Association between Blood Ammonia Level and Severity of Portal Hypertensive Gastropathy in Egyptian Patients with Post Hepatitis C Virus Cirrhosis

Original Article

Marwa Ahmed Mohamed, Moataz Mohamed Sayed, Eslam Safwat, Al sayed Hasan Mohamed Hasan and Nouran Mohamed Said

Department of Internal Medicine, Gastroenterology and Hepatology Unit, Ain Shams University, Cairo, Egypt

ABSTRACT

Background: Portal hypertensive gastropathy (PHG) is a prevalent consequence of portal hypertension (PHT), impacting between 20–98% of individuals with cirrhosis. Given that PHT arises as a result of liver cirrhosis, serum biomarkers such as blood ammonia levels may serve as non-invasive indicators for the presence and severity of PHG.

Aim of the Work: To evaluate the relationship between blood ammonia levels and the severity of PHG in Egyptian cirrhotic patients with hepatitis C virus (HCV) infection.

Patients and Methods: This case-control study included 100 HCV-related cirrhotic patients from Ain Shams University Hospital and Kafr-El Sheikh Liver Center. Patients were categorized into four groups based on the presence of esophageal varices (OV) and PHG. Clinical, laboratory, ultrasonographic, and endoscopic evaluations were performed. Serum ammonia levels were measured using EDTA-anticoagulated samples.

Results: Blood ammonia levels were significantly elevated in patients with severe PHG (154.9 ± 16.3 µg/dL) compared to mild PHG (110.8 ± 19.5 µg/dL, $P < 0.001$). Ammonia levels correlated with PHG severity score (r = 0.830, $P < 0.001$), Child-Pugh score (r = 0.554, $P = 0.004$), portal vein diameter (r = 0.540, $P = 0.005$), and spleen size (r = 0.778, $P < 0.001$). At a cutoff of >120 µg/dL, ammonia had 100% sensitivity, 92.3% specificity, and 96.2% accuracy in differentiating severe from mild PHG.

Conclusion: Serum ammonia is a strong predictor of PHG severity in cirrhotic patients, correlating with endoscopic and ultrasonographic parameters. It may serve as a valuable non-invasive biomarker for risk stratification in PHG.

Key Words: Ammonia, Cirrhosis, Non-Invasive Marker, Portal Hypertensive Gastropathy, Portal Hypertension.

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Corresponding Author: Marwa Ahmed Mohamed, Internal Medicine Department, Gastroenterology and Hepatology Unit, Ain Shams University, Cairo, Egypt, **Tel.:** +201014390050, **E-mail**: Marwasakr@med.asu.edu.eg

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INTRODUCTION

The final stage of chronic liver disease, cirrhosis, is marked by the formation of nodules and the liver's architectural deformity, which eventually results in portal hypertension (PHT). An increase in portal venous pressure that causes a hepatic venous pressure gradient (HVPG) more than 10 mmHg is known as clinically significant PHT (CSPH) [1].

Portal hypertensive gastropathy (PHG) is a prevalent stomach mucosal disorder found in individuals with PHT. Its pathophysiology is believed to involve both hyperemia and gastric congestion. Increased mucosal blood flow in cirrhotic patients with PHG compared to those without supports this hypothesis. Other contributing factors may include mucosal ischemia, heightened nitric oxide synthase activity, and inflammation resulting from altered blood flow due to PHT. The severity of gastropathy is influenced by portal pressure, hepatic vascular resistance, and the degree of hepatic perfusion impairment [2].

PHG is often identified after an endoscopy for another purpose (e.g., to check for esophageal varices) and is often asymptomatic. However, bleeding may happen when ectatic veins burst because the stomach mucosa is friable in the context of PHG. While severe and acute bleeding is certainly possible, chronic bleeding is more typical. Patients experiencing persistent bleeding often present with iron deficiency anemia and/or occult blood in their stool. In cases of acute hemorrhage, clinical manifestations such as hematemesis, melena, or hematochezia may occur, varying in severity based on the extent of blood loss [3].

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It is anticipated that 3 to 60% of PHG patients will experience chronic bleeding, and 2 to 12% may experience acute bleeding. Ninety to ninety-five percent of patients who experience acute bleeding have severe PHG [4].

The liver converts ammonia to urea, which is one of the primary products of nitrogen metabolism. Patients with cirrhosis have higher serum levels of this neurotoxin because to reduced hepatic function and the development of portosystemic shunts [5]. Hepatic stellate cells (HSC) are activated as a result of oxidative stress brought on by elevated blood ammonia levels in cirrhotic patients. Liver stiffness is increased and extracellular matrix deposition is induced by stellate cell activation. Considering the role stellate cell activation plays in PHT and hepatic fibrogenesis, elevated blood ammonia may contribute significantly to disease progression by inducing this cellular activation [6]. A study investigating the effects of ammonia reduction both in vitro and in vivo demonstrated a decline in HSC activation markers and the restoration of HSC function. These findings indicate that ammonia may serve as a potential therapeutic target for mitigating PHT[7].

AIM OF THE WORK

This study aimed to evaluate the predictive value of blood ammonia levels as a non-invasive marker for assessing the severity of PHG. Additionally, the correlation of this parameter with endoscopic findings, ultrasonographic features, and the Child-Pugh classification was investigated.

PATIENTS AND METHODS

This case-control study involved 100 Egyptian patients with cirrhosis, recruited from the Hepatology and Gastroenterology Unit of Ain Shams University Hospital and Kafr-El Sheikh Liver Center. It was carried out from October 2020 to November 2021.

ETHICAL CONSIDERATIONS

Approval was obtained from the Research Ethics Committee at the Faculty of Medicine, Ain Shams University (FMASU MSO 3/ 2025).

Grouping

One hundred HCV related cirrhotic patients were included in the current study. Participants in the study were subdivided into 4 equal groups: Group I: Patients exhibiting oesophageal varices (OV) and PHG. Group II: Patients with OV only. Group III: Patients with PHG only. Group IV: Patients with no OV or PHG as a control group.

Eligibility Criteria:

The study employed stringent exclusion criteria during participant selection to minimize confounding factors. Patients with hepatocellular carcinoma, hepatic encephalopathy, alcohol consumption, or concomitant medications that could affect outcomes were excluded. Additional exclusions included individuals undergoing primary prophylaxis for variceal bleeding with beta-blockers, those with portal vein thrombosis, patients on oral anticoagulants, and individuals with acute gastrointestinal hemorrhage within the prior two weeks. Moreover, patients with prior interventions for esophageal varices, such as band ligation or sclerotherapy, those with Gastric Antral Vascular Ectasia (GAVE) treated with argon photocoagulation, and individuals contraindicated for endoscopic evaluation—such as clinically unstable patients or those with severe cardiopulmonary disease or hematological disorders—were also excluded.

Patients underwent the following:

Full evaluation was performed, including meticulous history taking, clinical examination, and extensive laboratory tests. The tests included a complete blood count (CBC), liver function tests—consisting of serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), total and direct bilirubin, serum albumin, and international normalized ratio (INR)—and serum creatinine levels. Furthermore, viral serology for hepatitis C virus antibodies (HCV Ab) and hepatitis B surface antigen (HBsAg) was conducted, in conjunction with the assessment of serum blood ammonia levels.

Abdominal Ultrasonography and Portal Vein Duplex

Real time abdominal ultrasonography was done. The liver's size, echogenicity, parenchyma, and localized lesions were all examined by ultrasonography. The biliary system and portal vein were also inspected. The size and texture of the spleen were assessed. Ascites was assessed for presence. The pancreas, kidneys, and para-aortic lymph nodes were among the other abdominal organs that were inspected. Portal vein Doppler study was done: to determine the direction of portal vein blood flow and PV diameter, and to rule out PVT.

Upper Gastrointestinal Endoscopy (UGI)

All patients had upper GI endoscopy conducted by seasoned endoscopists who were unaware of group assignments to mitigate observer bias. The categorization and evaluation of PHG were founded on the Baveno III scoring system. A modest mucosal mosaic pattern was designated a value of 1, but a severe pattern was assigned a score of 2. Isolated red markings received a score of 1, whereas confluent red markings were assigned a value of 2. The existence of GAVE was noted, with an extra 2 points allocated if flat or slightly elevated red stripes extending from the pylorus to the antrum and gastric body were observed. PHG severity was classified as mild for scores ≤ 3 and severe for scores ≥ 4 [8].

Collection of samples and quantification of ammonia

Ethylenediaminetetraacetic acid (EDTA) was the preferred anticoagulant due to its ability to minimize

red blood cell ammonia synthesis. Blood samples were obtained from a stasis-free vein in fasting individuals, ensuring that smoking was prohibited for a minimum of nine hours before collection. The tubes were completely filled, securely stoppered, and immediately placed on ice. Centrifugation was performed at 4°C, and analysis was conducted within 30 minutes of venipuncture to maintain sample integrity.

Statistical analysis

The collected data were analyzed using SPSS version 26.00 software (Spss Inc, Chicago, ILL Company). Categorical data were presented as numbers and percentages while quantitative data were expressed as mean ± standard deviation or median, range, and IQR. Chi-square test (X^2), Fisher's exact test, "Z" test, Spearman's correlation coefficient (rho), student "t" test, Man Whitney U test, ANOVA and Kruskal Wallis test were used as tests of significance. Significant ANOVA and Krauskal Wallis tests were followed by post hoc multiple comparisons using Bonferroni and Bonferroni adjusted Mann Whitney respectively to detect the significant pairs. *P-value* <0.05 was considered significant.

RESULTS

Males constituted 60.0% in Group I, 76.0% in Group II, 56.0% in Group III, and 64.0% in Group IV, while females accounted for 40.0%, 24.0%, 44.0%, and 36.0%, respectively. The chi-square test indicated no statistically significant disparity in sex distribution among the groups ($\chi^2 = 2.431$, df = 3, $P = 0.488$), indicating that gender was similarly distributed across the study groups.

The analysis demonstrated a statistically significant difference among the study groups in terms of age, Child-Pugh score, spleen size, portal vein diameter (PVD), and portal vein blood flow velocity (PVV). The post hoc Tukey's test indicated that Group IV exhibited considerably lower values than the other groups ($P < 0.05$), especially for age, spleen size, PVD, and PVV (Table 1).

Table 1: Comparative analysis of the studied groups based on age, Child-Turcotte-Pugh score, and abdominal ultrasound findings.

	Age (Years)		ANOVA (F)	*P-value*
Study Group	Age Range	Mean ± SD		
Group I	49 – 70 [4]	57.28 ± 5.16 [4]		
Group II	41 – 67 [4]	54.64 ± 6.33 [4]	10.225	<0.001*
Group III	39 – 70 [4]	54.32 ± 7.55 [4]		
Group IV	32 – 70 [1,2,3]	46.76 ± 8.75 [1,2,3]		
	Child Pugh Score			
Study Group	Score Range	Mean ± SD		
Group I	5 – 11[4]	6.28 ± 1.67 [4]		
Group II	5 – 10 [4]	6.40 ± 1.71[4]	4.155	0.008*
Group III	5 - 10	6.08 ± 1.50		
Group IV	5 – 7 [1,2]	5.12 ± 0.44 [1,2]		
	Spleen size (cm)			
Study Group	Range	Mean ± SD		
Group I	14 - 21[4]	17.24 ± 1.62 [4]		
Group II	13.8 – 20 [4]	16.88 ± 1.89 [4]	13.595	<0.001*
Group III	13.5 – 19 [4]	16.61 ± 1.31 [4]		
Group IV	12.9 - 17.5 [1,2,3]	14.66 ± 1.23 [1,2,3]		
	PVD (mm)			
Study Group	Range	Mean ± SD		
Group I	10 – 18 [4]	14.62 ± 1.93 [4]		
Group II	11 – 17 [4]	14.28 ± 1.56 [4]	7.628	<0.001*
Group III	11 – 18 [4]	14.76 ± 1.45 [4]		
Group IV	10 – 15 [1,2,3]	12.82 ± 1.44 [1,2,3]		

	P.V blood Flow Velocity (cm/s)			
Study Group	Range	Mean ± SD		
Group I	9 - 24	14.60 ± 4.54		
Group II	9 - 26	16.72 ± 5.02	16.052	<0.001*
Group III	10 - 22	16.24 ± 3.60		

ANOVA: Analysis of Variance, cm: Centimeter, mm: Millimeter, P.V: Portal Vein, PVD: Portal Vein Diameter, SD: Standard Deviation, *: significant *p-value* <0.05, 1: significantly different from group I, 2: significantly different from group II, 3: significantly different from group III, 4: significantly different from group IV.

The direction of portal vein blood flow differed significantly among the studied groups ($P < 0.001$). Hepatopetal flow was most frequent in Group IV (96%), while it was less common in Groups I, II, and III (28%, 48%, and 56%, respectively). Hepatofugal flow was observed in 40% of patients in Groups I and II, 32% in Group III, and only 4% in Group IV. Bidirectional flow was detected in 32% of Group I and 12% of Groups II and III, but was absent in Group IV (Table 2).

Table 2: Comparison between studied groups regarding direction of portal vein blood flow.

P.V Flow direction	Study Group								Chi-Square	
	Group I		Group II		Group III		Group IV			
	N	%	N	%	N	%	N	%	X^2	*P-value*
Hepatofugal	10	40.00	10	40.00	8	32.00	1	4.00		
Bidirectional	8	32.00	3	12.00	3	12.00	0	0.00		
Hepatopetal	7	28.00	12	48.00	14	56.00	24	96.00	27.700	<0.001*
Total	25	100.00	25	100.00	25	100.00	25	100.00		

N: number, P.V: Portal Vein, *: significant *p-value* <0.05, X^2: Chi-Square

Hemoglobin levels were significantly lower in Groups I, II, and III compared to Group IV ($P = 0.006$). Platelet counts and white blood cell counts also showed statistically significant differences among groups ($P < 0.001$ for both). Significant group differences were also noted in total and direct bilirubin, urea, albumin, INR, and blood ammonia levels (all $P < 0.001$). However, there were no significant differences in ALT, AST, or creatinine levels (Table 3).

Table 3: Comparison between studied groups regarding different laboratory variables.

Parameter	Group I	Group II	Group III	Group IV	ANOVA (F)	*P-value*
HGB (g/dL)	10.17 ± 1.08 [4]	10.25 ± 1.19 [4]	10.56 ± 1.23	11.39 ± 1.71 [1,2]	4.437	0.006*
PLT (×10⁹/L)	108.04 ± 26.75 [4]	93.56 ± 16.5 [1,4]	109.52 ± 24.8	125.00 ± 18.50 [1,2]	8.492	<0.001*
WBC (×10⁹/L)	5.08 ± 1.24 [3,4]	4.79 ± 1.80 [3,4]	6.07 ± 1.10 [1,2]	6.36 ± 1.02 [1,2]	8.195	<0.001*
ALT (U/L)	23.48 ± 8.07 [4]	24.80 ± 8.18 [4]	23.96 ± 9.45	26.28 ± 7.75 [1,2]	0.536	0.659
AST (U/L)	24.16 ± 7.39 [4]	25.96 ± 6.74 [4]	25.16 ± 8.22	23.48 ± 7.58 [1,2]	0.530	0.663
BIL T (mg/dL)	1.85 ± 0.55 [4]	1.86 ± 0.57 [4]	1.53 ± 0.46	1.26 ± 0.35 [1,2]	8.634	<0.001*
BIL D (mg/dL)	0.63 ± 0.28 [4]	0.61 ± 0.26 [4]	0.47 ± 0.21	0.38 ± 0.13 [1,2]	7.088	<0.001*
Urea (mg/dL)	34.72 ± 7.32 [3,4]	33.68 ± 7.26 [3,4]	27.96 ± 5.44 [1,2]	29.04 ± 4.00 [1,2]	7.383	<0.001*
Creatinine (mg/dL)	1.07 ± 0.19 [4]	1.04 ± 0.16 [4]	1.02 ± 0.16	0.95 ± 0.12 [1,2]	2.424	0.070
Albumin (g/dL)	3.53 ± 0.43 [4]	3.46 ± 0.40 [4]	3.56 ± 0.31 [4]	3.98 ± 0.17 [1,2,3]	12.221	<0.001*
INR	1.35 ± 0.17 [4]	1.39 ± 0.19 [3,4]	1.28 ± 0.13 [2,4]	1.12 ± 0.10 [1,2,3]	15.264	<0.001*
Ammonia (µg/dL)	160.28 ± 29.08 [2,3,4]	134.84 ± 28.20 [1,4]	130.20 ± 28.56 [1,4]	78.08 ± 23.32 [1,2,3]	39.623	<0.001*

ALT: Alanine Aminotransferase, Albumin: Serum Albumin, AMMONIA: Serum Ammonia, ANOVA: Analysis of Variance, AST: Aspartate Aminotransferase, BIL D: Direct Bilirubin, BIL T: Total Bilirubin, Creatinine: Serum Creatinine, F: F-statistic (ANOVA), HGB: Hemoglobin, INR: International Normalized Ratio, PLT: Platelet Count, *P-value*: Probability Value, SD: Standard Deviation, TUKEY'S Test: Post Hoc Comparison Using Tukey's Method, Urea: Serum Urea, WBC: White Blood Cell Count, *: significant *p-value* <0.05, 1: significantly different from group I, 2: significantly different from group II, 3: significantly different from group III, 4: significantly different from group IV.

A significant relationship was found between PHG severity and several variables among Group III patients. Severe PHG was more frequently observed in patients with higher Child-Pugh classes (P = 0.024), those with mild to moderate ascites (P = 0.007), and those exhibiting hepatofugal or bidirectional blood flow (P < 0.001). Additionally, severe PHG was significantly associated with severe mosaic patterns (P < 0.001), red markings (P<0.001), and the presence of GAVE (P=0.009) (Table 4).

Table 4: Association between the Severity of Portal Hypertensive Gastropathy (Group III) and Demographic, Clinical, and Endoscopic Features.

Group III		PHG Severity				Chi-Square	
		Mild		Severe			
		N	%	N	%	X^2	*P-value*
Sex	Male	7	53.85	7	58.33	0.051	0.821
	Female	6	46.15	5	41.67		
Child Pugh class	Child A	12	92.31	5	41.67	7.426	0.024*
	Child B	1	7.69	6	50.00		
	Child C	0	0.00	1	8.33		
Ascites	No ascites	12	92.31	5	41.67	7.354	0.007*
	Mild to moderate	1	7.69	7	58.33		
P.V blood Flow direction	Hepatofugal	0	0.00	8	66.67	21.280	<0.001*
	Bidirectional	0	0.00	3	25.00		
	Hepatopetal	13	100.00	1	8.33		
PHG Mosaic pattern	Mild	13	100.00	1	8.33	21.280	<0.001*
	Severe	0	0.00	11	91.67		
PHG Red markings	Mild	13	100.00	1	8.33	21.280	<0.001*
	Severe	0	0.00	11	91.67		
GAVE	No	13	100.00	7	58.33	6.771	0.009*
	Yes	0	0.00	5	41.67		

GAVE: Gastric Antral Vascular Ectasia, HGB: Hemoglobin, INR: International Normalized Ratio, PHG: Portal Hypertensive Gastropathy, P.V: Portal Vein, *: significant *p-value* <0.05.

Blood ammonia levels among Group III patients showed a significant relationship with several clinical and endoscopic variables. Higher ammonia levels were observed in patients with advanced Child-Pugh class (P = 0.037), mild to moderate ascites (P = 0.011), hepatofugal or bidirectional flow (P < 0.001), severe mosaic pattern and red markings (P < 0.001 for both), and presence of GAVE (P = 0.032). No significant difference was observed based on sex (Table 5).

Table 5: Relationship of blood ammonia level with different variables (in group III).

Group III		AMMONIA (µg/dL)				T-Test or ANOVA	
		N	Mean	±	SD	T or F	*P-value*
Sex	Male	14	138.143	±	29.672	1.621	0.119
	Female	11	120.091	±	24.753		
Child Pugh class	Child A	17	120.588	±	28.957	3.829	0.037*
	Child B	7	149	±	13.589		
	Child C	1	162	±	0		
Ascites	No ascites	17	120.588	±	28.957	-2.774	0.011*
	Mild to moderate	8	150.625	±	13.394		
P.V blood Flow direction	Hepatofugal	8	151	±	16.767	19.169	<0.001*
	Bidirectional	3	165.333	±	10.693		
	Hepatopetal	14	110.786	±	19.498		
PHG Mosaic pattern	Mild	14	110.786	±	19.498	-6.029	<0.001*
	Severe	11	154.909	±	16.263		
PHG Red markings	Mild	14	109.929	±	18.04	-6.799	<0.001*
	Severe	11	156	±	15.08		
GAVE	No	20	124.2	±	28.31	-2.276	0.032*
	Yes	5	154.2	±	13.719		

GAVE: Gastric Antral Vascular Ectasia, HGB: Hemoglobin, INR: International Normalized Ratio, PHG: Portal Hypertensive Gastropathy, P.V: Portal Vein, *: significant *p-value* <0.05.

Total PHG score among Group III patients significantly varied based on Child-Pugh class ($P = 0.003$), ascites grade ($P = 0.001$), and portal vein blood flow direction ($P < 0.001$). Higher PHG scores were observed in patients with severe mosaic patterns, red markings (both $P < 0.001$), and GAVE ($P < 0.001$). No significant difference in PHG score was found between males and females (Table 6).

Table 6: Relationship of total PHG score (group III) with different variables.

Group III		PHG score				T-Test or ANOVA	
		N	Mean	±	SD	T or F	*P-value*
Sex	Male	14	4.214	±	1.311	0.630	0.535
	Female	11	3.909	±	1.044		
Child Pugh class	Child A	17	3.588	±	0.939	7.503	0.003*
	Child B	7	5.000	±	1.000		
	Child C	1	6.000	±	0.000		
Ascites	No ascites	17	3.588	±	0.939	-3.752	0.001*
	Mild to moderate	8	5.125	±	0.991		
P.V blood Flow direction	Hepatofugal	8	5.250	±	0.463	52.296	<0.001*
	Bidirectional	3	5.333	±	0.577		
	Hepatopetal	14	3.143	±	0.535		
	Small	0	3.000	±	0.000		
PHG Mosaic pattern	Mild	14	3.143	±	0.535	-10.441	<0.001*
	Severe	11	5.273	±	0.467		
PHG Red markings	Mild	14	3.143	±	0.535	-10.441	<0.001*
	Severe	11	5.273	±	0.467		
GAVE	No	20	3.700	±	0.979	-4.138	<0.001*
	Yes	5	5.600	±	0.548		

GAVE: Gastric Antral Vascular Ectasia, HGB: Hemoglobin, INR: International Normalized Ratio, PHG: Portal Hypertensive Gastropathy, P.V: Portal Vein, *: significant *p-value* <0.05.

In Group III patients, blood ammonia levels showed a strong positive correlation with PHG score, and both were significantly associated with markers of advanced liver disease and portal hypertension. Ammonia correlated positively with total bilirubin, Child-Pugh score, portal vein diameter, spleen size, and negatively with albumin and portal vein flow velocity. Similarly, PHG score correlated positively with total bilirubin, Child-Pugh score, portal vein diameter, spleen size, and negatively with albumin and portal vein flow velocity, indicating that both parameters reflect the severity of liver dysfunction and portal hypertension in this group (Table 7).

Table 7: Correlations of blood Ammonia level and PHG score with different variables among group (III) patients.

Correlations				
Group III	AMMONIA (µg/dL)		PHG score	
	r	*P-value*	r	*P-value*
PHG score	0.830	<0.001*		
HGB	-0.320	0.118	-0.396	0.050*
PLT	-0.408	0.043*	-0.287	0.164
WBC	-0.192	0.358	-0.158	0.452
ALT	-0.120	0.569	-0.349	0.088
AST	-0.035	0.866	-0.202	0.333
Total bilirubin	0.427	0.033*	0.439	0.028*
Direct bilirubin	0.320	0.119	0.346	0.091
Urea	0.231	0.267	0.349	0.087
Creatinine	0.350	0.086	0.381	0.060
Albumin	-0.481	0.015*	-0.697	<0.001*
INR	0.384	0.058	0.634	0.001*
Child Pugh score	0.554	0.004*	0.652	<0.001*
Portal vein diameter	0.540	0.005*	0.611	0.001*
Spleen size	0.778	<0.001*	0.679	0.001*
P.V flow Velocity (cm/s)	-0.776	<0.001*	-0.814	<0.001*

*: significant *p-value* <0.05, ALT: Alanine Aminotransferase, AMMONIA: Ammonia, AST: Aspartate Aminotransferase, HGB: Hemoglobin, INR: International Normalized Ratio, PHG: Portal Hypertensive Gastropathy, PLT: Platelet Count, P.V: Portal Vein, WBC: White Blood Cell Count.

At the best cut of value >120mg/dl, on comparing the sensitivity and specificity of serum ammonia for discriminating between mild and severe PHG, the sensitivity was 100%, specificity was 92.31% and accuracy of the test was 96.2% (Figure 1).

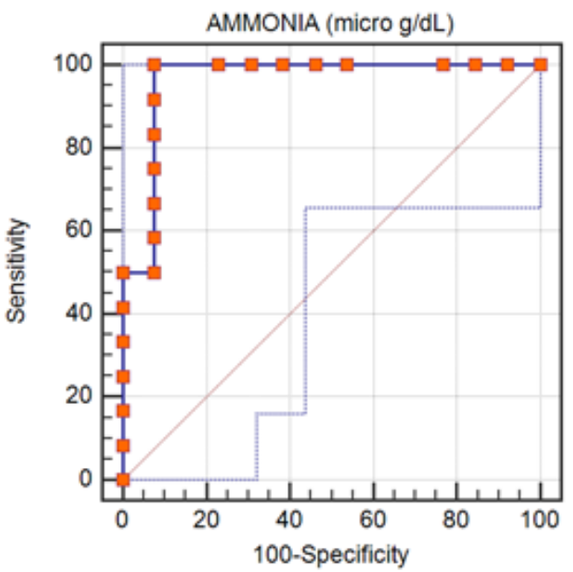

Fig. 1: ROC curve of Serum ammonia to discriminate between mild and severe PHG.

DISCUSSION

PHG is a known complication of both cirrhotic and non-cirrhotic PHT and carries the potential to cause either acute gastrointestinal bleeding or chronic blood loss. Endoscopic findings typically include a mosaic-like mucosal pattern resembling snake skin, often accompanied by red spots [9].

In cirrhotic patients, portosystemic shunting facilitates ammonia transfer into systemic circulation, contributing to elevated blood ammonia levels. This suggests that blood ammonia could serve as a useful marker for the presence and severity of PHT and PHG [10]. The study aimed to explore the relationship between blood ammonia and PHG severity.

The current results showed no statistically significant difference in gender distribution between the study groups, although a male predominance was observed. This finding was also noted by ***Kim et al.,*** who reported that over 60% of chronic liver disease and cirrhosis cases occurred in males [11].

A significant difference was observed in patient age across the groups. This was not consistent with the findings of ***Arulprakash et al.,*** who found no significant difference regarding age between cirrhotic patients with and without esophageal varices (OVs). This discrepancy could be attributed to the broader age range in Arulprakash's cohort (17–74 years) [12].

As regards platelet count, the current results showed significantly lower levels in patients with OVs and/or PHG compared to controls. This is consistent with ***Abd-Elsalam et al.***, who reported that patients with thrombocytopenia had a significantly higher frequency of large varices [13]. Similar results were observed by ***Abbasi et al.***, who found an inverse relationship between thrombocytopenia and variceal grade. The mechanisms behind thrombocytopenia in cirrhosis include splenic sequestration, reduced thrombopoietin production, and potential bone marrow suppression [14, 15].

Serum albumin levels were significantly lower in patients with OVs and PHG compared to controls, reflecting worsening liver function. This is in agreement with findings from ***Kazemi et al.***, who noted that hypoalbuminemia was associated with both the presence and severity of OVs [16]. On the other hand, studies by ***Duah et al.*** and ***El-Kalla et al.*** Found no significant differences in albumin levels between patients and controls, suggesting possible regional or methodological variations [17, 18].

Elevated INR levels were detected in patients with OVs and PHG, compared to those without. This aligns with the results of ***Fontana et al.***, who observed worsening coagulation profiles with increasing cirrhosis severity [19]. Conversely, ***El-Kalla et al.*** did not report significant INR differences between patients and controls [18].

The analysis also revealed significantly elevated bilirubin levels among patients with OVs and PHG. These findings are supported by studies such as ***Fontana et al.*** and ***El-Kalla et al.***, who also observed hyperbilirubinemia in patients with advanced portal hypertension [18, 19].

In terms of ultrasonographic findings, the current results indicated that PVD was significantly greater in patients with OVs and PHG. This was consistent with ***Sarwar et al.***, who concluded that a PVD >11 mm on ultrasound is predictive of esophageal varices [20]. This finding highlights the value of PVD as a non-invasive predictor of portal hypertension severity [21].

Splenic longitudinal diameter (SLD) was significantly increased in patients with PHG and OVs, supporting its value as a non-invasive indicator of portal pressure. This aligns with findings by ***Esmat et al.***, who noted a significant relationship between splenomegaly and variceal presence [22]. However, ***El-Kalla et al.*** found no significant association, which came in contrast to our findings [18].

Portal vein flow direction also showed marked differences between groups. Hepatopetal flow predominated in the control group, while altered flow patterns (hepatofugal or bidirectional) were more prevalent among those with OVs and PHG. These alterations have been previously described by von ***Herbay et al.*** and ***Mittal et al.***, who linked them to advanced liver dysfunction and increased PHT [23, 24].

PVV was significantly lower in groups with PHG and OVs, which reinforces the use of PVV as a non-invasive marker for evaluating variceal risk. This was supported by ***Elkenawy et al.*** and ***Shastri et al.***, who found that PVV correlated inversely with variceal severity and liver dysfunction [25, 26]. ***Kayacetin et al.*** further added that low PVV may also reflect bleeding risk in cirrhotic patients [27].

The current study highlighted a strong relationship between blood ammonia levels and the presence and severity of PHG. Mean serum ammonia was significantly higher in patients with both OVs and PHG, with the highest levels recorded in Group I. Elevated ammonia levels were also observed in previous studies, including by ***El-Kalla et al.*** and ***Ali et al.***, who both reported increased ammonia in cirrhotic patients with varices [18, 28].

Additional literature further supports the importance of ammonia in portal hypertension pathogenesis. ***Jalan et al.*** Demonstrated that ammonia induces HSC activation, contributing to fibrogenesis and increased portal pressure. This process includes metabolic disruption, cellular hypertrophy, and upregulation of pro-inflammatory

genes[7]. ***Bode et al.*** also suggested that ammonia affects hepatic stellate cell phenotype by altering glutamine synthetase expression, reinforcing its role in disease progression [29].

The current results showed that elevated ammonia is not only a consequence of portosystemic shunting but also a contributor to worsening portal hypertension. Therefore, measuring ammonia may have diagnostic and prognostic implications. These findings support exploring ammonia-lowering therapies as potential strategies to reduce PHT and PHG severity [7, 10, 28].

Among patients with PHG (Group III), 52% had mild PHG and 48% had severe PHG based on the Baveno III score. These distributions are comparable to previously reported prevalence ranges for PHG grades [9].

A significant relationship was observed between PHG severity and Child-Pugh score (P = 0.005), supporting previous findings by ***Taranto et al.***, who reported a clear association between PHG severity and hepatic functional reserve [30]. In contrast, studies by ***Abbasi et al.*** and ***El-Kalla et al.*** did not find a statistically significant relationship[18,31].

Discrepancies between studies may result from differences in PHG grading systems, variations in population characteristics, or differing use of medications such as beta-blockers or prior endoscopic interventions.

The present findings also indicated significantly larger spleen size and PVD, and lower PVV in patients with severe PHG compared to those with mild disease, indicating a direct relationship with portal hypertension severity. These observations are consistent with ***Kim et al.***, who reported that HVPG was significantly higher in patients with severe PHG [32].

Serum ammonia levels were markedly higher in patients with severe PHG than in those with mild PHG, and this difference was statistically significant ($P < 0.001$). A strong positive relationship was noted between blood ammonia and PHG score. This aligns with prior research by ***El-Kalla et al.***, supporting the hypothesis that elevated ammonia reflects both liver dysfunction and portosystemic shunting [18].

Moreover, ammonia-induced activation of hepatic stellate cells may represent a target for therapy, as demonstrated by ***Jalan et al.***, who reported that ammonia-lowering therapy led to reduced HSC activation and lower portal pressures in experimental models [7].

ROC analysis in this study identified a cutoff value of >120 µg/dL for distinguishing severe from mild PHG. At this threshold, serum ammonia demonstrated 100% sensitivity, 92.31% specificity, and 96.2% accuracy. While previous studies such as ***El-Hefny et al.*** and ***Montasser et al.*** reported thresholds for detecting esophageal varices using ammonia, to our knowledge, this is the first study to propose a cutoff for PHG severity [33, 34]. This highlights the clinical utility of serum ammonia as a potential non-invasive biomarker for risk stratification in PHG, supporting its incorporation into future diagnostic protocols.

Finally, there are several limitations to this study, including the small sample size and potential population heterogeneity. These limitations highlight the preliminary nature of our findings and underscore the need for future longitudinal studies.

CONCLUSION

Blood ammonia concentrations are associated with the occurrence, intensity, and grading of PHG in cirrhosis.

CONFLICTS OF INTEREST

There is no conflicts of interest.

DECLARATION OF CONFLICTING INTERESTS

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CONTRIBUTION

M.A.M., M.M.S., E.S.M., A.H.M. and A.E.M. conceived and planned the experiments. M.A.M. contributed to sample preparation. All authors provided critical feedback and helped shape the research, analysis and manuscript. All authors have read and approved the manuscript.

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دراسه مدى الارتباط بين مستوى الامونيا فى الدم و حده اعتلال المعدة الناتج عن ارتفاع الضغط البابى فى المرضى المصريين الذين يعانون من تليف كبدى ناتج عن فيروس (سى)

مروه احمد محمد، معتز محمد سيد، اسلام صفوت، السيد حسن محمد حسن و نوران محمد سعيد

قسم الطب الباطني، وحدة أمراض الجهاز الهضمي والكبد، جامعة عين شمس، القاهرة، مصر

المقدمة: يُعد اعتلال المعدة الناجم عن فرط ضغط الدم البابي أحد المضاعفات الرئيسية لفرط ضغط الدم البابي، حيث يحدث في حوالي ٢٠-٩٨٪ من مرضى تليف الكبد. ونظرًا لأن فرط ضغط الدم البابي هو نتيجة ثانوية لتليف الكبد، فإن المؤشرات الحيوية في الدم، مثل مستوى الأمونيا، قد تكون بمثابة مؤشر غير جراحي للتنبؤ بوجود اعتلال المعدة الناجم عن فرط ضغط الدم البابي وشدته.

هدف الدراسة: تقييم العلاقة بين مستوى الأمونيا في الدم وشدة اعتلال المعدة الناجم عن فرط ضغط الدم البابي لدى المرضى المصريين المصابين بتليف الكبد الناتج عن عدوى فيروس التهاب الكبد الوبائي سي.

المرضى والطرق: تم إجراء دراسة حالات وشواهد على مجموعة من المرضى المصابين بتليف الكبد، تم تجنيدهم من مستشفى جامعة عين شمس ومركز الكبد بكفر الشيخ بعد الحصول على الموافقة المستنيرة. تم تقسيم المشاركين إلى أربع مجموعات متساوية وفقًا لوجود دوالي المريء واعتلال المعدة الناجم عن فرط ضغط الدم البابي .تم قياس مستويات الأمونيا في الدم باستخدام عينات الدم المعالجة بمضاد التخثر إيثيلين دياميين رباعي الأسيتيك. كما شملت التقييمات الإضافية الفحوصات المخبرية الروتينية، وتصوير البطن بالموجات فوق الصوتية، ودراسة دوبلر للوريد البابي، وتنظير الجهاز الهضمي العلوي. تم تصنيف شدة اعتلال المعدة بناءً على النتائج التنظيرية، مع الأخذ في الاعتبار العوامل المتداخلة مثل استخدام الأدوية أثناء التحليل.

النتائج: أظهرت الدراسة ارتفاعًا ملحوظًا في مستوى الأمونيا في الدم لدى المرضى الذين يعانون من اعتلال المعدة الناجم عن فرط ضغط الدم البابي، سواء كان مصحوبًا بدوالي المريء أو غير مصحوب بها، مقارنة بالمرضى غير المصابين بهذه المضاعفات. كما تبين أن مستوى الأمونيا في الدم يمثل مؤشرًا عالي الدقة في التمييز بين الدرجات المختلفة لاعتلال المعدة. بالإضافة إلى ذلك، ارتبط ارتفاع مستوى الأمونيا في الدم بزيادة شدة تليف الكبد، وفقًا لتصنيف تشايلد-بوغ، كما أظهر علاقة إيجابية مع حجم الطحال.

الخلاصة: يُعد مستوى الأمونيا في الدم مؤشرًا واعدًا غير جراحي لتقييم شدة اعتلال المعدة الناجم عن فرط ضغط الدم البابي لدى مرضى تليف الكبد المصاحب لعدوى فيروس التهاب الكبد الوبائي سي. هناك حاجة إلى المزيد من الدراسات للتحقق من جدواه السريرية ووضع إرشادات لإدماجه في الممارسة الطبية الروتينية.