Serum serotonin as a non-invasive marker of portal hypertensive gastropathy in Egyptian patients with HCV-related liver cirrhosis

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Abstract

Background and study aims: **Portal hypertensive gastropathy (PHG) is an important complication of portal hypertension (PHT) in cirrhotic patients. We aimed in the current study to investigate the validity of serum serotonin as a probable non-invasive marker for PHG in cirrhotic patients with PHT. We conducted this study on 100 HCV-related cirrhotic patients divided into three groups according to their endoscopic findings; group I: patients with no endoscopic signs of PHG; group II: patients with mild PHG; and group III: patients with severe PHG. All subjects had routine laboratory investigations, serum serotonin level using ELISA kits, calculation of Child's score, abdominal ultrasound, and upper GIT endoscopy.**

Results: **Serum serotonin was significantly higher in those with PHG than those without (t= 5.128, p <0.001). Moreover, it was significantly higher in patients with severe degree of PHG than those with mild PHG (t=7.357, p<0.001). Furthermore, a significant positive correlation was observed between serum serotonin and Child Pugh score (t=7.357, p<0.001). Roc curve analysis revealed that serum serotonin at a level > 26.5 ng/ml had a 78.82% sensitivity, 73.33% specificity, and accuracy of 78% to discriminate between those with signs of PHG and those without.**

Conclusion: **Serum serotonin is a valuable non-invasive marker of PHG in HCV-cirrhotic patients. Furthermore, its serial measurements could be used to monitor disease progression.** (Acta gastroenterol. belg., **2022,** 85, **73-79**).

Keywords: Serotonin, PHG, portal hypertension, HCV, liver cirrhosis.

Introduction

Chronic Hepatitis C is one of the most important causes for liver cirrhosis, end-stage liver failure and hepatocellular malignancy (1,2). Portal hypertensive gastropathy (PHG) is an underappreciated complication of portal hypertension in cirrhotic patients. Erosive gastritis is seen in cirrhotic patients that is pathologically different from that gastritis seen in other patients without cirrhosis, as it results from mechanical backpressure from portal hypertension rather than mucosal derangement in non-cirrhotic patients. That was confirmed by reversal of erosive gastritis after lowering of elevated portal pressure by surgical decompression (3). PHG can affect any age with a prevalence that varies from 20% to 75% in portal hypertensive patients (4). The degree of portal hypertension and the severity of liver disease are the main predictors of PHG (5). The pathogenesis of PHG is inadequately understood. The most accepted underlying pathophysiology is hemodynamic changes that result in gastric mucosa congestion, which in turn activates the release of proinflammatory mediators rendering gastric mucosa vulnerable to ulceration and bleeding (6). PHG can be presented clinically with gastrointestinal bleeding with an incidence of about 2% to 20% of all cases of gastrointestinal bleeding (7). Upper GIT endoscopy is the most common diagnostic modality of PHG with multiple classifications emerged depending on the endoscopic findings (8-11).

Serotonin (5-hydroxytryptamine 5HT) is a molecule with dual function both as a central neurotransmitter and as a peripheral hormone (12). It binds to 5HT receptors on the membrane of the target cells. Serotonin as an enteric neurotransmitter exerts its function through modulation of the smooth muscles of the gut or through enteric nerves to influence blood flow (13). Excess serotonin in the serum is excreted in urine after converting to 5 hydroxy-indole acetic acid (14). In cirrhotic livers, the number of 5HT receptors in hepatic stellate cells (HSC) increases with an enhanced response to serotonin effect resulting in contraction of these cells and sinusoidal closure ending in elevation of portal pressure (15).

The current study aimed to evaluate the role of free serum serotonin in patients with HCV-related liver cirrhosis complicated with hypertensive gastropathy as a probable non-invasive diagnostic tool in such patients.

Methods

The current prospective case-control cross-sectional study was conducted on 100 HCV cirrhotic patients who were admitted to the Tropical Diseases and Internal Medicine Departments, Alexandria University Hospital, in the period from January 2018 to February 2020. Liver cirrhosis was diagnosed in participants of the study according to clinical characteristics, findings in

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abdominal ultrasonography and laboratory hepatic panel. Patients were divided according to Child's classification to those with well compensated liver disease, those with mild liver impairment and those with sever liver impairment. The proposal of the study was accepted by the Ethical Committee of Faculty of Medicine, Alexandria University according to the World Medical Association Declaration of Helsinki. Full description of the procedure was explained to the participants, and all of them signed the informed consent.

Exclusion criteria were hepatitis B viral infection (HBV), autoimmune hepatitis (AIH), alcohol intake, metabolic syndrome, hepatocellular carcinoma (HCC), portal vein or splenic vein thrombosis, neuropsychological disorders, schistosomiasis, and carcinoid syndrome. Patients receiving the following drugs were also excluded from the study; vasodilators, NSAIDs, and beta-blockers.

All participants were subjected to a full history taking and thorough clinical examination. Blood samples were collected from all participants, centrifuged, and stored at -20 C. Laboratory investigations include Complete blood picture, liver transaminases (ALT, AST), total and direct bilirubin, serum albumin, serum creatinine, blood urea, Prothrombin time (PT), HBsAg and HCV Abs by 3rd generation enzyme-linked Immunosorbent Assay (ELISA).

Measurement of serum serotonin level was done using ELISA kits obtained from LifeSpan BioSciences company (LS-F10593), with an assay range of 0.78-50 ng/ml.

Child turcotte-Pugh score (16) was calculated for all patients. Abdominal US was done for all patients to confirm liver cirrhosis, presence or absence of ascites, splenic size, splenic vein diameter, collateral, and portal hypertension.

Portal vein diameter caliber was used as an indirect tool to detect portal hypertension and thereby these patients were subjected to screening portal hypertensive gastropathy endoscopically.

Upper Gastrointestinal Endoscopy was done by an expert endoscopist using (Olympus GIF-Type Q240-Japan). After upper gastrointestinal tract endoscopy, the patients were classified into 3 groups according to Baveno III criteria (10); Group (I): HCV cirrhotic patients with no endoscopic signs of hypertensive gastropathy; group (II): HCV cirrhotic patients with mild hypertensive gastropathy; group (III): HCV cirrhotic patients with severe hypertensive gastropathy.

Signs in gastric endoscopy were mosaic-like or "snakeskin" patterns in mild PHG, cherry red spots in severe PHG, with signs of chronic bleeding and oozing being also seen.

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). The Kolmogorov- Smirnov was used to verify the normality of distribution of variables, Comparisons between groups for categorical variables were assessed using Chi-square test (Fisher's Exact or Monte Carlo correction). ANOVA was used for comparing the three studied groups and followed by Post Hoc test (Tukey) for pairwise comparison. Student t-test was used to compare two groups for normally distributed quantitative variables. Pearson coefficient was used to correlate between two normally distributed quantitative variables. Receiver operating characteristic curve (ROC) was used to determine the diagnostic performance of the markers, area more than 50% gives acceptable performance and area about 100% is the best performance for the test. Significance of the obtained results was judged at the 5% level.

Results

Study population

The current study involved 100 HCV-cirrhotic patients. According to the Child's classification, 13 patients were class A, 25 patients were class B, and 62 patients were class C.

Following upper gastrointestinal endoscopy, patients were divided into three groups according to Baveno III criteria: 15 patients with no signs of PHG (group I), 46 patients with signs of mild PHG (group II), and 39 patients with signs of severe PHG (group III). Table 1 represents the patients' distribution according to their Child's classification in relation to PHG.

Demographic data and clinical presentations

Demographic data, clinical presentations and laboratory findings of the studied patients were summarized in tables 2a, 2b and 3.

Table 1. — **Patients' distribution according to their Child's classification in relation to PHG:**

PORTAL HYPERTENSIVE GASTROPATHY (PHG)							
YES (85 patients)						No (15 patients)	
Child A		**Child B**	**Child C**			**Child A**	**Child B**
2		21	62			11	4
Mild PHG (46 patients**)**			**Severe PHG (**39 patients**)**				
Child A	**Child B**	**Child C**	**Child A**	**Child B**	**Child C**		
2	19	25	0	2	37		

Table 2a. — **Demographic data of the studied groups**

	Group I (n = 15)	Group II (n = 46)	Group III (n = 39)	Test of Sig.	p
Age (years)					
Mean ± SD. Median (Min. – Max.)	50.4 ± 6.3 51 (40-61)	46.5 ± 5.9 46.5 (33-58)	47.8 ± 5.1 50 (38-57)	F= 2.764	0.068
Sex					
Male Female	6 (40%) 9 (60%)	30 (65.2%) 16 (34.8%)	30 (76.9%) 9 (23.1%)	χ^2= 6.605*	0.037*

χ^2: **Chi square test. F**: **for ANOVA test. p:** p value for comparing between the three studied groups. *: Statistically significant at $p \leq 0.05$ **Group (I)**: HCV cirrhotic patients with no endoscopic signs of PHG. **Group (II)**: HCV cirrhotic patients with mild PHG. **Group (III)**: HCV cirrhotic patients with severe PHG.

Table 2b. — **Different clinical presentations in the studied groups**

Clinical presentation	Patient without PHG (n = 15)	Patient with PHG (n = 85)	χ^2	FEp
Ascites	0 (0%)	74 (87.1%)	50.226*	<0.001*
Dyspepsia	7 (46.7%)	63 (74.1%)	4.575	0.062
Abdominal pain	3 (20%)	32 (37.6%)	1.745	0.186
GIT bleeding	0 (0%)	14 (16.5%)	2.873	0.120
Altered bowel habits	1 (6.7%)	2 (2.4%)	0.815	0.389

χ^2: Chi square test FE: Fisher Exact. p: p value for comparing between the two studied groups. *: Statistically significant at $p \leq 0.05$

Table 3. — **Laboratory results of the studied groups**

	Group I (n = 15)	Group II (n = 46)	Group III (n = 39)	Test of Sig.	p
Hb (g/dL)					
Mean ± SD. Median (Min. – Max.)	12.8 ± 0.7 12.8(11.8-4.7)	10.1[a] ± 1.2 10.6(7.5-13.2)	8.8[ab] ± 1.3 8.7 (5.5-11.1)	F = 65.726*	<0.001*
Platelet (*10³/uL)					
Mean ± SD. Median (Min. – Max.)	195 ± 50.1 186 (145-350)	106.1[a] ± 31.5 99.5 (55-200)	86.9[ab] ± 23.6 87 (23-122)	F = 62.295*	<0.001*
Bilirubin (mg/dL)					
<2 2-3 >3 Mean ± SD. Median (Min. – Max.)	15 (100%) 0 (0%) 0 (0%) 1.4 ± 0.2 1.3 (1.1-1.9)	16 (34.8%) 29 (63%) 1 (2.2%) 2.1[a] ± 0.5 2.1 (1.2-3.5)	9(23.1%) 25 (64.1%) 5 (12.8%) 2.3[a] ± 0.5 2.2 (1.6-3.5)	χ^2= 31.064* F = 20.329*	MCp <0.001* <0.001*
Albumin (g/dL)					
<2.8 2.8-3.5 >3.5 Mean ± SD. Median (Min. – Max.)	3 (20.0%) 7 (46.7%) 5 (33.3%) 3.3 ± 0.5 3.5 (2.5-3.8)	27 (58.7%) 19 (41.3%) 24 (52.2%) 2.5[a] ± 0.5 2.7 (1.1-3.5)	36(92.3%) 3 (7.7%) 0 (0%) 1.9[ab] ± 0.5 1.9 (1-2.9)	χ^2= 37.141* F = 42.956*	MCp <0.001* <0.001*
INR					
<1.7 1.7-2.3 >2.3 Mean ± SD. Median (Min. – Max.)	9 (60.0%) 6 (40%) 0 (0%) 1.6 ± 0.3 1.6 (1.1-2.1)	1 (2.2%) 21 (45.7%) 0 (0%) 2.3[a] ± 0.4 2.4 (1.4-3.5)	0(0%) 1 (2.6%) 38 (97.4%) 3.2[ab] ± 0.6 3.1 (2.1-4.6)	χ^2= 67.385* F = 63.769*	MCp <0.001* <0.001*
Child's classification					
A B C	11 (73.3%) 4 (26.7%) 0 (0%)	2 (4.3%) 19 (41.3%) 25 (54.3%)	0 (0%) 2 (5.1% 37 (94.9%)	χ^2= 64.417*	MCp <0.001*
Sig. bet. grps. p_1<0.001* $^{MC}p_2$<0.001* $^{MC}p_3$<0.001*					
Child score					
Mean ± SD. Median (Min. – Max.)	6.2 ± 1.3 6 (5-9)	9.5[a] ± 1.5 10 (6-12)	10.7[ab] ± 0.7 11 (9-12)	F = 71.607*	<0.001*

F: F for ANOVA test, Pairwise comparison between each two groups was done using Post Hoc Test (Tukey). p: p value for comparing between the three studied groups. p1: p value for comparing between G I and G II. p2: p value for comparing between G I and G III. p3: p value for comparing between G II and G III. a: Significant with Group I b: Significant with Group II *: Statistically significant at $p \leq 0.05$. Group (I): HCV cirrhotic patients with no endoscopic signs of PHG. Group (II): HCV cirrhotic patients with mild PHG. Group (III): HCV cirrhotic patients with severe PHG.

Table 4a. — **Comparison between patients with PHG and cirrhotic patients without PHG regarding serum Serotonin levels**

Serotonin level ng/mL	Patient without PHG (n = 15)	Patient with PHG (n = 85)	t	p
Mean ± SD. Median (Min. – Max.)	27.4 ± 12.9 21.5 (11.9-49.2)	50.7 ± 16.7 52.6 (17.5-75.9)	5.128*	<0.001*

t: Student t-test. p: p value for comparing between the two studied groups. *: Statistically significant at $p \leq 0.05$

Table 4b. — **Comparison between patients with mild PHG and patients with severe PHG regarding serum Serotonin levels**

Serotonin level ng/mL	Group II (n = 46)	Group III (n = 39)	t	p
Mean ± SD. Median (Min. – Max.)	41.4 ± 16.4 51.8 (17.5-60.2)	61.7 ± 8.4 60.3 (50 – 75.9)	7.357*	<0.001*

t: Student t-test. p: p value for comparing between the two studied groups. *: Statistically significant at $p \leq 0.05$. **Group (II)**: HCV cirrhotic patients with mild PHG. **Group (III)**: HCV. cirrhotic patients with severe PHG.

Group I comprised of 15 subjects with a mean age of 50.4±6.3 years, they were 6 males and 9 females. Group II comprised of 46 subjects with a mean age of 46.5±5.9 years, they were 30 males and 16 females. Group III comprised of 39 patients with a mean age of 47.8±5.1 years, they were 30 males and 9 females (Table 2a).

Table 2b compared the clinical presentations between patients without PHG and patients with PHG. Ascites was the only statistically significant parameter between both groups ($p<0.001$). While dyspepsia, abdominal pain, GIT bleeding and altered bowel habits, although higher in patients with PHG, they did not show significant statistical relationship between both groups.

Table 3 showed that the Hb level was the lowest in Group III (8.8±1.3 mg/dl) with statistically significant association between the 3 groups ($p<0.001$). Platelets count was the lowest in Group III (86.9±23.6X10^3/uL) with statistically significant association between the 3 groups ($p<0.001$). Moreover, there was statistically significant relationship between the 3 studied groups regarding bilirubin, albumin and INR ($p<0.001$). There was also statistical significance between the study groups regarding their Child's classification and Child's score ($p<0.001$).

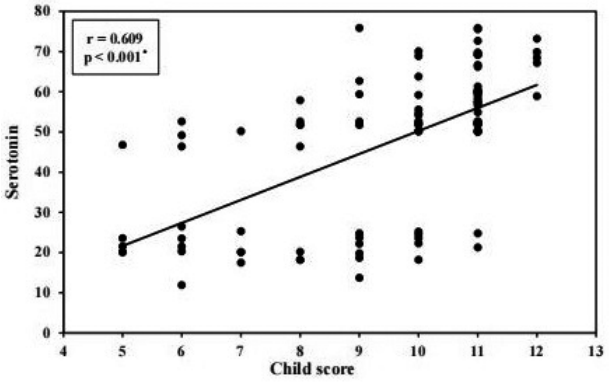

Figure 1. — Correlation between serum Serotonin and Child's score in the total sample (n = 100).

Table 5. — **Correlation between serum serotonin and different clinical presentations in patients with PHG (n = 85)**

		Serotonin level ng/mL			
Clinical presentation	**N**	**Mean ± SD.**	**Median (Min. – Max.)**	**t**	**p**
Ascites					
No	**11**	43.9 ± 18.6	51.8 (18.2-67.2)	1.464	0.147
Yes	**74**	51.7 ± 16.3	52.7 (17.5-75.9)		
Dyspepsia					
No	**22**	47.6 ± 18.2	52.2 (18.2-75.9)	1.020	0.311
Yes	**63**	51.8 ± 16.2	54.2 (17.5-5.9)		
Abdominal pain					
No	**53**	49 ± 17.6	52.5 (17.5-75.9)	1.221	0.226
Yes	**32**	53.6 ± 15	53.5 (18.2-5.9)		
GIT bleeding					
No	**71**	49.8 ± 17.5	52.6 (17.5-75.9)	1.109	0.271
Yes	**14**	55.3 ± 11.4	54.6 (23.6-69.8)		
Altered bowel habits					
No	**83**	50.5 ± 16.8	52.6 (17.5-75.9)	0.857	0.394
Yes	**2**	60.8 ± 11.5	60.8 (52.6-68.9)		

t: Student t-test. p: p value for comparing between **Serotonin** and clinical presentations.

Serum Serotonin level

Regarding serum serotonin levels, the mean values were significantly higher in patients with PHG than in patients without PHG (t= 5.128, p <0.001) (Table 4a).

Moreover, in patients with PHG, the mean serotonin level was significantly higher in severe PHG than in mild PHG (t=7.357, p<0.001) (Table 4b).

Serotonin correlations

A significant positive correlation was noted between serum serotonin levels and Child's score in the studied patients (r= 0.609, p<0.001) (Figure 1).

No significant difference was noted between serum Serotonin levels and any of the clinical presentations of the patients with PHG as shown in table 5.

Serotonin validity to discriminate between patients with PHG and patients without PHG

The validity of serum serotonin to discriminate patients with PHG (groups II and III) from patients with no endoscopic signs of PHG (group I) was evaluated using ROC curve analysis. This revealed that serum serotonin at a level more than 26.5 ng/ml had a 78.82% sensitivity, 73.33% specificity, and accuracy of 78% to discriminate between those with signs of PHG and those without PHG (AUC=0.877, p<0.001) (Table 6, Figure 2).

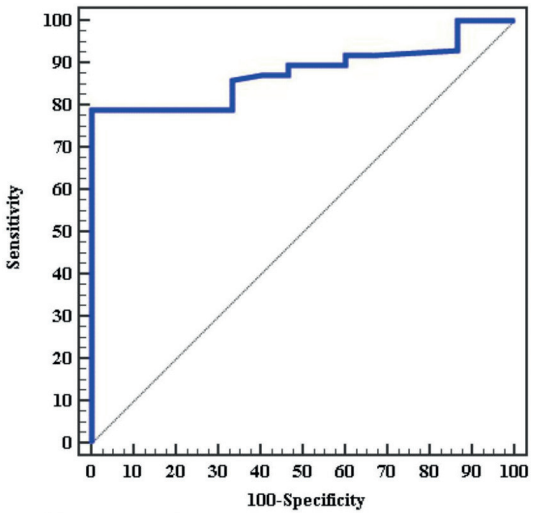

Figure 2. — ROC curve for serum Serotonin levels to discriminate patients with PHG (n = 85) from patients without signs of PHG (n = 15).

Discussion

Portal hypertensive gastropathy (PHG) is a complication of portal hypertension. It can be described as a mucosal and submucosal vascular ectasia due to mucosal gastric alteration resulting in acute or chronic gastrointestinal bleeding. The exact underlying pathophysiology of this condition is poorly understood, and several hypotheses were raised to explain it.

In the current study we tried to study a non-invasive marker that can detect the presence of PHG in patients with portal hypertension to decrease the need for upper gastrointestinal endoscopy in such patients especially if they are decompensated.

We studied the serum levels of serotonin in one hundred portal hypertensive HCV-related cirrhotic patients with variable degrees of PHG as detected by upper endoscopic findings.

Among the 100 patients included in the present study, 85 patients (85%) had signs of PHG, with 46% of them had mild PHG and 39% had severe PHG. Similar percentages were reported by other researchers (17-19).

In our patients, dyspepsia was by far the most common complaint described by our patients (74%), with a higher percentage observed in patients with severe PHG (84.6%). In a study by El-Bokl et al (20), dyspeptic symptoms were observed in 70% of their patient, (100% of patients with PHG and 40% of patients without PHG). Altered gastric motility has been noted in cirrhotic patients, although the exact mechanism is not fully understood, it was hypothesized that it may be due to alteration of microcirculation of gastric walls, neural and hormonal factors (21).

Ascites was the most observed sign in our patients observed in 88.2% of patients with PHG. It is known that portal hypertension in cirrhotic patients is responsible for

Table 6. — **Validity of serotonin level to discriminate patients with hypertensive gastropathy (n=85) from patients with no endoscopic signs of hypertensive gastropathy (n=15)**

	AUC	p	95% C.I	Cut off	Sensitivity	Specificity	PPV	NPV	Accuracy
Serotonin level 0.78-50 ng/mL	0.877	<0.001*	0.810-0.944	>26.5	78.82	73.33	94.4	37.9	78.0

AUC: Area Under a Curve. p value: Probability value. CI: Confidence Intervals. NPV: Negative predictive value. PPV: Positive predictive value.
*: Statistically significant at p ≤ 0.05.

about 75% of cases of ascites carrying a bad prognosis with mortality rate of approximately 50% (22).

Gastrointestinal bleeding in PHG is a serious complication. It was reported that PHG is responsible for about 2-20% of cases of non-variceal bleeding in cirrhotic patients (11). In our study, 16.5% of patients presented with gastrointestinal bleeding. In a study by Primignani et al. (23), acute gastrointestinal bleeding was reported in 2.7% of patients with PHG. Variable percentages were reported in other studies (24).

We detected a significant correlation between Child's score and the severity of PHG. As per our results, Sarin et al. reported a similar association between Child's classification and the severity of PHG (25). On contrary, another study reported an independent association of Child-Pugh C with PHG (19). While other studies failed to report a relation between Child's classification and the severity of PHG (26,27).

In the current study, serum serotonin level showed significant higher levels in patients with PHG than cirrhotic patients without PHG signs. Similar results were detected in other studies (28,29). While contradictory results were given by Yeoh S.W et al (30).

Serotonin is mainly synthesized by entero-chromaffin cells of the gastrointestinal tract. It binds to its receptors and mediates vascular contraction / relaxation, gastrointestinal motility, and platelet aggregation. The hepatic stellate cells control portal blood flow via its position in hepatic sinusoids. In cirrhotic livers, these cells transformed into myofibroblasts that secrete collagen like material (27). In cirrhotic patients, platelets sequestration resulted in release of serotonin which produce intense vasoconstriction in portal circulation (29). Furthermore, as serotonin binds to 5HT receptors on target cells, it exerts its action. This leads to releasing of calcium from the endoplasmic reticulum increasing intracellular calcium. This leads to a series of calcium dependent mechanisms on the cellular level leading to contraction of the smooth muscles of both the gut and the blood vessels enhancing gut motility and causing vasoconstriction, respectively. And this might partially explain the mechanical role of serotonin in PHG (31).

Platelets are one of the main storage sites of serotonin. Some researchers stated significant negative correlation between serum serotonin and platelet count (28, 32). While Rudic JS et al did not find any correlation between platelet count and serum serotonin (29).

On correlating serum serotonin levels with the degree of hepatic dysfunction as reflected by Child's classification and score, a significant positive correlation was noted. That indicates the significance of serum serotonin in monitoring the disease progression. Similar results were given by Hammam AA et al (31) while other researchers found that serum serotonin was significantly higher in cirrhotic patients with Child grade A than those with grade C (33).

In our research, a cut-off value of serum serotonin level of more than 26.5 ng/mL had a 78.82% sensitivity and 73.33% specificity to predict PHG. Accordingly, serum serotonin can be considered as a non-invasive biomarker to predict PHG in HCV related cirrhotic patients complicated with portal hypertension. Other studies gave similar assumption in cases with esophageal varices as a complication of portal hypertension in cirrhotic patients(28, 29, 34).

Conclusion

Serum serotonin is a valuable non-invasive marker of PHG in HCV-cirrhotic patients.

Furthermore, its serial measurements could be used to monitor disease progression.

Limitation of the study

Small sample size, and future study should be done on a larger number of patients.

Abbreviations

AIH: Autoimmune hepatitis; ALT: Alanine aminotransferase; AST: Aspartate aminotrans-ferase; GIT: Gastrointestinal tract.; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HCC: Hepatocellular carcinoma; INR: international normalizing ratio; PHG: Portal hypertensive gastropathy; PHT: Portal hypertension.

Ethics approval and consent to participate

The proposal of the current study was approved by the ethical committee of the Faculty of Medicine-Alexandria University. Informed written consent was signed by all participants or their caregivers before the study. The committee's reference number is not available. The current study is original and has not been published elsewhere in any form or language (partially or in full).

Consent for publication

Not applicable. Note**:** knowing that Dr Walid Ellakany had a past experience of being ex-researcher merging with Milano and endoscopy expertise in Gemelli, Rome, Italy.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

All authors declare no conflict of interests.

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Authors' contribution

Study concept and design: M.S, and W.E; Acquisition of data: M.S, and W.E; Analysis and interpretation of

data: M.S, and W.E; Drafting of the manuscript: M.S, and M.G; Critical revision of the manuscript for important intellectual content: M.S, and W.E; Statistical analysis: M.S, and W.E; Administrative, technical, and material support: M.S, R. A, M.G and W.E; Study supervision: M.S, and W.E. All authors have read and approved the manuscript.

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