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Small-bowel mucosal changes in Egyptian cirrhotic patients with portal hypertension using capsule endoscopy versus single-balloon enteroscopy

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Abstract

Background: Small-bowel mucosal abnormalities that may occur secondary to portal hypertension in patients with liver cirrhosis have an impact on health and quality of life. In spite of the importance of these changes, little is known about the frequency and features of small-bowel changes in cirrhotic patients with portal hypertension. Eighty cirrhotic patients with or without esophageal or gastric varices were recruited in this study as well as 60 age- and sex-matched controls. All study participants underwent capsule endoscopy. In addition, half of the patients and controls were randomized to receive single-balloon enteroscopy.

Results: The prevalence of small-bowel mucosal changes was statistically significantly higher in cirrhotic patients than in controls; 57% versus 6.7%, respectively ($p < 0.05$). Cirrhotic patients with portal hypertensive gastropathy showed a significant increase in the small-bowel changes ($p < 0.001$). Small-bowel changes were significantly higher in patients with higher MELD and Child-Pugh scores ($p < 0.001$). Moreover, capsule endoscopy was more effective in the detection of small-bowel changes than single-balloon enteroscopy.

Conclusions: Mucosal changes associated with portal hypertensive enteropathy are more prevalent in cirrhotic patients, regardless of the presence or absence of gastric varices. Small-bowel mucosal changes in patients with portal hypertensive enteropathy were more common in patients who suffered from portal hypertensive gastropathy and were positively correlated with advanced chronic liver disease.

Keywords: Cirrhosis, Portal hypertension, Small bowel, Capsule endoscopy, Balloon enteroscopy

Background

Liver cirrhosis represents a major public health problem in Egypt, due to the high prevalence of viral hepatitis; mainly chronic hepatitis C (up to 10%) [1], and less commonly chronic hepatitis B (approximately 1.4%) [2]. Liver cirrhosis result in scarring of normal liver tissue with loss of normal hepatic architecture which cause increased vascular resistance and contribute to subsequent portal hypertension [3]. Portal hypertension causes both mucosal and vascular changes along the entire

gastrointestinal tract including esophageal and gastric varices, portal hypertensive gastropathy (PHG), portal hypertensive colopathy (PHC), and portal hypertensive enteropathy (PHE), which refers to the mucosal and vascular changes of the small intestine that are associated with portal hypertension [4]. The identification and diagnosis of PHE have evolved over the past decade due to increased accessibility of the small intestine with the use of video capsule endoscopy (VCE) and deep enteroscopy [5].

There is no consensus classification of PHE. De Palma et al. classified endoscopic findings of PHE into two categories; mucosal inflammatory-like abnormalities (edema, erythema, granularity, friability), and vascular lesions

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(cherry-red spots, telangioectasia, or angiodysplasia-like lesions, varices) [6]. Meanwhile, Abdelaal et al. classified PHE lesions into 4 subtypes; inflammatory-like lesions, red spots, angioectasia, and small-bowel varices [7].

To the best of our knowledge, this is the first study of Egyptian patients with liver cirrhosis and portal hypertension using small-bowel capsule endoscopy or single-balloon enteroscopy. We aimed in this study to study the small-bowel mucosa of cirrhotic patients with portal hypertension and to compare the diagnostic accuracy between CE and enteroscopy.

Methods

Study design and data collection

This prospective, controlled study was carried out at Minia University Hospital, department of tropical medicine, and at Wadi Elneel Hospital, unit of gastroenterology and endoscopy. This study included 140 adult subjects, 80 known cirrhotic patients and 60 controls. All patients were selected from both the outpatient and inpatient clinics.

This study consisted of three groups: group one included 40 cirrhotic patients who did not suffer from any esophageal or gastric varices, group two included 40 cirrhotic patients who suffered esophageal or gastric varices (as previously diagnosed by upper gastroduodenal endoscopy), and group three included 60 controls who did not suffer from any chronic liver diseases and were indicated for small-bowel capsule endoscopy or enteroscopy either due to unexplained abdominal pain, chronic diarrhea, or obscure GIT bleeding.

Patients were excluded from the study if they had or suspected to have intestinal obstruction or strictures; they had recent history or current intake of medications which affect the degree of portal hypertension, such as beta-blockers, and affect the intestinal mucosa, such as non-steroidal anti-inflammatory drugs; they suffered from renal or cardiac impairment, hepatocellular carcinoma, and/or portal vein thrombosis; they suffered from enteritis from other causes, such as Crohn's disease; and if they suffered from swallowing disorders.

Data collected from patients included age; gender; presence or absence of chronic liver diseases documented by history; clinical examination; laboratory investigation including CBC, liver function, renal function, and viral hepatitis markers; presence or absence of cirrhosis documented by abdominal ultrasonography, presence or absence of GI-tract abnormalities; esophageal and gastric varices; and portal hypertensive gastropathy (PHG) documented by upper GIT endoscopy.

Liver cirrhosis was diagnosed using typical history and clinical features of chronic liver diseases, abnormal synthetic functions, typical radiological features, and/or histological data of liver cirrhosis or evidence

of cirrhosis by transient elastography. Liver cirrhosis severity was determined using Child-Pugh class and MELD score [8].

Small-bowel changes were defined as mucosal inflammatory-like abnormalities (edema, erythema, granularity, friability, and/or spontaneous bleeding) and/or vascular lesions (cherry-red spots, telangioectasia, or angiodysplasia-like lesions and varices). All patients received capsule endoscopy.

Twenty patients from group I, twenty patients from group II, and thirty controls from group III were randomly selected to receive single-balloon enteroscopy to study its accuracy of diagnosis with that of CE.

Capsule endoscopy of the small bowel was done using CAM SB2 Capsule, GIVEN IMAGING LTD, as it enabled minimally invasive visualization of the GI tract. Patients stopped taking any iron-containing medications 1 week before capsule endoscopy. Patients stopped taking any solid food and any dark food the night prior to the procedure, started a clear liquid diet, then started 1 L of polyethyl glycol plus simethicone to improve SB visualization. Then, patients fasted for 12 h before the procedure. The patient ingested the capsule with a cup of water then took nothing per mouth for 2 h, after 2 h one glass of water, light snack after 4 h, and regular diet after 6 h and was observed for 8 h at the study site. After 8 h, the sensor array and the recording device were removed. After completion of the imaging study, patients were permitted to return home. The CE digital image stream was reviewed and interpreted by two expert endoscopists.

Single-balloon enteroscopy was done using video scope OLYMPUS SIF Type Q260. No bowel preparation is generally recommended in most cases for single-balloon enteroscopy by the oral approach, except a minimum of 12 h fasting, deep monitored sedation with propofol or general anesthesia with intubation is recommended for antegrade approach.

Statistical analysis

Analyses of data were done using Statistical Package of Social Science (SPSS), version 20. Qualitative data expressed as proportions, while quantitative data expressed as the mean \pm standard deviation (SD). The Student's *t* test and one-way ANOVA were used for comparison of quantitative variables. Qualitative data was analyzed by chi-square (χ^2) test. Pearson's correlation coefficient was used to measure the strength of a linear association between two variables and is denoted by *r*. Logistic regression is a statistical method for analyzing a data set in which there are one or more independent variables that determine an outcome. Statistical significance was defined as *p* values less than 0.05.

Results

A total of 140 patients who fulfilled the inclusion criteria of the study, eighty of them were patients with liver cirrhosis that further divided into two groups, group I included forty cirrhotic patients without esophageal or gastric varices. Group II included forty cirrhotic patients with esophageal and gastric varices (as diagnosed by upper endoscopy). Group III (control group) included sixty non-cirrhotic patients who underwent capsule endoscopy for causes like anemia (obscure GIT bleeding) chronic diarrhea or chronic abdominal pain.

All the studied groups completed the CE and single-balloon enteroscopy uneventfully without complications.

Characteristics and small-bowel findings of the studied groups are listed in Table 1.

The mean of the age was 34.85 ± 6.32 years old in group I, 35.85 ± 9.3 years old in group II, and 37.67 ± 8 years old in group III with insignificant difference $p = 0.45$.

According to sex, in group I 20 M/20F, in group II 22 M/18F, in group III 32 M/28F without significant difference $p = 0.95$.

The etiology of liver cirrhosis in all patients was post hepatitis distributed as in group I 36/40 (90%) HCV and

4/40 (10%) HBV. In group II 34/40(85%) HCV and 6/40(15%)HBV, with insignificant difference.

Using capsule endoscopy, small-bowel changes were detected in 22/40 (55%) in group I, 24/40 (60%) in group II, and 4/60 (6.6%) in group III with insignificant difference between groups I and II but highly significant difference when compared with the control group $p < 0.001$.

Inflammatory changes were associated with vascular changes in 10/40 (25%) in group I and in 16/40 (40%) in group II.

The pattern of small-bowel mucosal changes was assessed according to inflammatory and vascular changes.

Edematous villi and erosions were detected in 4/40 (10%) in group I and 10/40 (25%) in group II, in 2/60 (3.3%) in group III.

Angioectasia in 6/40 (15%) in group I, and not detected in group II OR III.

Varices in 2/40(5%) in group I, 4/40(10%) in group II, not in group III. Edematous villi and erosions + angioectasia 4/40 (10%) in group I, 4/40 (10%) in group II, not in group III (Fig. 1).

Edematous villi and erosions + varices in 2/40 (5%) in group I, 2/40 (5%) in group II.

Table 1 Characteristics and small bowel changes in studied groups

	Group I No varices N = 40	Group II With varices N = 40	Group III Control N = 60	p value
Age				
Range	26–48	25–50	25–54	0.45
Mean \pm SD	34.85 ± 6.32	35.85 ± 9.3	37.67 ± 8	
Sex				
Male N (%)	20 (50%)	22 (55%)	32 (53.3%)	0.9
Female N (%)	20 (50%)	18 (45%)	28 (46.7%)	
Etiology				ns
HCV	36 (90%)	34 (85%)		
HBV	4 (10%)	6 (15%)		
Small bowel changes	22 (55%)	24 (60%)	4 (6.6%)	0.001
Inflammatory/vascular (%)	10/40 (25%)	16/40 (40%)		
SB finding				
Edematous villi and erosions	4 (10%)	10 (25%)	2 (3.3%)	I vs II
Angioectasia	6 (15%)	0 (0%)		
Varices	2(5%)duodenal	4 (10%) duodenal jejunal varix		0.58
Edematous villi and erosions + angioectasia	4 (10%)	4 (10%)		I vs II vs III
Edematous villi and erosions + varices	2 (5%) jejunal varix	2(5%) duodenal varix		0.006
Angiodysplasia	4(10%)	4(10%)	2(3.3%)	

HCV hepatitis C virus, HBV hepatitis B virus, SB small bowel

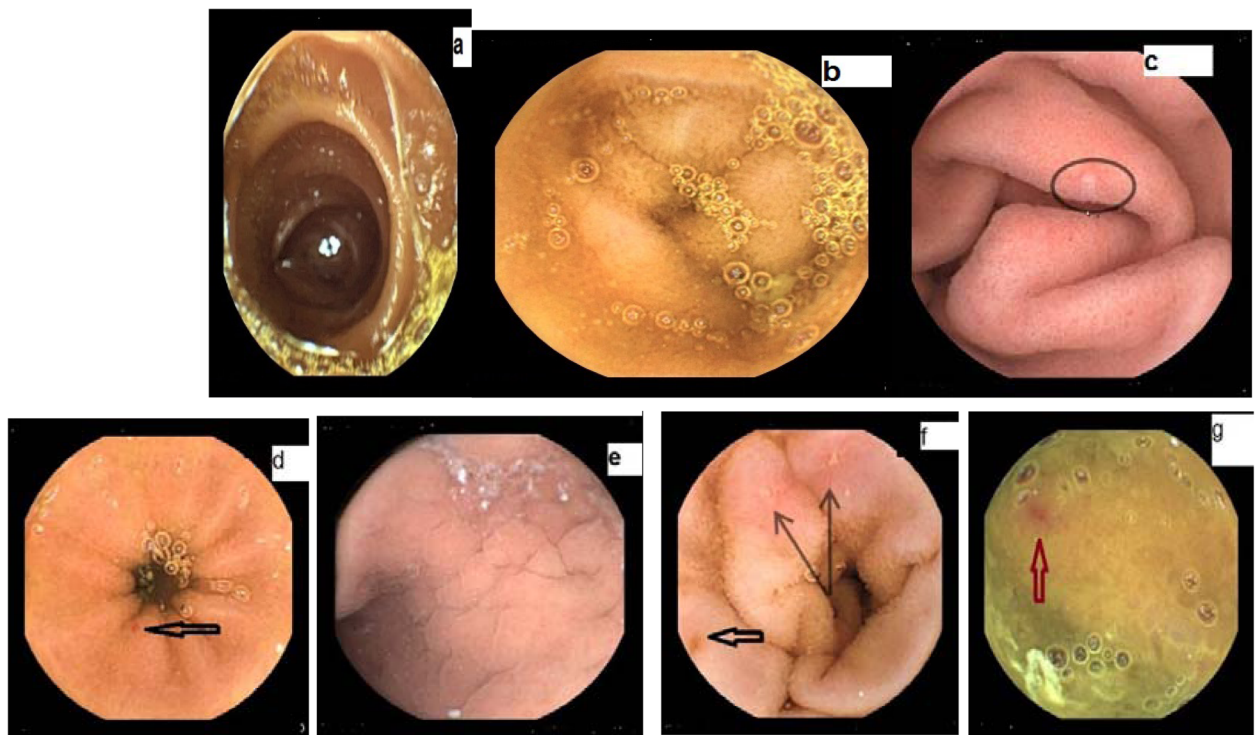


Fig. 1 Mucosal changes in portal hypertensive enteropathy. **a** Normal intestinal mucosa. **b** mucosal edema with absence of the lumen. **c** Superficial erosion. **d** Red spot (arrow). **e** Mosaic appearance of edematous mucosa. **f** Superficial erosion (thin arrow) and angioectasia (thick arrow). **g** Angiodysplasia (arrow)

Angiodysplasia 4/40 (10%) in group I, 4/40 (10%) in group II, and 2/60 (3.3%) in group III.

There was insignificant difference between small-bowel changes between groups I and II ($p = 0.58$) indicating that even in case of absence of esophageal and gastric varices, the small-bowel changes coexist and may cause complications like anemia or obscure GIT bleeding.

We compared between cirrhotic patients with small-bowel changes (PHE) and those cirrhotic without SB changes (Table 2). Small-bowel changes were found in 46/80 (57.5%) of cirrhotic patients. We assessed the cirrhotic patients' laboratory results and assessed them clinically using MELD score and Child's classification. Patients with small-bowel changes had a MELD score higher than patients without SB changes (19.52 ± 4.03 vs 11.06 ± 3.79 $p < 0.001$).

SB changes were found in patients with Child's class B and C than class A with a significant difference ($p < 0.001$), whereas all patients with Child's class C show small-bowel changes (Fig 2).

By comparing the HB levels, it was significantly lower in cirrhotic patients with SB changes than those without (6.93 ± 1.49 vs 9.08 ± 1.12 $p < 0.001$)

According to portal hypertensive gastropathy, it was found to be present in all patients with SB changes (PHE) 46/46 (100%) (Table 2).

In univariate analysis, we studied different factors (age, sex, Child score, MELD score, portal hypertensive gastropathy, and gastric or esophageal varices); out of these factors, Child score, MELD score, portal hypertensive gastropathy, and gastric or esophageal varices were the statistically significant predictors for the occurrence of portal hypertensive enteropathy (OR (95% CI) 25

Table 2 Comparison between cirrhotic patients with and without small bowel changes

	Small bowel finding 46/80 (57.5%)	No small bowel finding 34/80 (42.5%)	<i>p</i> value
MELD score			
Mean ± SD	19.52 ± 4.03	11.06 ± 3.79	0.001*
Child score			
A	4	24	0.001*
B	24	10	
C	18	0	
HB level			
Mean ± SD	6.93 ± 1.49	9.08 ± 1.12	0.001*
Portal hypertensive gastropathy			
Yes	46(100%)	18(53%)	
No	0(0%)	16(47%)	

MELD model of end-stage liver disease

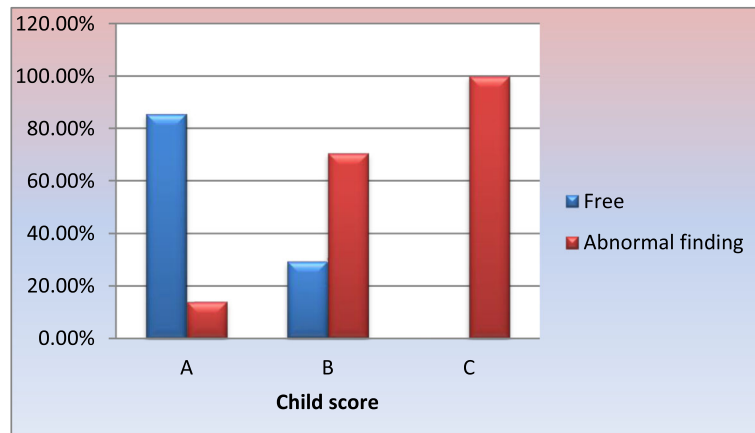


Fig. 2 Percentage of Child score in small-bowel findings

(4.222–150.4), 1.425 (1.239–1.640), 46 (9.112–232.2), 0.291 (0.146–0.578) respectively) $p < 0.001$ for all (Table 3).

Multivariate analysis model further showed that portal hypertensive gastropathy is the independent indicator for portal hypertensive enteropathy OR (20.133) 95% CI (1.129–358.9) $p = 0.041^*$ (Table 4).

Small-bowel findings were positively correlated with Child Score and MELD score with significant value($r = 0.670, 0.737$,respectively, $p < 0.001$), and negatively correlated with HB Level($r = - 0.665, p = 0.001$) (Table 5).

By comparing the diagnostic accuracy of CE and single-balloon enteroscopy, we found that CE detected SB abnormalities in 75% vs 40% for enteroscopy with a significant difference $p = 0.025$ (Fig. 3).

Discussion

Liver cirrhosis is the most advanced stage of chronic liver disease that is defined as a diffuse disorganization of hepatic architecture by extensive fibrosis associated with regenerative nodules [3]. Cirrhosis is associated with high morbidity and mortality, mainly from hepatic insufficiency and portal hypertension (PHT) [9]. Portal

hypertension leads to mucosal abnormalities of the gastrointestinal tract, which are named according to the anatomical site. While portal hypertensive gastropathy and colopathy are considered sources of non-variceal bleeding in patients with liver cirrhosis and portal hypertension, data on portal hypertensive enteropathy (PHE) are limited [10]. This is important in the view of the massive surface area of the small bowel and its unreachability during conventional gastrointestinal endoscopy [11]. The development of capsule endoscopy (CE) and balloon-assisted enteroscopy (BAE) has enabled easy access to the small bowel [12].

In this prospective case-controlled study, 80 cirrhotic patients with portal hypertension with or without gastric or esophageal varices, as well as age- and sex-matched 60 controls, were recruited. We evaluated the small-bowel changes in all study participants using capsule endoscopy or single-balloon enteroscopy.

In our study, we found that the prevalence of small-bowel changes that meet the definition of portal hypertensive enteropathy (PHE) to be statistically significantly higher in cirrhotic patients than controls ($p < 0.001$).

Table 3 Simple logistic regression analysis of factors affecting PHE

Variable	OR	95% CI	p value
Age	0.957	(0.897–1.021)	0.183
Sex	0.821	(0.308–2.194)	0.695
Child score			
A	1	Ref	–
B/C	25	4.222–150.4	0.0001*
MELD score	1.425	(1.239–1.640)	0.0001*
PHG	46	(9.112–232.2)	0.0001*
Gastric esophageal varices	0.291	(0.146–0.578)	0.0001*

Table 4 Multiple logistic regression analysis of variables affecting PHE

Variable	OR	95% CI	p value
Age(years)	1.033	(0.921–1.158)	0.583
Sex	0.144	(0.016–1.268)	0.0081
Child score			
A	1	Ref	–
B/C	0.009	0000–2.394	0.099
MELD score	1.786	(0.881–3.62)	0.107
PHG	20.133	(1.129–358.9)	0.041*
Gastric esophageal varices	2.803	(0.537–14.64)	0.222

OR odds ratio, CI confidence interval, MELD model of end-stage liver disease, PHG portal hypertensive gastropathy

Table 5 Correlation between small-bowel findings and Child score, Meld score, and HB level

Child score	<i>r</i>	0.670
	<i>p</i>	< 0.001*
Meld score	<i>r</i>	0.737
	<i>p</i>	< 0.001*
HB level	<i>r</i>	- 0.665
	<i>p</i>	< 0.001*

MELD model of end-stage liver disease, PHG portal hypertensive gastropathy, HB hemoglobin

*Significant difference (*p* value ≤ 0.05)

PHE was seen in 57.5% of cirrhotic patients versus in 6.6% of control subjects. Our data are consistent with previous studies showed that the prevalence of PHE was significantly higher in cirrhotic patients than in control group [5–7]. Abdelaal et al. found relatively similar results with PHE found in 67.7% of cirrhotic patients vs 6.9% in control; *p* = 0.001 [7]. On the contrary, in a study by Kodama et al. and colleagues, they showed higher results in cirrhotic patients up to 90%, and they didn't find any small-bowel changes in control subjects [13]. Also, in a study by Akyuz et al., they found small-bowel changes in 92.8% of cirrhotic patients and in 85.7% of non-cirrhotic patients who suffered portal hypertension for various reasons [14]. A study by Kovacs et al. showed the same results of our study in cirrhotic patients but much higher percent was seen in the control group than in our study [15], but this was attributed to phenotype of the control group in that study who were non cirrhotic but with PHT.

In our study, there were no significant differences between cirrhotic patients with known esophageal or gastric varices and those without esophageal or gastric varices regarding the prevalence of small-bowel changes

(*p* = 0.58). Our data are consistent with many studies [13, 14, 16]. On the other hands, studies by De Palma et al., Abdelaal et al., Goulas et al., and Aoyama et al. showed that there was a correlation between the presence of esophageal or gastric varices and the prevalence of small-bowel changes especially in cases of large esophageal varices and in patients who had history of endoscopic variceal injection sclerotherapy or ligation [6, 7, 17, 18].

In this study, the detected SB mucosal changes in cirrhotic patients with esophageal or gastric varices were identical to those seen in cirrhotic patients without varices. The observed changes include edematous villi and erosions in 25% of cirrhotic patients with varices and in 10% of cirrhotic patients without varices, angioectasia in 15% of cirrhotic patients without varices and not detected in cirrhotic patients with varices, small-bowel duodenal varices in 5% of cirrhotic patients without esophageal varices, and in 10% of those with known esophageal varices; however, jejunal varices detected to be 5% in group I. Small-bowel varices were found mainly in duodenal and jejunal regions. This in agreement with Aoyama et al., who found that the proximal and middle small intestines to be the most common sites of involvement by PHE especially varices formation [18]. Patterns of SB changes in our study were similar to other studies [9, 16, 19]. However, in a study published by Figueiredo et al., they showed a higher percentage of SB varices than in our study [20].

In our study, capsule endoscopy has detected small-bowel changes in 75% of cirrhotic patients, while ante-grade single-balloon enteroscopy has detected small-bowel changes in only 40% of cirrhotic patients (*p* = 0.025). These results indicate that capsule endoscopy is more efficient in detection of small-bowel changes in cirrhotic patients than single-balloon enteroscopy. Our

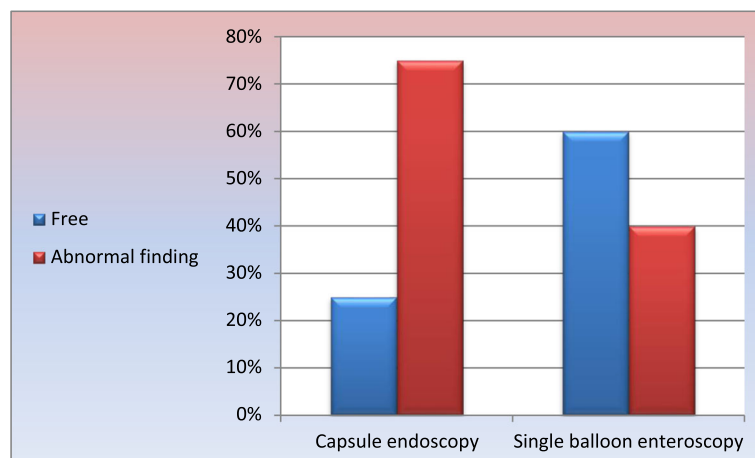


Fig. 3 Capsule endoscopy versus single-balloon enteroscopy in small-bowel findings

results are consistent with many studies which confirm that capsule endoscopy is a non-invasive technique that is effective in the detection of small-bowel changes and also safe for patients with small-bowel varices who are at high risk of hemorrhage [11, 14, 16, 21]. On the other hand, a study by Jeon et al. showed a limitation of CE with inability to do repeated examination and to perform concurrent treatment [22].

In our study, all patients with SB changes were found to have portal hypertensive gastropathy. While those who did not have any small-bowel changes, 53% of them were found to have PHG. The occurrence of PHG with PHE in previous studies has led to the suggestion that they may not be separate entities but, instead, may be regional indicators of PHT [11, 13, 17]. On the contrary, studies by Kovacs et al., Akyuz et al., and Jeon et al. demonstrated that the presence of small-bowel changes was not related to the presence of portal hypertensive gastropathy [14, 22].

Our study is consistent with several other studies which revealed that patients with advanced cirrhotic status (higher MELD and child Pugh scores) have a higher prevalence of PHE. These data indicate that the presence of small-bowel changes due to portal hypertensive enteropathy is related to the severity of underlying chronic liver disease [10, 16, 18, 23].

We found that the hemoglobin level was significantly lower in cirrhotic patients with small-bowel changes than in those without small-bowel changes ($p < 0.001$). This may be attributed to chronic gastrointestinal bleeding from vascular mucosal lesions that could be concealed and detected only by occult blood in stool [5, 6, 13].

We studied the effect of different variables on the presence of portal hypertensive enteropathy; we found that by univariate analysis, Child class B or C, high MELD score, portal hypertensive gastropathy, and esophageal and gastric varices could be an indicator of the presence of small-bowel changes ($p < 0.05$), while by multivariate analysis, portal hypertensive gastropathy is the only variable which was related to the presence of small-bowel changes (OR = 20.133, $p = 0.41$), this in agreement with many previous studies [6, 7, 15, 19–23].

Conclusion

Portal hypertensive enteropathy is found in about half of the studied cirrhotic patients. The presence of current or previous esophageal or gastric varices does not affect the presence of PHE and does not have influence on the type of small bowel mucosal changes. PHG was an independent variable indicating the presence of PHE, but the presence of PHG does imply the absolute presence of PHE. The presence of PHE may be a marker of severity since the prevalence of PHE is higher in patients with advanced

chronic liver disease. Regarding diagnosis, small-bowel capsule endoscopy is a more reliable and superior diagnostic modality of PHE than single-balloon enteroscopy. We recommend the use of capsule endoscopy in screening and initial diagnosis of the small-bowel changes in cirrhotic patients especially in patients either advanced chronic liver disease and unexplained GI blood loss, or portal hypertensive gastropathy. Further studies on a larger number of patients are needed to compare the diagnostic accuracy of small-bowel capsule endoscopy and balloon enteroscopy.

Abbreviations

CBC: Complete blood count
GIT: Gastrointestinal tract
HBV: Hepatitis B virus
HCV: Hepatitis C virus
PHC: Portal hypertensive colopathy
PHE: Portal hypertensive enteropathy
PHG: Portal hypertensive gastropathy
MELD: Model of end-stage liver disease
SBS: Small bowel
VCE: Video capsule endoscopy

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Authors' contributions

ZS: study concept and design, writing paper; AE: critical revision of the manuscript; HK: statistical analysis, revision of the manuscript; AME: technical and material support; IM, NF: analysis and interpretation of data. All authors have read and approved the manuscript.

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Availability of data and materials

Available.

Ethics approval and consent to participate

This study was conducted in accordance with the principles established by the 18th World Medical Assembly (Helsinki, 1964). This study was conducted in compliance with all national and international laws and regulations. Written informed consent was obtained from all participants in this study. Ethical committee referral number 198.2017, Minia University, Minya Egypt.

Consent for publication

All patients included in this research gave written informed consent to publish the data contained within this study. Patients involved in this study agree for publication of data.

Competing interests

The authors declare that they have no competing interests.

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