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Prevalence and risk factors of endoscopically confirmed gastroesophageal reflux disease (GERD) in patients with liver cirrhosis

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Abstract

Background: Gastroesophageal reflux disease (GERD) is one of the most common diseases in modern civilization that originates basically from a disturbance in the structure and function of the lower esophageal sphincter (LES). Liver cirrhosis with or without esophageal varices (EV) may predispose to GERD, and GERD may precipitate rupture of esophageal varices. As variceal bleeding is a serious life-threatening complication of liver cirrhosis, GERD prevalence among cirrhotic patients is continuously subjected to research. We aimed to determine the prevalence of endoscopy-confirmed GERD in patients with liver cirrhosis and its possible risk factors. So, one hundred patients with HCV-related liver cirrhosis were consecutively enrolled in this study. They were subjected to history taking {including Reflux Disease Questionnaire}, thorough clinical examination, abdominal ultrasound, and lab investigations and then referred for upper endoscopy to screen for GERD and/or esophageal varices.

Results: GERD was endoscopically confirmed in 83 patients (83%) and the highest prevalence was in patients with Child B and C. Among 82 patients with esophageal varices, there were 68 patients who had endoscopic GERD (82.9%), and among 62 patients with ascites, there were 56 patients who had endoscopic GERD (90.3%).

Conclusion: We found a high prevalence of GERD (83%) among patients with liver cirrhosis. The severity of GERD was significantly related to the Child grade, the grade of varices, and the degree of ascites but ascites was the only significant risk factor for GERD development in cirrhotic patients.

Keywords: Liver cirrhosis, Gastroesophageal reflux disease, Prevalence, Risk factors, Ascites

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Main points

1- Endoscopically confirmed GERD is highly prevalent among cirrhotic patients (83%).
2- Ascites, Child grade, and esophageal varices grade were significantly related to the grade of GERD in cirrhotic patients.
3- Ascites was the only independent predictor for presence of GERD, and it correlates significantly with the presence of GERD and the severity of GERD.
4- Accordingly, cirrhotic patients should be advised to do upper endoscopy to screen for GERD; otherwise, physician should empirically treat cirrhotic patients as GERD especially if they are symptomatic.

Background

Gastroesophageal reflux disease (GERD) is one of the most common diseases in modern civilization, which greatly affects people's health and quality of life [1]. GERD originates from a disturbance in the structure and function of the lower esophageal sphincter (LES). Disturbed esophageal motility in addition to weak LES can cause regurgitation of gastric and/or duodenal contents into the esophagus [2]. Many factors are involved in the GERD pathophysiology including prolonged lower esophageal sphincter relaxation, presence of hiatus hernia, low basal LES pressure, delayed esophageal clearance, and delayed gastric emptying [3, 4]. In Egypt, liver cirrhosis is a major health problem owing to high prevalence of HCV infection [5]. Liver cirrhosis with or without esophageal varices was found to decrease the LES pressure, worsen the esophageal motility, delay the esophageal clearance, and delay the gastric emptying and eventually lead to reflux [6–8]. Some studies reported high incidence of GERD in patients with liver cirrhosis (65%) [9, 10], while others reported a lower percentage (33%) [6]. Moreover, asymptomatic GERD was found to be common in patients with liver failure [11]. The highest prevalence of GERD was found among patients with Child B and C liver cirrhosis with positive relationship between the severity of liver damage and GERD [12]. A significant relationship between ascites and GERD was reported as ascites increases the intra-abdominal pressure, compressing the stomach and its contents, and this may alter the anatomic anti-reflux measures naturally occurring against reflux [11, 12], and reflux symptoms tend to decrease when intra-abdominal pressure was reduced by paracentesis [13]. Esophageal varices—independent of liver cirrhosis—lead to LES dysfunction, which make the stomach contents reflux easily, and also EV lead to delay in esophageal clearance, which increases the contact time of acid reflux with the esophageal mucosa [8, 14]. On the other hand, GERD may be a risk factor for esophageal varices bleeding as the increased contact time between acid reflux and EV may lead to erosion of the esophageal mucosa and increase the risk of variceal rupture [15–17]. This study was designed to evaluate the prevalence of endoscopy confirmed GERD in patients with liver cirrhosis and its possible risk factors.

Methods

The present study included 148 patients with HCV-related liver cirrhosis. They were consecutively enrolled from those attending the liver cirrhosis clinic at Minia University Hospital for regular medical follow-up. Only 100 patients completed the study (48 patients refused to participate in the study or refused to do endoscopy). Patients with other systemic diseases like systemic sclerosis, diabetes mellitus, hypertension or neuromuscular disorders, alcohol abusers, and chronic users of drugs that influence esophageal motility like calcium channel blockers, theophylline, or nitrates were excluded from the study. Patients included in the study were subjected to history taking {including Reflux disease questionnaire [18], emphasizing on typical GERD symptoms, such as heartburn and/or acid regurgitation}, thorough clinical examination, abdominal ultrasound, and lab investigations and then referred for upper endoscopy to screen for GERD and/or esophageal varices. All patients had blood drawn for routine investigations including liver function tests using an OLYMPUS automatic biochemical analyzer (OLYMPUS-AU640). The diagnosis of liver cirrhosis was based on clinical examination, laboratory findings, and ultrasonographic study, while its severity was assessed by Child-Turcotte-Pugh scoring system [19]. Ascites was classified as mild, moderate, or marked according to clinical and ultrasonographic criteria [20].

Upper gastrointestinal endoscopy

All patients underwent upper gastrointestinal endoscopy (Olympus XQ260; Olympus, Japan). GERD was classified according to Los Angeles Classification into grade A—mucosal erosion < 5 mm, which does not extend between the tops of two mucosal folds; grade B—mucosal erosion > 5mm, but does not extend between the tops of two mucosal folds; grade C—confluent erosion that is continuous between the tops of two or more mucosal folds but involves < 75% of the esophageal circumference; and grade D—confluent and circumferential erosion that involves 75% or more of the esophageal circumference [21]. Esophageal varices were classified into grade 1 (small), straight small caliber varices; grade 2 (medium), moderately enlarged, beady varices covering less than one third of the lumen; and grade 3 (large), markedly enlarged, nodular or tumor-shaped varices occupying more than one third of the lumen [22]. Esophageal varices and GERD grading were evaluated by 2 senior endoscopists.

Statistical analysis

The collected data were coded, tabulated, and statistically analyzed using SPSS program (Statistical Package for Social Sciences) software version 23. Descriptive statistics were done for parametric quantitative data by mean, standard deviation. Categorical variables were given as number and percentages and chi-square test and Fisher's exact test were used for comparison between categorical variables. Multivariate logistic regression analysis model was performed using endoscopic GERD as a dependent variable. P value ≤ 0.05 was considered significant.

Results

A total of 100 patients who met the inclusion criteria were included in this study. Sixty-eight were males and thirty-two were females, with a mean age of 57.2 ± 7.9 years (range, 41–72 years). Seventy-one patients were above 50 years old. According to Child-Pough scoring system, 36 patients were Child A; 41 patients Child B; and 23 patients Child C. Typical symptoms of GERD (heart burn and regurgitation) were present in 42 patients, while GERD was endoscopically confirmed in 83 of patients. Ascites was present in 62 patients while esophageal varices were present in 82 patients (Table 1). The present study showed a significant relation between typical GERD symptoms and Child grades (P <0.05), but there was no significant relation between typical symptoms of GERD and grades of ascites or grades of GERD (P <0.06, P <0.07, respectively) (Table 2). There was no significant relation between the mere presence of varices and presence of endoscopically confirmed GERD (Table 3). However, there was significant relationship between the grade of GERD and the grade of varices (P<0.0001) (Table 4). Regarding to ascites, there was significant relationship between the mere presence of ascites and endoscopic GERD (P < 0.001) (Table 5), and significant relationship between grade of ascites and grade GERD (P < 0.0001) as shown in Table 4. Multivariate analysis model further showed that only ascites was the independently predictor for presence of GERD [OR (95% CI) 1.22 (0.429–1.799) {p <0.01}] (Table 6).

Table 1 Demographic data, symptoms, signs, and lab findings of the studied patients

Variable	Cirrhotic patients (n=100)
Age, range / mean ± SD	41–72 / 57.2±7.91
Sex, male / female	68 (68%) / 32 (32%)
Smokers	43 (43%)
Typical GERD symptoms (heart burn and regurgitation)	42 (42%)
Ascites (n = 62)	
Mild	29 (46.8%)
Moderate	22 (35.5%)
Marked	11 (17.7%)
Child class	
Class A	36 (36%)
Class B	41 (41%)
Class C	23 (23%)
Esophageal varices (n = 82)	
Grade 1	14 (17.1%)
Grade 2	16 (19.5%)
Grade 3	52 (63.4%)
Endoscopic GERD (n = 83)	
Grade A	24 (28.9%)
Grade B	29 (34.9%)
Grade C	23 (27.7%)
Grade D	7 (8.5%)
Laboratory findings	
Serum albumin, mean ± SD	(2.5±0.3)
Total bilirubin, mean ± SD	(3.1±0.4)
INR, mean ± SD	(1.5±0.25)
Platelets, mean ± SD	(116.3±7.4)

GERD gastroesophageal reflux disease, *INR* international normalization ratio

Discussion

A total of 100 cirrhotic patients were endoscopically assessed according to Los Angelos classification, and GERD with its variable grades was detected in 83 patients (83%). Some researchers reported GERD prevalence among liver cirrhosis patients to be as high as 65% [9, 10]. But lower percentage was reported by other researchers: 33% [6] and 43% [11]. The higher prevalence in our study (83%) may be explained by the fact that our patients had more advanced liver cirrhosis as most of them had esophageal varices (82%) and ascites (62%), which act as positive mechanical factors contributing to GERD. In addition, administration of PPI before enrollment was one of our exclusion criteria. Moreover, more than one third of our patients were smokers (42%) and smoking is a well-known risk factor for GERD [23]. Our data revealed that GERD was more prevalent in male patients than females; however, it was statistically insignificant. The high prevalence of GERD among males may be attributed to the high prevalence of liver cirrhosis and its complications among males than females [12] and to smoking which is highly prevalent in males. However, Kotzan et al. [24] found no correlation between sex and reflux. This study showed that GERD was significantly higher in elderly patients above 50 years old than in younger patients and this agrees with Li et al. [12], who found a significant relationship between reflux esophagitis and age among patients with chronic liver disease. Similarly, earlier studies found a more severe

Table 2 Relation between typical reflux symptoms and Child grades, ascites grades, and grades of GERD

Patients	Typical reflux symptoms		*P* value
	No (58)	Yes (42)	
Child grade A (*n* = 36)	16 (44.4%)	20 (55.6%)	**0.037**
Child grade B (*n* = 41)	24 (58.5%)	17 (41.5%)	
Child grade C (*n* =23)	18 (78.3%)	5 (21.7%)	
Ascites (*n* = 62)			**0.064**
No ascites (*n* =38)	18 (47.4%)	20 (52.6%)	
Mild (*n* =29)	16 (55.2%)	13 (44.8%)	
Moderate (*n* =22)	14 (63.6%)	8 (36.4%)	
Marked (*n* =11)	10 (90.9%)	1 (9.1%)	
Endoscopic GERD (*n* = 83)			**0.072**
No GERD (*n* =17)	10 (58.8%)	7 (41.2%)	
Grade A (*n* =24)	12 (50%)	12 (50%)	
Grade B (*n* =29)	14 (48.3%)	15 (51.7%)	
Grade C (*n* =23)	19 (82.6%)	4 (17.4%)	
Grade D (*n* =7)	3 (42.9%)	4 (57.1%)	

gastroesophageal reflux in elderly patients when compared with younger patients [25, 26]. We found that GERD grade (B) was the most frequent grade existing in 29 out of 83 of cirrhotic patients with endoscopic GERD (35%), and this agrees with other reports that found GERD grade (B) the most frequent grade (43.9%) in patients with chronic liver diseases [16]. We found that 42 patients (42%) with liver cirrhosis experienced typical symptoms of GERD (heartburn and regurgitation) and this is in accordance with other studies who found that the percentage of cirrhotic patients who experienced typical symptoms for GERD was (48%) and (32%) respectively [8, 12]. As we mentioned before, GERD was endoscopically confirmed in 83 patients while only 42 patients had typical GERD symptoms and this means that 41 patients with confirmed GERD did not complain of typical GERD symptoms and this is in accordance with other researchers who reported that asymptomatic GERD might occur in patients with more severe liver cirrhosis [11, 12]. Also, Ahmed et al. [16] reported that there is no relationship between GERD symptoms and the severity of liver cirrhosis. This may be explained by the fact that patients with severe liver cirrhosis had more severe symptoms and complications such as fatigue, ascites, and bleeding that usually mask other relatively milder complains like heart burn or regurgitation. In addition, this finding confirms the literature stating that there is no correlation between endoscopic findings and the intensity or frequency of GERD symptoms in non-cirrhotic patients [27].

Our study showed no significant relation between typical GERD symptoms and different grades of GERD, denoting that there is no relationship between GERD symptoms and GERD severity. But we found that GERD grades (C) and (D) were more frequent in Child (B) and (C) patients than in Child (A) patients, with a significant relationship between the grades of GERD and the severity of liver cirrhosis as graded by the Child scoring system ($P < 0.0001$). Similar results were reported [8, 12, 16]. This may be due to the presence of ascites and esophageal varices that were frequent findings in our cases. In addition, liver cirrhosis itself—regardless the mechanical effects of esophageal varices or ascites—could be an important cause explaining the high incidence of GERD in patients with liver cirrhosis owing to neural and humoral factors [16]. For example, nitrous oxide (NO) was found in large amounts in the systemic circulation of cirrhotic patients. NO has been shown to decrease the amplitude of distal esophageal peristaltic

Table 3 Relation between the presence of esophageal varices and endoscopic GERD

Esophageal varices	Endoscopic GERD		*P* value
	Yes *N*= 83	No *N*= 17	
Presence of varices *N*= 82	**68 (82.9%)**	**14 (17.1%)**	**0.9**
No varices *N*=18	**15 (83.3%)**	**3 (16.7%)**	

Table 4 Relation between grades of GERD and Child grade, degree of ascites, and grades of varices

G Grades of endoscopic GERD:	Grade 0 (*n*=17)	Grade A (*n* = 24)	Grade B (*n* = 29)	Grade C (*n* = 23)	Grade D (*n* = 7)	*P* value
Child grading						**< 0.0001**
Child grade **A (*n* = 36)**	11 (30.6)	9 (25%)	12 (33.3%)	3 (8.3%)	1 (2.8%)	
Child grade **B (*n* = 41)**	6 (14.6)	13 (31.7%)	15 (36.6%)	7 (17.1%)	0 (0%)	
Child grade **C (*n* =23)**	0(0%)	2 (8.7%)	2 (8.7%)	13 (56.5%)	6 (26.1%)	
Ascites						**< 0.0001**
No (38)	11 (28.9%)	9 (23.7%)	13 (34.3%)	4 (10.5 %)	1 (2.6%)	
Mild (29)	6 (20.7%)	10 (34.5%)	9 (31%)	4 (13.8%)	0 (0%)	
Moderate (22)	0 (0%)	5 (22.7%)	7 (31.8%)	8 (36.4%)	2 (9.1%)	
Marked (11)	0 (0%)	0 (0%)	0 (0%)	7 (63.6%)	4 (36.4%)	
Esophageal varices						**< 0.0001**
No varices (18)	3 (16.7%)	6 (33.3%)	7 (38.9%)	2 (11.1%)	0 (0%)	
Grade 1 (14)	1 (7.2)	4 (28.5%)	3 (21.4%)	5 (35.7%)	1 (7.2%)	
Grade 2 (16)	1 (6.3%)	3 (18.7%)	4 (25%)	7 (43.7%)	1 (6.3%)	
Grade 3 (52)	12 (23.1%)	11 (21.2%)	15 (28.8%)	9 (17.3%)	5 (9.6%)	

waves, and the velocity of the peristaltic contractions in the proximal esophagus, and all these can attribute to the high incidence of GERD in patients with liver cirrhosis [28, 29]. Other studies have shown plasma vasoactive peptide and neurotensin in cirrhotic patients are significantly higher than in the normal population, and these substances are known to reduce the pressure of the lower esophageal sphincter [30, 31].

Our study showed that out of 82 patients with esophageal varices, 68 patients (82.9%) had endoscopic GERD with insignificant relationship between the mere presence of esophageal varices and GERD in univariate and multivariate analysis (P = 0.9, P = 0.5 respectively) but there was significant relation between grade of EV and grade of GERD (P<0.0001). This is contradictory to some studies that reported a significant relationship between the presence of esophageal varices, independent of their caliber, and GERD [10]. But another study revealed no relation between occurrence of GERD and existence of esophageal varices [12] even in patients with sequential endoscopic variceal ligation [32]. The explanation of correlation between grade of EV and GERD severity could be attributed to the ability of EV to delay the esophageal clearance and increases the contact time between acid and mucosa [11]. Furthermore, some researchers reported that cirrhotic patients with esophageal varices were more prone to develop esophageal motor disorders, a delay in the esophageal clearance time, and abnormal gastroesophageal reflux [33, 34]. Moreover, it was reported that the high mechanical effect of large esophageal varices has significantly decreased the peristaltic wave amplitude in middle and distal esophagus predisposing to GERD [35].

This study showed that the presence of ascites was a risk factor for occurrence of GERD in patients with cirrhosis in univariate and multivariate analyses ($P \leq 0.001$, P= 0.01 respectively). In other words, patients with cirrhosis and ascites had nearly 4 times risk for developing GERD in comparison with those with cirrhosis without ascites. These results agreed with Bhatia et al. [36], who showed a significant relationship between esophageal motility changes and the changes in intraabdominal and intragastric pressure due to ascites. In addition, they found that duration and amplitude of esophageal body peristaltic contraction wave was increased in the presence of ascites and decreased after its control [36]. This agrees with Navarro-Rodriguez et al. [13] who observed that there was a trend of reduced reflux when intraabdominal pressure was reduced by paracentesis. However, in an Egyptian study done by Iman et al. [35], they

Table 5 Relation between the presence of ascites and endoscopically confirmed GERD

Ascites	Endoscopically confirmed GERD		*P* value
	Yes *N*= 83	No *N*= 17	
Presence of ascites (*N*= 62)	**56 (90.3%)**	**6 (9.7%)**	**< 0.001**
No ascites (*N*= 38)	**27 (71%)**	**11 (29%)**	

Table 6 Multivariate logistic regression for prediction of endoscopic GERD in cirrhotic patients

Baseline characteristic	Multivariate analysis[a]	
	OR (95% CI)	*P* value
Ascites	3.8 (1.27–11.3)	0.01
E. varices	0.97 (0.24–3.8)	0.5
Child grade	0.88 (0.56–3.1)	0.2

OR odds ratio, *CI* confidence interval, *E* esophageal
[a]Variables with *P* values < 0.05 in univariate are included in the equation

found that ascites had no effect on the esophageal motility or the LES pressure. We also found that GERD grades (C) and (D) were more frequently found in patients with moderate and marked ascites with significant relationship between the degree of ascites and the grade of GERD (*P* value < 0.0001). These results were similar to a previous study reporting a significant relation (*P*< 0.001) between the degree of ascites and the grade of GERD [16]. It was suggested that ascites could induce an increase in the intra-abdominal pressure, compressing the stomach and its contents [12] and paracentesis induces improvement of reflux symptoms in patients with ascites by reduction of intra-abdominal pressure [13].Contradictory, some studies found no significant difference in the esophageal motility and LES pressure in patients with or without ascites [35, 37].

Conclusion

Our study showed that endoscopically confirmed GERD is highly prevalent in cirrhotic patients (83%). Ascites, Child grade, and esophageal varices grade were significantly related to the grade of GERD in cirrhotic patients, but ascites was the only independent risk factor for development of GERD, and it correlates significantly with the presence of GERD and the severity of GERD.

Abbreviations

GERD: Gastroesophageal reflux disease; LES: Lower esophageal sphincter; EV: Esophageal varices; HCV: Hepatitis C virus

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Authors' contributions

HM and *YF* were responsible for the concept and design of the study; *WS* and *HM* were responsible for data acquisition; *YF* and *AE* performed upper endoscopy; *SR* was responsible for statistical analysis; *TH* and *YF* analyzed the data, interpreted the results, and drafted the manuscript. All authors critically revised the manuscript, approved the final version to be published, and agree to be accountable for all aspects of the work

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Availability of data and materials

Data will not be shared as it is part of a multicenter study we arrange to publish soon.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the ethics of good clinical practice and Helsinki Declaration after approval of the local ethical committee of Minia Faculty of Medicine but unfortunately the committee's reference number is not available. Written, informed consent was obtained from every patient to participate in the study.

Consent for publication

Every patient gave written, informed consent to publish the results

Competing interests

Authors agreed that there is no conflict of interest.

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