

Gastro-oesophageal reflux disease in liver cirrhosis: Possible pathogenesis and clinical intervention (Review)

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Abstract. Oesophageal variceal bleeding is a common complication of decompensated liver cirrhosis (LC). Some studies have reported that reflux oesophagitis (RE) is a risk factor for upper gastrointestinal bleeding, and greatly impacts the quality of life. However, the frequency and mechanism of gastro-oesophageal reflux disease (GERD) in LC remain unclear. The present review explored the possible pathogenesis, and analysed the advantages and disadvantages of the interventional measures and the need for implementation of these measures. By combining the comprehensive terms associated with LC, GERD and RE, EMBASE, Medline/PubMed and the Cochrane Library were systematically searched. The underlying pathological mechanism of GERD in LC was summarized: Transient relaxation of the lower oesophageal sphincter, delayed gastric emptying, increased intra-abdominal pressure, increased intragastric pressure and excessive nitric oxide production destroyed the ‘anti-reflux barrier’, causing gastric content reflux. Proton pump inhibitors (PPIs) have been widely used empirically to lower the risk of oesophageal venous rupture and bleeding. However, long-term use of acid inhibitors in patients with LC may induce complications, such as spontaneous bacterial peritonitis. The metabolic half-life of PPIs is prolonged in patients with severe liver function impairment. Therefore, the indications for using acid inhibitors lack

clarity. However, after endoscopic oesophageal variceal eradication, additional benefits may be gained from the long-term use of PPIs in small doses.

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1. Introduction

The term gastro-oesophageal reflux disease (GERD) refers to a set of syndromes that include the signs and symptoms associated with any pathological process, with retrosternal burning (heartburn) and reflux as the characteristic symptoms. The Montreal definition of GERD states that GERD is a disease that develops when the reflux of stomach contents causes troublesome symptoms or complications. The word ‘trouble’ in the definition accurately captures how negative the symptoms appear to patients. The symptoms of GERD are classified by this international evidence-based consensus into oesophageal symptom syndrome (with oesophageal symptoms but no evidence of oesophageal injury, including non-erosive reflux disease) and oesophageal injury syndrome [mucosal injury is a recognised aspect, and the most common manifestation is reflux oesophagitis (RE), including stenosis, Barrett’s oesophagus, and adenocarcinoma], while the recognised extra-oesophageal symptoms include reflux cough syndrome, reflux laryngitis syndrome, reflux asthma syndrome, reflux tooth erosion syndrome, etc. (1). In addition, this new definition acknowledges that the reflux causing symptoms might be weakly acidic or gaseous. According to extensive population-based studies, the prevalence of GERD in Western Europe and North America is 10-20% (2). Symptomatic GERD adversely affects the quality of life of patients with chronic liver disease (as affects the mood and general health perception) (3).

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Abbreviations: LC, liver cirrhosis; GERD, gastro-oesophageal reflux disease; TLESR, transient lower oesophageal sphincter relaxation; UGIB, upper gastrointestinal bleeding; RE, reflux oesophagitis; LES, lower oesophageal sphincter; LESP, LES pressure; EGJ, oesophagogastric junction; EV, oesophageal varices; IAP, intra-abdominal pressure; NOS, nitric oxide synthase; PPI, proton pump inhibitor; EVS, endoscopic variceal sclerotherapy; EVL, endoscopic variceal ligation

Key words: LC, GERD, RE, TLESR, nitric oxide, PPIs

The pathophysiology of GERD comprises several factors, such as low basal pressure of the lower oesophageal sphincter (LES), prolonged LES relaxation time, delayed oesophageal clearance, and delayed gastric emptying (4). In addition, GERD is also closely associated with unhealthy lifestyle habits, such as smoking, obesity, strenuous exercise after meals, consumption of carbonated drinks, poor eating habits, and excessive alcohol and coffee consumption. Individuals with diabetes and metabolic syndrome are more likely to experience GERD. RE is the most common manifestation of oesophageal injury. RE is a risk factor for upper gastrointestinal bleeding (UGIB) and greatly impacts the quality of life. Patients with decompensated liver cirrhosis (LC) often experience oesophageal variceal bleeding, and it appears that effective anti-reflux treatment should be used. However, the frequency and specific mechanism of RE in LC have not been elucidated. Patients with LC might be prone to GERD, and some studies indicate that the prevalence of GERD in patients with LC is high (5-7). What factors cause GERD in LC? Is it necessary to employ anti-reflux measures? Some studies have reported that GERD might promote the rupture of oesophageal varices (EV) in patients with LC, resulting in an increased risk of UGIB (7-10). In recent years, proton pump inhibitors (PPIs) have been widely used empirically to lower the risk of oesophageal venous rupture and bleeding in patients with LC. Herein, we attempt to explain the possible pathogenesis of GERD in LC and discuss whether anti-reflux measures should be employed.

2. Epidemiological investigation

GERD is very common worldwide, and the prevalence of gastro-oesophageal reflux symptoms varies greatly among countries. A recent survey indicates that the GERD prevalence in China is approximately 2.5% (11). According to a systematic review, the prevalence of GERD in East Asia ranges from 2.5 to 6.7%; however, the data lacks quality (12). A study comprehensively analysed the epidemiological trend of GERD in 204 countries and regions in the past 20 years and reported that the age-standardised prevalence rate (ASPR) increased globally from 2015 to 2019. The risk of GERD is closely associated with age, and the incidence of GERD in women is marginally higher. In the past 20 years, the ASPRs of Latin America, the Caribbean, South Asia, North Africa, and the Middle East were the highest, while those of East Asia and China were the lowest (below 5%) (13). The increased risk of GERD in these areas is associated with potential risk factors, such as obesity, alcohol consumption, and smoking, which is consistent with the findings of previous studies (11). The study conducted in 2018 also reported that despite the lack of clear evidence indicating the high-risk factors of GERD, the observed prevalence rate of individuals over 50 years of age, smokers, users of non-steroidal anti-inflammatory drugs, and obese individuals is significantly higher (14). Eating habits, such as irregular eating patterns, large meals, and bedtime meals, might be associated with GERD symptoms (15). In a prospective study in China, 1280 patients with chronic liver disease (879 patients with LC) were endoscopically assessed, and a RE prevalence of 36.4% was reported in patients with chronic liver disease (6). A recent retrospective study reported that the 10-year incidence of RE in patients with LC was similar to that of the general

population (4.79%) (16). Currently, there are a few studies on the prevalence and associated factors of GERD in patients with LC, and a more representative research population and standardised methods are warranted for further epidemiological study. There is a lack of evidence proving the positive correlation between LC and GERD to date because patients with LC are often accompanied by complications, such as EV and portal hypertension (PHT), several high-risk factors, such as previous endoscopic injection sclerotherapy and portal vein thrombosis (PVT) exist, which might result in severe RE in patients with LC. As most patients with RE lack GERD symptoms and do not take acid inhibitors before the onset of severe UGIB, the prevalence of severe RE that causes UGIB has increased significantly in the past three decades (8). Ethanol can damage the mucosal barrier, cause oesophageal mucosal inflammation, increase the risk of oesophageal acid damage, and increase the prevalence of GERD or RE among alcoholics (17,18). Alcohol is a risk factor for LC, which might be one of the reasons why some patients with LC are likely to develop GERD.

3. Pathophysiological changes of GERD

Under normal conditions, the intra-abdominal pressure (IAP) is positive, and the intra-thoracic pressure is negative, which is the physical basis of promoting the reflux of stomach contents into the oesophagus. A small amount of reflux occurs in all individuals throughout the day, and the primary mechanism resulting in most physiological reflux events is referred to as transient LES relaxation (TLESR). However, the normal anatomy and physiology of the oesophagus, LES, diaphragm at hiatus, and stomach can prevent pathological GERD. The most common causes of pathological reflux are the destruction of the LES normal reflux barrier and the pressure gradient change in the thoracic and abdominal cavities (19,20). Several studies have reported that ascites can increase intragastric and IAP (21-23). Patients with LC have a high incidence of acid reflux (23) and oesophagitis (24). In patients with LC, a decreased LES pressure is observed with increased ascitic fluid (23,25). Therefore, ascites in patients with LC is a potentially important factor for GERD development (7,21,23,26).

Fluctuations are observed in the normal oesophageal mucosal environment between destruction and repair; therefore, physiological TLESR occurs (20). The LES function is closely associated with the incidence and severity of GERD. The LES is the annular muscle layer at the distal end of the oesophagus, which generates resting pressure higher than the IAP, and the resting pressure generated by the LES is sufficient to prevent the back-flow of gastric contents to the oesophagus (27). The LES, diaphragm, and the normal anatomy of the oesophagus and stomach are involved in the anti-reflux mechanism.

Severe RE and UGIB are often observed in patients with LC owing to EV, PVT, PHT, etc., thereby deserving the attention of hepatologists and gastroenterologists. However, the existing research on GERD-related LC is scarce. Some studies employed endoscopy and oesophageal manometry to demonstrate that patients with LC have lower oesophageal motility disorder, abnormal changes in the potential of hydrogen (pH) in the lower oesophageal segment, and varying degrees of oesophageal mucosal injury (Table I) (5-7, 26, 28).

Table I. Related research on oesophageal monitoring in patients with LC.

First author/s, year	Country	Research objective	Observation methods and outcome indicators	Related prevalence rate	(Refs.)
Hassanin <i>et al</i> , 2021	Egypt	A total of 100 patients with HCV-associated LC were enrolled in the study and underwent clinical examination, imaging examination and upper gastrointestinal endoscopy.	Oesophageal mucosal lesions were classified according to the Los Angeles classification system as follows: Grade A, mucosal erosion <5 mm, not extending between the upper limit of two mucosal folds; grade B, mucosal erosion >5 mm, not extending between the upper limit of two mucosal folds; grade C, confluent erosion that is continuous between the upper limit of two or more mucosal folds but involves <75% of the oesophageal circumference; and grade D, confluent and circumferential erosion that involves ≥75% of the oesophageal circumference.	83 patients (83%) were diagnosed with GERD by endoscopy, and the prevalence rates of grades B and C were the highest. Among 62 patients with ascites, 56 patients (90.3%) were diagnosed with GERD under endoscopy. This study reported that ascites are the only risk factor for GERD in patients with LC.	(7)
Zhang <i>et al</i> , 2011	China	A total of 78 patients with LC and 30 healthy controls confirmed to be EV-free by endoscopy were included.	LESP, PA, PD, PV, dynamic 24-h oesophageal pH and bilirubin monitoring were measured. i) In the LC group, the LESP was 15.32 ± 2.91 mmHg, the PA was 61.41 ± 10.52 mmHg, the PD was 5.32 ± 1.22 s, and the PV was 5.22 ± 1.11 cm/s. ii) 24-h oesophageal pH and bilirubin monitoring results: Compared with those in the control group, pathological oesophageal pH and bilirubin measurements increased in the LC group, while bile reflux events also increased.	The incidences of RE and pathological reflux were 37.18 and 55.13%, respectively.	(5)
Li <i>et al</i> , 2010	China	Experimental group: 1,280 patients with chronic liver disease (879 patients with LC and 401 patients with chronic hepatitis). Control group: 29 patients with acute hepatitis A or E.	Referring to the Los Angeles classification scheme, the degree and scope of oesophageal mucosal injury were observed by endoscopy, and RE was classified into grades A, B, C and D. In the experimental group, 43% of the patients with LC (378/879) had different degrees of oesophageal mucosal damage compared with 22% of the patients with chronic hepatitis (91/401).	In this clinical study, the prevalence of RE in patients with chronic liver disease was 36.4% (469/1280), while it was 10.3% (3/29) in the control group.	(6)

Table I. Continued.

First author/s, year	Country	Research objective	Observation methods and outcome indicators	Related prevalence rate	(Refs.)
Schechter <i>et al</i> , 2007	Brazil	A total of 51 patients with LC with EV confirmed by endoscopy were included in the study.	By manometry, pH recording was performed by placing the probe 5 cm above the upper limit of the LES. Reflux episodes and abnormal reflux were defined according to the duration of oesophageal pH <4 in different positions. Abnormal reflux of pH records was observed in 19 patients with LC with EV (37%), and 1 of the patients developed erosive oesophagitis during endoscopy.	27 patients (53%) had typical GERD symptoms. An association was observed between typical GERD symptoms and abnormal reflux.	(28)
Navarro-Rodriguez <i>et al</i> , 2003	Brazil	LESP and 24-h oesophageal pH of 16 patients with ascites were monitored before and after the puncture.	According to the degree of intra-abdominal pressure reduction achieved, the patients were divided into group A (decreased by >70%) and group B (decreased by <70%). Before and after the reduction of intra-abdominal pressure, the LESP in the two groups was as follows: Group A, before puncture, 15.60 mmHg, after puncture, 18.09 mmHg; and group B, before puncture, 23.09 mmHg, after puncture, 20.40 mmHg. However, 24-h pH monitoring showed pathological reflux in patients with ascites that was reduced with the paracentesis. In 16 patients, the mean total number of reflux episodes before puncture was 520.26, and that after was 136.26. In group A, the mean total number of reflux episodes was as follows: Before puncture, 661.27; after puncture, 99.45.	The results revealed that a reduction in intra-abdominal pressure of >70% decreased gastro-oesophageal reflux.	(26)

LC, liver cirrhosis; HCV, hepatitis C virus; RE, reflux esophagitis; EV, oesophageal varices; LESP, lower oesophageal sphincter pressure; PA, peristaltic amplitude; PD, peristaltic duration; PV, peristaltic velocity; GERD, gastro-oesophageal reflux disease; LES, lower oesophageal sphincter.

4. Mechanism

Relevant biological findings and clinical mechanism analysis have been reported concerning GERD's abnormal mechanism. GERD can be associated with bile (alkaline) reflux, gastric or oesophageal distension, and dyskinesia. The LES plays a crucial role in the incidence and severity of GERD. Currently, the mechanism of RE in patients with LC has not been fully elucidated. However, the incidence of RE in patients with LC is associated with the following factors: i) Patients with LC often experience delayed gastric emptying and might develop corresponding gastrointestinal symptoms (29). ii) Ascites result in an increased IAP, compressing the stomach and causing reflux of the stomach contents (26). iii) The existence of tense ascites results in decreased LES pressure. During swallowing or coughing, the intragastric pressure instantaneously increases, which might cause gastro-oesophageal reflux (23,25). iv) With pathological changes in the livers of patients with LC, the inducible nitric oxide (NO) synthase (NOS) (iNOS) expression increases, and the endothelial NOS (eNOS) activity decreases, resulting in a large number of harmful pro-inflammatory NO mediators. On the one hand, the visceral artery vessels dilate, and the plasma osmotic pressure decreases, resulting in ascites (30-33). On the other hand, excessive NO, promoting an increase in the TLESR frequency, results in an increase in the total number of reflux episodes (34,35).

Increased IAP and GERD. LC causes increased intrahepatic resistance, a gradual increase in portal pressure, systemic visceral arterial dilatation, and effective circulating blood volume insufficiency. Through the antidiuretic process of the renin-angiotensin-aldosterone pathway, the sympathetic nervous system, and renal vasoconstriction, the human body increases the total plasma volume through water-sodium retention to maintain sufficient effective arterial blood volume. However, other factors, such as hypoalbuminaemia and changes in intestinal capillary pressure and permeability, can cause an accumulation of free fluid in the abdominal cavity (36). A study measuring the LES pressure (LESP) in patients with LC reported that 10 control participants had a LESP of 21 ± 1 mmHg, whereas, among 15 patients with LC, 10 had a LESP of 22 ± 1 mmHg, while five LC patients with massive tension ascites had a LESP of 16 ± 2 mmHg. After the resolution of ascites through diuresis, the LESP increased to 25 ± 3 mmHg in all LC patients with massive tension ascites. Additionally, the remission of ascites not only increased the LESP but also decreased the gastric pressure significantly, with a significant linear correlation between the mean increase in LESP and the mean decrease in gastric pressure (25). The results of another experimental study revealed that intragastric pressure in patients with LC and ascites is proportional to the volume of ascites, particularly in patients with tension ascites; a sudden, transient increase in the intragastric pressure during swallowing or vigorous coughing might cause gastric oesophageal reflux (23). When abdominal compression is applied, the LES relaxes, and gastro-oesophageal reflux prolongs after swallowing (37). Twenty-four-hour dynamic monitoring of oesophageal pH in patients with ascites revealed that gastro-oesophageal reflux significantly decreased when the IAP decreased by

more than 70% of the pre-puncture baseline, implying that a significant reduction in the IAP significantly decreased gastro-oesophageal reflux (26).

Increased IAP, formation of hiatal hernia, and GERD. When the IAP increases, the oesophagogastric junction (EGJ) actively contracts, and the tonic contraction of the diaphragm results in increased LESP (38). During swallowing, the oesophageal body is shortened due to contraction of the longitudinal muscles of the oesophagus, causing the LES to move proximally, and a small part of the proximal stomach enters the thoracic cavity through the diaphragmatic hiatus. After swallowing, due to the elasticity of the phreno-oesophageal ligament, all structures return to their original anatomical positions. However, due to factors such as excessive contraction of the longitudinal oesophageal muscles, increased IAP, and age-related degeneration, these ligaments might lose their elasticity, resulting in a hiatal hernia (39). The existence of a hiatal hernia alters the pressure topography of the EGJ, which might increase the susceptibility of gastro-oesophageal reflux events. When the LES relaxes during swallowing, the LESP decreases, and when the pressure of the hiatal hernia exceeds the LESP, barium back-flow occurs from the hiatal pouch to the oesophagus (40). It is well known that GERD is associated with the formation of hiatal hernia caused by increased IAP; however, few studies have confirmed that hiatal hernia is directly associated with LC. More evidence based on standardised methods is required.

Excessive NO production and GERD. Several studies have revealed that liver pathology varies in patients with LC, resulting in high NO levels and elevated exhaled NO (eNO) (32,34,35,41-43). NO is a novel signalling molecule associated with inflammation and tissue damage and is the most known effective vasodilator. It can dilate visceral blood vessels, increase visceral blood flow, and aggravate PHT (44,45). In view of factors such as decreased hepatic metabolism, toxin accumulation, increased intestinal permeability, impaired intestinal motility, and changes and translocation of the intestinal flora, endotoxins, and other intestinal-derived metabolites, the blood vessels could be directly stimulated *in vivo* or cytokines could be stimulated to produce NOS. During NOS catalysis, L-arginine interacts with oxygen to increase NO synthesis and release *in vivo* (46,47). Does a change in the microbial community in patients with LC affect ammonia metabolism? Compared with normal individuals, the structure of the duodenal mucosal microflora in LC changes, and with the development of LC, the intestinal microflora exhibits an increase in Enterobacteriaceae, Staphylococcus, Streptococcus, and other microflora, and these microflorae produce endotoxins and ammonia through their urease activities, respectively (48,49). A study revealed that gut urease-containing bacteria Streptococcus salivarius was observed in patients with LC, and it was revealed that a change in the salivary bacteria number in patients with LC was positively correlated with ammonia accumulation (50). However, aseptic animals can also produce ammonia through intestinal glutaminase activity. Therefore, it is unclear whether the change in the intestinal microecology in LC has additional effects on ammonia accumulation and excessive NO production.

The increase in NO concentration increases the risk of hepatic encephalopathy. Hyperammonaemia could increase NO, and the NO concentration in brain regions with acute ammonia toxicity increases, resulting in common learning and memory disorders and brain oedema (51,52).

NO is produced by three isoforms of NOS: neuronal NOS, iNOS, and eNOS. eNOS is constitutively expressed in hepatic sinusoidal endothelial cells (LSECs) and produces a small amount of NO. A small amount of NO keeps hepatic stellate cells (HSCs) and Kupffer cells still, which is essential for controlling vascular tension and blood flow in hepatic sinuses, and plays a crucial role in vascular homeostasis and inhibiting hepatic pathological conditions. However, iNOS is not expressed under normal conditions, but its expression is induced by bacterial endotoxin lipopolysaccharide secondary to intestinal bacterial translocation and pro-inflammatory cytokines associated with liver ischaemia-reperfusion injury. iNOS is up-regulated in various hepatic cells (including LSECs, Kupffer cells, HSCs, smooth muscle cells, bile duct cells (cholangiocytes), and other immune cells), which produce a large amount of NO and promote liver injury. Under pathological conditions, eNOS activity decreases, iNOS is up-regulated, and NO production in LSECs decreases, resulting in capillarisation of endothelial cells and HSC activation, accompanied by extracellular matrix deposition, HSC contraction and proliferation, finally resulting in increased intrahepatic resistance and sinusoidal blood flow disorder (33,53-58). Hepatic microvascular dysfunction and excessive NO production result in apoptosis, inflammation, deoxyribonucleic acid damage, and hepatocellular carcinoma.

A small increase in portal vein pressure and the increase of related blood flow is first sensed by the intestinal microcirculation. This increases vascular endothelial growth factor production, triggering eNOS activation and subsequent NO overproduction (30-32,41). Therefore, excessive NO production might be associated with ascites. Multiple studies (42,43) demonstrated that NO, eNO, and plasma NO levels in peripheral and hepatic veins of patients with LC patients are significantly elevated, and NO is closely associated with TLESR. Reportedly, NO can decrease the peristaltic wave amplitude in the distal oesophagus and the peristaltic contraction rate in the proximal oesophagus. NO plays a crucial role in TLESR secondary to fundus distension, which is secondary to reflux attack (34). A study on healthy volunteers revealed (35) that the use of substances that inhibit NO synthesis [NG-monomethyl-L-arginine (L-NMMA)] can significantly lower the TLESR frequency after ingestion of solid food, and reduce the total reflux attack. It can then be confirmed laterally that excessive NO might result in an increase in the transient relaxation frequency of LES, thereby resulting in an increase in the total number of reflux attacks.

Another study reported that L-NMMA inhibited the increase in the number of TLESRs caused by gastric distension by inhibiting NO synthesis (34). The findings of Boulant's research on dogs also demonstrated that L-NMMA reduces the gastric distension controlled by pressure in dogs and reduces the number of TLESRs caused by gastric distension (59). NO is involved in the maintenance of basal gastric fundic tension and human diet-induced gastric fundal relaxation. Prolonged L-NMMA infusion inhibits NO synthesis, causing fundic contraction, which results in a decrease in the basal fundus

volume (60). Non-adrenergic nerve mechanism involving the NO nerve can regulate gastrointestinal smooth muscles and then affect the gastric fundus tension (61).

Bad lifestyle and eating habits. A study on the risk factors of GERD reported that unhealthy lifestyles, such as obesity; smoking; after-dinner and strenuous physical activity; consumption of high-fat, fried, and spicy food; excessive coffee/tea consumption; and consumption of carbonated drinks and alcohol, contribute to GERD (15). Being overweight and obese increases the risk of various digestive system-related diseases, such as GERD and erosive oesophagitis (62). In particular, diabetes, metabolic syndrome, and obesity might also increase the risk of GERD (63). On the other hand, metabolic syndrome, hyperglycaemia, and obesity are independent risk factors for L of chronic hepatitis B (64). Therefore, metabolic factors might reveal the relationship between GERD and chronic liver disease. Several studies have indicated that ethanol can damage the mucosal barrier, cause oesophageal mucosal inflammation, and increase the risk of oesophageal acid injury. Alcohol-induced acute oesophageal necrosis might occur in patients with high alcohol intake, particularly in patients with immunosuppressive alcoholic hepatitis, which further reveals that excessive alcohol intake might be the key factor for oesophageal lesions and cirrhosis (17,18,65). In addition, a prospective study reported that there is a significant correlation between chronic hepatitis B virus (HBV) infection and GERD, particularly in women and HBV carriers with a high aspartate aminotransferase to platelet ratio, and the incidence of erosive oesophagitis increases (66).

The potential interactions between LC, TLESR, increased IAP, increased intragastric pressure, excessive NO production, and unhealthy lifestyle and eating habits are presented in Fig. 1.

5. Clinical intervention

RE might result in haemorrhagic oesophagitis and variceal bleeding in patients with LC (8,67-69). Although PPIs have been widely used in LC patients with EV in recent years, it lacks strong evidence-based practice. On the one hand, most patients with RE lack reflux symptoms; on the other hand, almost two-thirds of the untreated patients with typical GERD symptoms do not take acid inhibitors because of normal endoscopic findings (70,71), thereby increasing the risk of oesophageal bleeding. In a study on RE, only 36% of all RE patients with UGIB were taking acid inhibitors before severe UGIB bleeding, which might have resulted in an increase in UGIB incidence caused by RE in recent years (8). The question remains whether LC patients with reflux tendencies should use acid inhibitors. A recent report on optimising GERD patient management stated that if GERD diagnosis is clear after oesophageal gastroscopy, PPIs can be used twice a day (before breakfast and dinner). If necessary, another PPI should be administered. In the case of nocturnal symptoms, any histamine-2 receptor antagonist and/or alginate could be administered before bedtime (72). These drugs could alleviate the symptoms of most patients with reflux, as they help cure oesophageal injuries (such as oesophagitis and stenosis), improve the quality of life, and improve sleep difficulties (73).

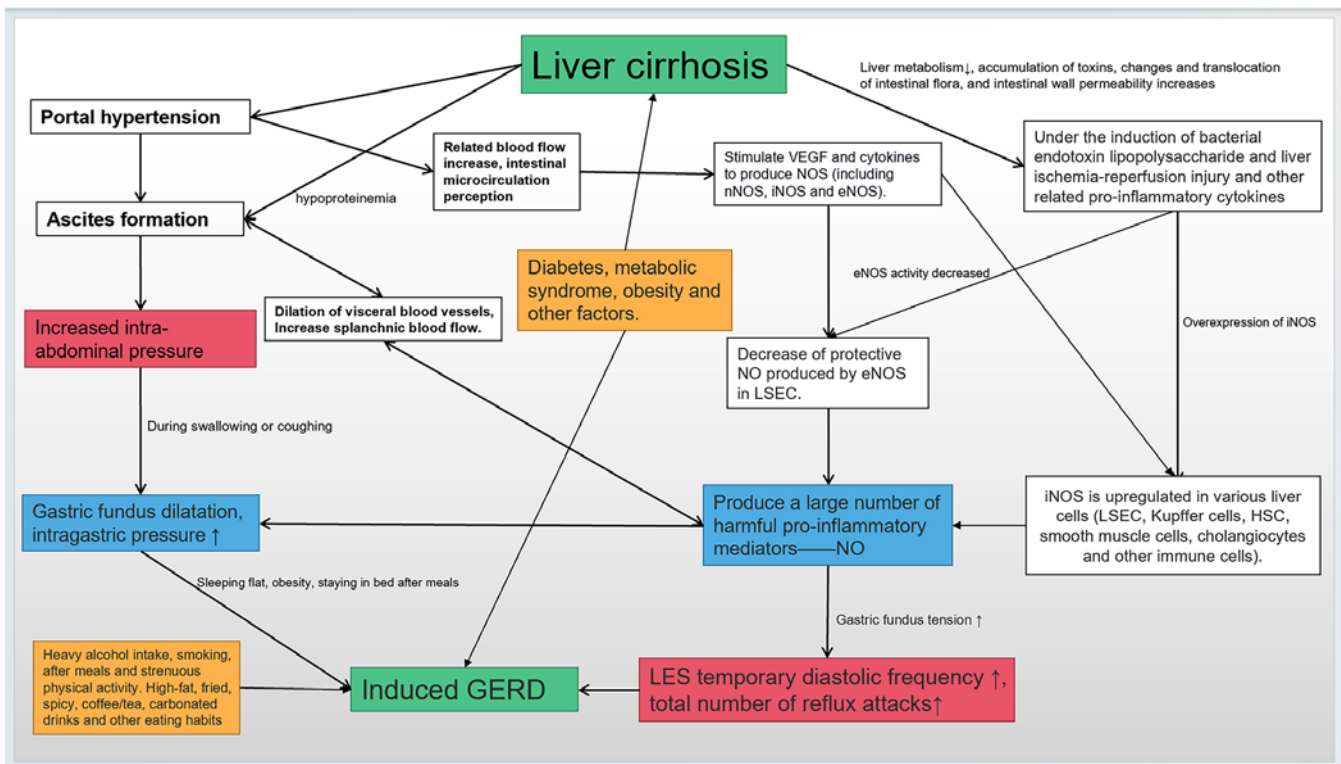


Figure 1. Potential interactions exist among ascites, gastric fundus dilatation, excessive nitric oxide production, increased LES relaxation frequency, metabolic diseases and unhealthy lifestyle, among which the increase in transient LES relaxation frequency is the key link, and ascites are a potentially important factor affecting GERD development. Green indicates the two diseases discussed, blue represents important factors that can induce GERD in the progression of liver cirrhosis, red emphasizes the key links in the pathogenesis, and yellow indicates the adjustable lifestyle and metabolic factors. GERD, gastro-oesophageal reflux disease; VEGF, vascular endothelial growth factor; NOS, nitric oxide synthase; nNOS, neuron NOS; iNOS, inducible NOS; eNOS, endothelial NOS; NO, nitric oxide; LSEC, hepatic sinusoidal endothelial cells; LES, lower oesophageal sphincter; HSC, hepatic stellate cells.

However, long-term PPI use is associated with spontaneous bacterial peritonitis (SBP) in patients with LC. SBP is one of the most common complications in patients with LC. At present, a popular dogma holds that frequent PPI use could aggravate SBP occurrence. A recent meta-analysis reported a weak correlation between SBP occurrence and PPI use; therefore, this meta-analysis suggested that PPIs should be administered with caution in patients with ascites in LC (74). Similar suggestions were made by some other researchers. PPI should be administered to patients who will benefit from its use. In elderly patients with severe liver injury, particularly those with ascites in LC, PPI treatment should be avoided or administered with caution to lower the risk of SBP (75-77).

In the past decades, several studies have reported a significant increase in the prevalence of RE that causes UGIB (8-10). Therefore, for LC patients with severe reflux tendency, surgical treatment might be considered to reduce the risk of variceal bleeding (78,79). The results of a recent study on refractory GERD revealed that during the 12-month follow-up period, patients who underwent laparoscopic fundoplication had the best control of reflux symptoms compared with those who received anti-reflux drugs (78). UGIB following variceal rupture is the main cause of death in patients with LC (80). Two types of endoscopic treatments are considered the first choice to control oesophageal variceal bleeding, namely endoscopic variceal sclerotherapy (EVS) and endoscopic variceal ligation (EVL) (81,82). However, several research findings have reported that EVL is more effective and safer than EVS

in improving oesophageal motility disorder and eradicating EV (83-85). Once varicose veins are treated, patients should undergo an upper gastrointestinal endoscopy every 3-6 months to evaluate the recurrence of varicose veins and the need for repeated treatment (86). However, although EVL is a relatively safe surgical method, there is a risk of postoperative bleeding. In rare cases, early spontaneous slippage of the rubber band or rupture of the residual vein at the base of the oesophageal ulcer could cause fatal bleeding (87,88).

The question remains whether long-term PPI use can prevent varicose vein rupture and bleeding. Although there is insufficient evidence currently, additional benefits might be obtained from consistent PPI use after the endoscopic intervention of varicose veins. Ulcer bleeding might rupture varicose veins after EVL treatment, and the combination of PPIs and surgical treatment might help lower the risk. The best evidence supports that short-term (10 days) PPI use for patients with EV and oesophageal ulcers after EVL treatment could decrease the oesophageal ulcer size after selective oesophageal ligation and even cure the ulcers after EVL (89,90). Long-term PPI use (>1 month) could decrease the rebleeding rate of patients with LC after endoscopic treatment while not affecting bleeding-related mortality. Therefore, acid inhibition should also be considered as a supplementary therapy after endoscopic treatment (91-93). Reportedly, chronic PPI use could increase the severity of hepatic encephalopathy in patients with LC compared with patients who do not use PPI (94). However, there is a lack of higher-quality evidence proving the existence

of an association between them. Two isoenzymes (CYP2C19 and CYP3A4) are involved in PPI metabolism in the liver, of which CYP2C19 is the main metabolic pathway (95,96). Older PPIs (including omeprazole, lansoprazole, and pantoprazole) are primarily metabolised by CYP2C19, while rabeprazole is primarily metabolised via the non-enzymatic pathway, which has advantages over old PPIs. In the standard dose (20 mg once a day), rabeprazole and esomeprazole provide better acid control than omeprazole (97,98). Severe liver damage results in a 7- to 9-fold increase in the area under the curve of all PPIs and an extended half-life of 4 to 8 h (95). Therefore, when PPIs are used in patients with LC, the increased half-life of these drugs in this group of patients should be considered, and the dosage should be reduced.

Brain toxicity caused by hyperammonaemia should also be avoided in LC patients with excessive NO production. Several studies have reported that the serum ammonia level can be decreased by using lactulose, probiotics, and prebiotics. This is because these agents regulate the intestinal flora and normalise the intestinal flora. The reduction of blood ammonia level, endotoxemia, and neurocognitive impairment lower the risk of hepatic encephalopathy (99-101).

6. Lifestyle adjustment

Several patients with LC are accustomed to a sedentary lifestyle owing to the decreased quality of life, which might be associated with the occurrence of GERD. During drug treatment, lifestyle changes such as weight loss, raising the bedside, avoiding strenuous activities for a few hours after meals, and refraining from consuming alcohol, coffee, carbonated drinks, etc., should be incorporated before or during drug treatment. This combination therapy helps relieve GERD symptoms (102). LC patients with varicose veins should eat digestible soft food, stop alcohol consumption, avoid staying up late, and be administered multivitamins. Patients with hepatic encephalopathy should strictly limit their protein intake.

7. Summary and comments

Herein, we outlined the possible relationship between LC and GERD in terms of the pathological mechanisms. The pathogenesis of GERD in LC is multifactorial. There are potential interactions among TLESR, increased IAP, increased intragastric pressure, and excessive NO production in patients with LC. Increased intragastric pressure and an increased TLESR frequency might be key factors for GERD development in LC. In view of the evidence, we recommend that for LC patients with reflux tendency (without ascites and EV), without other contraindications, acid inhibitors are the appropriate choice for early protection of the oesophageal mucosa, preferably with regular upper gastrointestinal endoscopy for dynamically monitoring the oesophagus. For patients with decompensated LC, such as portal hypertension, coagulation dysfunction, and ascites (without EV), particularly those with severe liver function damage, long-term PPI use should be avoided to reduce the risk of SBP occurrence and further liver function damage. In contrast, for decompensated patients with EV with a high risk of bleeding, endoscopic oesophageal variceal eradication should be considered, and acid

inhibitors might be considered postoperatively to reduce the rate of rebleeding after endoscopic treatment in patients with LC. At the same time, LC patients with unhealthy lifestyles should be given health education for lifestyle modification. Finally, we eagerly anticipate more new evidence of GERD in LC.

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Availability of data and materials

All data generated and/or analyzed during this study are included in this published article.

Authors' contributions

FY, XYH and YZ conceived the entire article, and designed and drafted the manuscript. NL and HFF revised it critically for important intellectual content. NL, HFF, ZJ and XYZ investigated the present area of research and gathered relevant and important information. LZ edited and modified the mechanism diagram and table. FY and XYH approved the final version of the review. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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