**Name of journal:** **World Journal of Gastroenterology**

**ESPS Manuscript No: 6749**

**Columns: TOPIC HIGHLIGHTS**

WJG 20th Anniversary Special Issues (11): Cirrhosis

**Gastrointestinal dysfunction in liver cirrhosis**

Kalaitzakis E. Gut dysfunction in liver cirrhosis

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**Received:** October 25, 2013 **Revised:** April 27, 2014

**Accepted:** June 2, 2014

**Published online:**

**Abstract**

Patients with liver cirrhosis exhibit several features of gut dysfunction which may have an impact on health-related quality of life and nutritional status as well as contribute to the development of cirrhosis complications. Gastrointestinal symptoms are common in cirrhosis and their pathophysiology probably involves factors related to liver disease severity, psychological distress, and gut dysfunction (*e.g.,* increased gastric sensitivity to distension and delayed gut transit). They may lead to reduced food intake and, thus, may contribute to the nutritional status deterioration in cirrhotic patients. Although tense ascites appears to have a negative impact on meal-induced accommodation of the stomach, published data on gastric accommodation in cirrhotics without significant ascites are not unanimous. Gastric emptying and small bowel transit have generally been shown to be prolonged. This may be related to disturbances in postprandial glucose, insulin, and ghrelin levels, which, in turn, appear to be associated to insulin resistance, a common finding in cirrhosis. Furthermore, small bowel manometry disturbances and delayed gut transit may be associated with the development of small bowel bacterial overgrowth. Finally, several studies have reported intestinal barrier dysfunction in patients with cirrhosis (especially those with portal hypertension), which is related to bacterial translocation and permeation of intestinal bacterial products, *e.g.,* endotoxin and bacterial DNA, thus potentially being involved in the pathogenesis of complications of liver cirrhosis.

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**Key words:** Liver cirrhosis; Gut motility; Gastric accommodation; Malnutrition; Gastrointestinal symptoms; Intestinal permeability

**Core tip:** Features of gut dysfunction are common in patients with cirrhosis and may have an impact on quality of life and nutritional status as well as contribute to the development of cirrhosis complications. Cirrhotic patients often report gastrointestinal symptoms. Their pathophysiology is complex, probably involving factors related to liver disease severity, psychological distress, and increased gastric sensitivity to distension as well as delayed gut transit. The latter is common in cirrhosis and may be related to postprandial glucose and hormone disturbances due to insulin resistance. Intestinal barrier dysfunction, potentially leading to bacterial translocation and permeation of bacterial products, has been frequently reported in cirrhotic patients, especially those with portal hypertension.

Kalaitzakis E. Gastrointestinal dysfunction in liver cirrhosis. *World J Gastroenterol* 2014; In press

**Introduction**

In recent years it has become widely recognized that liver cirrhosis may affect several organ systems such as the cardiovascular system[[1](#_ENREF_1),[2](#_ENREF_2)], the respiratory system[[3](#_ENREF_3)], the kidneys[[4](#_ENREF_4),[5](#_ENREF_5)], and the skeletal system[[6](#_ENREF_6),[7](#_ENREF_7)]. Cirrhosis has also been associated with varying degrees of malnutrition[[8](#_ENREF_8)] and with alterations in the gastrointestinal (GI) tract[[9](#_ENREF_9)]. Apart from the presence of structural changes in the GI tract, such as esophageal varices and portal hypertensive gastropathy, that may be the cause of GI bleeding and anemia, there have also been described abnormalities in the sensorimotor and barrier function of the gut in liver cirrhosis. These changes are of importance as they might contribute to malnutrition and health-related quality of life impairment in these patients, while impaired gut barrier function may also contribute to the development of cirrhosis complications, in particular bacterial infections.

**Malnutrition in liver cirrhosis**

Malnutrition is common in cirrhosis with a reported prevalence as high as 80%[[8](#_ENREF_8),[10-13](#_ENREF_10)]. It is associated with increased morbidity and mortality[[8](#_ENREF_8)] and it can compromise liver transplantation results[[11](#_ENREF_11)]. Recently, severe muscle wasting (sarcopenia) has been shown to be present in 30%-41% of patients with cirrhosis and to be independently related to mortality in general[[14](#_ENREF_14)] as well as in patients with hepatocellular cancer[[15](#_ENREF_15)] and those listed for liver transplantation[[16](#_ENREF_16)]. Lean-mass depletion is also related to hepatic encephalopathy in liver transplant candidates with cirrhosis[[17](#_ENREF_17)].

The pathogenesis of malnutrition in liver cirrhosis is not fully understood but poor dietary intake[[8](#_ENREF_8),[18](#_ENREF_18)], increased energy expenditure[[11](#_ENREF_11),[19-21](#_ENREF_19)], malabsorption[[8](#_ENREF_8),[22](#_ENREF_22)] and poor synthetic capacity of the cirrhotic liver may be involved. Potential reasons for low energy intake include reduced appetite possibly associated with increased brain tryptophan availability[[23](#_ENREF_23)], satiety due to ascites[[24](#_ENREF_24)], poor palatability of low-sodium diets, and hepatic encephalopathy[[8](#_ENREF_8)], GI symptoms[[25](#_ENREF_25),[26](#_ENREF_26)], and gut dysfunction[[27](#_ENREF_27)]. Increased glucose and lower ghrelin levels postprandially have also been suggested to be related to poor food intake and weight loss in cirrhosis[[28](#_ENREF_28)]. Postprandial glucose and ghrelin alterations are probably associated with insulin resistance which is common in these patients[[28](#_ENREF_28)].

Increased energy expenditure, although not a constant feature of cirrhosis, has also been reported to contribute to a negative energy balance[[8](#_ENREF_8),[11](#_ENREF_11),[19-21](#_ENREF_19),[29-31](#_ENREF_29)]. Last, fat malabsorption has been reported to be frequent (especially in those with evidence of malnutrition)[[22](#_ENREF_22)]. This may be related to the cholestasis often present in cirrhosis, but a reduction in the area of the intestinal absorptive surface has also been proposed in cirrhotis[[32](#_ENREF_32)]. However, not all studies have found defective active absorption in these patients[[22](#_ENREF_22),[33](#_ENREF_33)].

**GI symptoms in patients with liver cirrhosis**

GI symptoms are common in cirrhotics compared to healthy controls (Figure 1)[[25](#_ENREF_25)]. Overall, up to 80% of patients with cirrhosis have been reported to have one or more relevant GI symptoms[[34](#_ENREF_34)]. The most common GI symptoms reported include abdominal bloating in 49.5% of patients, abdominal pain in 24%, belching in 18.7%, diarrhea in 13.3%, and constipation in 8%[[34](#_ENREF_34)]. GI symptom severity appears to be related to liver disease severity[[25](#_ENREF_25)], lactulose use[[25](#_ENREF_25)], the presence of ascites[[25](#_ENREF_25)], and psychological distress[[26](#_ENREF_26),[34](#_ENREF_34)] as well as low serum testosterone levels[[26](#_ENREF_26)]. The pathophysiology of GI symptoms, however, appears to be complex, and to also involve abnormalities in gut motility function as outlined later in this review. Although they improve following liver transplantation, GI symptoms remain of concern post-transplant, mainly due to diarrhea[[26](#_ENREF_26)].

GI symptoms in cirrhosis are related to recent weight loss[[25](#_ENREF_25),[26](#_ENREF_26)]. In an experiment in which subjects underwent a caloric satiation drinking test, patients with significant symptoms reached satiation earlier compared to patients without symptoms and healthy controls (Figure 2)[[26](#_ENREF_26)]. Thus, GI symptoms appear to have an impact on meal induced satiety which may limit food intake. Last but not least, GI symptoms are associated with impaired physical and mental health-related quality of life in cirrhosis[[25](#_ENREF_25)].

**Structural changes of the GI tract in liver cirrhosis**

The structural effects of liver cirrhosis on the GI tract have been considered to be mainly associated with portal hypertension. A major endoscopic finding is varices most commonly located in the esophagus and/or the fundus of the stomach. Occasionally varices may be found in “ectopic” locations such as in the duodenum or in the rectum[[35](#_ENREF_35)]. Esophageal varices develop in the majority of patients with cirrhosis, provided a long enough follow-up period[[36](#_ENREF_36),[37](#_ENREF_37)]. They can be the site of GI bleeding, a potentially lethal complication[[36](#_ENREF_36),[37](#_ENREF_37)].

Mucosal changes are also frequently encountered upon endoscopic examination of the GI tract in patients with cirrhosis[[9](#_ENREF_9),[38](#_ENREF_38)]. Portal hypertensive intestinal vasculopathy is a term used to describe changes in the intestinal microcirculation secondary to longstanding portal hypertension[[9](#_ENREF_9)]. Signs of portal hypertensive intestinal vasculopathy may be observed in all parts of the GI tract[[9](#_ENREF_9)]. The prevalence of portal hypertensive gastropathy, with its characteristic mosaic appearance, has been reported in 20%-98% of cirrhotic patients[[39](#_ENREF_39)], the wide variation probably being due to varying study quality and the different characteristics of the studied cirrhotic cohorts. Among 222 patients with cirrhosis without a history of variceal bleeding, medium or large esophageal varices, previous endoscopic therapy, or propranolol treatment, the prevalence of portal hypertensive gastropathy was reported to be 21.6%[[40](#_ENREF_40)]. Major predictors of portal hypertensive gastropathy are the presence of esophageal varices and increased severity of cirrhosis[[40](#_ENREF_40)]. Thus it has been found to be associated to poor prognosis in cirrhotic patients[[41](#_ENREF_41)]. Acute bleeding from portal hypertensive gastropathy has been reported to occur infrequently but may be severe[[40](#_ENREF_40),[42](#_ENREF_42)], while chronic bleeding resulting in anemia may be a concern[[40](#_ENREF_40),[42](#_ENREF_42)].

In cirrhotics compared to healthy controls, there have been shown have higher plasma gastrin[[43](#_ENREF_43)] and higher prevalence of peptic ulcers[[44](#_ENREF_44),[45](#_ENREF_45)]. In an endoscopic study, the annual incidence rate of peptic ulcer observed in 140 patients undergoing endoscopic follow-up was 4.3%[[46](#_ENREF_46)]. Ulcers are associated with decompensated cirrhosis[[47](#_ENREF_47)] but are asymptomatic in up to 2/3 of cases[[46](#_ENREF_46)]. In a meta-analysis, the prevalence of helicobacter pylori infection has been found to be higher in cirrhotics with compared to those without peptic ulcer disease[[48](#_ENREF_48)], but its role in the pathogenesis of peptic ulcers in these patients has been questioned[[49](#_ENREF_49)] with alcohol consumtion and portal hypertension being hypothsized as major contributing factors[[50](#_ENREF_50)]. Cirrhotic patients have a significantly increased risk of peptic ulcer bleeding and re-bleeding compared to the general population[[51](#_ENREF_51),[52](#_ENREF_52)]. However, their prognosis during an ulcer bleeding episode may not differ drastically from that of non-cirrhotic patients experiencing bleeding from a peptic ulcer[[50](#_ENREF_50)].

**Gastric sensorimotor function**

***Gastric accommodation***

In the fasting state, the proximal stomach smooth muscle maintains a tonic contractile activity[[53-55](#_ENREF_53)]. During and after food ingestion, a relaxation of the proximal stomach occurs, providing the meal with a reservoir and enabling a volume increase without a rise in pressure (gastric accommodation reflex)[[53](#_ENREF_53),[54](#_ENREF_54),[56-59](#_ENREF_56)].

Impaired gastric accommodation has been associated with upper GI symptoms, such as early satiety, bloating, and epigastric pain, in patients with functional dyspepsia[[60](#_ENREF_60),[61](#_ENREF_61)], diabetes[[62](#_ENREF_62)], prior fundoplication surgery[[63](#_ENREF_63)], vagotomy and partial gastrectomy[[64](#_ENREF_64)].

Gastric barostat studies, using a polyethylene balloon placed in the fundus of the stomach, are generally considered to be the gold standard for the evaluation of gastric accommodation[[59](#_ENREF_59)]. However, other types of tests such as abdominal ultrasound, magnetic resonance imaging, and single-photon emission computed tomography (SPECT) are also commonly used[[59](#_ENREF_59)].

Thus far, three studies have assessed gastric accommodation in cirrhosis. In an ultrasonographic study, performed in patients with alcoholic cirrhosis (*n =* 21), meal-induced accommodation was found to be reduced compared to controls[[65](#_ENREF_65)]. Similarly, in a study employing SPECT, cirrhotic patients with tense ascites (*n =* 15) were found to have impaired accommodation compared to healthy controls[[66](#_ENREF_66)]. Not unexpectedly, accommodation improved following large-volume paracentesis, resulting in an increase in caloric intake[[66](#_ENREF_66)]. In a third study, in which a gastric barostat was employed, meal-induced accommodation was found to be increased in patients with cirrhosis (*n =* 16, none with tense ascites) compared to healthy controls[[27](#_ENREF_27)]. Although energy intake (assessed by means of food diaries) was related to gastric accommodation in controls (*r* = 0.67, *p <* 0.05), this relationship was found to be disrupted in cirrhotic patients (*p* > 0.1). Thus, although it appears reasonable that meal-induced accommodation is impaired in the presence of tense ascites[[66](#_ENREF_66)], to date, it remains unclear how it is affected in patients with cirrhosis of different etiologies without significant ascites.

***Gastric sensitivity to distension***

Gut stimuli, specifically gastric distension by food ingestion, may induce GI symptoms. It has been reported that gastric tone is important in determining gastric sensitivity to distension[[55](#_ENREF_55),[67](#_ENREF_67)] and that in particular gastric wall tension determines perception of gastric distension, at least below nociception levels[[68](#_ENREF_68)].

Hypersensitivity to gastric distension, defined as enhanced sensitivity to balloon distension of the proximal stomach, is present in a subset of functional dyspepsia patients[[69](#_ENREF_69),[70](#_ENREF_70)] and it is associated with weight loss[[69](#_ENREF_69)]. In a single study investigating sensory thresholds at gastric distention, no significant difference was found between patients with cirrhosis (*n =* 16) and healthy controls[[27](#_ENREF_27)]. However, sensory thresholds were related to gastrointestinal symptom severity and liver disease severity, expressed as the Child-Pugh and MELD scores (lower threshold with increasing symptom and liver disease severity)[[27](#_ENREF_27)].

***Gastric emptying***

Another way of assessing gastric motor function is measurement of gastric emptying. Delayed gastric emptying has traditionally been considered a mechanism that contributes to symptom generation in patients with GI motility disorders and systemic diseases affecting the GI tract[[71](#_ENREF_71)].

Most studies in cirrhosis have found gastric emptying to be delayed[[72-76](#_ENREF_72)], but some controversy exists with other studies reporting normal[[77-80](#_ENREF_77)], or accelerated[[81](#_ENREF_81)] gastric emptying. Several factors may account for the divergence of results hitherto published, including selection of patient groups with different characteristics, selection of small patient groups or small control groups and use of different measurement methods. In a recent study from our group almost a quarter of stable patients with cirrhosis had delayed gastric emptying (Figure 3), which was associated with postprandial fullness and bloating[[76](#_ENREF_76)]. Delayed gastric emptying was also related to postprandial hyperglycemia, hyperinsulinemia, and hypoghrelinemia[[76](#_ENREF_76)]. The latter abnormalities appear to be associated to insulin resistance, which is frequent in cirrhosis. These findings are in accordance with published data showing that induced hyperglycemia is associated with reduced gut motility[[82](#_ENREF_82)], delayed gastric emptying, decreased hunger[[83](#_ENREF_83)], and increased postprandial symptoms[[84](#_ENREF_84)] in healthy subjects. Physiological hyperglycemia has been shown to slow gastric emptying in diabetes mellitus[[85](#_ENREF_85)] and healthy volunteers[[86](#_ENREF_86)]. Experimental euglycemic hyperinsulinemia also impairs stomach and duodenal motility[[87](#_ENREF_87)] and prolongs gastric emptying[[87](#_ENREF_87),[88](#_ENREF_88)]. Gastric emptying time in cirrhosis has not been found to be related to portal pressure expressed as variceal pressure, as measured with a small pressure-sensitive capsule attached to a gastroscope[[72](#_ENREF_72)] or as hepatic venous pressure gradient[[80](#_ENREF_80)]. Finally, a role for autonomic dysfunction in the pathophysiology of delayed gastric emptying has also been proposed in these patients[[89](#_ENREF_89)].

***Small bowel motility***

Manometry studies have shown disturbed gut motility in liver cirrhosis[[90-93](#_ENREF_90)]. An abnormal propagation pattern of pressure waves with a high number of long clusters and frequent waves propagating in a retrograde fashion have been reported in cirrhotics, in particular those with portal hypertension[[93](#_ENREF_93)]. Small bowel manometry disturbances have, anecdotally, been reported to improve following liver transplantation[[94](#_ENREF_94)]. However, similar to investigations on gastric emptying, gut transit studies have shown contradictory results[[72](#_ENREF_72),[77](#_ENREF_77),[79](#_ENREF_79),[80](#_ENREF_80),[95-97](#_ENREF_95)] in these patients, with most reporting prolonged small bowel transit times. In a recent study on gut transit in cirrhosis, about 35% of patients showed delayed small bowel residence times (Figure 3), which was related to increased diarrhea and abdominal pain[[76](#_ENREF_76)]. These findings are in accordance with data from non-cirrhotic patients with unexplained GI symptoms whose small bowel transit was frequently slow in unexplained diarrheal disease[[98](#_ENREF_98)]. Small bowel bacterial overgrowth is also common in cirrhosis[[92](#_ENREF_92),[99](#_ENREF_99)] and appears to be related to liver disease severity[[100](#_ENREF_100)], although it was only observed in patients with portal hypertension in one study[[93](#_ENREF_93)]. Interestingly, patients with small bowel bacterial overgrowth have been also shown to have slower small bowel transit[[72](#_ENREF_72)]. Furthermore, it has been reported that acceleration of orocecal transit using cisapride is associated with the abolishment of bacterial overgrowth in 80% of cirrhotic patients with bacterial overgrowth[[101](#_ENREF_101)]. It is thus possible that delayed small bowel transit in cirrhosis may lead to the development of small bacterial overgrowth, which could contribute to the symptoms of abdominal pain and diarrhea. More importantly, small bacterial overgrowth has been speculated to be related to bacterial translocation and infectious complications, such as spontaneous bacterial peritonitis[[92](#_ENREF_92)].

**Intestinal permeability:** The gut barrier includes immunogenic factors (such as mucosal lymphocytes and immunoglobulins) and the epithelial barrier (*i.e.* epithelial cells allowing selective intestinal permeability and their mucus layer)[[102-104](#_ENREF_102)]. Central to the role of barrier function of the epithelial cells are the tight junctions and adherens junctions regulating paracellular transport[[104](#_ENREF_104)]. As a barrier, the gut prevents the permeation of microorganisms or substances, such as luminal antigens and proinflammatory factors. At the same time it allows for selective permeation of certain substances such as nutrients[[102](#_ENREF_102),[103](#_ENREF_103)].

Non-invasive methods have been used to assess gut barrier function by measuring the urinary excretion of orally administered test substances such as monosaccharides, disaccharides, and 51Cr-EDTA[[102](#_ENREF_102),[105](#_ENREF_105)]. To address the complexity of factors affecting the results of gut permeability tests, the principle of differential urinary excretion of several test substances administered at the same time has been developed[[105](#_ENREF_105)].

Bacterial infections are of concern in patients with cirrhosis, with spontaneous bacterial peritonitis being the most relevant[[106](#_ENREF_106),[107](#_ENREF_107)]. They may occur as a consequence of repeated access of bacteria from the lumen to the mesenteric lymph nodes (translocation), and thereby to the ascitic fluid[[108](#_ENREF_108)]. Intestinal permeability in liver cirrhosis has been variably reported as increased or normal[[32](#_ENREF_32),[33](#_ENREF_33),[109-117](#_ENREF_109)]. Discrepancies among published studies may be partly explained by patient selection and choice of different measurement methods. A recent report on intestinal permeability in cirrhosis with and without ascites by means of a four-sugar permeability-absorption test has shown increased permeability in the former group only[[114](#_ENREF_114)]. Recent evidence suggests the presence of gut barrier dysfunction in patients with cirrhosis, especially those with severe liver disease[[118](#_ENREF_118)]. For example Campillo et al have found increased intestinal permeability in cirrhotics, particularly in those with bacterial infections[[32](#_ENREF_32)].Intestinal hyperpermeability has also been shown to be more common in patients with a history of spontaneous bacterial peritonitis[[117](#_ENREF_117)]. Increased permeability upon hospital admission has also been reported to be a predictor of bacterial infections in cirrhosis[[119](#_ENREF_119)] and to be related to cirrhosis complications in general[[118](#_ENREF_118)], although published studies are not unanimous[[120](#_ENREF_120)].

Furthermore, permeation of intestinal bacterial products, *e.g.* endotoxin and bacterial DNA, may contribute to the activation of the immune system, derangement of the circulatory status, and induction of renal failure[[108](#_ENREF_108),[121](#_ENREF_121)] as well as the development of hepatic encephalopathy in patients with cirrhosis[[96](#_ENREF_96),[122](#_ENREF_122),[123](#_ENREF_123)]. This may occur through reduced hepatic clearance of endotoxin (component of the Gram negative bacterial wall) in cirrhotic patients and/or by means of increased cytokine production by the gut, for example by endotoxin-primed macrophages releasing nitric oxide and proinflammatory cytokines[[124-127](#_ENREF_124)]. The proinflammatoy status and nitric oxide release in cirrhosis may, in turn, disrupt further the gut barrier function[[125](#_ENREF_125)], contribute to immune and hemodynamic derangement and cardiac dysfunction[[124](#_ENREF_124),[126](#_ENREF_126),[128](#_ENREF_128),[129](#_ENREF_129)] as well as predict progression of liver disease[[127](#_ENREF_127)]. Bacterial overgrowth, in particular overgrowth of pathogenic E.coli and Staphylococcal species, has been reported to be more frequent in cirrhotics with compared to those without minimal hepatic encephalopathy[[96](#_ENREF_96),[122](#_ENREF_122)]. In a recent meta-analysis, the use of probiotics, prebiotics, and symbiotics, which have an effect on gut flora, was shown to be associated with significant improvement in hepatic encephalopathy[[123](#_ENREF_123)]. Alcohol misuse in patients with liver disease is associated with increased intestinal permeability[[130-132](#_ENREF_130)] and endotoxemia, which in turn may contribute to alcohol-induced liver damage by means of hepatic fibrosis stimulation[[130](#_ENREF_130)]. Recent studies have shown that alcohol-induced gut leakiness and endotoxemia precedes steatohepatitis in patients with alcoholic liver disease and, thus, they are not a consequence of the latter[[133](#_ENREF_133)]. This further suggests that a “leaky” gut may play an important role in the pathogenesis of of chronic liver injury. Several mechanisms have been proposed to explain bacterial translocation such as intestinal bacterial overgrowth in conjunction with intestinal motility disturbances (outlined above), impairment of the intestinal barrier function, and alterations in the local immune defenses[[121](#_ENREF_121),[134](#_ENREF_134)].

The pathophysiology of intestinal barrier dysfunction in cirrhosis is complex. First, alcohol and its metablites, acetaldehyde and fatty acid ethyl esters, may contribute to the disruption of tight junctions, mainly through nitric oxide mediated oxidative stress and the generation of reactive oxygen species, and alterations in the cytoskeleton, but also through direct cell damage[[135](#_ENREF_135),[136](#_ENREF_136)]. Portal hypertension *per se* may affect the integrity of intestinal barrier by causing edema in the gut wall with dilatation of the intercellular spaces[[137](#_ENREF_137)]. Several studies have shown increased intestinal permeability in patients with portal hypertension compared to those without[[114-116](#_ENREF_114)]. A recent study has shown that treatment with non-selective beta blockers reduces intestinal permeability as well as bacterial translocation in patients with cirrhosis[[116](#_ENREF_116)]. Furthermore, microbial changes in the intestine, and in particular small intestinal bacterial overgrowth, may also affect the gut barrier[[138](#_ENREF_138)], thereby increasing permeability, while compromised Paneth cell antimicrobial host defense has been shown to predispose to bacterial translocation in experimental cirrhosis[[139](#_ENREF_139)]. Finally, altered expression of enterocyte tight junction proteins has been reported in patients with liver cirrhosis, in particular those with decompensated cirrhosis, and is correlated with levels of endotoxemia in these patients[[140](#_ENREF_140)]. In particular, although tight junctions have been found to be normal ultrastructurally, claudin-2 a pore forming protein of tight junctions, is increased in decompensated cirrhosis[[125](#_ENREF_125)] whereas the expression of the tight junction proteins occludin and claudin-1 have been shown to be significantly decreased[[140](#_ENREF_140)]. These changes may, at least in part, explain the observed increased paracellular permeability in cirrhosis[[125](#_ENREF_125),[40](#_ENREF_140)].

**Conclusion**

GI symptoms are common in patients with liver cirrhosis. Their pathophysiology is complex and probably involves factors related to liver disease severity, psychological distress, and gut dysfunction. GI symptoms are related to reduced energy intake and, thus, may contribute to weight loss and malnutrition. Identification of patients with GI symptoms could therefore help select candidates for nutritional therapy. Gastric sensorimotor function appears also to be altered. Although published data on gastric accommodation are not unanimous, not unexpectedly, tense ascites appears to have a negative impact on meal-induced accommodation of the stomach. Gastric emptying and small bowel transit are delayed, which may be related to disturbances in postprandial glucose, insulin, and ghrelin levels. These alterations, in turn, appear to be associated to insulin resistance, which is common in patients with cirrhosis. Delayed gut transit as well as small bowel manometry disturbances may be associated with the development of small bowel bacterial overgrowth. Future interventional studies should address potential causes of delayed gut transit, such as diabetes and insulin resistance. This could, possibly, help develop specific therapies improving energy intake but also reducing bacterial overgrowth. Finally, several studies have reported intestinal barrier dysfunction in patients with liver cirrhosis (especially those with portal hypertension), which is related to bacterial translocation and permeation of intestinal bacterial products, *e.g.* endotoxin and bacterial DNA, thus potentially being involved in the pathogenesis of complications of liver cirrhosis.

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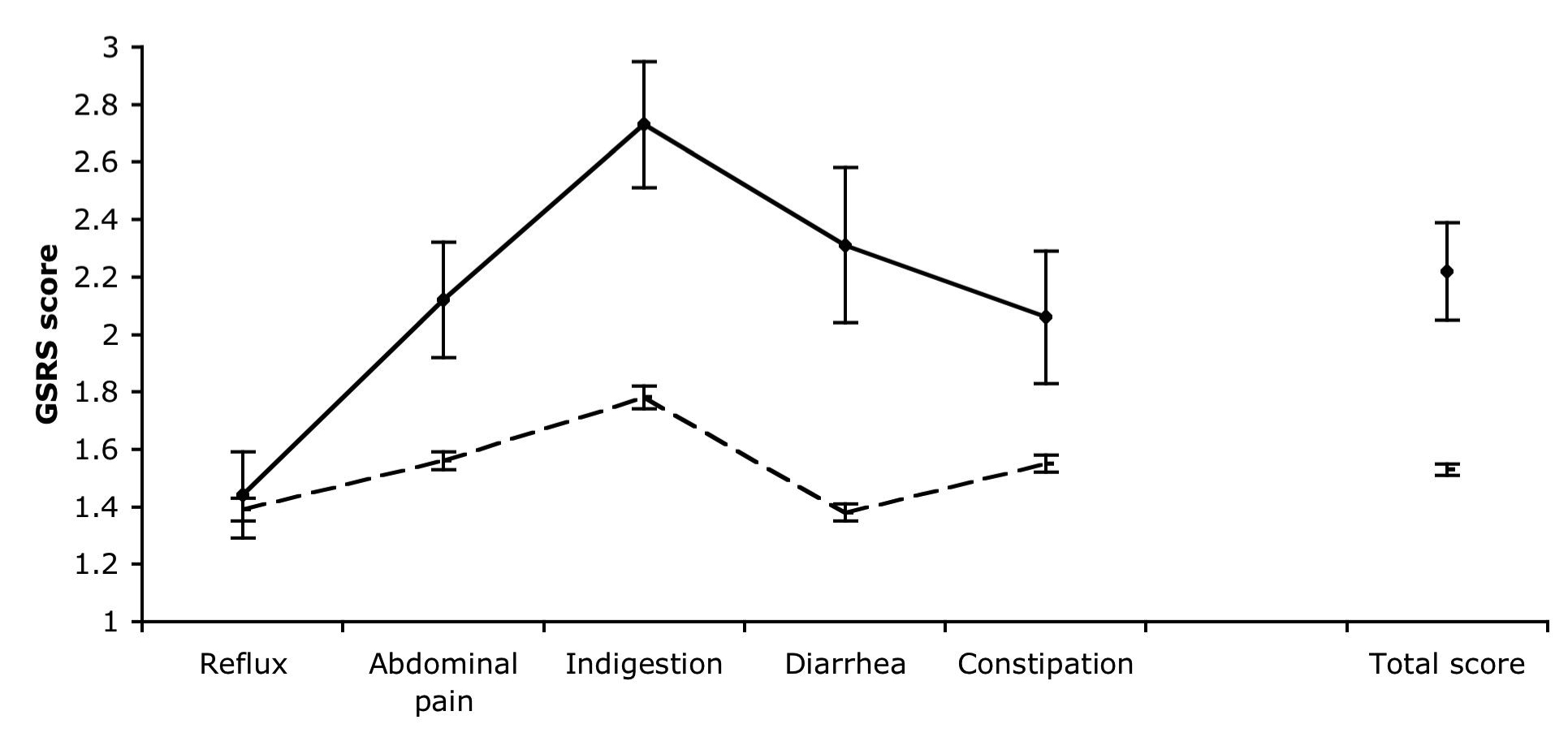
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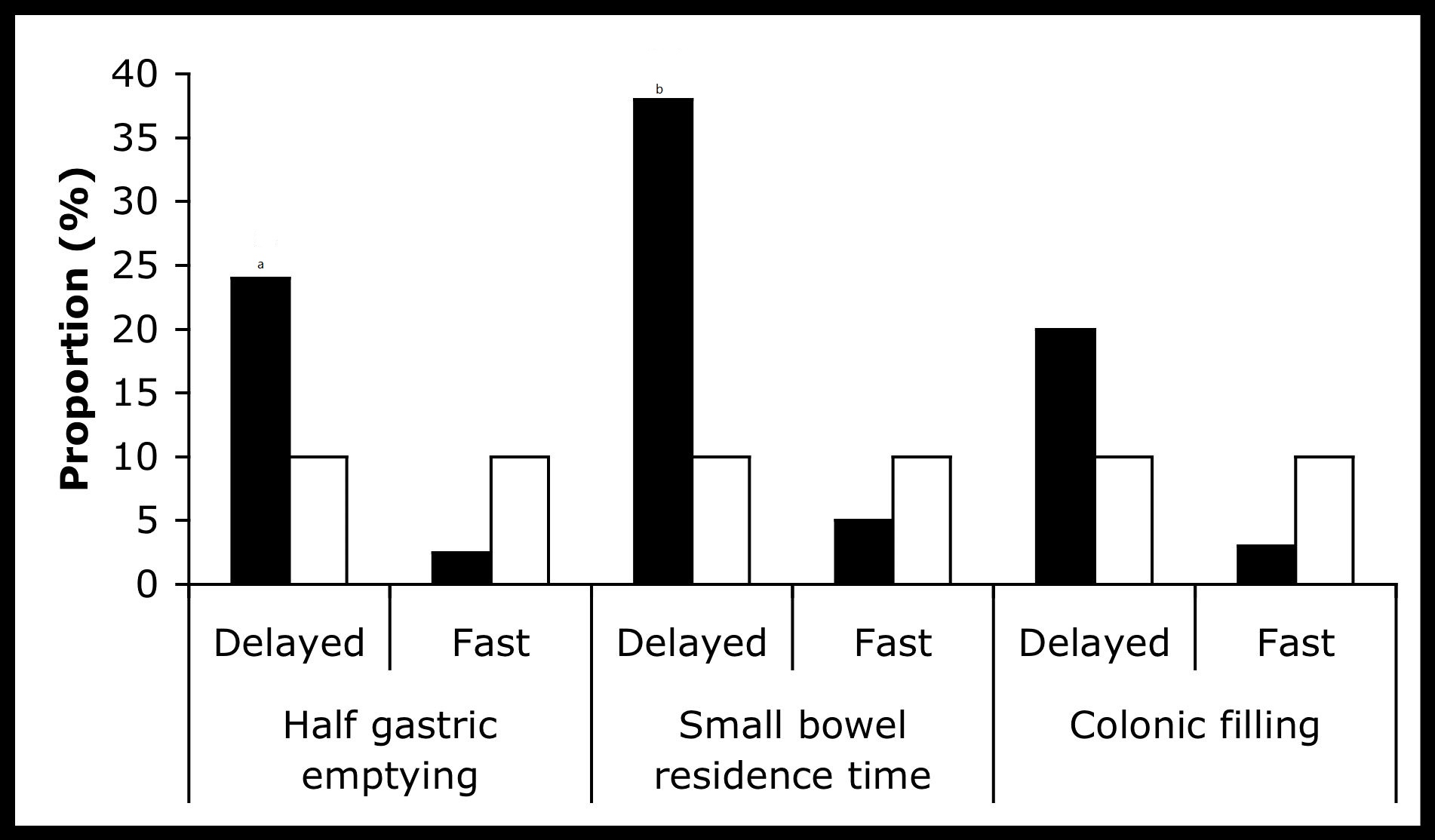
**P-Reviewers:** Festi D, Li YH, Mach TH, Manesis EK, Yang YP **S-Editor:** Ma yj **L-Editor:** **E-Editor:**

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**Figure 1 Gastrointestinal symptom severity assessed as gastrointestinal symptom rating scale scores (means and 95%CI) in patients with liver cirrhosis (continuous line, *n =* 128) and healthy controls (dashed line, *n =* 2162).** The higher the score in gastrointestinal symptom rating scale (GSRS) the higher the severity of gastrointestinal symptoms. Adapted from the reference [25].



**Figure 2 Cumulative percentage of cirrhotics with significant symptoms (*n =* 16, dotted line), cirrhotics without significant symptoms (*n =* 24, dashed line) and healthy controls (*n =* 11, continuous line) reaching maximum satiety during a caloric satiation drinking test.** In a caloric satiation drinking test, subjects are asked to consume a liquid caloric meal at a constant rate, scoring their satiation level at 5-min intervals. The test is terminated when the subject reaches maximal satiation. Adapted from the reference [26].



**Figure 3 Frequency of transit abnormalities in patients with liver cirrhosis (black bars, *n =* 42) and healthy controls (white bars, *n =* 83).** Reference values were based on percentiles 10 and 90 of the transit values of healthy controls (*n =* 83) a*p <* 0.05, b*p <* 0.01, patients group *vs* healthy controls. Adapted from the reference [76].