

Gut-liver axis in cirrhosis: Are hemodynamic changes a missing link?

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Abstract

Recent evidence suggests that the condition of the gut and its microbiota greatly influence the course of liver disease, especially cirrhosis. This introduces the concept of the gut-liver axis, which can be imagined as a chain connected by several links. Gut dysbiosis, small intestinal bacterial overgrowth, and intestinal barrier alteration lead to bacterial translocation, resulting in systemic inflammation. Systemic inflammation further causes vasodilation, arterial hypotension, and hyperdynamic circulation, leading to the aggravation of portal hypertension, which contributes to the development of complications of cirrhosis, resulting in a poorer prognosis. The majority of the data underlying this model were obtained initially from animal experiments, and most of these correlations were further reproduced in studies including patients with cirrhosis. However, despite the published data on the relationship of the disorders of the gut microbiota with the complications of cirrhosis and the proposed pathogenetic role of hemodynamic disorders in their development, the direct relations between gut dysbiosis and hemodynamic changes in this disease are poorly studied. They remain a missing link in the gut-liver axis and a challenge for future research.

Key Words: Gut microbiota; Gut dysbiosis; Small intestinal bacterial overgrowth; Intestinal barrier; Bacterial translocation; Vasodilation; Hyperdynamic circulation; Gut microbiome; Cardiac output; Systemic vascular resistance

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Core Tip: Recent evidence suggests that the condition of the gut and its microbiota greatly influence the course of liver disease, especially cirrhosis. This introduces the concept of the gut–liver axis, which can be imagined as a chain connected by several links. However, despite the published data on the relationship of the disorders of the gut microbiota with the complications of cirrhosis and the proposed pathogenetic role of hemodynamic disorders in their development, the direct relations between gut dysbiosis and hemodynamic changes in this disease are poorly studied. They remain a missing link in the gut–liver axis and a challenge for future research.

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INTRODUCTION

The last decade has been marked by an intensive study of the role of the gut microbiota in norm and pathology. It has been shown that the gut bacteria not only mechanically reside in the gut, but also have a variety of effects on the body, both positive and negative. Moreover, the gut microbiota play an important role in the development of diseases of the gut as well as distant organs such as the joints, heart, liver, brain, and others[1]. This led to introduction of the concepts of the gut–joint[2–3], gut–heart[4], gut–liver[5], and gut–brain axes[6], and others[7]. The importance of the gut–liver axis is evidenced by the fact that a separate conference of the European Association for the Study of the Liver, which took place in 2018, was dedicated to this axis.

Gut bacteria and their cell components when they enter human tissues (bacterial translocation) lead to the development of systemic inflammation of varying degrees of intensity, which has a complex effect on the body. Lipopolysaccharide (LPS) is the most well studied and one of the most reactogenic of such components[8]. Normally, bacterial translocation inhibits by the predominance of strict anaerobes and bacteria without active LPS in the gut microbiome and low permeability of the intestinal barrier. With pathology, the proportion of facultative anaerobes (*Bacilli* and *Proteobacteria*) and bacteria with active LPS (*Proteobacteria*) capable of bacterial translocation increases in the intestinal microbiome (gut dysbiosis), the total number of bacteria in the small intestine increases [small intestinal bacterial overgrowth (SIBO)], and intestinal permeability also increases, which contributes to the development of bacterial translocation and systemic inflammation. The latter triggers a chain of events that contribute to the decompensation of liver function in cirrhosis[8]. An important link in this chain is hemodynamic disorders, which are often underestimated.

GUT DYSBIOSIS IN CIRRHOSIS

Alteration of the gut microbiota composition in cirrhosis has been established in a number of studies (Table 1)[8–23]. Despite some inconsistencies in the results obtained, there was an increase in the abundance of taxa capable of bacterial translocation (*Bacilli*, *Streptococcaceae*, *Lactobacillaceae*, *Enterococcaceae*, *Proteobacteria*, *Enterobacteriaceae*), as well as those with active LPS (*Proteobacteria*, *Enterobacteriaceae*), with a decrease in the abundance of autochthonous taxa incapable of bacterial translocation and not containing LPS (*Clostridia*, *Ruminococcaceae*, *Lachnospiraceae*, etc.) in cirrhosis in most reports.

The Model for End-stage Liver Disease (MELD) score was negatively correlated with the abundance of *Clostridiales* XIV, *Lachnospiraceae*, and *Ruminococcaceae*, and positively correlated with the abundance of *Staphylococcaceae*, *Enterococcaceae*, and *Enterobacteriaceae*[16]. Patients with acute-on-chronic liver failure (ACLF) had a significantly lower abundance of gram-positive organisms that had no LPS[16]. The abundance of *Lachnospiraceae* was negatively related to the Child–Turcotte–Pugh (CTP)

Table 1 Changes in the gut microbiome in cirrhosis according to data from different studies

Ref.	Taxa that increased in cirrhosis	Taxa that decreased in cirrhosis
Zhang <i>et al</i> [9], 2019	<i>Bacteroidaceae</i>	<i>Prevotellaceae</i>
Jin <i>et al</i> [10], 2019	<i>Proteobacteria, Granulicatella</i>	<i>Bacteroidetes, Ruminococcaceae, Barnesiellaceae, Faecalibacterium, Dorea, Anaerostripes, RuminococcusButyricoccus, Bilophila</i>
Zeng <i>et al</i> [11], 2020	<i>Proteobacteria, Bacteroides, Atopobium, Akkermansia, Prevotella, Parabacteroides</i>	
Kajihara <i>et al</i> [12], 2019	<i>Enterobacteriaceae</i>	<i>Akkermansia, Rikenellaceae, Erysipelotrichales</i>
Chen <i>et al</i> [13], 2020	<i>Gammaproteobacteria, Bacilli, Erysipelotrichi</i>	<i>Clostridia</i>
Zheng <i>et al</i> [14], 2020	<i>Verrucomicrobia, Proteobacteria, Phyllobacterium, Sphingomonas, Enterococcus, Erysipelatoclostridium, and Romboutsia</i>	<i>Firmicutes, Tenericutes, Ralstonia, Catenibacterium, and Lachnospira</i>
Lapidot <i>et al</i> [15], 2020	<i>Gammaproteobacteria, Enterobacteria, Bacilli, Streptococcaceae, Alloscardovia, Atopobium</i>	<i>Ruminococcaceae and Lachnospiraceae</i>
Bajaj <i>et al</i> [16], 2014; Bajaj <i>et al</i> [17], 2015	<i>Staphylococcaeae, Enterococcaeae, Enterobacteriaceae</i>	<i>Porphyromonadaceae, Clostridiales XIV, Lachnospiraceae, Ruminococcaeae, Veillonellaceae</i>
Ahluwalia <i>et al</i> [18], 2016	<i>Lactobacillaceae, Enterococcaeae, Enterobacteriaceae</i>	<i>Clostridiales XIV, Lachnospiraceae, Ruminococcaeae</i>
Liu <i>et al</i> [19], 2018	<i>Firmicutes, Peptostreptococcaeae, Streptococcaeae, Erysipelotrichaceae, Clostridiaceae_1, Pasteurellaceae</i>	<i>Bacteroidetes, Bacteroidaceae, Prevotellaceae, Porphyromonadaceae, Acidaminococcaeae</i>
Inoue <i>et al</i> [20], 2018	<i>Bacilli, Streptococcus, Lactobacillus</i>	
Maslennikov <i>et al</i> [21], 2021	<i>Bacilli, Bifidobacteriaceae, Streptococcaceae, Lactobacillaceae, Enterococcaceae, Enterobacteriaceae, Proteobacteria</i>	<i>Clostridia, Ruminococcaceae, Lachnospiraceae</i>
Chen <i>et al</i> [22], 2011	<i>Proteobacteria, Fusobacteria, Bacilli, Enterobacteriaceae, Pasteurellaceae, Streptococcaceae, Fusobacteriaceae, Veillonellaceae</i>	<i>Bacteroidetes, Lachnospira, Bacteroidaceae</i>
Kakiyama <i>et al</i> [23], 2013	<i>Enterobacteriaceae and Veillonellaceae</i>	<i>Blautia, Ruminococcaceae, Lachnospiraceae</i>

score, but an opposite tendency was observed for the abundance of *Streptococcaceae* [22].

Gut dysbiosis was more pronounced in patients with hepatic encephalopathy [18]. Patients with severe dysbiosis had lower serum albumin and cholinesterase levels, higher CTP scale values, higher C-reactive protein (CRP) levels, and poorer long-term prognosis [21]. A higher abundance of *Lachnospiraceae* was negatively correlated with the risk of hospitalization in the intensive care unit [24]. There were positive correlations of the abundance of *Enterobacteriaceae* with hepatic encephalopathy, the abundance of *Enterococcaceae* with circulatory failure, and the abundance of *Streptococcaceae* with respiratory failure within 30 d of hospitalization [24].

SIBO IN CIRRHOSIS

The prevalence of SIBO in cirrhosis is approximately 40%, higher (approximately 50%) in decompensated cirrhosis and lower (approximately 30%) in compensated cirrhosis [25]. SIBO in cirrhosis is associated with ascites, minimal hepatic encephalopathy, bacterial translocation, spontaneous bacterial peritonitis (SBP), prolonged orocecal transit time, systemic inflammation, hyperdynamic circulation, vasodilation, and arterial hypotension, but is not associated with hypocoagulation [25-26]. Further studies are required to clarify the relationship of SIBO with hyperbilirubinemia, hypoalbuminemia, previous overt hepatic encephalopathy, and esophageal varices [25].

INTESTINAL BARRIER DYSFUNCTION IN CIRRHOSIS

The intestinal barrier is represented by antimicrobial proteins secreted into the intestinal lumen, intestinal epithelial cells connected by tight and other intercellular junctions, intraepithelial lymphocytes, and other structures [27]. Its dysfunction

manifests in an increase in intestinal permeability, the biomarkers of which are an increase in the level of proteins of tight junctions (claudins, zonulin, occludin, and others) in blood as well as substances that are normally poorly absorbed from the intestinal lumen (D-lactate, lactulose, polyethylene glycol, and others)[27].

Short-chain fatty acids (SCFA) produced by the gut microbiota, especially butyrate, play an important role in maintaining the intestinal barrier[28]. This effect is possibly associated with an increase in the production of proteins of tight junctions which was observed in the culture of epithelial cells after the addition of SCFA[28]. However, the exact mechanism for this has not yet been established.

D-lactate is formed only during the metabolism of bacteria and cannot be used by the human body. A small amount of D-lactate enters the blood from the intestines[29]. With an increase in intestinal permeability, its level in the blood increases, which is observed in patients with cirrhosis[30]. Moreover, it becomes higher with an increase in the CTP class of cirrhosis[30].

Intestinal permeability measured by the urinary excretion of oral polyethylene glycol and lactulose with mannitol was also higher in cirrhosis[31-32]. The ratio of the urinary excretion of lactulose to mannitol gradually increased with disease severity[32] and was higher in patients with ACLF[33].

The blood level of claudin 3 was higher in patients with cirrhosis than in healthy individuals. It was also higher in patients with decompensated cirrhosis, SBP, and ACLF than in those with compensated cirrhosis and chronic hepatitis without cirrhosis [34].

The contents of claudin 1 and occludin in duodenal biopsy specimens were lower in patients with cirrhosis than in healthy individuals and lower in patients with decompensated cirrhosis than in those with compensated cirrhosis. The expression of occludin gradually decreased from the crypt to the tip of the villi that have maximal contact with gut microbiota. Occludin and claudin 1 expression were inversely correlated with the CTP score, grade of esophageal varices, and blood LPS level[35].

The blood zonulin level was significantly higher in patients with cirrhosis[36]. It was higher in patients with CTP C cirrhosis than in those with CTP A and B cirrhosis and did not differ significantly between patients with CTP A and B cirrhosis[37]. The level of this biomarker was significantly positively correlated with the blood LPS level in decompensated cirrhosis[36].

The intestinal mucosal mitotic count was significantly lower in patients with cirrhosis than in the controls, and a trend toward increased apoptosis was recorded. Lipid peroxidation in the intestinal cells increased in decompensated cirrhosis but not in compensated cirrhosis[38]. These changes (increased death and decreased renewal of intestinal cells and increased oxidative stress in these cells) also predispose to a decrease in the gut barrier function.

The blood level of diamine oxidase (DAO), a biomarker of intestinal damage[39], was higher in patients with cirrhosis than in healthy individuals and patients with chronic hepatitis without cirrhosis[40]. It increased with an increase in the CTP class and was higher in patients with decompensated cirrhosis, SBP, bleeding from esophageal varices, and hepatic encephalopathy and patients who were re-hospitalized within the next 6 mo[40]. No difference in the DAO level was noted between patients with and without ascites[40]. The DAO level was positively correlated with aspartate aminotransferase (AST), total bilirubin[40], and D-lactate[30] levels and negatively correlated with serum albumen level and prothrombin activity. However, no significant associations were noted between the DAO level and alanine aminotransferase (ALT)[40]. The DAO level in blood was an independent marker of the development of complications of cirrhosis during the next 12 mo and death[32].

Patients with cirrhosis had a diminished expression of the antibacterial peptides defensin 5 and 6 at the intestinal crypts compared with healthy controls, and this was negatively correlated with blood LPS levels. In addition, the content of intraepithelial lymphocytes in the duodenal biopsy specimen was lower in patients with decompensated cirrhosis than in healthy controls[41]. Thus, the protective properties of the intestinal epithelium against bacterial invasion are reduced in patients with cirrhosis and this also predisposes to a decrease in the effectiveness of the intestinal barrier.

The total stool content of SCFA was lower in patients with cirrhosis than in healthy controls. Lower levels of propionate, butyrate, valerate, isobutyrate, and isovalerate were noted, while there were no differences in acetate content[10]. Fecal microbiota from patients with CTP class A produced SCFA comparable with those in the controls, whereas those from patients with CTP classes B and C produced them with a moderate and a profound reduction, respectively[10]. The abundance of *Bacteroidetes*, *Lachnospiraceae*, and *Faecalibacterium* was the most consistent positive association with

SCFA production. *Granulicatella*, which had a strong correlation with the severity of liver disease, showed a negative association with SCFA production[10]. The blood butyrate level was inversely correlated with the MELD score[42] and blood LPS, tumor necrosis factor alpha (TNF- α), interleukin 6 (IL-6), and nitric oxide (NO) levels[38] and was significantly lower in patients with a history of ascites, SBP, and previous episodes of hepatic encephalopathy[42].

BACTERIAL TRANSLOCATION IN CIRRHOSIS

Bacterial translocation is the penetration of living bacteria (cellular bacterial translocation) and their cell components (molecular bacterial translocation) from the gut lumen into its wall, mesenteric lymph nodes, ascitic fluid, liver tissue, and portal and systemic blood flow[43]. The most used biomarkers of bacterial translocation are LPS, soluble SD14, lipopolysaccharide binding protein (LBP), and bacterial DNA[43-45]. In addition, modern metagenomic technologies make it possible to assess the total genome of bacteria in ascitic liquid and blood (ascitic and blood microbiome)[46]. Endogenous infections (*e.g.*, SBP) can develop as complications of cellular bacterial translocation[47].

The blood LPS level was higher in patients with cirrhosis than in healthy individuals. It was also higher in patients with decompensated cirrhosis, SBP, and ACLF compared to those with compensated cirrhosis and chronic hepatitis without cirrhosis[16,30,34]. Moreover, it was higher in patients with clinical portal hypertension (esophageal varices, portal gastropathy, thrombocytopenia, and/or ascites) than in those without it[41]. The greater the size of esophageal varices and the higher the degree of ascites is accompanied by higher blood LPS levels[41].

Direct correlations of blood LPS level with the level of intestinal permeability (D-lactate[30] and claudin 3[34]) and intestinal damage (DAO[30]) biomarkers, pro-inflammatory cytokines (TNF- α and IL-6)[42], endothelial dysfunction biomarker NO [42], and CTP[30] and MELD[16] scores have been identified.

Serum LPS levels as well as TNF- α , IL-6, and NO levels were significantly higher in the portal blood than in the hepatic and peripheral blood, without significant differences in the latter two sites[42]. This proves the predominantly intestinal origin of blood LPS, NO, and pro-inflammatory cytokines in cirrhosis.

The blood LPS level was positively correlated with the abundance of gram-negative bacteria *Enterobacteriaceae* and *Bacteroidaceae* and negatively correlated with the abundance of gram-positive bacteria *Clostridiales* XIV, *Lachnospiraceae*, and *Ruminococcaceae* in the gut microbiome[16].

Patients who died within 30 d after admission compared with those who survived had a significantly higher blood LPS level and an abundance of gram-negative bacteria that had LPS in the gut microbiome[16]. In patients with infectious complications of cirrhosis (*e.g.*, SBP), the abundance of potential pathogenic bacteria *Enterobacteriaceae* was higher, and the abundance of autochthonic bacteria *Lachnospiraceae*, *Ruminococcaceae*, *Veillonellaceae*, and *Clostridiales* XIV was lower[16]. These patients had a higher blood LPS level[16]. The content of the genetic material of *Enterobacteriaceae* increased in the blood of patients with cirrhosis[12].

Bacterial DNA was detected in ascitic fluid and blood in 30% of patients with decompensated cirrhosis, only in ascitic fluid in 30% of these patients, only in blood in 20% of these patients, and not in one of them in 20% of these patients[48]. The presence of bacterial DNA in blood and ascitic fluid was associated with a significantly higher prevalence of systemic inflammatory response syndrome[48]. A significantly higher number of patients with bacterial DNA in ascitic liquid needed transjugular intrahepatic portal shunting, while the presence of serum bacterial DNA was associated with an increased number of episodes of hepatic encephalopathy[48]. Bacterial DNA in blood and/or ascitic fluid was more often detected in patients with SBP, systemic inflammatory response syndrome, and ACLF[49]. The presence of bacterial DNA in blood and ascitic fluid was associated with higher blood IL-6 and IL-10 levels[49].

It is striking that there is a huge difference in the composition of the gut microbiome on the one hand and the ascitic and blood microbiome on the other. *Firmicutes* and *Bacteroidetes* represented mainly by strict anaerobes were dominant, while mainly facultative anaerobes *Proteobacteria*, as a rule, occupied less than 10% in the gut microbiome in cirrhosis. However, *Proteobacteria* accounted for 75%-90%, *Firmicutes* (rather as facultative anaerobes *Bacilli*) for 5%-10%, and *Bacteroidetes* for 3%-4% in the ascitic and blood microbiomes in cirrhosis. The aerotolerant bacteria *Actinobacteria*

were represented many times more (5%-10% *vs* < 2%) in the ascitic and blood microbiome than in the gut microbiome[49-50]. No significant differences were noted between the microbiota compositions of ascites and blood samples at the phylum level [49]. The main families of bacteria in the ascitic and blood microbiome were facultative anaerobes *Pseudomonadaceae*, *Oxalobacteraceae*, *Neisseriaceae*, *Enterobacteriaceae*, *Sphingomonadaceae*, and *Moraxellaceae*, which are relatively poorly represented in the gut microbiome[50]. These data prove the hypothesis that facultative anaerobes are the main translocating bacteria, while dominant in the gut microbiome of healthy persons, strict anaerobes almost never translocate.

Thus, bacterial translocation is associated with gut dysbiosis, impaired intestinal barrier function, systemic inflammation, endothelial dysfunction, infectious and non-infectious complications of cirrhosis.

SYSTEMIC INFLAMMATION IN CIRRHOSIS

The pro-inflammatory cytokine TNF- α level was higher in patients with cirrhosis than in healthy individuals. It was also higher in patients with decompensated cirrhosis, SBP, and ACLF compared to those with compensated cirrhosis and chronic hepatitis without cirrhosis[34]. The blood TNF- α level was positively correlated with the blood level of the intestinal permeability biomarker claudin 3 and bacterial translocation biomarker LPS[34].

Patients with systemic inflammation (blood CRP level above 25 mg/L) had higher MELD and CTP scores, and they were more often diagnosed with SBP[50].

The blood CRP level was higher in cirrhosis with SIBO and in cirrhosis with severe dysbiosis[21,26]. *Porphyromonadaceae* was negatively correlated with the anti-inflammatory cytokine IL-10 and positively correlated with IL-13 in cirrhosis[17]. The pro-inflammatory cytokine and NO levels were lower in patients receiving antibiotic treatment[42].

The blood levels of the biomarkers of macrophage activation sCD163 and soluble mannose receptor and biomarkers of systemic immune activation IL-6 and IL-8 were significantly higher in patients with cirrhosis than in healthy controls and gradually increased with disease severity (CTP classes B and C *vs* A)[32]. The blood levels of sCD163 and soluble mannose receptor were significantly positively correlated with the values of other biomarkers of systemic inflammation (IL-6 and IL-8), bacterial translocation (LPS and soluble CD14), intestinal permeability (test with urinary lactulose/mannitol excretion), and intestinal damage (DAO) and were higher in patients who developed complications of cirrhosis (ascites, hepatic encephalopathy, or jaundice) within 12 mo[32].

Thus, systemic inflammation is associated with SIBO, gut dysbiosis, impaired intestinal barrier function, bacterial translocation, infectious and non-infectious complications of cirrhosis.

HEMODYNAMIC CHANGES IN CIRRHOSIS

The main hemodynamic changes in cirrhosis are systemic vasodilation, arterial hypotension, and hyperdynamic circulation (increased cardiac output and index). It is believed that vasodilation is the primary condition and leads to arterial hypotension and an increase in the heart function and fluid retention (hyperdynamic circulation) through activation of the renin, angiotensin, and aldosterone and other systems to compensate for it[51].

N-terminal prohormone of brain natriuretic peptide (NT-proBNP) can be used as a biomarker of hyperdynamic circulation in cirrhosis. This protein is considered a biomarker of heart failure. However, its level was not correlated with a decrease in ejection fraction but correlated with an increase in cardiac output and a decrease in systemic vascular resistance (SVR) in cirrhosis[52]. Patients with hyperdynamic circulation had a higher NT-proBNP level regardless of the presence of diastolic dysfunction[52]. Patients with refractory ascites, severe esophageal varices, hepatorenal syndrome, and hypoalbuminemia had a higher NT-proBNP level, but patients with pre-ascites had a lower NT-proBNP level. The NT-proBNP level was correlated with the CTP and MELD scores, serum albumin level, and portal vein diameter[53].

Patients with hyperdynamic circulation had a higher MELD score, serum total bilirubin level, international normalized ratio, and massive ascites. These patients more often developed ACLF and died within 1 year of follow-up[54]. The mean arterial pressure (MAP) decreased progressively from the prognostic stages of cirrhosis 1 to 5, and the cardiac index increased progressively from stages 1 to 4 but decreased in stage 5[55].

The blood flow increased in the abdominal aorta and common hepatic and superior mesenteric arteries, decreased in the renal arteries, and did not change significantly in the portal vein and carotid arteries in cirrhosis. Moreover, the flow through the abdominal aorta and common hepatic and superior mesenteric arteries was higher in patients with a higher MELD score than in those with a low score[56]. In cirrhosis, the blood flow increases in the organs that are most susceptible to the effects of bacterial translocation and the inflammatory response to it: the intestine (superior mesenteric artery) and liver, into which the portal vein carries blood rich in LPS and pro-inflammatory cytokines[42]. As a result, the kidneys are affected by the steal syndrome, which predisposes to the development of hepatorenal syndrome[57]. The excess blood that enters the intestine through the superior mesenteric artery does not increase the flow in the portal vein due to increased resistance to portal blood flow through the liver. This leads to increased pressure in the portal vein (increased portal hypertension), the equivalent of which is the wedged hepatic venous pressure (WHVP), and shunting of portal blood, which predisposes to the development of esophageal varices and hepatic shunt encephalopathy[58]. Patients with clinically significant portal hypertension had higher cardiac output and index and lower SVR than those with preclinical portal hypertension. Moreover, these changes were greater in patients with esophageal varices than in those without[59]. The shunted fraction (ratio of the splenorenal shunt flow to portal vein flow) was directly correlated with the cardiac index and inversely correlated with SVR. Moreover, the blood ammonia level and incidence of hepatic encephalopathy were higher in patients with a higher shunted fraction[60]. WHVP and hepatic venous pressure gradient (HVPG) (the main indicator of hepatic portal hypertension—the difference between the pressure in the portal vein, the equivalent of which is WHVP, and the pressure in the hepatic veins) were positively correlated with cardiac output and negatively correlated with SVR[61]. Cardiac output was independently associated with higher hepatic blood flow[61]. The platelet count was inversely correlated with the value of the cardiac index[60].

It is assumed that the main mechanism of vasodilation in cirrhosis is the release of NO from the vascular wall under the action of pro-inflammatory cytokines[62-64]. However, this process is obviously more complex, and other molecules, including carbon monoxide, may be involved in its implementation[52,62-65]. The blood NO level was positively correlated with stroke volume, arterial compliance, total blood plasma volume, and WHVP[66]. There was a positive correlation between the blood CRP level and cardiac output and total arterial compliance and a negative correlation between the blood CRP level and SVR in cirrhosis[26]. IL-6 and IL-8 were significantly correlated with HVPG, whereas IL-8 was significantly correlated with cardiac output. SVR and MAP showed a negative correlation with IL-6 and IL-8[54]. The blood level of nitrates (stable metabolites of unstable NO) was higher in patients with decompensated cirrhosis (maximal in CTP C) than in those with compensated cirrhosis and chronic hepatitis without cirrhosis and healthy individuals (it did not differ significantly among these two groups)[67]. Moreover, it was higher in patients with ascites or large esophageal varices[67]. The blood renin level was higher in patients with cirrhosis compared to healthy individuals and increased with the CTP class. There was a positive correlation between the blood renin and nitrate levels. The pro-inflammatory cytokine IL-6 level was positively correlated with both nitrate and renin levels[67]. The CTP score was found to be directly related to serum levels of angiotensin-I and aldosterone and the cardiac index[68].

Carbon monoxide (CO) is formed as a by-product of the breakdown of heme by heme oxygenase, the activity of which is increased in the liver with cirrhosis[69,70]. The CO concentration in exhaled air was higher in patients with cirrhosis than in healthy individuals, and it was even higher in patients with ascites than in those without ascites. The level of this biomarker correlated with Child-Pugh score, prothrombin time, serum bilirubin and albumin level[71]. No correlation was found between CO concentration and blood pressure, heart rate, or plasma renin activity [71]. However, plasma CO levels directly correlated with the serum LPS level, cardiac output, and inversely with SVR and MAP[65]. This and other vasodilators are much less studied in patients with cirrhosis than NO.

Table 2 Correlation matrix of links of the gut-liver axis in cirrhosis (data from human studies)

	Gut dysbiosis	Small intestinal bacterial overgrowth	Intestinal barrier dysfunction	Bacterial translocation	Systemic inflammation	Hyperdynamic circulation	Severity of cirrhosis	Complications of cirrhosis	Prognosis
Gut dysbiosis		NR	+	+	+	NR	+	+	+
Small intestinal bacterial overgrowth	NR		NR	+	+	+	+	+	NR
Intestinal barrier dysfunction	+	NR		+	+	NR	+	+	+
Bacterial translocation	+	+	+		+	+	+	+	+
Systemic inflammation	+	+	+	+		+	+	+	+
Hyperdynamic circulation	NR	+	NR	+	+		+	+	+
Severity of cirrhosis	+	+	+	+	+	+		+	+
Complications of cirrhosis	+	+	+	+	+	+	+		+
Prognosis	+	NR	+	+	+	+	+	+	

+: Relations are reported; NR: Not reported.

Despite the established correlations between the levels of proinflammatory cytokines and vasodilators in cirrhosis, the exact mechanisms of increasing the concentration of the latter remains to be determined[72].

CONNECTING THE LINKS OF THE GUT–LIVER AXIS

The following model of the gut–liver axis was proposed. Gut dysbiosis, SIBO, and intestinal barrier alteration lead to bacterial translocation, resulting in systemic inflammation in cirrhosis. The latter leads to vasodilation, arterial hypotension, and hyperdynamic circulation, the consequence of which is the aggravation of portal hypertension, which contributes to the development of complications of cirrhosis, resulting in a poorer prognosis[64]. The gut-liver axis can be simplified as a chain with the aforementioned links (Figure 1).

Most of the data underlying this model were obtained initially from animal experiments and were further reproduced in studies including patients with cirrhosis (Table 2), the results of which are described in this article. However, the clustering of the described data is noteworthy. Thus, the cluster of pathogenetic relations between the pathology of the gut microbiota, intestinal barrier disorders, bacterial translocation, and systemic inflammation and that between systemic inflammation, increased formation of vasodilators (*e.g.*, NO), hemodynamic changes, and complications of cirrhosis are well described. Several studies have shown that the pathology of the gut microbiota, intestinal barrier disorders, and bacterial translocation are associated with the development of complications of cirrhosis and poor prognosis. However, the direct relations between the pathology of the gut microbiota, intestinal barrier disorders, and bacterial translocation on the one hand and hemodynamic changes on the other in patients with cirrhosis have been poorly studied. Only the following relations have been reported: HVPG was positively correlated with blood LPS level and negatively correlated with blood butyrate levels[42]. The blood isobutyrate levels were directly correlated with SVR and inversely correlated with cardiac index[42]. The blood butyrate level was inversely correlated with NO levels[38]. There were correlations between blood LPS and NO levels[42]. The portal venous LPS levels were inversely correlated with systolic blood pressure and portal venous blood flow velocity[73].

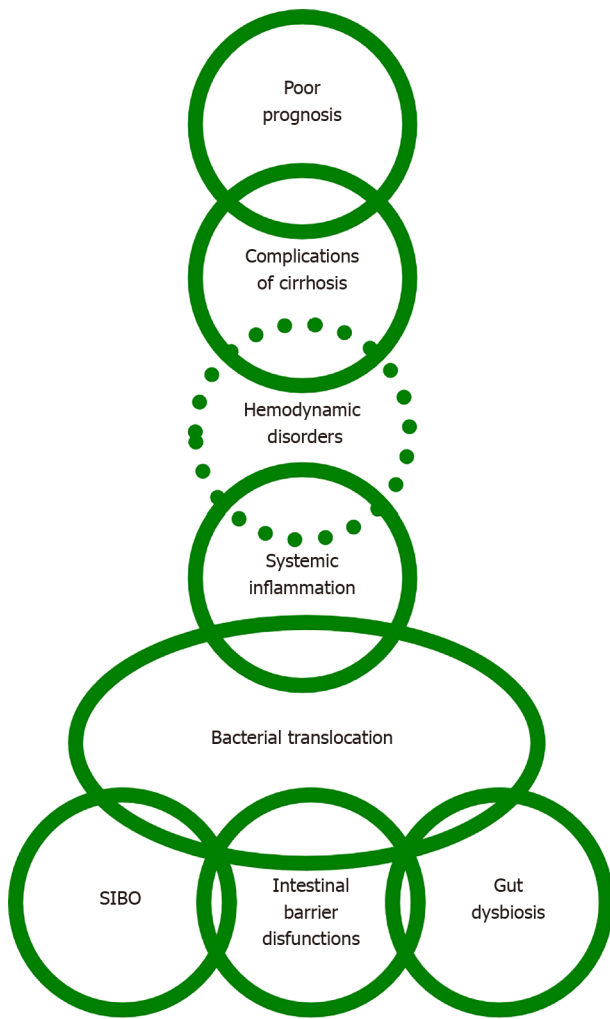


Figure 1 Links of the gut-liver axis in cirrhosis. SIBO: Small intestinal bacterial overgrowth.

Cirrhosis with SIBO had a significantly higher incidence of hyperdynamic circulation and vasodilatation compared with cirrhosis without SIBO. Cardiac output was higher and SVR was lower in cirrhosis with SIBO than in cirrhosis without SIBO [26]. Patients with detected bacterial DNA in blood had lower MAP and SVR and higher blood levels of NO, renin, TNF- α , and IL-12. No significant differences in cardiac output, heart rate, stroke volume, WHVP, and HVPG were noted between patients with and without bacterial DNA in blood[74]. In addition, there were no significant differences in the hemodynamic parameters and blood levels of NO, TNF- α , IL-12, and renin between patients who had DNA of gram-positive bacteria and who had DNA of gram-negative bacteria in their blood[74]. Patients with ascites and a higher level of the bacterial translocation marker LBP had lower MAP and SVR and higher cardiac index and blood levels of renin, aldosterone, and NO metabolites[75]. The blood levels of LBP, TNF- α , and NO metabolites and SVR were correlated with each other[75]. The TNF- α levels were also inversely correlated with MAP[74].

No studies on the association of gut dysbiosis (except for reports of the association of the increased abundance of *Enterococcaceae* with circulatory failure[24]) with hemodynamic disorders have been described in cirrhosis. The only study on the association of SIBO and hemodynamic disorders in cirrhosis was published[26]. An uncontrolled small study showed that probiotics can correct hemodynamic changes in cirrhosis[76]. Randomized controlled trials are required to confirm these findings.

CONCLUSION

In conclusion, hemodynamic changes remain a missing link of the gut-liver axis in cirrhosis, which should be studied in future research.

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