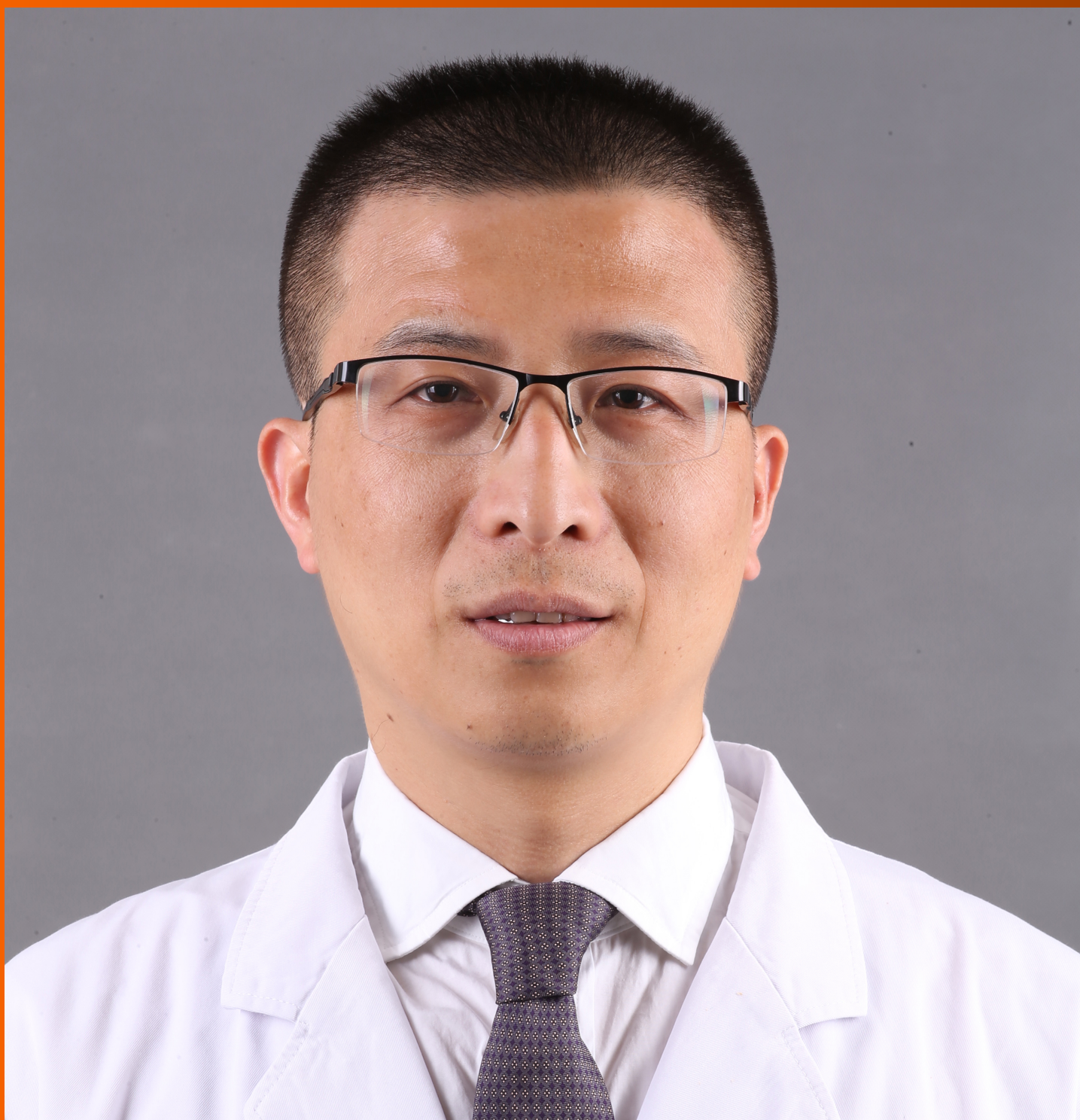


# World Journal of *Hepatology*

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**ABOUT COVER**

Editorial Board Member of *World Journal of Hepatology*, Fan-Pu Ji, MD, PhD, Professor, Doctor, Department of Infectious Diseases, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710004, Shaanxi Province, China. [infection@xjtu.edu.cn](mailto:infection@xjtu.edu.cn)

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## Hepatocellular carcinoma and microbiota: Implications for clinical management and treatment

Dario Spanu, Andrea Pretta, Eleonora Lai, Mara Persano, Clelia Donisi, Stefano Mariani, Marco Dubois, Marco Migliari, Giorgio Saba, Pina Ziranu, Valeria Pusceddu, Marco Puzzone, Giorgio Astara, Mario Scartozzi

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Dario Spanu, Andrea Pretta, Eleonora Lai, Mara Persano, Clelia Donisi, Stefano Mariani, Marco Dubois, Marco Migliari, Giorgio Saba, Pina Ziranu, Valeria Pusceddu, Marco Puzzone, Giorgio Astara, Mario Scartozzi, Medical Oncology Unit, University Hospital and University of Cagliari, Monserrato 09042, Cagliari, Italy

**Corresponding author:** Mario Scartozzi, MD, Chairman, Full Professor, Medical Oncology Unit, University Hospital and University of Cagliari, SS 554 km 4500 Bivio per Sestu, Monserrato 09042, Cagliari, Italy. [marioscartozzi@gmail.com](mailto:marioscartozzi@gmail.com)

### Abstract

Gut microbiota plays an essential role in host homeostasis. It is involved in several physiological processes such as nutrients digestion and absorption, maintenance of intestinal epithelial barrier integrity and immune system self-tolerance. Especially the gut microbiota is assumed to play a crucial role in many gastro-intestinal, pancreatic and liver disorders. Its role in hepatic carcinogenesis is also gaining increasing interest, especially regarding the development of therapeutic strategies. Different studies are highlighting a link between some bacterial strains and liver disease, including hepatocellular carcinoma (HCC). Indeed, HCC represents an interesting field of research in this perspective, due to the gut-liver axis, to the implication of microbiota in the immune system and to the increasing number of immunotherapy agents investigated in this tumour. Thus, the assessment of the role of microbiota in influencing clinical outcome for patients treated with these drugs is becoming of increasing importance. Our review aims to give an overview on the relationship between microbiota and HCC development/progression and treatment. We focus on potential implications on the available treatment strategies and those under study in the various stages of disease. We highlight the pathogenic mechanisms and investigate the underlying molecular pathways involved. Moreover, we investigate the potential prognostic and/or predictive role of microbiota for target therapies, immune checkpoint inhibitors and loco-regional treatment. Finally, given the limitation of current treatments, we analyze the gut microbiota-mediated therapies and its potential options for HCC treatment focusing on fecal microbiota transplantation.

**Key Words:** Hepatocellular carcinoma; Gut microbiota; Gut-liver axis; Fecal microbiota transplantation; Carcinogenesis; Immune checkpoint inhibitors

**Core Tip:** The gut-liver axis plays an important role in the pathogenesis of liver diseases, including hepatocellular carcinoma (HCC). Growing evidence has supported the role of the gut microbiota in the development of HCC and as a prognostic and predictive factor. Thus, manipulation of the gut microbiota might represent a novel way to treat or prevent HCC.

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## INTRODUCTION

Hepatocellular carcinoma (HCC) is an aggressive malignancy and almost exclusively develops in patients with chronic liver disease and cirrhosis. While viral hepatitis, especially hepatitis B virus (HBV) infection and hepatitis C virus (HCV) infection represent one of the most important cause of cirrhosis and HCC in low-income countries and Asia, alcoholic liver disease (ALD) and nonalcoholic fatty liver disease (NAFLD) are the main cause for developing cirrhosis and HCC in high income countries. The pathogenesis of HCC is multi factorial, driven by a circle of liver injury, inflammation, and regeneration that typically spans decades. Next to predisposing factors, as already mentioned, increasing evidence points towards a key role of the bacterial microbiome and bacterial metabolites in the development of chronic liver disease (CLD).

The human gut is one of the most complex structures in the body and is colonized by trillions of microorganisms including bacteria, fungi, viruses and protists. Among them, bacteria are the main inhabitants[1]. In recent years there has been increasing attention to the possible relationship between the gut microbiota and the process of carcinogenesis. Increasing data have suggested that the gut microbiota is related to a variety of cancers, particularly of the gastrointestinal tract, and consequently it has been hypothesized that this link may lead to the development of targeted therapies against the gut microbiome[2,3].

Among the various types of cancer, hepatocellular carcinoma is also included. As is known, the liver does not contain a microbiome, but is closely connected to the gut *via* the portal venous system, constituting the intestine – microbiota – liver axis[4].

The balance of the intestinal microbiota is essential for a physiological and correct functioning of the metabolism and immunity and, even more importantly, of the intestinal barrier[5]. In fact, homeostasis between the host and the microbiota is maintained precisely by the multilayered intestinal barrier. A disruption in this balance can lead to a malfunction of the intestinal barrier, resulting in chronic inflammation and dysbiosis. Although the mechanisms by which the microbiota is related to cancer are not yet fully understood, the above two are key factors in the carcinogenesis process[6] and several studies have observed significant alterations in the composition of gut microbiota in patients with chronic liver disease especially with a reduction in beneficial bacteria and an increase in pathogenic bacteria[7]. For this reason, numerous studies have investigated the potential use of therapies targeting the microbiota, such as prebiotics, probiotics and fecal microbiota transplantation (FMT). In particular, their potential role in the treatment of different liver diseases (such as hepatic encephalopathy, steatohepatitis and cirrhosis) and in different types of cancer (such as gastrointestinal cancers, breast cancer and melanoma) has been studied[8].

Indeed, in recent years, researchers have focused their attention on the possible prognostic and predictive role of gut microbiota composition, in particular in the response to therapy with immune checkpoint inhibitors (ICIs). It seems that a variation in the composition of the gut microbiota can influence the efficacy of treatments, in particular of immunotherapy, and the presence of specific gut microbes increases this efficacy[9].

## IMPACT OF MICROBIOTA IN HCC DEVELOPMENT

Microbiome role in the development and growth of neoplastic lesions has assumed ever greater interest in recent studies. Human microbiota, defined as the population of microorganisms that colonize the body, has in fact been shown to play a crucial role both in physiological and pathological mechanisms. In addition to bacteria, the gut microbiota also contains eukaryotes as fungi, and some types of viruses.

Bacterial gut microbiota promotes disease development and progression not only locally, such as inflammatory bowel disease (IBD)[10,11], but also in distant locations such as the brain, heart, hematopoietic system and liver[12-16].

Given its direct anatomical connection through the portal vein, the liver is closely connected to the intestine. This is called "intestine-microbiota-liver axis"[6,17]. In fact, the liver receives blood rich in nutrients absorbed by the intestine, but it is also the first "filter" organ for the intestinal microbiota, of the MAMP (microbe-associated molecular pattern), toxins and bacterial metabolites. These products can subsequently trigger inflammatory responses *via* pattern recognition receptors.

Damage to the intestinal barrier, associated with alterations of the intestinal microbiota in CLD contribute to the onset of chronic inflammation. The inflammation, in turn, progresses, leading to tissue reworking with fibrosis. The processes of rehashing on an inflammatory basis increase the risk of developing HCC as the last step of the entire pathological process[7,18-20].

Bile acids represent another factor that acts in this complex system. In fact, these have the function of regulating the intestinal epithelial barrier, the proliferation of epithelial cells of the mucosa *via* the farnesoid X-activated receptor - dependent and the epidermal growth factor receptor - dependent pathways and controlling the growth and adhesion of intestinal bacteria[21,22].

At the hepatic level, bacterial products activate toll-like receptors (TLRs), in particular TLR-4, which, in turn, activates the NF- $\kappa$ B pathway, which determines the constitutive initiation of a mitogenic signal that is associated with an inhibition of programmed cell death. Chronic damage exposes the liver to a prolonged action of several TLR ligands and other bacterial substances, which represent inflammatory mediators that promote the development of chronic liver disease as well as laying the foundations for the subsequent development of hepatocellular cancer[20] (Figure 1).

Most cases of HCC develop on a basis of fibrosis and cirrhosis, which is the most important risk factor for the development of liver cancer. However, the presence of underlying liver diseases of various etiologies may contribute to the increased specific risk for developing HCC on a cirrhotic basis[23] (Table 1).

### NAFLD

Although the percentage of NAFLD patients who develop HCC is small, the high incidence carries a high risk of developing hepatocellular carcinoma. Several studies in animal models have shown that the microbiome of obese patients has the ability to extract more nutrients, and in mice deprived of bacterial flora there was a reduction in body weight despite an increased caloric intake[24,25].

In dysbiotic mice fed a high-fat diet, choline is converted to methylamine, which involves a reduction in circulating plasma levels of phosphatidylcholine. Subsequently, low phosphatidylcholine levels lead to impaired secretion of VLDL, reducing hepatic lipid export, inducing hepatic steatosis[26,27].

The contribution of gut microbiota to non alcoholic steatosis hepatitis, a progressive form of NAFLD, is not as well documented as its role in earlier disease stages. An high-fat diet (HFD) increases intestinal permeability in mice with a noticeable increase in LPS serum levels[28,29].

### ALD

About half of the cases of cirrhosis are caused by alcohol consumption. Indeed, serum LPS levels are increased in patients who have made chronic use of alcohol. Ethanol and its metabolite acetaldehyde have the ability to interrupt the intercellular junctions in the intestine, allowing bacteria and their products to pass into the bloodstream[30].

The microbiota-TLR4 axis plays an important role in this process. In fact, in several studies conducted on animal models, TLR4 deprived mice, subjected to intestinal disinfection, have shown a reduction in inflammation and oxidative stress[31-33].

### Liver fibrosis

Fibrosis represents a risk factor for the development of HCC. Literature data highlight an important contribution of the microbiota-TLR4 axis to liver fibrosis[34].

Studies in knockout mice have shown a key role for TLR4 and other mediators in the TLR4 signaling pathway, such as CD14 and lipopolysaccharide binding protein, in experimental models of hepatic fibrosis.

Conversely, other studies have shown a protective role of bacterial flora against the development of liver inflammation and fibrosis[35,36].

Evidence supports the role of the commensal microbiota as a hepatoprotective, although an alteration in its internal balance can lead to the prevalence of harmful species that can cause liver damage.

### Viral Hepatitis

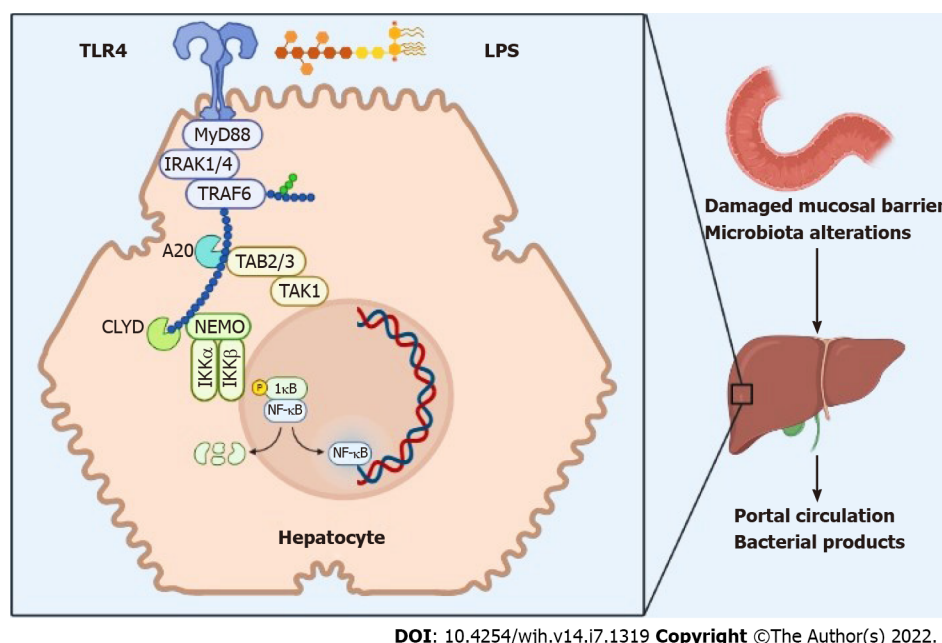
There is currently little data on the role of the microbiota in chronic viral hepatitis at the moment. Current data suggests that dysbiosis in patients with viral hepatitis cirrhosis is similar to that in patients with cirrhosis from other causes[37]. Further studies will be needed to investigate the close interconnections between microbiome composition and tumor development and growth.



**Table 1 Human studies involving gut microbial composition in various hepatocellular carcinoma-related etiologies**

Microbiota balance			
Ponziani <i>et al</i> [38]	Cirrhosis + HCC	↑ <i>Bacteroides</i> ; ↑ <i>Ruminococcus</i> ; ↑ <i>Enterobacteriaceae</i>	↓ <i>Bifidobacterium</i> ; ↓ <i>Akkermansia</i>
Ren <i>et al</i> [41]	HBV cirrhosis + HCC	↑ <i>Actinobacteria</i>	↓ <i>Verrucomicrobia</i>
Liu <i>et al</i> [97]	NBNC cirrhosis + HCC	↑ <i>Escherichia</i> ; ↑ <i>Enterococcus</i>	↓ <i>Faecalibacterium</i> ; ↓ <i>Ruminococcus</i> ; ↓ <i>Ruminoclostridium</i>
Huang <i>et al</i> [39]	HBV cirrhosis + HCC	↑ <i>Bacteroides</i> ; ↑ <i>Lachnospiraceae incertae sedis</i> ; ↑ <i>Clostridium XIVa</i>	

↑: Increased; ↓: Decreased; NBNC: Non-hepatitis B virus non-hepatitis C virus; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma.



**Figure 1 Interaction between Bacterial Lipopolysaccharides and Toll-like receptor 4 signaling pathway in hepatocellular carcinoma development.** LPS: Lipopolysaccharides; MyD88: Myeloid differentiation primary response protein 88; IRAK1/4: IL-1 receptor associated kinase 1/4; TRAF6: TNF receptor associated factor 6; TAK1: TGF-activated kinase 1; TAB2/3: TAK1-binding protein 2/3; NEMO: NF-kappa-B essential modulator; IKK: Inhibitor of nuclear factor kappa-B; NF-κB: Nuclear factor kappa B.

## PREDICTIVE AND PROGNOSTIC ROLE OF MICROBIOTA

Given the important role of the gut microbiota in liver carcinogenesis, growing attention towards using microbiome patterns as a predictive, prognostic or diagnostic biomarker of HCC is observed. The gut microbiome dysbiosis has been evaluated in NAFLD- and HBV/HCV-related HCC patients to find new clinical features and outcomes biomarkers in this setting [38,39]. In 2019, Ponziani *et al* [38] found that cirrhotic patients with NAFLD and HCC lack protective bacteria and have an enhanced intestinal inflammation with an increased level of IL8, IL13, CCL3, CCL4, CCL5, and faecal calprotectin concentration. HCC was associated with increased abundance of Bacteroidetes together with a reduction of Verrucomicrobiaceae, Bifidobacteriaceae, Akkermansia, Bifidobacterium.

In a more recent study, HCC tumour burden was associated with the presence of specific gut microbes, distinguished by the enrichment of *Bacteroides*, *Lachnospiraceae incertae sedis*, and *Clostridium XIVa*. Patients with these three genera mounted a weaker host liver anti-tumour inflammatory response [39]. Primary bile acids increased CXCL16 expression, which regulates NK cell accumulation, whereas secondary bile acids showed the opposite effect. Feeding secondary bile acids or colonization of bile acid-metabolizing bacteria reversed both NK cell accumulation and inhibition of liver tumour growth in mice with altered gut commensal bacteria. Removing gram-positive bacteria by antibiotic treatment with vancomycin, which contains the bacteria mediating primary-to-secondary bile acid conversion, induced hepatic NK cell accumulation and decreased liver tumour growth in mice. These data suggest that *Clostridium XIVa* influences bile acid-controlled NK cell accumulation. In normal liver tissue from human HCC patients, primary bile acid cheno-deoxycholic acid levels

correlated with CXCL16 expression, whereas an inverse correlation was observed with secondary bile acid glycolithocholate[40]. Higher bile acid levels ( $\geq 16 \mu\text{mol/L}$ ) indicated worse clinical outcomes among HBV-related HCC patients with enrichment of *Bacteroides*, *Lachnospiracea incertae sedis*, and *Clostridium XIVa*. These results show that correlation between gut microbiota and serum bile acids in tumour immune microenvironment could potentially influence tumour burden and clinical outcomes in HBV-related HCC[40].

In 2019, Ren *et al*[41] evaluated the potential role of microbiome as a non-invasive biomarker for HCC. The authors collected 486 faecal samples from East, Central, and Northwest China. Using 16S rRNA Miseq sequencing, 3 groups were identified: early HCC, cirrhosis, and healthy controls. Actinobacteria, 13 genera including *Gemmiger* and *Parabacteroides* were increased in HCC compared with cirrhosis. Additionally, butyrate-producing genera was decreased, and lipopolysaccharide-producing was increased in HCC in comparison to healthy controls. Interestingly, 30 microbial markers were identified through a fivefold cross-validation on a random forest model between 75 early HCC and 105 non-HCC samples. This was the first study characterizing the gut microbiome in early HCC as a non-invasive tool to diagnosed early stage of HCC.

In literature, three studies analysed the potential predictive and prognostic role of gut microbiota in HCC.

Zheng *et al*[42] analyzed the characteristics and changes in the gut microbiota during treatment with anti-PD-1 immunotherapy drugs in eight patients with HCC. Responders (R) had, during the entire treatment, a higher richness of taxa and a greater number of genes than the no-responder (NR). Before the start of treatment, *Bacteroidetes* was the most abundant phylum, followed by *Firmicutes* and *Proteobacteria* in both R and NR[41]. As treatment progressed, the microbial composition at the phylum level in R remained relatively stable, while *proteobacteria* often increased in NR, with a prevalence of *Escherichia coli*. Furthermore, the methanogenesis pathway was found to be correlated with *R. obeum* and *Lactobacillus* species, and furthermore the generated methane would appear to improve oxidative stress damage and suppress host inflammatory response. Other pathways with potential benefits include sulfate reduction and carbon fixing functions that were correlated with *R. obeum*, carotenoid biosynthesis correlated with *B. cellulosilyticus* and *A. colihominis*, and unsaturated fatty acid metabolism associated with *C. comes*[42].

Li *et al*[9] collected microbiome samples from 65 patients with metastatic HCC being treated with ICI therapy. The analyzes showed that patients with a high presence of *Faecalibacterium* had a significantly prolonged PFS compared to those with low presence ( $P = 0.006$ ). In contrast, patients with a high presence of *Bacteroidales* had a reduced PFS compared with those with low presence ( $P = 0.002$ ).

Chung *et al*[43] studied the effects of the gut microbiota in eight adult patients with HCC treated with nivolumab (anti PD-1). Reported data showed that responder patients had a significantly lower *Firmicutes/Bacteroidetes* ratio (10% *vs* 66.7%,  $P < 0.05$ ) and a higher *Prevotella/Bacteroides* ratio (22.99 *vs* 2.312,  $P = 0.024$ ) than non-responders. These results indicate that the F/B ratio and P/B ratio could serve as predictive markers of non-response to nivolumab therapy. *Akkermansia* species was also found in two responders, indicating that this could also be a useful prognostic marker of response to nivolumab therapy in patients with advanced HCC.

In the last decade, several research efforts have been made to identify potential prognostic and predictive biomarkers of response with target therapy[44-46]. In this perspective, interest in interaction between the gut microbiome and HCC targeted therapy is increasing, even if no data are available up to date. It has been shown that among anthocyanins, delphinidin possesses strong antitumor activity through various mechanisms such as downregulation of matrix metalloproteinase (MMP)[47], inhibition of angiogenesis and tumour cell migration[48], growth suppression of ER $\alpha$ -positive cancer both *in vitro* and *in vivo*[49] and apoptosis promotion[50,51].

These mechanisms are, in turn, the target of targeted therapies. Therefore, a possible implementation of the targeted therapies activity can be profoundly influenced by the composition of the intestinal microbiome. Furthermore, particular microbes could become a future therapeutic target to potentially improve the effectiveness of cancer treatment. However, further studies are needed to better understand the predictive and prognostic role of the gut microbiome in HCC and to investigate the potential benefits of microbiome modulation.

## THE ROLE OF GUT MICROBIOTA IN PATIENTS WITH HEPATOCELLULAR CARCINOMA TREATED WITH IMMUNE CHECKPOINT INHIBITORS

Gut microbiota dysfunction is known to lead to dysfunction of local, locoregional, and systemic immune systems, causing the dissolution of epithelial barriers, and as a consequence, transfers biofilm microbes and their components into mesenteric lymph nodes and peripheral circulation. Furthermore, dysbiosis may induce a neutrophils gathering into the intestinal epithelium that modifies the profiles of inflammatory cytokine and chemokine, stimulates the T helper 17 and effector T-cells, resulting in a negative feedback control of the microbiota[52]. Aging, antibiotics, xenobiotics, smoking, hormones, and diet can be responsible for dysbiosis which is a risk factors for cancer onset and, on the other hand, influences

the therapeutic outcomes, as for chemotherapy or immunotherapy, interfering directly or indirectly with therapeutic mechanisms[53].

ICIs are promising anticancer agents and according to several recent studies, the gut micro-biome may play a critical role in regulating immunotherapy responses. Thus, the microbiome can influence the host response to ICIs (PD-1/ PD-L1 blockade, or CTLA-4 inhibition)[52,53] (Table 2).

CD152, well known as CTLA-4, a T-cell surface receptor activated by two ligands (CD80 or CD86) expressed on antigen-presenting cells, induces an inhibitory signal in the early activated T-cell[54,55]. The other immune checkpoint repressing T-cell response is PD-1 (programmed death cell 1) sided is on the surface of activated T-cells, whereas its ligand PD-L1 is expressed on tumor cells surfaces and antigen-presenting cells (macrophages and dendritic cells). Their bond induces T-cell inactivation[56].

Various studies have recently examined the role of gut microbiota in melanoma patients treated with ICIs showing a strict correlation between gut microbiota and response to immunotherapy and how differences in microbiome composition could influence treatment efficacy[56-60].

Notably, *Akkermansia muciniphila* was associated with a better response to ICIs. In metastatic melanoma patients with a benefit from ICIs treatment, the so-called responders, several bacteria phyla were detected in abundance: *Faecalibacterium*, *Ruminococcaceae*, and *Clostridiales*. Nevertheless, non-responder patients had a higher amount of *Bacteroidales*.

According to several studies, both preclinical and clinical, *A. muciniphila*, *Alistipes indistinctus*, *Bacteroides*, *B. cepacia*, *D. formicigenerans*, *Parabacteroides merdae/distasonis*, *C. aerofaciens*, *Eubacterium* spp., *Veillonella parvula*, *Klebsiella pneumoniae*, *Bifidobacterium* spp., *Lactobacillus* spp., *Streptococcus parasanguinis*, *Blautia* spp., *E. hirae*, *E. faecium*, *H. filiformis*, *Faecalibacterium prausnitzii*, *Gemmiger formicilis*, and *Ruminococcaceae* family seems to improve the effectiveness of ICIs facilitating antitumor immunity.

Gut microbiota enhanced with *B. thetaiotaomicron*, *Roseburia intestinalis*, *Anaerotruncus colihominis*, *Blautia obeum*, and some combination of antibiotics were associated with a compromised ICIs' efficacy[53].

Changes in the expression of cytokines and immune cells due to alterations in the gut microbiota induced distinct therapeutic responses[61].

As for HCC, ICIs are approved for clinical practice usage[62-64]. Up to now, programmed cell death (PD) ligand-1 (PD-L1) expression, tumor mutation burden, and microenvironmental immune cells have been associated with ICIs effectiveness. A previous study conducted by Shen *et al*[65] investigated the relationship between the gut microbiome, analyzed through 16S rRNA and shotgun whole-genome sequencing on stool samples collected at baseline and after eight weeks treatment, and the effectiveness of immunotherapy in patients with advanced HCC. The study enlisted thirty-six patients (31 males and 5 females). There was no difference in the baseline gut microbiome between responders and non-responders. Also, the composition of gut microbiota showed no difference induced by ICIs. The study failed to demonstrate an association between gut microbiota and ICI efficacy, maybe due to the size of the sample examined, the different treatment, and the host factors influencing and affecting the gut microbiota, along with a non-standardized method to collect and process the stool samples leading to poor reproducibility. Also, dysbiosis is common in patients with chronic liver diseases. Therefore, it may affect the response to ICIs treatment as the study results, too.

On the contrary, a study by Chung *et al*[43] enrolled eight patients with HCC who received nivolumab as second- or third-line treatment after sorafenib. At baseline and after three months of treatment, fecal samples to assess the microbiome were collected. Patients with Child-Pugh A were 87.5%. Various bacterial taxa, like *Dialister pneumosintes*, *Lactobacillus reuteri*, *Enterococcus faecium*, *Streptococcus Gordonii*, *Streptococcus mutans*, *Escherichia coli*, *Veillonella atypica*, *Granulicatella* sp., and *Trichuris trichiura*, were detected in non-responders. *Citrobacter freundii*, *Azospirillum* sp., and *Enterococcus durans* were part of responders' microbiota. Yet, the bacteria detected didn't match with the species found in previous studies. A skewed Firmicutes/Bacteroidetes ratio seems related to a scarcity of response to immunotherapy. Moreover, a high *Prevotella*/*Bacteroides* ratio seems associated with a better response to nivolumab as proved in a study that examined fecal samples in patients with advanced gastrointestinal cancer treated with ICIs[66]. However, the exiguity of the samples examined leads to low statistical power. Dysbiosis appears as an element that plays a critical role in the immunotherapy response in patients affected with hepatocellular carcinoma.

A retrospective study by Li *et al*[9] focused on the composition of gut microbiota in patients with HCC treated with ICIs. In particular, patients were gathered on the basis of the abundance of *Bacteroidales* in nonresponders and *Faecalibacterium* in responder patients. As a result, an abundance of *Faecalibacterium* correlated with an increased PFS, while a great amount of *Bacteroidales* is associated with low PFS. However, the small size of the sample and the retrospective nature of this study limited the validity of the results observed.

Another study by Zheng *et al*[42] enlisted eight patients with HCC, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and a Child-Pugh Class A receiving camrelizumab, an anti-PD-1 agent, after progression to sorafenib. Stool samples were collected and analyzed at baseline and week 3 and 12, respectively. In the responders patients the species that composed the gut microbiota were: *Bacteroidetes*, *Firmicutes* and *Proteobacteria*. In non-responder *Proteobacteria* were predominant. Oral intake of *Bifidobacterium* may promote antitumor growth induced by ICIs. *A. muciniphila* and

**Table 2 Correlation studies between intestinal microbial composition and response to immune checkpoint inhibitors**

	Treatment	Responder	Non responder
Zheng <i>et al</i> [42]	Anti-PD1	↑ <i>Akkermansia muciniphila</i> ; ↑ <i>Ruminococcaceae</i>	↑ <i>Proteobacteria</i>
Li <i>et al</i> [9]	Anti-PD1	↑ <i>Faecalibacterium</i>	↑ <i>Bacteroidales</i>
Chung <i>et al</i> [43]	Anti-PD1	<i>Dialister pneumosintes</i> ; <i>Escherichia coli</i> ; <i>Lactobacillus reuteri</i> ; <i>Streptococcus mutans</i> ; <i>Enterococcus faecium</i> ; <i>Streptococcus gordonii</i> ; <i>Veillonella atypica</i> ; <i>Granulicatella sp.</i> ; <i>Trichuris trichiura</i> ; ↑ <i>Firmicutes/Bacteroidetes</i> ratio; ↓ <i>Prevotella/Bacteroides</i> ratio	<i>Citrobacter freundii</i> ; <i>Azospirillum sp.</i> ; <i>Enterococcus durans</i> ; ↑ <i>Akkermansia</i> species

↑: Increased; ↓: Decreased.

*Ruminococcaceae* were observed in the intestinal microbiota and have a role in immunomodulatory functions. Oral *A. muciniphila* could revive the effectiveness of ICIs.

A clinical trial was recently opened at the National Cancer Institute that aims to combine vancomycin-based antibiotic treatment with immune checkpoint inhibitors (NCT03785210). This study may attempt to answer the question of whether the combination of immunotherapy with microbiota selection could have a beneficial effect in HCC patients[67].

Summing up, evidence with low statistical power is available up to now. Further studies are warranted for the time being. Also, a standardized method to collect and analyze fecal samples may help obtain reproducibility.

## HCC AND MICROBIOTA TRANSPLANT

Curative options for advanced HCC are very limited, and driving the need to develop new therapeutics. Greater understanding about bacterial function, its impact on the host, its contribution to the loss of barrier function and the gut-liver immune system will lay the foundations for novel therapeutic approaches to the treatment of chronic liver disease that will attenuate progression to cirrhosis and HCC. To improve their efficacy, these therapies should focus on preventing the progression from chronic liver disease to cirrhosis and from compensated to decompensated cirrhosis. Bacteriotherapy could restore microbiome composition, reduce intestinal permeability (and thus reduce endotoxemia) and attenuate the chronic inflammatory environment in the liver; in this way, there is the potential that progression of disease and tumour development could be delayed or halted. Ideally, these therapeutic approaches would be more effective if they targeted earlier stages of disease and aimed to reduce chronic inflammation and cirrhosis, rather than directly reduce tumour mass[68].

Potential routes to target intestinal microbiota community include diet, probiotics, prebiotics, antibiotics[69-73] and FMT.

FMT aims to replenish the gut with a “physiological” microbiome taken from the stool of healthy subjects. Fecal donors are carefully selected[74], with exclusion criteria such as a low or high body mass index (new-onset obesity has been reported in a transplant recipient of fecal microbiota isolated from an overweight donor[75]), high risk behavior for infectious diseases, gastro-intestinal disease, recent microbiota-altering treatment (antibiotics, immunosuppressive medication, antineoplastic agents), presence of specific medical issues such as auto-immune, atopic or neurologic disorders, cancer, or chronic pain syndrome. The method for microbiota isolation is simple: fecal matter is collected from selected donors, suspended (usually in saline solution) and mixed in a blender; the resulting liquefied stool is filtered through a strainer to remove fibers, and thus ready for transplant[8]. Currently, FMT has been approved as a clinical method for treating recurrent *Clostridium difficile* infection by 2013 guidelines[76] and its clinical effectiveness has reached approximately 90%[77]. Fecal microbiota can be delivered *via* endoscopy (*e.g.*, colonoscopy or nasojejunal), enema or colonic transendoscopic enteral tubing[78-80]. Oral capsules has been developed showing efficacy comparable to delivery by colonoscopy regardless of whether fresh, frozen or lyophilised stools were used[81-83]. However, frequency of doses and optimal overall duration is still unclear as study parameters were not directly comparable across different studies.

There are several clinical studies regarding the use of probiotics as a novel and effective approach to treat or prevent chronic liver disease and HCC. Probiotic VSL#3, a combination of *Bifidobacteria*, *Lactobacilli* and *Streptococcus thermophilus*, could short inpatient time for patients with liver cirrhosis and hepatic encephalopathy[84]. A randomized controlled multicenter study investigates the role of probiotics in patients with alcoholic hepatitis (AH)[85]. The 117 patients were prospectively randomized to receive the 7 d of cultured *Lactobacillus subtilis*/*Streptococcus faecium* (1500 mg/d) or placebo (probiotics 60 and placebo 57). In the probiotics group albumin and TNFα showed significant difference. In addition, 7 d of oral supplementation with cultured *L. subtilis*/*S. faecium* was associated with restoration of bowel flora and improvement of microbial lipopolysaccharide in patients with AH.



Another study in mice aimed to evaluate the role of FMT in reducing HFD-induced steatohepatitis in mice. The analysis was conducted by examining the microbiota structure of the rodents, the butyrate present in the caecal content, the intrahepatic lipids and the liver pathological conditions 8 weeks after FMT. The results documented a reduction in the degree of steatohepatitis after FMT, as indicated by the finding of a decrease in intrahepatic lipids, NAS score and intrahepatic pro-inflammatory cytokines (INF- $\gamma$  and IL-17), with an increase in Foxp3, IL-4 and IL-22 [86]. Another study investigate the role of FMT in patients with untreated severe alcoholic hepatitis (SAH). Philips *et al* [87] discovered that Indices of liver disease severity improved significantly within the first week after FMT compared to HC and even survival was better in patients treated with FMT (87.5% *vs* 33.3%,  $P = 0.018$ ). Philips *et al* [88] reported a case of a young male patient with corticosteroid nonresponsive severe alcoholic hepatitis in 2017. FMT led to rapid amelioration of appetite and hyperbilirubinemia. Notably, FMT was performed in 18 patients with persistent positive HBeAg [89]. FMT was effective for these patients *via* inducing HBeAg clearance, suggesting that regulating intestinal microbiota might be beneficial to chronic hepatitis B treatment. A Phase I clinical trial demonstrated that FMT restored antibiotic-induced microbial dysbiosis in patients with advanced liver cirrhosis [90]. Even more, the effect of FMT on hepatic encephalopathy has been confirmed in both animal models and human beings. FMT alleviated cognitive function and prevented hepatic necrosis in animal models, thereby triggering improvement of hepatic encephalopathy [91]. Kao *et al* [92] reported a significant improvement in serum ammonia and quality of life in a patient with hepatic encephalopathy after performing FMT. Bajaj *et al* [93] conducted a randomized clinical trial, which suggested that FMT has the potential to improve cognition and reduce hospitalizations in hepatic encephalopathy patients.

Recently, Baruch *et al* [94] reported the first-in-human clinical trials where they discovered how treatment with FMT was associated with favorable changes in immune cell infiltrates and gene expression profiles in both the gut lamina propria and the tumor microenvironment. These early findings have implications for modulating the gut microbiota in cancer treatment.

These results encourage further studies on the possible beneficial impact of gut microbiota “resetting” by FMT in HCC.

## LIMITATIONS AND FUTURE PERSPECTIVES

Despite the abundance of studies in the literature, the understanding of the mechanisms of the alteration of the gut microbiota in HCC remains incomplete and inadequate. Most clinical studies have limitations due to the fact that they are single center studies with small population samples, which compromises the applicability of the results. Furthermore, it is often complex to analyze the various etiologies of the hepatic disease, the stage of cirrhosis, the diet, the use of antibiotics for other causes, the consumption of alcohol; all these elements represent confounding factors that can determine important variations in the intestinal microbiota. Therefore these factors should be considered in the design of future studies, which would involve multiple centers, on a large scale.

The characteristics of dysbiosis change among patients with hepatocellular carcinoma depending on the different etiologies. Despite this, some studies have shown that the different etiology of HCC is not related to a condition of intestinal microbial dysbiosis [95], while other studies are conflicting. Chen *et al* [96] evaluated the differences in the gut microbiota in consideration of the etiology of liver disease. they found that the discriminant between HBV-related cirrhosis and primary biliary cirrhosis was indicated by two operative taxonomic units (OTU), OTU-23 (*Neisseria*) and OTU-36 (*Gemella*). Furthermore, the level of bacterial diversity and composition varied differently between patients with non-HBV and non-HCV HCC (NBNC-HCC) and patients with HBV-HCC [97], and between patients with HBV-HCC and NAFLD-HCC [41,98]. Therefore, these data suggest that in designing future studies, the underlying etiology of liver disease should also be taken into account for identifying patterns of dysbiosis in HCC.

Currently, although several studies on the association between intestinal microbiota and HCC are emerging, data analyzing the causal relationship are still very limited [99]. From a methodological point of view, traditional sequencing technology and 16S rRNA sequencing (the most established genetic marker used for bacterial identification and classification), does not take into account rare eukaryotic cells and the absence of which could lead to loss of important information. Furthermore, it is necessary to consider that the use of low biomass samples, such as blood, can lead to contamination in the microbiome analysis [100].

Finally, despite extensive preclinical evidence, clinical trials focusing on the prevention and treatment of HCC by modulating the microbiota are still lacking. The greatest difficulties are found, in this sense, in the applicability of *in vitro* or *in vivo* studies to the human context.

To optimize the therapeutic response it could be useful to host protective intestinal bacteria depending on the type of treatment proposed. To confirm this, despite the current lack of clinical studies, the data obtained up to now with animal models have given interesting results in increasing the efficacy of treatments by modulating the bacterial flora. Some studies suggest that to increase the efficacy of the treatments it is necessary to keep intact the commensal microbiota which would mediate the cellular functions of the myeloid-derived cells present in the tumor microenvironment [101]. The



results obtained from the implantation of fecal material of patients with melanoma in germ-free mice, led to an improvement in tumor control, increased the response of T lymphocytes and obtained a greater efficacy of treatment with the anti programmed cell death protein 1 (PD-1)[59]. Among these, *Bifidobacterium* spp. has been identified. as a component of the microbiota that improved the efficacy of treatment with anti programmed death-ligand 1 (PD-L1)[58], while several species of *Bacteroides* appear to have an implication in the antitumor effect of antigen-blocking anti-cytotoxic T cells (CTLA ) - 4[57].

As regards hepatocarcinoma, a recent study has documented that the intestinal microbiota can increase the effectiveness of treatment with anti PD-1, increasing the sensitivity to immunotherapy[42, 102]. Given the important results obtained from immunotherapy treatment in patients with advanced HCC[103], it is important to explore the data relating to the microbiota and the bacterial species interested in contributing to the beneficial effects of the immunotherapy. Furthermore, in patients with NAFLD-HCC, given the immunosuppressive phenotype exerted in peripheral blood mononuclear cells from a bacterial extract of these patients, the possible modulation of the microbiota could help in overcoming any resistance to immunotherapy in HCC[98].

## CONCLUSION

In recent years, enormous progress has been made in the characterization of the gut microbiota and its association with different etiologies and severity of cancer diseases; various hypotheses have also been advanced in chronic liver disease and in the development of HCC and studies have been launched to characterize it. Furthermore, the work in rodent models and the greater understanding of the etiology of bacterial pathogens affecting liver disease has established the contribution of the gut microbiome in the progression of liver disease and its potential role as predictive and prognostic biomarkers.

Considering that patients with HCC and other CLDs are prone to alterations in the intestinal microbiota, it is tempting to assume that dysbiosis affects the efficacy of anticancer treatments including ICI in some categories of patients and that consequently the modulation of components of the microbiota can be managed to increase the activity of available treatments. Despite the growing interest on the part of researchers on the subject, for now it remains to be clarified whether the recent data obtained through animal models on the interaction of the immune response and the microbiota in some types of tumors, can also be applied to patients with hepatocarcinoma. Therefore, the orientation of research towards the intestinal microbiota, in particular the use of probiotics or the transplantation technique of the fecal microbiota, will be able to better direct towards new paradigms and personalized treatments with the aim of improving the effectiveness of the treatments available for HCC.

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**Country/Territory of origin:** Italy

**ORCID number:** Dario Spanu 0000-0003-2968-6811; Andrea Pretta 0000-0002-0262-9270; Eleonora Lai 0000-0002-0275-8187; Mara Persano 0000-0003-3600-0232; Clelia Donisi 0000-0003-4129-3375; Stefano Mariani 0000-0002-2513-1408; Marco Dubois 0000-0001-6728-2944; Marco Migliari 0000-0002-7730-4235; Giorgio Saba 0000-0003-2356-4477; Pina Ziranu 0000-0002-5659-7366; Valeria Pusceddu 0000-0003-4167-9091; Marco Puzzoni 0000-0001-5880-4309; Giorgio Astara 0000-0002-3949-3354; Mario Scartozzi 0000-0001-5977-5546.

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