ChatGPT 结果：

Yes. The *gut microbiome has been studied directly in human hepatocellular carcinoma (HCC)*, and the literature now covers several clinically distinct HCC settings: *HBV-related HCC, HCV-related HCC, NAFLD/MASLD/NASH-related HCC, alcohol-related HCC, cirrhosis-associated HCC of mixed etiologies, and HCC treated with immune-checkpoint inhibitors*. The strongest human evidence so far is for NAFLD/MASLD-associated HCC and for microbiome associations with immunotherapy response.

“strongest human evidence”属于证据强度比较，但未提供系统检索或比较依据支持该判断

HCC setting	Human gut-microbiome evidence	Rep
HBV-related HCC	Yes	Fecal m… HBV-HCC, non-HBV/non-viral HCC, and healthy controls; distinct bacterial taxa and ecological patterns have been reported.
HCV-related HCC	Yes	Recent shotgun-metagenomic work has specifically profiled HCV-HCC, finding enrichment of potentially pathogenic/inflammatory organisms and functional pathways.
NAFLD/MASLD/NASH-related HCC	*Yes—relatively well studied*	Multiple studies show an HCC-associated microbiome distinct from NAFLD cirrhosis without cancer, with alterations in *Bacteroides*, *Veillonella*, Enterobacteriaceae, *Bifidobacterium*, SCFA-producing pathways, and immune phenotypes.
Alcohol-related HCC	Yes	A recent case-control study using 16S sequencing plus microbial culturomics identified an ALD-HCC microbiome signature, including enrichment of *Thomasclavelia ramosa*.
Cirrhosis-associated HCC,	Yes	Studies matching HCC and

mixed etiologies		non-HCC cirrhosis suggest microbiome differences associated with the presence of HCC even after accounting for cirrhosis severity and etiology.
Early/resectable and advanced HCC receiving immunotherapy	*Yes*	Gut microbiome composition and diversity have been associated with response or resistance to anti-PD-1/PD-L1 therapy.

1. HBV-associated HCC

One of the earlier studies specifically compared *HBV-related HCC* with *non-hepatitis-virus-related HCC* and healthy individuals. Liu et al. used fecal microbiome profiling and found that the microbial communities differed among the groups, supporting the idea that HCC etiology may influence its associated microbiome.

Reference

Liu Q, Li F, Zhuang Y, et al. *Alteration in gut microbiota associated with hepatitis B and non-hepatitis virus related hepatocellular carcinoma. Gut Pathogens.* 2019;11:1. doi:10.1186/s13099-018-0281-6.

This study is particularly relevant if your question is whether microbiome findings have been investigated in a *viral-etiology-defined HCC subtype*: the answer is clearly yes.

2. NAFLD/MASLD/NASH-related HCC

This is probably the *best-characterized etiologic HCC subgroup* in the gut-microbiome literature.

Ponziani et al. compared patients with *NAFLD-related cirrhosis plus HCC*, NAFLD cirrhosis without HCC, and healthy controls. HCC wa
Bacteroides and Ruminococcaceae and decreased *Bif*
changes were also correlated with intestinal inflamma
markers.

“best-characterized”属于跨HCC亚组的比较性判断，缺少直接文献比较支持

Reference

Ponziani FR, Bhoori S, Castelli C, et al. *Hepatocellular carcinoma is associated with gut microbiota profile and inflammation in nonalcoholic fatty liver disease. Hepatology.* 2019;69(1):107-120. doi:10.1002/hep.30036.

An especially important later study by Behary et al. used *shotgun metagenomics plus metabolomics*, rather than only 16S profiling. It compared patients with NAFLD cirrhosis with versus without HCC. The NAFLD-HCC microbiome had distinct taxonomic and functional features; *Bacteroides caecimuris* and *Veillonella parvula*, for example, were enriched in the HCC group. Microbial functional pathways and fecal metabolites indicated increased SCFA production, and bacterial extracts from NAFLD-HCC patients promoted a more immunosuppressive T-cell phenotype ex vivo, including expansion of regulatory T cells and attenuation of CD8+ T-cell responses.

Reference

Behary J, Amorim N, Jiang XT, et al. *Gut microbiota impact on the peripheral immune response in non-alcoholic fatty liver disease related hepatocellular carcinoma. Nature Communications.* 2021;12:187. doi:10.1038/s41467-020-20422-7.

Thus, there is good evidence that the gut microbiome has been studied specifically in what would now generally be termed *MASLD/MASH-associated HCC*, although older papers use the terminology NAFLD/NASH.

3. Alcohol-related HCC

This has also now been examined directly.

A case-control study compared patients with alcohol-related liver disease without HCC, *alcohol-related HCC*, and healthy controls using both 16S rRNA sequencing and microbial culturomics. *Thomasclavelia ramosa* was particularly enriched in the alcohol-related HCC group.

Reference

Thomasclavelia ramosa and alcohol-related hepatocellular carcinoma: a microbial culturomics study. Gut Pathogens. 2025. doi:10.1186/s13099-025-00703-6.

This is notable because it goes beyond sequence-based detection and incorporates culturomics, providing evidence for viable bacterial organisms associated with alcohol-related HCC.

Reference书目信息不完整：该论文已有明确作者及卷/文章号（2025;17:27），此处仅列题名、期刊、年份和DOI

4. HCV-related HCC

HCV-related HCC has also been studied, although the literature is smaller than that for MASLD-HCC.

A recent Egyptian shotgun-metagenomic study included a dedicated *HCV-HCC group* and compared it with healthy participants and several HCV/liver-disease groups. HCC

samples showed enrichment of organisms such as *Escherichia* and microbial genes associated with inflammatory pathways, including lipopolysaccharide biosynthesis.

Reference

Metagenomic profiling of gut microbiome signatures across liver disease stages and HCV-related hepatocellular carcinoma in Egyptian patients. 2026. PMID: 42131203.

So HCV-HCC should also be considered a specifically investigated microbiome-defined clinical subgroup.

Reference信息不完整：仅提供题名、年份和PMID，缺少作者、期刊及已有DOI

5. Cirrhosis-associated HCC independent of a singl

Several studies have attempted to distinguish microbiome changes associated with *HCC itself* from those caused simply by cirrhosis.

For example, Grąt et al./the corresponding observational cohort study compared 25 patients with cirrhosis plus HCC against 25 patients with cirrhosis but no HCC, matched for age, sex, etiology, Child-Pugh class, and portal-hypertension severity, as well as healthy subjects. The investigators identified differences in microbial communities linked to HCC and inflammatory status.

作者归属错误：该研究实际第一作者为 Federico Piñero，论文作者列表中无 Grąt

Reference

A different gut microbiome linked to inflammation found in cirrhotic patients with and without hepatocellular carcinoma. Annals of Hepatology. 2019;18(3):480-487. doi:10.1016/j.aohep.2018.10.003.

This kind of design is important because *cirrhosis itself produces major gut dysbiosis*, making cirrhotic controls preferable to healthy controls when trying to identify an HCC-specific signature.

Effenberger et al. have additionally demonstrated bacterial signatures in *blood and liver tissue* in cirrhosis/HCC, reinforcing the concept of microbial translocation along the gut-liver axis, although this study is not purely a fecal-microbiome study.

Reference

Effenberger M, Waschina S, Bronowski C, et al. *A gut bacterial signature in blood and liver tissue characterizes cirrhosis and hepatocellular carcinoma. Hepatology Communications.* 2023;7(7):e00182. doi:10.1097/HC9.0000000000000182.

6. Gut microbiome and immunotherapy-treated HCC

This is another major branch of the literature.

Zheng et al. performed longitudinal metagenomic sequencing in HCC patients receiving *anti-PD-1 immunotherapy*. Responders had greater microbial richness and gene counts than nonresponders, while taxa including *Akkermansia muciniphila* and members of Ruminococcaceae were enriched among responders. Proteobacteria progressively increased in nonresponders.

Reference

Zheng Y, Wang T, Tu X, et al. *Gut microbiome affects the response to anti-PD-1 immunotherapy in patients with hepatocellular carcinoma. Journal for ImmunoTherapy of Cancer.* 2019;7:193. doi:10.1186/s40425-019-0650-9.

More recent work has extended this observation to several clinical HCC cohorts. A study using 81 stool samples from 50 HCC patients included *early-stage resectable HCC receiving perioperative checkpoint blockade as well as advanced unresectable HCC receiving anti-PD-1/PD-L1-based therapy*, and found microbiome signatures associated with immune-checkpoint-blockade response.

This means microbiome research in HCC is no longer restricted to cancer risk or diagnosis; it is increasingly being studied as a *predictive biom response*.

给出具体样本量及研究结论，但未提供对应Reference，无法直接建立“结论—文献”映射

Overall conclusion

So, *yes—quite extensively*. Based on published human literature, the gut microbiome has been investigated in at least:

1. *HBV-associated HCC*
2. *HCV-associated HCC*
3. *NAFLD/NASH/MASLD/MASH-associated HCC*
4. *Alcohol-related HCC*
5. *Cirrhosis-associated HCC of mixed etiologies*
6. *Early-stage/resectable HCC*
7. *Advanced/unresectable HCC*
8. *HCC treated with anti-PD-1/PD-L1 immune-checkpoint therapy*

Among these, *MASLD/NAFLD-related HCC currently has some of the strongest etiologically controlled human evidence*, because investigators have compared patients with the same underlying liver disease and cirrhosis *with versus without HCC*. Immunotherapy-treated HCC is another rapidly developing area.

A key caveat is that there is *not yet a universally reproducible "HCC microbiome signature."* Individual studies report different taxa, partly because of HCC etiology, geography, diet, cirrhosis severity, medication/antibiotic exposure, sequencing methodology, and relatively small cohort sizes. The most convincing emerging signal

is therefore not one individual bacterium, but a combination of *community dysbiosis, microbial metabolic functions—especially bile-acid and SCFA metabolism—and altered host immunity*. Recent reviews summarize this field and emphasize the same limitations.

If your purpose is *designing an HCC gut-microbiome study or writing the introduction for an SCI paper*, I can next compile a more systematic table of the published human studies—*authors, year, HCC etiology, cohort size, control group, sample type, sequencing method, altered taxa/metabolites, and DOI/PMID*—which would make it easier to identify the research gap.

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