

## The Gut Microbiome in Cirrhosis and Hepatocellular Carcinoma: Characterization of Disease-Related Microbial Signature and the Possible Impact of Life Style and Nutrition

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**Abstract :** Introduction: Hepatocellular carcinoma (HCC) is one of the leading causes of cancer related mortality worldwide. Liver Cirrhosis is the main predisposing risk factor for the development of HCC. The factor(s) influencing disease progression from Cirrhosis to HCC remain unknown. Gut microbiota has recently emerged as a major player in different liver diseases, however its association with HCC is still a mystery. Moreover, there might be an important association between the gut microbiota, nutrition, life style and the progression of Cirrhosis and HCC. The aim of our study was to characterize the gut microbial signature in association with life style and nutrition of patients with Cirrhosis, HCC-Cirrhosis and healthy controls. Design: Stool samples were collected from 95 individuals (30 patients with HCC, 38 patients with Cirrhosis and 27 age, gender and BMI-matched healthy volunteers). All participants answered lifestyle and Food Frequency Questionnaires. 16S rRNA sequencing of fecal DNA was performed (MiSeq Illumina). Results: There was a significant decrease in alpha diversity in patients with Cirrhosis (qvalue=0.033) and in patients with HCC-Cirrhosis (qvalue=0.032) compared to healthy controls. The microbiota of patients with HCC-cirrhosis compared to patients with Cirrhosis, was characterized by a significant overrepresentation of *Clostridium* (pvalue=0.024) and CF231 (pvalue=0.010) and lower expression of Alphaproteobacteria (pvalue=0.039) and Verrucomicrobia (pvalue=0.036) in several taxonomic levels: Verrucomicrobiae, Verrucomicrobiales, Verrucomicrobiaceae and the genus *Akkermansia* (pvalue=0.039). Furthermore, we performed an analysis of predicted metabolic pathways (Kegg level 2) that resulted in a significant decrease in the diversity of metabolic pathways in patients with HCC-Cirrhosis (qvalue=0.015) compared to controls, one of which was amino acid metabolism. Furthermore, investigating the life style and nutrition habits of patients with HCC-Cirrhosis, we found significant correlations between intake of artificial sweeteners and Verrucomicrobia (qvalue=0.12), High sugar intake and Synergistetes (qvalue=0.021) and High BMI and the pathogen *Campylobacter* (qvalue=0.066). Furthermore, overweight in patients with HCC-Cirrhosis modified bacterial diversity (qvalue=0.023) and composition (qvalue=0.033). Conclusions: To the best of the our knowledge, we present the first report of the gut microbial composition in patients with HCC-Cirrhosis, compared with Cirrhotic patients and healthy controls. We have demonstrated in our study that there are significant differences in the gut microbiome of patients with HCC-cirrhosis compared to Cirrhotic patients and healthy controls. Our findings are even more pronounced because the significantly increased bacteria *Clostridium* and CF231 in HCC-Cirrhosis weren't influenced by diet and lifestyle, implying this change is due to the development of HCC. Further studies are needed to confirm these findings and assess causality.

**Keywords :** Cirrhosis, Hepatocellular carcinoma, life style, liver disease, microbiome, nutrition

**Conference Title :** ICM 2018 : International Conference on Microbiome

**Conference Location :** Amsterdam, Netherlands

**Conference Dates :** December 03-04, 2018