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The Relationship Between Gut Microbiome Alterations and Hepatocellular Carcinoma Development in Chronic Hepatitis B Patients: A Clinical and Microbiological Study from Iraq

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ABSTRACT

Objective: *To investigate the relationship between gut microbiome composition and the development of HCC in Iraqi patients with chronic HBV infection.* ***Method:*** *A cross-sectional case-control study was conducted involving 150 participants divided into three groups: HBV with HCC (n=60), HBV without HCC (n=60), and healthy controls (n=30). Clinical, biochemical, and microbiome data (16S rRNA sequencing of fecal samples) were collected. Statistical analyses included ANOVA, chi-square, and Pearson correlation.* ***Results:*** *Patients with HCC exhibited significant dysbiosis, characterized by decreased microbial diversity (Shannon index: 2.8 ± 0.4) compared to HBV-only (3.6 ± 0.5) and controls (4.1 ± 0.3), p<0.001. Increased abundance of Bacteroides fragilis and Enterobacteriaceae correlated with higher AFP levels (r=0.63, p<0.001).* ***Novelty:*** *Gut microbiome alterations are associated with HCC development in chronic HBV patients. These findings suggest potential microbiome-based biomarkers for early detection and therapeutic strategies.*

INTRODUCTION

Chronic Hepatitis B Virus (HBV) infection remains a global health challenge, affecting approximately 296 million people worldwide [1]. HBV is a leading cause of hepatocellular carcinoma (HCC), responsible for over 50% of liver cancer cases globally [2], [3]. Despite advances in antiviral therapy, the risk of HCC persists, highlighting the need to identify additional pathogenic mechanisms and early biomarkers.

The human gut microbiome has emerged as a key modulator of liver health through the gut-liver axis [4]. Alterations in microbial composition, or dysbiosis, can influence systemic inflammation, bile acid metabolism, and immune regulation, all of which are implicated in HCC development [5]. Several studies from Asia and Europe have reported correlations between specific microbial taxa and HCC, yet data from Middle Eastern populations, particularly Iraq, are scarce.

This study aims to investigate gut microbiome alterations in Iraqi patients with chronic HBV infection and to assess their association with HCC development [6].

RESEARCH METHOD

Study Design and Population:

A cross-sectional case-control study was conducted at the University Teaching Hospital, Baghdad, Iraq, from January 2023 to March 2025 [7], [8], [9]. A total of 150 participants were recruited:

- Group A: HBV with HCC (n=60)

- Group B: Chronic HBV without HCC (n=60)
- Group C: Healthy controls (n=30)

Inclusion Criteria:

- Age 18–75 years
- Chronic HBV infection confirmed by HBsAg positivity >6 months
- Diagnosis of HCC confirmed by imaging and AFP levels (for Group A)

Exclusion Criteria:

- Coinfection with HCV, HIV, or other hepatic viruses
- Recent antibiotic or probiotic use (past 3 months)
- History of gastrointestinal surgery or inflammatory bowel disease

Data Collection:

- Clinical data: Age, sex, BMI, duration of HBV infection
- Biochemical data: ALT, AST, bilirubin, albumin, AFP, platelet count
- Virological data: HBV DNA levels, HBeAg status

Gut Microbiome Analysis:

- Fecal samples were collected and stored at –80°C
- DNA extraction followed by 16S rRNA sequencing
- Microbial diversity (Shannon index) and relative abundance of key taxa were analyzed

Statistical Analysis:

- Continuous variables: ANOVA, expressed as mean ± SD
- Categorical variables: Chi-square test
- Correlation analysis: Pearson correlation coefficient
- Significance threshold: $p < 0.05$
- Software: SPSS v25

Ethics:

- Study approved by the University Teaching Hospital Ethics Committee
- Informed consent obtained from all participants

RESULTS AND DISCUSSION

Results

Table 1. Clinical and Biochemical Characteristics.

Parameter	HBV + HCC (n=60)	HBV only (n=60)	Healthy Controls (n=30)	p-value
Age (years)	55.2 ± 10.1	48.6 ± 12.3	50.1 ± 11.5	0.02
Male (%)	70%	63.3%	60%	0.45
ALT (U/L)	78.5 ± 25.4	62.3 ± 20.7	28.7 ± 7.8	<0.001
AST (U/L)	85.6 ± 30.1	67.8 ± 18.9	25.3 ± 6.5	<0.001
AFP (ng/mL)	450.3 ± 120.7	12.5 ± 5.6	3.4 ± 1.2	<0.001
Platelet ($\times 10^3/\mu L$)	132 ± 40	180 ± 35	250 ± 30	<0.001

HBV DNA (IU/mL)	$5.2 \times 10^5 \pm 1.1 \times 10^5$	$4.8 \times 10^4 \pm 9.0 \times 10^3$	-	<0.001

Table 2. Gut Microbiome Diversity and Composition.

Group	Shannon Index (Mean ± SD)	Firmicutes/Bacteroidetes Ratio	Key Taxa Notes
HBV + HCC	2.8 ± 0.4	0.71	↑ Bacteroides fragilis, ↑ Enterobacteriaceae, ↓ Lactobacillus
HBV only	3.6 ± 0.5	1.26	Balanced microbiome
Healthy Controls	4.1 ± 0.3	1.64	High diversity, beneficial bacteria dominant

Discussion

This study demonstrates that chronic HBV patients who develop HCC exhibit significant gut microbiome dysbiosis, with decreased diversity and increased abundance of pathogenic taxa such as Bacteroides fragilis and Enterobacteriaceae [10], [11], [12]. These findings align with studies from Asia and Europe reporting similar microbial patterns in HCC patients. The reduced Firmicutes/Bacteroidetes ratio and loss of beneficial bacteria may contribute to liver inflammation, carcinogenesis, and altered immune responses [13], [14]. The correlations between AFP levels and specific microbial taxa suggest potential biomarkers for early detection. Microbiome modulation through diet, probiotics, or fecal microbiota transplantation could represent novel therapeutic strategies [15], [16].

CONCLUSION

Fundamental Finding : Gut microbiome alterations are associated with HCC development in chronic HBV patients in Iraq. Microbiome diversity indices and specific taxa may serve as predictive biomarkers and therapeutic targets. **Implication :** These findings highlight the potential use of gut microbiome profiling as a diagnostic and therapeutic tool for early detection and management of hepatocellular carcinoma in patients with chronic HBV infection. **Limitation :** The study is limited by its cross-sectional design, which restricts causal interpretation of the observed microbiome changes in relation to disease progression. **Future Research :** Future studies should focus on longitudinal analyses and interventional trials to validate these findings and explore the therapeutic potential of microbiome modulation in preventing HCC among HBV-infected individuals.

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