BMC Cancer

RESEARCH Open Access

Dietary intervention reshapes gut microbiota and lipid metabolism to enhance anti-tumor immunity and prognosis in hepatocellular carcinoma: a randomized controlled trial

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Abstract

Background The gut microbiota is increasingly recognized as a key modulator of cancer pathogenesis and treatment response. We aimed to investigate the efficacy of a targeted dietary intervention on clinical outcomes, gut microbiota, lipid metabolism, and systemic immunity in patients with hepatocellular carcinoma (HCC).

Methods In this single-center, prospective, randomized controlled trial, 100 patients with primary HCC were enrolled and randomly assigned (1:1) to an experimental group ($n=50$), receiving a structured dietary intervention including probiotics, prebiotics, and specific dietary advice, or a control group ($n=50$), receiving routine dietary care. The primary endpoints were progression-free survival (PFS) and overall survival (OS). Secondary endpoints included changes in gut microbiota composition (16S rRNA sequencing), serum lipid profiles, immune cell subsets (flow cytometry), and quality of life (WHOQOL-100).

Results After a median follow-up of 12 months, the experimental group showed significantly longer median PFS (9.4 vs. 7.3 months; Hazard Ratio [HR] = 0.52, 95% CI: 0.34–0.79, $P<0.01$) and median OS (27.7 vs. 22.6 months; HR = 0.61, 95% CI: 0.42–0.88, $P=0.008$). The intervention significantly increased microbial α-diversity and enriched beneficial genera such as *Bifidobacterium* and *Lactobacillus*. This was accompanied by improved lipid metabolism (reduced serum cholesterol and triglycerides) and a shift towards an anti-tumor immune profile, including increased CD8 + T cells and decreased regulatory T cells (Tregs). Quality of life scores were also significantly higher in the experimental group ($P<0.001$).

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Conclusion A targeted dietary intervention effectively modulates the gut microbiota, lipid metabolism, and systemic immunity in HCC patients, translating into significant improvements in survival and quality of life. These findings support microbiota-targeted dietary therapy as a promising adjunctive strategy in HCC management.

Trial registration This study was registered with ClinicalTrials.gov (Identifier: NCT07143955; date: 19/08/2025).

Keywords Gut Microbiota, Hepatocellular Carcinoma, Lipid Metabolism, Immunomodulation, Probiotics, Randomized Controlled Trial

Background

Hepatocellular carcinoma (HCC) accounts for 75–85% of primary liver cancers and remains a major global health challenge, characterized by high incidence, insidious onset, and poor prognosis [1]. Globally, HCC is the sixth most common cancer and the third leading cause of cancer-related mortality [2]. The pathogenesis of HCC is a complex, multistep process almost invariably developing on a background of chronic liver disease and cirrhosis, driven by factors such as viral hepatitis (HBV, HCV), alcohol abuse, and non-alcoholic fatty liver disease (NAFLD) [3, 4].

Emerging evidence highlights the critical role of the "gut-liver axis," a bidirectional communication network where the gut microbiota and its metabolites profoundly influence liver homeostasis and pathology [5]. Dysbiosis, an imbalance in the gut microbial community, is increasingly recognized as a key contributor to liver diseases, including NAFLD progression and HCC development [6]. Through the portal vein, microbial products such as lipopolysaccharide (LPS) can translocate to the liver, activating pattern recognition receptors like Toll-like receptor 4 (TLR4). This triggers persistent low-grade inflammation, promotes hepatic stellate cell activation, and drives fibrogenesis, creating a pro-carcinogenic microenvironment [7, 8]. Patients with cirrhosis and HCC often exhibit reduced microbial diversity and an enrichment of pathogenic bacteria, which exacerbates inflammation and immune dysregulation [9, 10].

The interplay between gut microbiota, host metabolism, and anti-tumor immunity is particularly crucial. Microbial metabolites, such as short-chain fatty acids (SCFAs) and secondary bile acids, can exert systemic effects. While SCFAs generally have anti-inflammatory properties, altered bile acid profiles, specifically elevated deoxycholic acid (DCA), have been linked to HCC progression [11, 12]. Moreover, dysregulated intestinal lipid metabolism, influenced by the microbiota, can impact systemic lipid profiles and immune function [13]. The tumor immune microenvironment in HCC is typically immunosuppressive, characterized by an exhausted cytotoxic T cell phenotype and an accumulation of regulatory T cells (Tregs) [14, 15]. The intratumoral Treg/CD8 + T cell ratio is a potent independent prognostic factor in HCC [15].

Given these connections, modulating the gut microbiota has emerged as a novel therapeutic strategy. Preclinical studies have shown that probiotic interventions can reshape the gut microbial landscape and suppress tumor burden [16, 17]. However, robust clinical evidence from randomized controlled trials (RCTs) demonstrating the impact of such interventions on clinical outcomes in HCC patients remains scarce. This study was designed to address this gap by investigating whether a targeted dietary intervention could rebalance the systemic immune profile, thereby improving survival and quality of life in patients with HCC.

Methods

Study design and participants

This study was a single-center, prospective, randomized controlled trial conducted at The First Hospital of Hebei Medical University. A total of 100 patients with a pathologically confirmed diagnosis of primary HCC were enrolled between May 2022 and September 2023. The study protocol was approved by the Institutional Review Board of The First Hospital of Hebei Medical University. All participants provided written informed consent before enrollment.

Inclusion criteria were: (1) Age between 18 and 80 years; (2) Pathologically confirmed primary HCC; (3) Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; (4) Adequate organ function; (5) Life expectancy of at least 3 months; (6) Willingness to provide informed consent.

Exclusion criteria were: (1) Concurrent malignancies other than HCC; (2) Severe, uncontrolled comorbidities; (3) Known history of severe intestinal diseases; (4) Use of antibiotics, probiotics, or other microbiota-altering agents within 4 weeks prior to enrollment; (5) Cognitive impairment; (6) Refusal to provide consent.

Randomization and blinding

Eligible patients were randomly assigned in a 1:1 ratio to either the experimental or control group using a computer-generated block randomization sequence (block size of 4). Allocation concealment was maintained using sequentially numbered, opaque, sealed envelopes. Due to the nature of the intervention, participants

and investigators were not blinded. However, outcome assessors, laboratory personnel, and data analysts were blinded to group assignments.

Interventions

Control group (n = 50)

Patients received routine dietary care and counseling according to institutional guidelines for HCC patients.

Experimental group (n = 50)

In addition to routine care, patients received a structured dietary intervention. The intervention consisted of three components: (1) Dietary Modification: A personalized diet plan designed to align with the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines for cancer patients [18], emphasizing high-fiber foods (≥ 30 g/day), lean proteins, and reduced intake of red/processed meats and refined sugars. (2) Probiotic Supplementation: A daily multi-species probiotic supplement administered as a freeze-dried, enteric-coated capsule (total ≥ 1×10^{10} CFU/day) containing *Bifidobacterium longum*, *Lactobacillus acidophilus*, and *Lactobacillus rhamnosus*. Patients were instructed to take one capsule daily with their morning meal at home. Product viability was ensured by refrigerated storage and transport. (3) Prebiotic and Fatty Acid Intake: Patients were provided with a daily 10 g powder sachet of a prebiotic blend (inulin and fructooligosaccharides) to be mixed with water. They also received counseling on incorporating foods rich in unsaturated fatty acids (e.g., olive oil, nuts). Adherence was monitored through bi-weekly dietary logs and pill/sachet counts.

Outcomes and assessments

The primary endpoints were progression-free survival (PFS) and overall survival (OS). Secondary endpoints included changes in gut microbiota, serum lipid markers, immunological profiles, health-related quality of life (QOL) assessed by the WHOQOL-100 questionnaire [19], and safety. Assessments were performed at baseline and at predefined intervals, with the main analyses conducted at 12 months (end-of-study). The median follow-up was 12 months (range: 6–18 months).

Sample collection and laboratory analysis

Gut microbiota analysis

Fecal samples were collected at baseline and 12 months. Bacterial DNA was extracted, and the V4 region of the 16S rRNA gene was sequenced on an Illumina NovaSeq platform. Bioinformatic analysis was performed using QIIME2.

Fecal SCFA analysis

Fecal concentrations of acetate, propionate, and butyrate were measured in a subset of samples ($n = 30$ per group) at 12 months using gas chromatography-mass spectrometry (GC–MS), as previously described [20].

Biochemical and immunological assays

Fasting blood samples were collected at baseline and 12 months. Serum cholesterol, phospholipids, and triglycerides were quantified using standard enzymatic assays. Lipase and fatty acid synthase (FAS) activities were measured enzymatically. Total serum bile acids were analyzed via HPLC. Peripheral blood mononuclear cells (PBMCs) were isolated for T-cell subset quantification (CD8 +, CD4 + CD25 + FoxP3 + Tregs) and NK cells by flow cytometry. Serum immunoglobulins (IgA, IgG, IgM) were measured by ELISA.

Statistical analysis

The sample size was calculated based on the primary endpoint of PFS. All analyses were conducted on the intention-to-treat (ITT) population. Continuous variables were compared using the independent t-test or Mann–Whitney U test. Categorical variables were compared using the Chi-square test or Fisher's exact test. Survival curves were generated using the Kaplan–Meier method and compared with the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using a Cox proportional hazards model. A multivariable Cox model was used to adjust for potential confounders, including baseline BCLC stage and concurrent oncologic treatments. A two-tailed P-value < 0.05 was considered statistically significant. All analyses were performed using R (version 4.2.1) and SPSS (version 27.0).

Results

Patient disposition and baseline characteristics

Patient recruitment followed the CONSORT 2010 guidelines [21]. Between May 2022 and September 2023, 132 patients were assessed for eligibility, and 100 were randomized (Fig. 1). The baseline demographic and clinical characteristics were well-balanced between the groups (Table 1 and Supplementary Table S1). Concurrent oncologic treatments received during the study period, including transarterial chemoembolization (TACE), sorafenib, and lenvatinib, were also similarly distributed between the two groups (Supplementary Table S2).

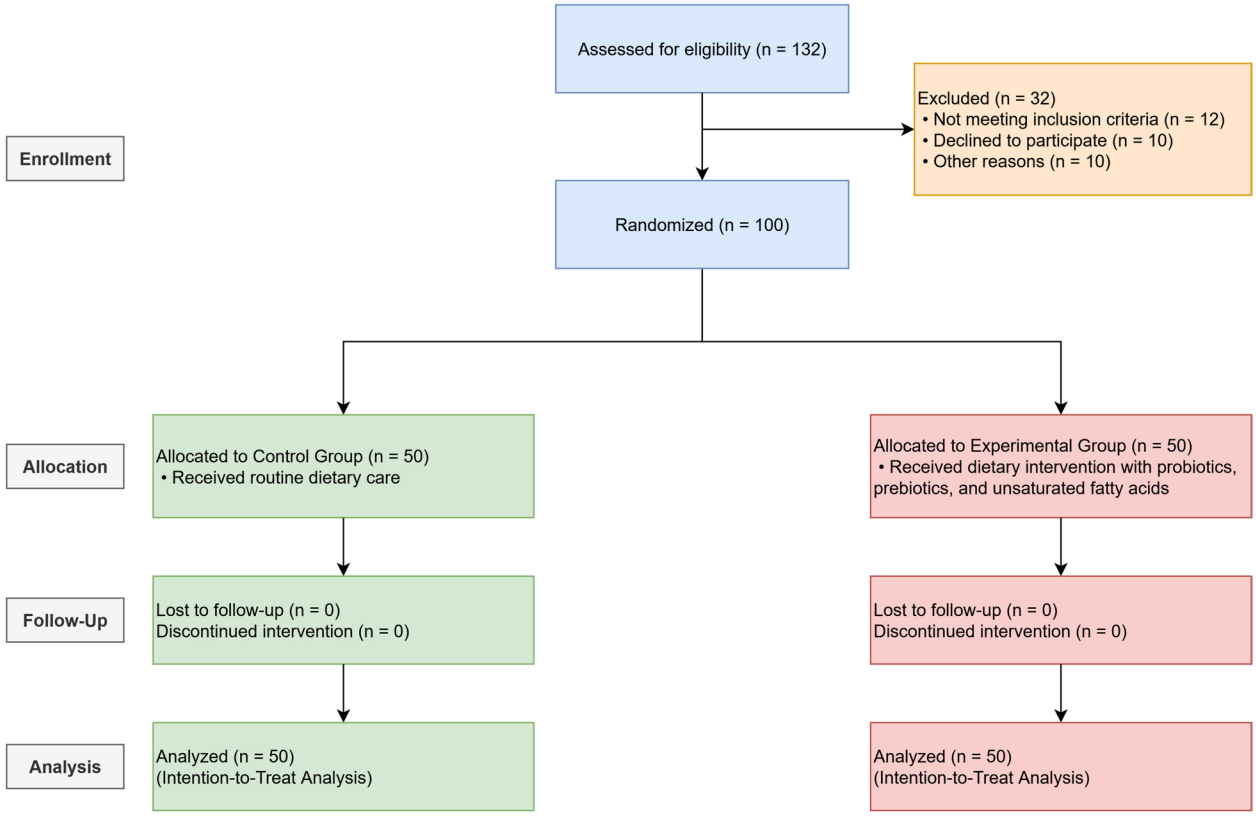

Fig. 1 CONSORT 2010 Flow Diagram. The diagram illustrates participant flow through the trial

Table 1 Baseline Demographics and Clinical Characteristics of Patients

Parameter	Experimental Group ($n=50$)	Control Group ($n=50$)	Statistic Value	*P*-Value
Sex (Male/Female)	33 (66.0%)/17 (34.0%)	35 (70.0%)/15 (30.0%)	$\chi^2=0.162$	0.687
Age (years), mean ± SD	63.39 ± 5.67	61.67 ± 5.38	t = 1.565	0.121
BMI (kg/m^2), mean ± SD	23.42 ± 2.15	22.35 ± 1.76	t = 2.651	0.099
TNM Stage			$\chi^2=0.151$	0.985
I-II	26 (52.0%)	24 (48.0%)	-	-
III-IV	24 (48.0%)	26 (52.0%)	-	-
Hypertension, n (%)	10 (20.0%)	8 (16.0%)	$\chi^2=0.340$	0.560
Diabetes, n (%)	3 (6.0%)	4 (8.0%)	$\chi^2=0.155$	0.694
Alcohol Use, n (%)	19 (38.0%)	22 (44.0%)	$\chi^2=0.370$	0.543

Data are presented as mean ± SD or n (%). *P*-values were calculated using independent t-test for continuous variables and Pearson's χ^2 test for categorical variables. BMI, body mass index; TNM, Tumor, Node, Metastasis

Intervention modulates gut microbiota composition and diversity

After 12 months, the experimental group showed a significant increase in gut microbial alpha-diversity compared to the control group, as measured by both the Shannon index ($P<0.001$) and Simpson index ($P<0.001$) (Fig. 2A, Table 2). Taxonomic analysis revealed significant enrichment of *Bifidobacterium* ($P<0.001$) and *Lactobacillus* ($P<0.001$), and a reduction of *Escherichia coli* ($P<0.001$) in the experimental group (Fig. 2B, Table 2).

Intervention improves systemic lipid metabolism

At 12 months, the experimental group demonstrated significantly lower serum levels of cholesterol, phospholipids, and triglycerides (all $P<0.001$). In contrast, markers of lipid catabolism, including lipase activity, FAS activity, and total bile acids, were significantly higher in the intervention group (all $P<0.001$) (Fig. 3, Table 3).

Intervention increases fecal short-chain fatty acid production

To assess the functional metabolic output of the altered microbiota, we measured fecal SCFA concentrations at 12 months. The experimental group had significantly higher levels of acetate (18.7 ± 3.1 vs. 12.4 ± 2.5 μmol/g, $P<0.001$), propionate (7.9 ± 1.8 vs. 5.1 ± 1.5 μmol/g, $P<0.001$), and butyrate (8.5 ± 2.0 vs. 4.8 ± 1.6 μmol/g, $P<0.001$) compared to the control group (Fig. 4).

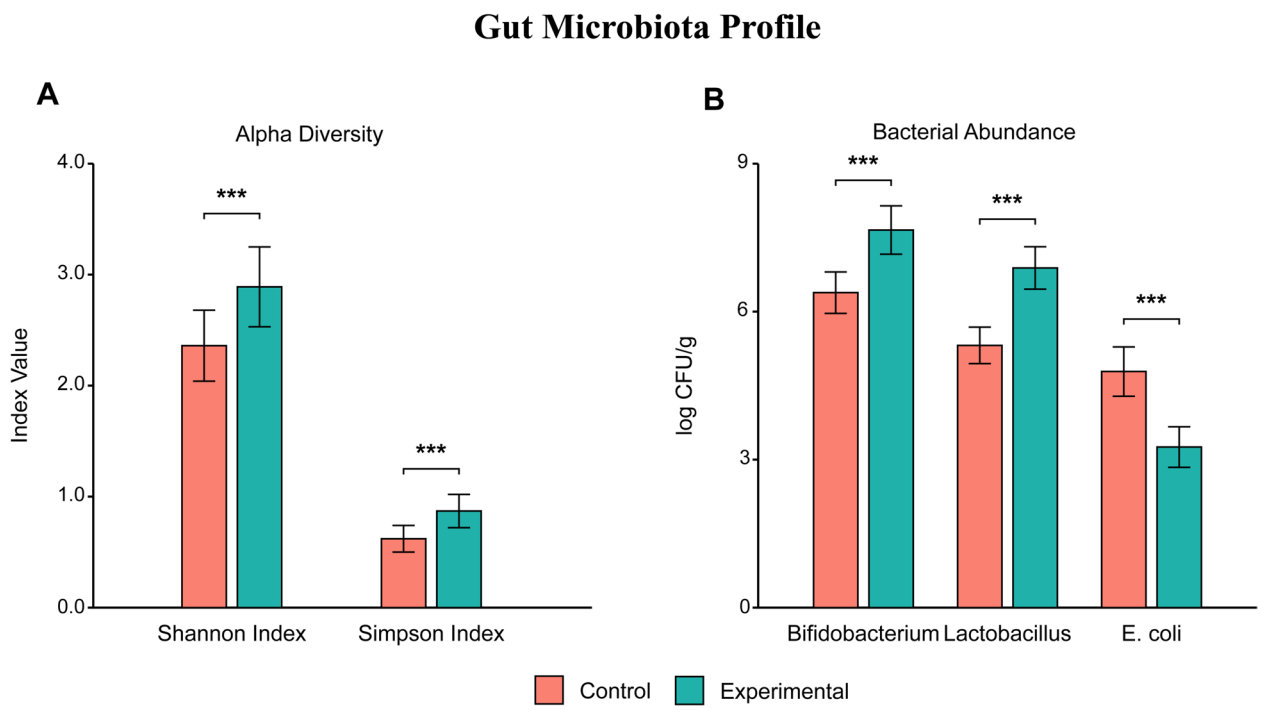

Fig. 2 Dietary Intervention Reshapes Gut Microbiota Profile. **A** Alpha-diversity indices and **B** abundance of key bacterial genera in the experimental and control groups at 12 months. Data are mean ± SD. ***$P < 0.001$

Table 2 Gut Microbiota Diversity and Abundance Post-Intervention

Microbiota Parameter	Experimental Group ($n = 50$)	Control Group ($n = 50$)	t-Value	*P*-Value
Shannon Index	2.89 ± 0.36	2.36 ± 0.32	7.531	< 0.001
Simpson Index	0.87 ± 0.15	0.62 ± 0.12	9.112	< 0.001
Bifidobacterium (log CFU/g)	7.58 ± 0.49	6.31 ± 0.42	13.120	< 0.001
Lactobacillus (log CFU/g)	6.81 ± 0.43	5.24 ± 0.37	19.014	< 0.001
E. coli (log CFU/g)	3.18 ± 0.41	4.71 ± 0.50	−15.823	< 0.001

Data are presented as mean ± SD. *P*-values were calculated using independent t-test

Intervention enhances systemic anti-tumor immune response

The dietary intervention prompted a robust systemic immune response. At 12 months, the experimental group had significantly higher levels of serum IgA, IgG, and IgM (Fig. 5A, Table 4). Flow cytometry analysis revealed a significantly higher absolute count of cytotoxic CD8 + T cells and a significantly lower count of immunosuppressive Tregs in the experimental group. NK cell counts were also elevated (Fig. 5B, Table 4).

Intervention improves clinical outcomes

The primary endpoints of survival were significantly improved in the experimental group. Kaplan–Meier analysis showed a longer median PFS (9.4 months vs. 7.3 months; HR = 0.52, 95% CI: 0.34–0.79; log-rank $P < 0.01$) (Fig. 6A, Table 5) and median OS (27.7 months vs. 22.6 months; HR = 0.61, 95% CI: 0.42–0.88; log-rank $P = 0.008$) (Fig. 6B, Table 5). Crucially, in a multivariable Cox proportional hazards model adjusting for concurrent oncologic treatments and baseline BCLC stage, the dietary intervention remained an independent predictor of improved PFS (Adjusted HR = 0.55, 95% CI: 0.36–0.85; $P = 0.007$) and OS (Adjusted HR = 0.63, 95% CI: 0.43–0.94; $P = 0.023$). In an exploratory subgroup analysis, the beneficial effect of the dietary intervention on PFS was observed in both male (HR = 0.54, 95% CI: 0.32–0.91) and female (HR = 0.49, 95% CI: 0.21–1.15) patients, with no significant interaction between treatment effect and sex (P for interaction = 0.82) (Supplementary Figure S1).

Intervention enhances quality of life

At 12 months, patients in the experimental group reported significantly higher quality of life scores across all six domains of the WHOQOL-100 questionnaire compared to the control group (all $P < 0.001$) (Fig. 7, Table 6).

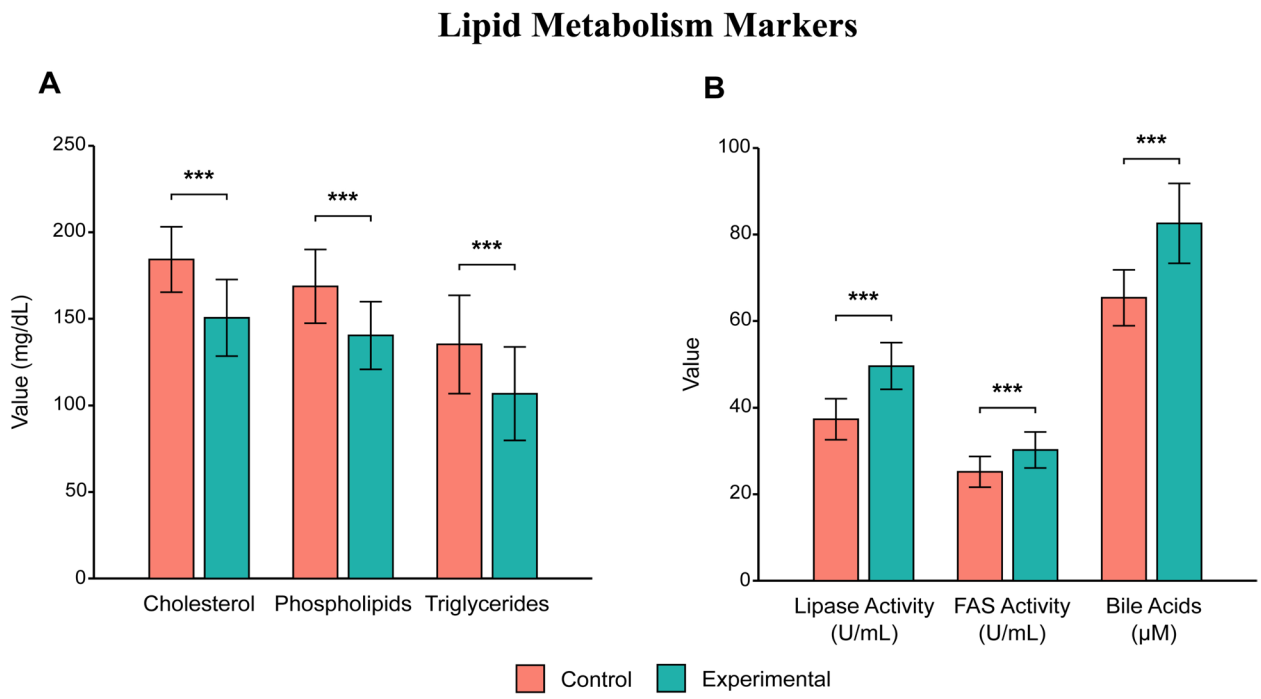

Fig. 3 Intervention Improves Systemic Lipid Metabolism. Serum levels of (**A**) lipids and (**B**) metabolic enzymes/acids in both groups at 12 months. Data are mean ± SD. ***$P < 0.001$

Table 3 Serum Lipid Metabolism Markers Post-Intervention

Lipid Marker	Experimental Group ($n = 50$)	Control Group ($n = 50$)	t-Value	*P*-Value
Cholesterol (mg/dL)	150.54 ± 22.14	184.27 ± 18.93	−8.114	< 0.001
Phospholipids (mg/dL)	140.39 ± 19.46	168.72 ± 21.32	−6.887	< 0.001
Triglycerides (mg/dL)	106.77 ± 26.93	135.21 ± 28.32	−5.161	< 0.001
Lipase Activity (U/mL)	49.63 ± 5.37	37.35 ± 4.74	12.181	< 0.001
FAS Activity (U/mL)	30.24 ± 4.16	25.19 ± 3.55	6.533	< 0.001
Bile Acids (μM)	82.57 ± 9.24	65.37 ± 6.46	10.379	< 0.001

Data are presented as mean ± SD. *P*-values were calculated using independent t-test. FAS, Fatty Acid Synthase

Safety and tolerability

The dietary intervention was well-tolerated. No serious adverse events were reported. Mild gastrointestinal symptoms were reported by a small number of patients in both groups (8% vs. 4%; $P = 0.677$). Routine laboratory safety monitoring revealed no significant differences in liver function tests between the groups over the study period, indicating the intervention was not associated with hepatotoxicity (Supplementary Table S3).

Discussion

This randomized controlled trial demonstrates that a targeted dietary intervention can significantly remodel the gut microbiota, optimize systemic lipid metabolism, foster an anti-tumor immune environment, and ultimately improve survival and quality of life in patients with HCC.

Our finding that the intervention increased microbial alpha-diversity is consistent with literature associating higher diversity with improved cancer outcomes [22]. The enrichment of *Bifidobacterium* and *Lactobacillus* is a key outcome, as these genera are known to produce SCFAs, which modulate immune function [23, 24]. To provide initial mechanistic insight, we measured fecal SCFA levels and found a significant increase in butyrate, propionate, and acetate in the intervention group (Fig. 7), which supports the hypothesis that the observed microbial shifts had a functional metabolic impact.

The immunological changes, particularly the increased CD8 +/Treg ratio, suggest a shift from an immunosuppressive to a cytotoxic immune state, which is a strong predictor of better prognosis in HCC [14]. The rationale for our bundled approach was to target the gut-liver axis through multiple complementary mechanisms simultaneously—providing beneficial microbes (probiotics), nourishing them (prebiotics), and promoting an

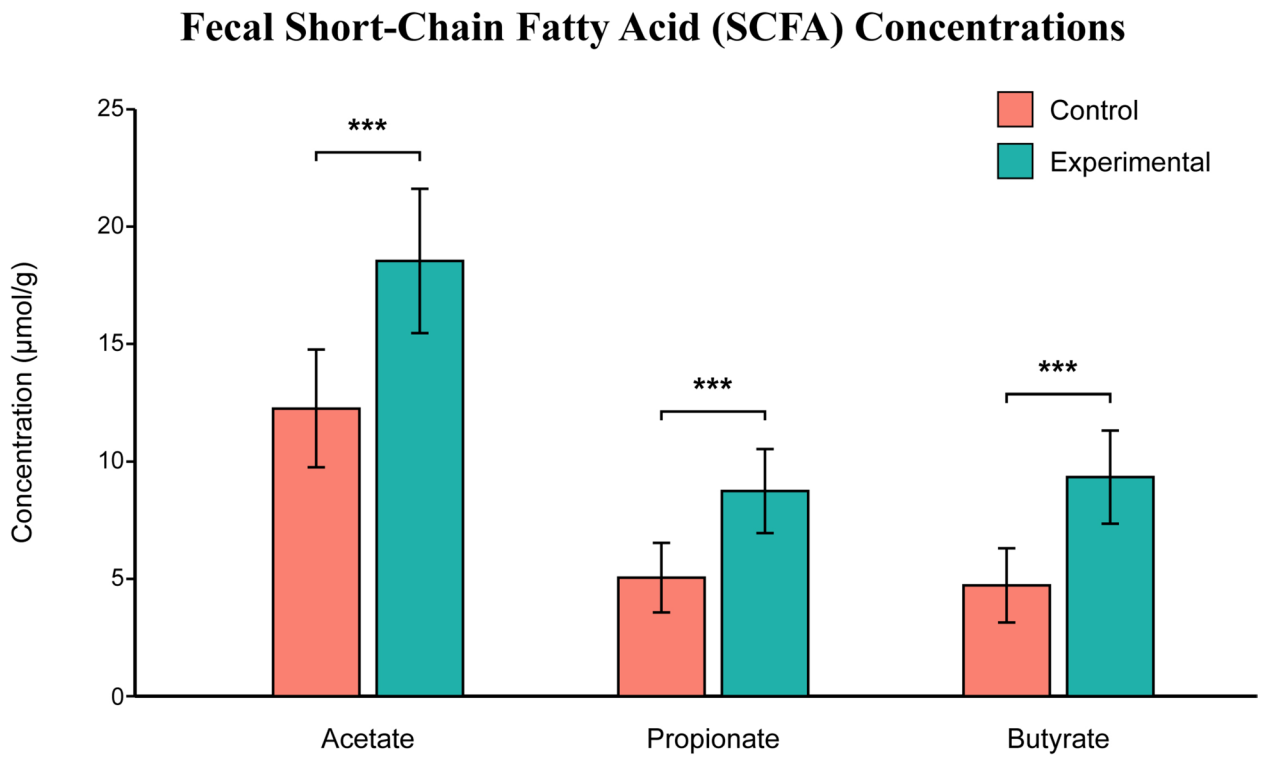

Fig. 4 Fecal Short-Chain Fatty Acid (SCFA) Concentrations. Levels of acetate, propionate, and butyrate in fecal samples from both groups at 12 months. Data are mean ± SD. ***$P < 0.001$

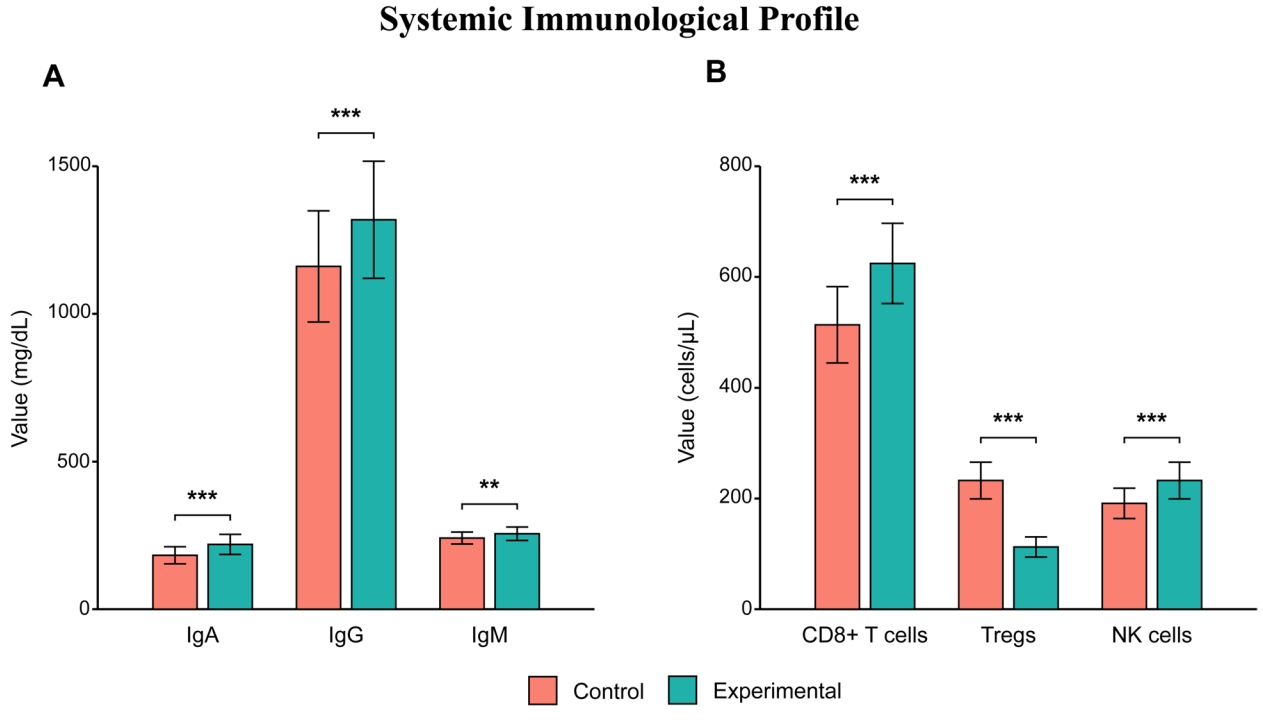

Fig. 5 Intervention Modulates Systemic Immune Responses. **A** Serum immunoglobulin levels and **B** peripheral immune cell counts in both groups at 12 months. Data are mean ± SD. **$P < 0.01$, ***$P < 0.001$

Table 4 Systemic Immunological Profile Post-Intervention

Immunological Parameter	Experimental Group ($n=50$)	Control Group ($n=50$)	t-Value	*P*-Value
Serum Immunoglobulins				
IgA (mg/dL)	98.43 ± 15.33	82.18 ± 13.82	5.452	< 0.001
IgG (mg/dL)	1241.59 ± 188.43	1098.24 ± 178.78	3.896	< 0.001
IgM (mg/dL)	120.31 ± 21.55	108.68 ± 19.24	2.766	0.007
Immune Cell Subsets				
CD8 + T cells (cells/μL)	624.36 ± 72.54	513.41 ± 68.97	7.821	< 0.001
Tregs (cells/μL)	112.43 ± 18.24	232.55 ± 33.19	−22.618	< 0.001
NK cells (cells/μL)	232.56 ± 33.14	191.28 ± 27.46	6.621	< 0.001

Data are presented as mean ± SD. *P*-values were calculated using independent t-test. Treg, regulatory T cell (CD4 + CD25 + FoxP3 +); NK, Natural Killer

Table 5 Survival Outcomes

Outcome	Experimental Group ($n=50$)	Control Group ($n=50$)	HR (95% CI)	*P*-Value
Median PFS (months)	9.4	7.3	0.52 (0.34–0.79)	< 0.01 (Log-rank)
Median OS (months)	27.7	22.6	0.61 (0.42–0.88)	0.008 (Log-rank)

PFS, Progression-Free Survival; OS, Overall Survival; HR, Hazard Ratio; CI, Confidence Interval. HRs and *P*-values were derived from Cox proportional hazards model and log-rank test, respectively

anti-inflammatory metabolic milieu (high-fiber, unsaturated fatty acids)—hypothesizing a synergistic effect. Recent work has increasingly highlighted such complex interactions, where gut and even oral microbiota can influence gynecological cancers, and gut dysbiosis is linked to intratumoral microbiota profiles in HCC, underscoring the systemic nature of microbial influence [25, 26].

The significant improvements in PFS and OS provide strong clinical validation for our approach. Importantly, this survival benefit persisted after adjusting for concurrent oncologic treatments, strengthening the evidence that the intervention itself conferred the advantage. The hazard ratios in our study align with the magnitude of benefit seen in trials of novel cancer therapies [27] and microbiota-modulating interventions [28].

Limitations

This study has several limitations. First, it was a single-center trial with a modest sample size. Second, a primary consideration of this study is its bundled intervention design, combining dietary modification, probiotics, prebiotics, and unsaturated fatty acids. While this holistic approach reflects a practical clinical strategy, it inherently limits our ability to attribute the observed benefits to a single component. Third, the mechanistic investigation was exploratory and limited to 16S rRNA gene sequencing, peripheral immune profiling, and fecal SCFAs. This approach cannot fully elucidate the functional metabolic pathways or immune interactions within the tumor microenvironment. We did not perform profiling of specific bile acid species such as DCA, which would have provided deeper mechanistic insights. Fourth, the follow-up period may not capture the full long-term OS benefit. Fifth, the open-label design introduces a potential for bias, particularly for subjective outcomes like quality of life. Sixth, the study was not powered to detect

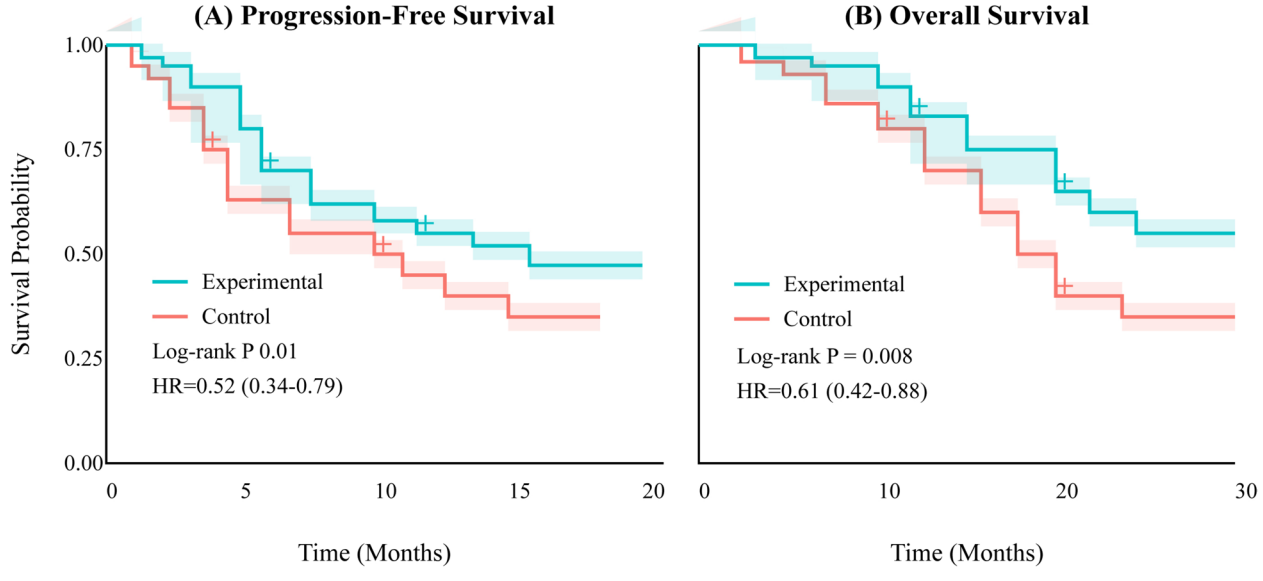

Fig. 6 Kaplan–Meier Curves for Clinical Outcomes. **A** Progression-Free Survival (PFS) and **B** Overall Survival (OS) in both groups

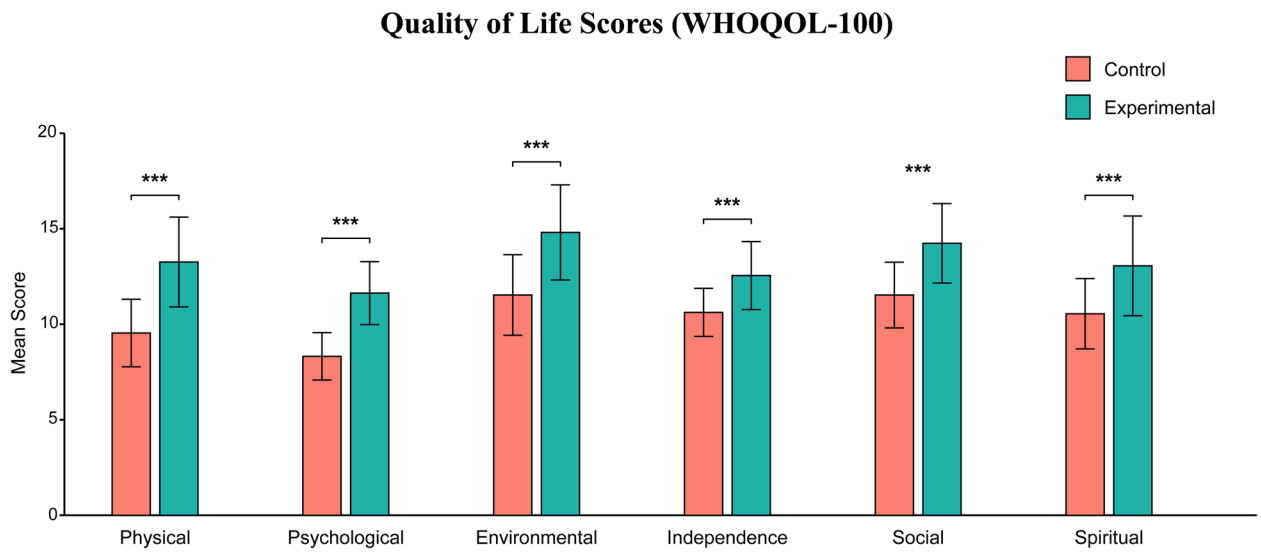

Fig. 7 Improvement in Quality of Life. Mean scores for the WHOQOL-100 domains in both groups at 12 months. Data are mean ± SD. ***$P < 0.001$

Table 6 Quality of Life Scores (WHOQOL-100) Post-Intervention

QOL Domain	Experimental Group ($n = 50$)	Control Group ($n = 50$)	t-Value	*P*-Value
Physical	13.26 ± 2.35	9.54 ± 1.77	8.851	< 0.001
Psychological	11.63 ± 1.65	8.32 ± 1.24	10.741	< 0.001
Environmental	14.81 ± 2.49	11.53 ± 2.11	6.883	< 0.001
Independence	12.55 ± 1.78	10.62 ± 1.26	6.012	< 0.001
Social Relationships	14.24 ± 2.08	11.53 ± 1.72	6.889	< 0.001
Spiritual	13.06 ± 2.61	10.55 ± 1.84	5.429	< 0.001

Data are presented as mean ± SD. *P*-values were calculated using independent t-test. QOL, Quality of Life

statistically significant differences in subgroup analyses, such as by sex, and these findings should be considered exploratory. Finally, dietary adherence relied on patient self-reporting, which is subject to bias. Future studies could incorporate objective biomarkers of adherence.

Conclusions

In conclusion, this randomized controlled trial provides compelling evidence that a structured dietary intervention targeting the gut microbiota can serve as a potent adjunctive therapy for HCC. By enhancing microbial diversity, optimizing metabolism, and reversing immune suppression, this approach significantly improves clinical survival and quality of life. These findings support integrating microbiota-targeted strategies into the standard of care for HCC.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-15325-z.

Supplementary Material 1: Supplementary Figure S1. Subgroup Analysis of Progression-Free Survival by Sex. Forest plot showing Hazard Ratios (HRs) and 95% Confidence Intervals (CIs) for PFS in male and female subgroups.

Supplementary Material 2

Supplementary Material 3

Acknowledgements

Not applicable.

Authors' contributions

XS and DZ designed the study, collected and analyzed the data, and were major contributors in writing the manuscript. FW and XL participated in data collection and patient follow-up. KS was responsible for data management and statistical analysis. HD and SS designed and supervised the dietary intervention protocol. LN and CW conceived the study, supervised the project, and critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Funding

This research was supported by the Medical Science Research Project of Hebei (Grant No. 20242312). The funder had no role in the study design, data collection, analysis, decision to publish, or preparation of the manuscript.

Data availability

The datasets generated and/or analysed during the current study are not publicly available due to patient privacy and confidentiality concerns but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of The First Hospital of Hebei Medical University (NO. 20211107). This study was

conducted in accordance with the ethical principles of the Declaration of Helsinki. All participants provided written informed consent before enrollment and any study-related procedures.

Consent for publication
Not applicable. This manuscript does not contain any individual person's data in any form (including any individual details, images, or videos).

Competing interests
The authors declare no competing interests.

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Received: 18 August 2025 / Accepted: 10 November 2025
Published online: 06 January 2026

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