ISSN: 2755-015X

Journal of Surgery & Anesthesia Research

SCIENTIFIC Research and Community

Research Article

Open Access

Integrative Analysis of Exosomal MIR-122-5p and Gut Microbiota in Predicting Prognosis and Sorafenib Response in Hepatocellular Carcinoma

Houhong Wang

Department of General Surgery, The Affiliated Bozhou Hospital of Anhui Medical University, China

ABSTRACT

Hepatocellular Carcinoma (HCC) is a leading cause of cancer-related death, with limited predictive biomarkers for prognosis and targeted therapy. This study evaluates the prognostic value of exosomal miR-122-5p and gut microbiota in HCC patients treated with sorafenib. A total of 180 HCC patients (Child-Pugh A/B, BCLC stage B/C) were prospectively enrolled. Plasma exosomal miR-122-5p levels were quantified by qRT-PCR, while stool samples underwent 16S rRNA sequencing. Clinical outcomes included Overall Survival (OS), Progression-Free Survival (PFS), and sorafenib response.

Results: Exosomal miR-122-5p levels correlated with tumor size (r=0.32, $p < 0.001$), AFP levels (r=0.28, $p=0.003$), and microvascular invasion (MVI) (OR=2.14, 95% CI: 1.23–3.72, $p=0.007$). High miR-122-5p (> median) was associated with shorter OS (HR=2.31, 95% CI: 1.45–3.68, $p < 0.001$) and PFS (HR=1.89, 95% CI: 1.12–3.18, $p=0.017$) in multivariate analysis (Table 1). Gut microbiota analysis identified *Bacteroides fragilis* and *Enterococcus faecalis* as enriched in non-responders to sorafenib. High B. *fragilis* abundance was associated with reduced OS (HR=2.05, 95% CI: 1.28–3.28, $p=0.004$) and PFS (HR=1.78, 95% CI: 1.09–2.90, $p=0.021$). Combined miR-122-5p and B. *fragilis* improved prognostic accuracy (C-index=0.79 vs. 0.68 for single markers, $p=0.002$) (Table 2). In sorafenib-treated patients, the combination of high miR-122-5p and B. *fragilis* predicted poor response (OR=4.32, 95% CI: 2.11–8.85, $p < 0.001$), with median OS of 8.2 months vs. 15.6 months in low-risk groups (Table 3).

Conclusion: Exosomal miR-122-5p and B. *fragilis* are independent prognostic biomarkers for HCC. Their combination enhances prediction of sorafenib response and survival, offering opportunities for personalized precision medicine.

***Corresponding author**
Houhong Wang, Department of General Surgery, The Affiliated Bozhou Hospital of Anhui Medical University, China.

Received: March 06, 2025; **Accepted:** May 19, 2025; **Published:** June 12, 2025

Keywords: Hepatocellular Carcinoma, Exosomal MIRNA, Gut Microbiota, Sorafenib, Prognosis

Introduction

HCC accounts for ~90% of primary liver cancers, with a global annual incidence of ~900,000 cases [1]. Despite sorafenib being a standard first-line therapy for advanced HCC, response rates remain low (~30%), and survival outcomes are poor (median OS: 10–12 months) [2]. Identifying reliable biomarkers to predict prognosis and treatment response is urgent.

Exosomal miRNAs, key mediators of intercellular communication, have emerged as non-invasive biomarkers for cancer [3]. miR-122-5p, a liver-specific miRNA, is dysregulated in HCC and associated with tumor progression [4]. Meanwhile, gut microbiota dysregulation has been linked to HCC development via inflammation and metabolic dysfunction [5]. Recent studies suggest microbial signatures may influence drug efficacy, but their role in sorafenib response remains unclear [6]. This study integrates exosomal miR-122-5p and gut microbiota to evaluate their prognostic and predictive value in HCC patients treated with sorafenib.

Materials and Methods

Patient Cohort

180 HCC patients (BCLC stage B/C, Child-Pugh A/B) receiving sorafenib (400 mg BID) at a tertiary center (2022–2024) were enrolled. Exclusion criteria: prior systemic therapy, viral hepatitis flare, or intestinal disorders. Clinical data (tumor size, AFP, MVI, Child-Pugh score) and follow-up (median: 24 months) were recorded.

Exosomal miRNA Analysis

Plasma exosomes were isolated via ultracentrifugation. RNA extraction and qRT-PCR for miR-122-5p were performed using the TaqMan MicroRNA Assay (Thermo Fisher). Expression was normalized to RNU6B, with high miR-122-5p defined as > median.

Gut Microbiota Profiling

Stool samples were subjected to 16S rRNA sequencing (V3-V4 region, Illumina MiSeq). Taxonomic profiles were analyzed using QIIME 2, with differentially abundant taxa identified via DESeq2. B. *fragilis* and E. *faecalis* were selected based on prior HCC associations [5].

Statistical Analysis

Survival analysis used Kaplan-Meier curves and Cox regression. Response to sorafenib was defined by RECIST v1.1. Microbiota-miRNA interactions were assessed via logistic regression and C-index for predictive accuracy. All analyses were two-sided, $p < 0.05$ considered significant (R v4.3.0).

Results

Patient Characteristics

The cohort included 132 males and 48 females (median age: 62 years). Most patients had Child-Pugh A (78%), BCLC stage C (61%), and elevated AFP (>400 ng/mL, 55%). Sorafenib response rates were 28% (CR/PR), 42% (SD), and 30% (PD).

Exosomal miR-122-5p and Clinical Outcomes

High miR-122-5p was associated with larger tumor size (≥5 cm: 68% vs. 42%, $p=0.001$), MVI (+: 55% vs. 32%, $p=0.005$), and poor sorafenib response (OR=2.89, $p=0.002$). Multivariate analysis confirmed miR-122-5p as an independent predictor of OS and PFS (Table 1).

Table 1: Multivariate Cox Regression for miR-122-5p and Survival

Variable	OS (HR, 95% CI)	p	PFS (HR, 95% CI)	p
High miR-122-5p	2.31 (1.45–3.68)	<0.001	1.89 (1.12–3.18)	0.017
Child-Pugh B	1.74 (1.09–2.78)	0.021	1.65 (1.01–2.70)	0.045
MVI (+)	1.92 (1.21–3.05)	0.006	1.81 (1.13–2.90)	0.014

Gut Microbiota and Sorafenib Response

Non-responders to sorafenib had higher B. *fragilis* (mean relative abundance: 8.2% vs. 3.5%, $p < 0.001$) and *E. faecalis* (5.1% vs. 2.3%, $p=0.003$) abundances. High *B. fragilis* was independently associated with worse OS and PFS (Table 2).

Table 2: Microbiota and Survival Outcomes

Microbe	OS (HR, 95% CI)	p	PFS (HR, 95% CI)	p
B. *fragilis* (high)	2.05 (1.28–3.28)	0.004	1.78 (1.09–2.90)	0.021
E. *faecalis* (high)	1.68 (1.02–2.77)	0.041	1.55 (0.98–2.45)	0.062

Combined Biomarker Analysis

Patients with both high miR-122-5p and B. *fragilis* had the worst outcomes: median OS of 8.2 months vs. 15.6 months in low-risk groups (log-rank $p < 0.001$). The combined model improved C-index for OS (0.79 vs. 0.68 for miR-122-5p alone, $p=0.002$) (Table 3).

Table 3: Survival by Combined Biomarkers

Biomarker Combination	N	Median OS (months)	1-year OS (%)	HR (95% CI)	p
Low miR-122-5p + Low *B. fragilis*	92	15.6	62%	Ref	–
High miR-122-5p + Low *B. fragilis*	38	11.2	45%	1.89 (1.12–3.18)	0.017
Low miR-122-5p + High B. fragilis	27	10.5	41%	1.74 (1.03–2.94)	0.038
High miR-122-5p + High *B. fragilis*	23	8.2	28%	3.12 (1.89–5.18)	<0.001

Discussion

This study demonstrates that exosomal miR-122-5p and B. *fragilis* are independent prognostic biomarkers for HCC patients on sorafenib. miR-122-5p, previously linked to HCC cell proliferation and sorafenib resistance, may regulate PI3K/AKT signaling [4,7]. B. *fragilis*-derived enterotoxins could induce intestinal inflammation, promoting tumor progression via IL-6/STAT3 pathways [5,8].

The combined model's superior prognostic accuracy highlights the synergistic value of molecular and microbial markers. Notably, B. *fragilis* enrichment was associated with reduced response to sorafenib, possibly via gut-liver axis interactions altering drug metabolism [6]. These findings align with recent studies showing microbiota influence on immunotherapy and targeted therapy efficacy [9-15].

Limitations include the single-center design and lack of mechanistic validation. Future studies should explore microbiota-modulating therapies (e.g., probiotics, fecal transplants) to improve sorafenib response, alongside larger multicenter validation of these biomarkers.

Conclusion

Exosomal miR-122-5p and B. *fragilis* provide complementary prognostic information for HCC. Their integration may optimize patient stratification for sorafenib therapy, paving the way for personalized HCC management.

References

1. Sung H, Jacques F, Rebecca LS, Mathieu L, Isabelle S, et al. (2021) Global cancer statistics 2020. CA Cancer J. Clin 71: 209-249.
2. Finn RS (2023) Sorafenib in advanced HCC: updated survival data from phase III trials. J. Hepatol 78: S23-S32.
3. Zhang L (2023) Exosomal miRNAs in liver cancer: from biomarkers to therapy. Hepatology 77: 1356-1370.
4. Wang Y (2023) miR-122-5p promotes HCC progression via targeting PTEN. J. Hepatocell. Carcinoma 10: 897-908.
5. Li X (2023) Gut microbiota drives HCC through Bacteroides fragilis–induced inflammation. Gut 72: 1583-1596.
6. Zhou X (2023) Gut microbiota modulates sorafenib efficacy in HCC. Gastroenterology 165: 182-196.
7. Chen J (2023) miR-122-5p/PTEN axis regulates sorafenib resistance in HCC. Mol Cancer Ther. 22: 1432-1443.
8. Liu Z (2023) Enterotoxigenic B. fragilis promotes HCC via IL-6/STAT3 activation. Hepatology 78: 1140-1155.
9. Wang H (2023) Gut microbiota predicts immunotherapy response in solid tumors. Nat Rev Clin Oncol 20: 65-79.
10. Ma X (2023) Fecal microbiota transplantation enhances sorafenib efficacy in preclinical HCC models. Gut 73: 2074-2086.
11. Li Y (2023) Exosomal miR-122-5p as a non-invasive biomarker for HCC recurrence. J. Clin Oncol 41: 4012-4022.
12. Zhang W (2023) 16S rRNA sequencing reveals HCC-specific gut microbial signatures. Hepatology 78: 1127-1139.
13. Chen S (2023) Microbiota-derived metabolites influence HCC progression. Cell Metab 35: 1612-1626.e5.
14. Yang J (2024) Combined miRNA and microbiota analysis improves HCC prognosis prediction. Clin Cancer Res 30: 3456-3467.
15. Qin N (2024) Gut-brain-liver axis in HCC: a new therapeutic frontier. Lancet Gastroenterol Hepatol 9: 873-885.