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ORIGINAL RESEARCH

Circulating Fibroblast Growth Factor 21 (FGF21) as a Prognostic and Diagnostic Biomarker in Hepatocellular Carcinoma

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Purpose: Fibroblast growth factor 21 (FGF21) is a hormone synthesized and released by liver cells. Deficiency in FGF21 has been shown to be associated with steatosis, inflammation, fibrosis, and increased risk of hepatocellular carcinoma (HCC) development. Moreover, recent evidence suggests that elevated FGF21 levels may paradoxically correlate with worse outcomes in HCC. We aimed to evaluate the association between serum FGF21 levels, clinicopathological parameters, and overall survival (OS) in HCC patients.

Patients and Methods: From 2001 to 2014, newly diagnosed HCC patients were recruited as part of an IRB-approved protocol. Blood samples were prospectively collected and a CLIA-certified lab measured serum FGF21 concentrations. Using FGF21 median as a cutoff point, all patients were categorized into subjects with low and high levels. The primary endpoint was OS.

Results: A total of 767 HCC patients were analyzed. Mean age was 65 years, and 74% were male. Median FGF21 value was 0.41 ng/mL. Our data showed that patients with advanced HCC including those with multinodular tumors, vascular invasion, distant metastasis, a higher Child-Pugh score, CLIP, BCLC, TNM, and ECOG stage had significantly increased FGF21 serum levels ($p < 0.05$ for all parameters). OS was significantly shorter in patients with high FGF21 compared to those with low FGF21 (24 months OS 28% vs 43%; $p < 0.001$). On multivariate analysis, high FGF21 was significantly associated with worse OS (HR: 1.422; 95% CI: 1.180–1.714; $p < 0.001$).

Conclusion: Elevated circulating FGF21 levels correlate with advanced clinicopathologic features and poor OS in HCC patients. Because elevated FGF21 during liver stress may indicate significant metabolic disruption, our data provides strong evidence that FGF21 may represent a valuable prognostic and potentially therapeutic biomarker in HCC. Future independent studies are required to validate our results.

Keywords: hepatocellular carcinoma, fibroblast growth factor 21, prognostic biomarker, overall survival

Introduction

Hepatocellular carcinoma (HCC), the predominant form of primary liver cancer, poses a substantial global health challenge, contributing significantly to the overall cancer burden with projections indicating continued rise in incidence and mortality.[1,2] While landmark studies demonstrating the efficacy of novel immunotherapy combinations have revolutionized HCC management,[3,4] overall survival rates and treatment responses remain suboptimal, underscoring the critical importance of developing more precise prognostic tools and biomarker-driven therapeutic strategies.

Fibroblast Growth Factor 21 (FGF21) is an endocrine hormone that is predominantly expressed in the liver. It plays a crucial role in metabolic homeostasis by regulating lipid and glucose metabolism,[5–8] and has emerged as

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a promising biomarker with potential anti-tumoral properties in HCC and other obesity-related malignancies.[9–12] A recent animal study suggested that lack of FGF21 may increase nonalcoholic fatty liver disease severity and promote transition to HCC.[13] There are also studies demonstrating that FGF21 reduces lipid concentration in the liver and inhibits inflammation by regulation of several signaling pathways.[14,15] FGF21 has been well-studied in fatty liver disease,[16] however, there is also accumulating evidence regarding its involvement in HCC pathogenesis. It has been shown that FGF21 is induced in functional hepatocytes during liver stress conditions including hepatitis, fatty degeneration, cirrhosis and liver tumors,[17] and is upregulated during mitochondrial stress responses such as the unfolded protein response, potentially serving as a biomarker for HCC development, progression and metastasis.[18] Another study revealed that serum FGF21 levels dramatically increase in chronic hepatitis B patients who develop HCC, suggesting FGF21 may serve as a useful biomarker for monitoring tumorigenesis.[19] Given this mechanistic and pathophysiologic relevance, we chose to investigate its association with survival outcomes in HCC.

Recent insights into novel molecular mechanisms in HCC pathogenesis, including PANoptosis, a newly identified form of inflammatory programmed cell death, highlight the ongoing need to identify and validate additional biomarkers such as FGF21 that could improve patient stratification and treatment outcomes.[20] In a prospective study that included 825 newly diagnosed HCC patients, higher serum FGF21 levels were associated with worse overall survival (OS), and more interestingly, this effect on survival was more pronounced in patients having more than three metabolic disorders.[21] In a retrospective study that included 82 patients with unresectable HCC treated with lenvatinib, using artificial intelligence algorithms, authors demonstrated that baseline AFP was the most significant predictor of OS, followed by albumin-bilirubin grade and FGF21.[22] The REFLECT study demonstrated that while higher baseline FGF21 levels were associated with shorter OS in both sorafenib and lenvatinib treatment groups, patients with elevated baseline FGF21 showed longer survival with lenvatinib compared to sorafenib, suggesting FGF21 may serve as a predictive biomarker for lenvatinib efficacy in HCC patients.[23] In a study that compared advanced HCC patients treated by transcatheter arterial chemoembolization with drug-eluting beads plus lenvatinib versus sorafenib, OS was better with lenvatinib, particularly in patients with FGF21 amplification and portal vein thrombus.[24] Another study identified FGF21 as a key molecule that promotes sorafenib resistance in HCC, suggesting FGF21 targeting as a promising strategy to overcome sorafenib resistance.[25] Collectively, these clinical observations suggest that FGF21 may not only serve as a prognostic biomarker but also as a predictive marker of treatment efficacy in HCC. However, the evidence remains limited and further clinical studies are needed to validate its therapeutic implications. In light of these findings, we sought to demonstrate the prognostic and diagnostic value of FGF21 in HCC patients and determine its potential role as a clinically relevant biomarker.

Materials and Methods

Patient Selection

This retrospective cohort study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocol was reviewed and approved by the Institutional Review Board at MD Anderson Cancer Center (MDACC), and all patients provided informed written consent prior to study commencement. This study enrolled patients with pathologically or radiologically confirmed HCC at MDACC from 2001 to 2014. In addition, this study included control participants who were selected from healthy spouses of patients who were diagnosed with cancers other than liver and gastrointestinal cancers. Clinicopathologic data and serum samples were collected prospectively from the patients during their first visit and before any treatment was administered. The following demographic and clinicopathologic data were recorded at the first visit: age, sex, race, HCC risk factors, presence of vascular invasion, number of nodules, extrahepatic metastases, and tumor differentiation. Classification systems for HCC staging were also used: Child-Turcot Pugh score (CTP), Cancer of the Liver Italian Program (CLIP), Barcelona Clinic Liver Cancer score (BCLC), and the American Joint Committee on Cancer (AJCC) tumor node metastasis (TNM) system.

Measurement of Serum FGF21

Serum FGF21 (ng/mL) was measured by Myriad RBM (Austin, TX), a Clinical Laboratory Improvement Amendments (CLIA)–certified biomarker testing laboratory. A multiplexed immunoassay panel (DiscoveryMAP v.3.3; Myriad RBM) was used to quantitate FGF21 on an automated, Luminex xMAP-based platform (Austin, TX). All results are given in ng/mL.

Statistical Analysis

The software SPSS version 29 (IBM, Aramark, NY) and GraphPad Prism version 10.0.3 for Windows (GraphPad Software, Boston, MA) were used for statistical analysis. Categorical variables were tabulated with frequency and percent. Independent *t*-test was used to determine and compare the mean and standard deviation of FGF21 levels between the different subgroups by patient clinical factors. A $p < 0.05$ was considered statistically significant.

Prognosis Analysis

To our knowledge, no consensus cutoff value has been established for FGF21 in HCC patients. In the absence of an externally validated threshold, we used the median value of our cohort to define "high" vs "low" groups, which is a common practice in exploratory biomarker analyses. Future validation studies are, therefore, essential. The OS curve was constructed using the Kaplan–Meier method and compared using the Log rank test. The univariate and multivariate analyses for OS utilized Cox proportional hazards models and were used to evaluate the association of OS with covariates. Hazard ratios (HRs) along their respective 95% confidence intervals were calculated for each factor on univariate analyses. Factors with $p < 0.05$ were added to the multivariate regression model. We evaluated whether FGF21 levels could provide additional prognostic value to each of the existing HCC staging systems by fitting Cox regression models including FGF21 and each of the scoring systems.

Diagnosis Analysis

A receiver operating characteristic (ROC) analysis was conducted, and Youden index was used to determine the ideal cutoff value for FGF21 to separate the cases from the controls.

Results

Baseline Characteristics

The study included 767 HCC patients. Table 1 summarizes the patients' demographic and clinicopathologic data. Seventy-four percent of patients were male and 57.4% were older than the age of 60. Fifty-one percent of patients had underlying HCC causes including hepatitis B or C, and 63.8% had concomitant cirrhosis. Sixty-two percent had multinodular tumors, 31% had vascular invasion, 20.4% had lymph node metastasis, and 24.6% had extrahepatic metastases. Staging the patients demonstrated that 53.7% were CTP A, 63.2% were CLIP stage 0–2, 76.6% were BCLC stage C-D, and 86.7% of patients had an ECOG of either 0 or 1.

Table 1 Demographic and Clinicopathologic Characteristics of Patients with Hepatocellular Carcinoma (n = 767)

Variable	Frequency (%)
Age	
≤ 60 y	327 (42.6)
> 60 y	440 (57.4)
Sex	
Male	567 (73.9)
Female	200 (26.1)

(*Continued*)

Table 1 (Continued).

Variable	Frequency (%)
Race	
Asian	57 (7.4)
Black	85 (11.1)
White	520 (67.8)
Hispanic	105 (13.7)
Comorbidities	
History of Tobacco Use	498 (64.9)
History of Alcohol Use	560 (73.0)
History of Hypertension	426 (55.5)
Obesity (BMI ≥ 30)	249 (32.5)
History of Diabetes Mellitus	271 (35.3)
Viral etiology	389 (50.7)
Gross Liver Cirrhosis	489 (63.8)
AFP level > 400 ng/dL	251 (32.7)
Tumor Factors	
Multinodular Tumors	474 (61.8)
Vascular Invasion	241 (31.0)
Lymph node Metastases	157 (20.4)
Distant Metastases	189 (24.6)
Tumor differentiation	
Well differentiated	193 (25.2)
Moderately differentiated	211 (27.5)
Poorly differentiated	120 (13.0)
Non differentiated	68 (8.9)
Fibrolamellar	13 (1.6)
Clear cell	7 (0.9)
Child-Pugh score	
A	412 (53.7)
B	299 (39.0)
C	56 (7.3)
CLIP staging	
Stage 0–2	485 (63.2)
Stage 3–6	282 (36.8)

(*Continued*)

Table 1 (Continued).

Variable	Frequency (%)
BCLC staging	
Stage 0–B	172 (22.4)
Stage C–D	588 (76.6)
ECOG	
0-1	665 (86.7)
2+	102 (13.3)
TNM staging	
Stage I–II	253 (33)
Stage IIIA–IIIB	225 (29.3)
Stage IIIC–IVB	266 (34.7)

Abbreviations: BMI, Body Mass Index; AFP, alpha-fetoprotein; CLIP, The Cancer of the Liver Italian Program; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; TNM, tumor, node, metastasis.

Table 2 compares the mean FGF21 between the different subgroups of patients' clinical parameters. Patients with history of tobacco or alcohol use had significantly lower FGF21 levels compared to patients without ($p = 0.037$ and $p = 0.044$ respectively). Patients with liver cirrhosis had significantly lower FGF21 levels, while patients with AFP levels >400 ng/mL had significantly higher circulating FGF21 ($p = 0.035$ and $p = 0.005$ respectively). Regarding other clinicopathologic features, having multinodular tumors, vascular invasion, and distant metastases correlated with significantly higher FGF21 levels ($p < 0.05$ for all). Patients classified as CTP B had significantly higher FGF21 when compared to CTP A ($p = 0.030$). Significantly higher FGF21 levels were also observed in patients with a CLIP score of 3

Table 2 Comparison of FGF21 Levels Between the Different Subgroups by Patient Clinical Factors

Characteristic	n	FGF21 Levels in ng/mL (Mean ± SD)	P-value
Age			
≤ 60 y	327	1.57 ± 4.25	0.716
> 60 y	440	1.47 ± 3.75	
Sex			
Male	567	1.50 ± 3.98	0.865
Female	200	1.55 ± 3.93	
Race			
Asian	57	2.47 ± 5.51	0.201
Black	85	1.40 ± 3.09	
White	520	1.37 ± 3.66	
Hispanic	105	1.80 ± 4.93	

(*Continued*)

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Table 2 (Continued).

Characteristic	n	FGF21 Levels in ng/mL (Mean ± SD)	P-value
History of Tobacco Use			
Yes	498	1.26 ± 3.04	0.037
No	269	1.99 ± 5.24	
History of Alcohol Use			
Yes	560	1.31 ± 3.67	0.044
No	207	2.04 ± 4.65	
History of Hypertension			
Yes	426	1.66 ± 4.31	0.254
No	341	1.33 ± 3.48	
Obesity (BMI ≥ 30)			
Yes	249	1.41 ± 3.59	0.599
No	518	1.57 ± 4.14	
History of Diabetes Mellitus			
Yes	271	1.73 ± 4.20	0.271
No	496	1.40 ± 3.83	
Viral etiology			
Yes	389	1.27 ± 3.61	0.090
No	378	1.76 ± 4.30	
Gross Liver Cirrhosis			
Yes	489	1.27 ± 3.44	0.035
No	278	1.95 ± 4.73	
AFP level > 400 ng/dL			
Yes	251	2.16 ± 4.83	0.005
No	516	1.20 ± 3.43	
Multinodular Tumors			
Yes	474	1.74 ± 4.39	0.031
No	293	1.15 ± 3.13	
Vascular Invasion			
Yes	241	2.02 ± 4.87	0.033
No	526	1.28 ± 3.46	
Lymph node Metastases			
Yes	157	1.90 ± 5.04	0.173
No	610	1.41 ± 3.64	

(*Continued*)

Table 2 (Continued).

Characteristic	n	FGF21 Levels in ng/mL (Mean ± SD)	P-value
Distant Metastases			
Yes	189	2.24 ± 5.38	0.021
No	578	1.28 ± 3.35	
Pathology			
Moderately/Well differentiated	404	1.63 ± 4.09	0.803
Non/Poorly differentiated	188	1.54 ± 4.21	
Child-Pugh class			
A	412	1.20 ± 3.07	0.030
B	299	1.99 ± 5.10	
C	56	1.26 ± 2.47	
CLIP staging			
Stage 0–2	485	0.87 ± 2.17	<0.001
Stage 3	147	3.01 ± 6.51	
Stage 4–6	109	2.67 ± 5.16	
BCLC staging			
Stage 0–B	172	0.74 ± 1.34	<0.001
Stage C–D	588	1.76 ± 4.45	
ECOG			
0-1	665	1.24 ± 3.34	<0.001
2+	102	3.32 ± 6.50	
TNM staging			
Stage I–II	253	0.85 ± 2.52	0.003
Stage IIIA–IIIB	225	1.89 ± 4.09	
Stage IIIC–IVB	266	1.91 ± 4.94	

Abbreviations: FGF21, Fibroblast Growth Factor 21; BMI, Body Mass Index; AFP, alpha-fetoprotein; CLIP, The Cancer of the Liver Italian Program; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; TNM: tumor, node, metastasis.

or higher than in those with a CLIP score of 0–2 ($p < 0.001$). Similarly, this was noted among BCLC and ECOG staging systems, with stages C-D in BCLC and 2+ in ECOG having higher levels than stages 0–B in BCLC and stage 0–1 in ECOG ($p < 0.001$ for both). In addition, patients with tumors stage III–IV on TNM staging had significantly higher FGF21 than those with tumors stage I–II ($p = 0.003$).

Prognostic Significance of FGF21

Kaplan–Meier analysis was conducted to compare OS between patients in the FGF21-low and patients in the FGF21-high group (Figure 1). The 50th percentile (median) of 0.41 ng/mL was used as a cutoff for the comparison. The median OS was significantly higher in the FGF21-low group (20.1 months) compared with the FGF21-high group (10.7 months,

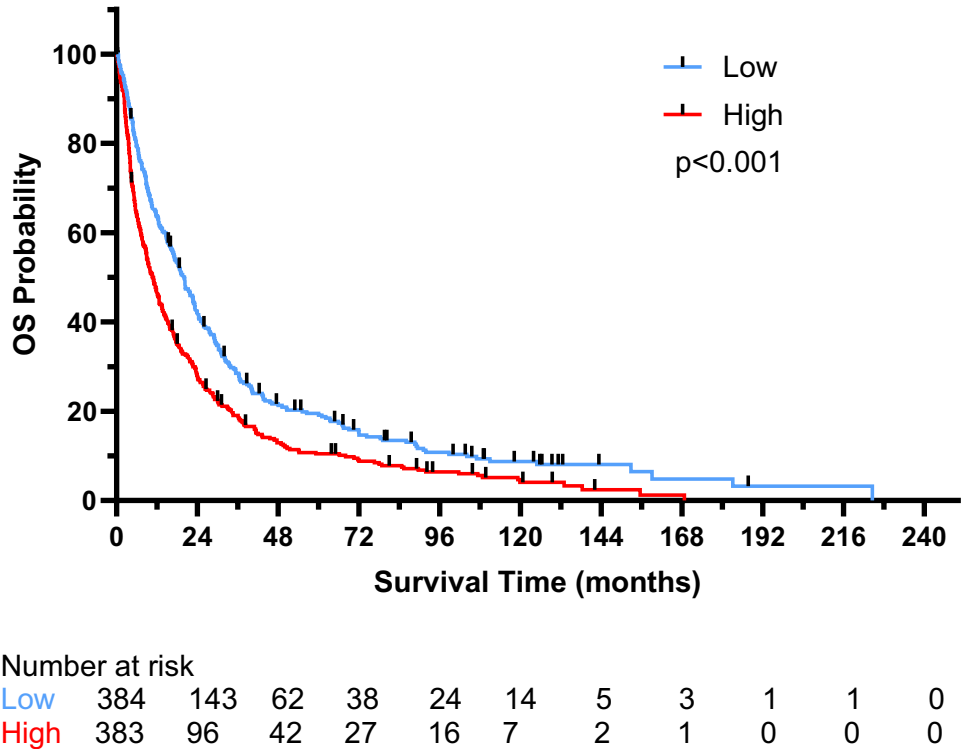

Figure 1 Kaplan–Meier curve representing OS among FGF21-Low and FGF21-High groups.

$p < 0.001$). Evaluating survival at 24 months, 43% of patients in the FGF21-low group were still alive, which is higher than the 28% of patients alive in the FGF21-high group ($p < 0.001$) (Table 3).

Other parameters were evaluated for their impact on OS (Table 4). On univariate Cox analysis, elevated FGF21 was a significant predictor of poor OS (HR: 1.449; 95% CI: 1.243–1.690; $p < 0.001$). Multiple other factors including male sex, alcohol use, cirrhosis, viral etiology, multinodular tumors, vascular invasion, lymph node metastases, distant metastases, no or poor differentiation, CTP B/C, ECOG of 2+, and TNM stage III–IV were all predictors of poor OS ($p < 0.05$ for all). On multivariate Cox analysis (Table 4) elevated FGF21 remains a significant predictor of poor OS (HR: 1.422; 95% CI: 1.180–1.714; $p < 0.001$). In addition, other factors that are poor predictors of OS on multivariate Cox analysis include male sex, multinodular tumors, vascular invasion, distant metastases, no or poor differentiation, CTP B/C, ECOG of 2+, and TNM stage III–IV ($p < 0.05$ for all).

In Table 5, we assessed whether FGF21 could provide additional prognostic value to each of the existing HCC staging systems. Patients with BCLC stages C and D had a higher HR than those with BCLC stage A ($p < 0.001$). Elevated FGF21 levels remained significantly associated with poor OS after adjusting for the effect of the BCLC classification system (HR: 1.375; 95% CI: 1.176–1.607; $p < 0.001$). Similarly, higher CLIP stages (1–6) were associated with significantly higher HRs than stage 0 ($p < 0.001$). After adjusting for the effect of the CLIP classification system, high

Table 3 Comparison of OS Between FGF21-Low and FGF21-High Groups

FGF21	Frequency (n)	Event	Median (95% CI)[a]	24 Months Rate	72 Months Rate	P-value
OS	767					
Low[b]	384	313	20.1 (17.3–23.0)	43%	15%	<0.001
High[b]	383	345	10.7 (9.0–12.4)	28%	8%	

Note: [a]Median survival in months [b]Low FGF21 defined as ≤0.41 ng/mL and high FGF21 > 0.41 ng/mL.

Table 4 Univariate and Multivariate Analysis: Predictors of OS in Patients with HCC (n = 767)

Factor	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
FGF21 > 0.41 ng/mL	1.449 (1.243–1.690)	<0.001	1.422 (1.180–1.714)	<0.001
Age: >60 y vs ≤ 60 y	0.938 (0.803–1.096)	0.421		
Sex: male vs female	1.304 (1.090–1.559)	0.004	1.249 (1.006–1.550)	0.044
Race				
Asian	1.273 (0.951–1.704)	0.104		
Black	1.166 (0.919–1.479)	0.207		
Hispanic	1.166 (0.934–1.455)	0.174		
White	0.798 (0.677–0.940)	0.007	0.865 (0.713–1.048)	0.138
Comorbidities				
History of Tobacco Use	1.115 (0.947–1.312)	0.191		
History of Alcohol Use	1.213 (1.017–1.448)	0.032	1.110 (0.896–1.376)	0.339
History of Hypertension	0.864 (0.740–1.008)	0.062	0.846 (0.706–1.014)	0.071
Obesity (BMI ≥ 30)	0.899 (0.764–1.058)	0.201		
History of Diabetes Mellitus	1.054 (0.899–1.235)	0.518		
Viral etiology	1.368 (1.172–1.595)	<0.001	1.188 (0.976–1.447)	0.086
Gross Liver Cirrhosis	1.367 (1.163–1.607)	<0.001	1.195 (0.980–1.458)	0.078
Tumor Factors				
Multinodular Tumors	1.651 (1.403–1.942)	<0.001	1.441 (1.182–1.756)	<0.001
Vascular Invasion	2.017 (1.713–2.374)	<0.001	1.432 (1.162–1.765)	<0.001
Lymph node Metastases	1.472 (1.221–1.773)	<0.001	1.060 (0.839–1.339)	0.625
Distant Metastases	1.931 (1.621–2.302)	<0.001	1.573 (1.252–1.975)	<0.001
Pathology: Non/poor vs well/moderate	1.352 (1.124–1.627)	<0.001	1.215 (1.000–1.477)	0.050
Child-Pugh class: B/C vs A	1.657 (1.419–1.935)	<0.001	1.338 (1.106–1.617)	0.003
ECOG: 2+ vs 0-1	2.166 (1.739–2.699)	<0.001	1.911 (1.458–2.505)	<0.001
TNM Stage: III–IV vs I–II	2.435 (2.047–2.897)	<0.001	1.502 (1.164–1.938)	0.002

Abbreviations: FGF21, Fibroblast Growth Factor 21; BMI, Body Mass Index; ECOG, Eastern Cooperative Oncology Group; TNM, tumor, node, metastasis.

circulating FGF21 levels remained significantly associated with poor OS (HR: 1.251; 95% CI: 1.066–1.468; p = 0.006). In addition, both CTP B and C had a higher HR than CTP A (p < 0.001 for both), and high circulating FGF21 was a significant predictor of poor OS (HR: 1.517; 95% CI: 1.300–1.771; p < 0.001) after adjusting for CTP.

Diagnostic Significance of FGF21

The mean circulating FGF21 levels are significantly higher among HCC cases (1.51 ± 3.97 ng/mL; n = 767) when compared to the control group (0.30 ± 0.72 ng/mL; n = 200) (p < 0.001). As Figure 2 demonstrates, ROC curve analysis

Table 5 Association Between FGF21 Levels and OS After Adjusting for the Effects of Each of the HCC Scoring Systems

Factor	Multivariate Analysis	
	HR (95% CI)	P-value
BCLC		
Stage 0 vs Stage A	0.291 (0.089–0.954)	0.042
Stage B vs Stage A	1.318 (0.878–1.978)	0.183
Stage C vs Stage A	2.419 (1.679–3.486)	<0.001
Stage D vs Stage A	6.605 (4.021–10.850)	<0.001
FGF21 after adjusting for BCLC		
High vs Low	1.375 (1.176–1.607)	<0.001
CLIP		
1 vs 0	1.671 (1.264–2.210)	<0.001
2 vs 0	2.117 (1.612–2.780)	<0.001
3 vs 0	3.862 (2.889–5.163)	<0.001
4 vs 0	5.788 (4.132–8.098)	<0.001
5 vs 0	18.634 (11.704–29.668)	<0.001
6 vs 0	36.412 (16.303–81.324)	<0.001
FGF21 after adjusting for CLIP		
High vs Low	1.251 (1.066–1.468)	0.006
Child-Pugh score (CPS)		
B vs A	1.472 (1.250–1.733)	<0.001
C vs A	5.424 (4.002–7.351)	<0.001
FGF21 after adjusting for CPS		
High vs Low	1.517 (1.300–1.771)	<0.001

Abbreviations: FGF21, Fibroblast Growth Factor 21; BCLC, Barcelona Clinic Liver Cancer; CLIP, The Cancer of the Liver Italian Program.

was performed and the area under the curve was found to be 0.728. The Youden index was calculated, and the ideal diagnostic cutoff was 0.385 ng/mL. The sensitivity for this cutoff is 52% and the specificity is 87%.

Discussion

In this study, we present evidence that serum FGF21 levels serve as a significant independent prognostic biomarker in HCC patients. Our findings demonstrate that elevated FGF21 levels are associated with more advanced clinicopathologic features of HCC. Most notably, patients with high FGF21 levels exhibited a substantially reduced median OS. In multivariable analysis, FGF21 remained an independent predictor of OS even after adjustment for Child-Pugh score (CPS), ECOG performance status and disease stage, underscoring its potential as a valuable addition to current risk stratification models.

While FGF21 has been characterized as a key metabolic regulator in glucose and lipid homeostasis with established roles in hepatic metabolism,[5–8,16] its prognostic significance in HCC remains incompletely understood. Although the

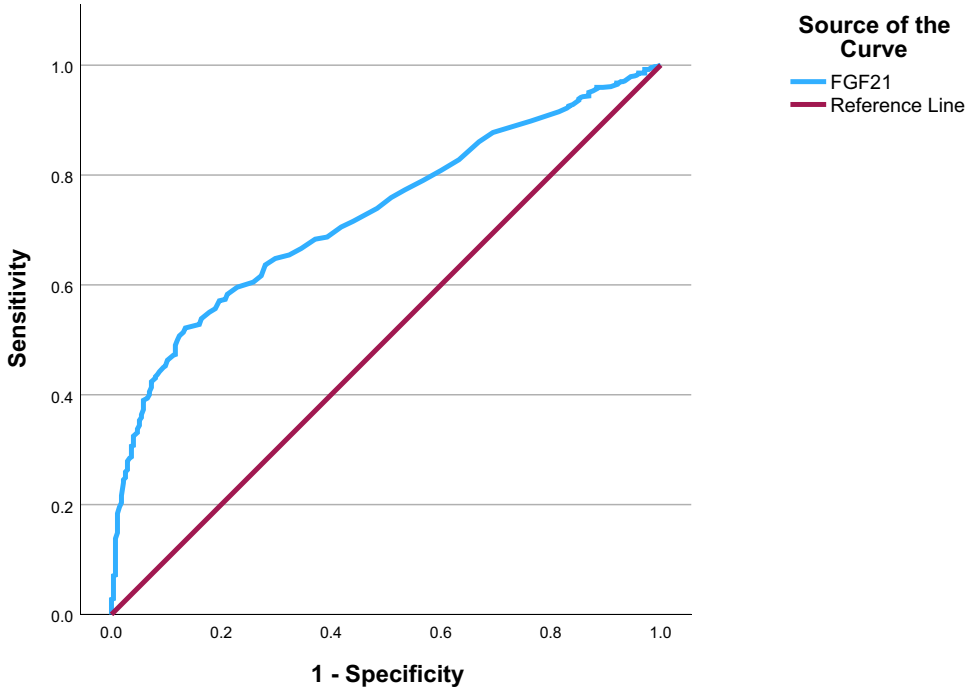

Figure 2 Diagnostic performance of serum FGF21 level generated by ROC curve values.

precise mechanisms underlying FGF21's role in tumorigenesis are not fully elucidated, evidence has demonstrated its involvement in various malignancies beyond HCC, including pancreatic,[12] breast,[26] and colorectal cancers,[27] suggesting a broader oncological relevance that warrants further investigation. Some studies have suggested plausible pathways by which elevated FGF21 could contribute to worse outcomes in HCC. FGF21 has been shown to act as a tumor-derived immune suppressor: tumor-secreted FGF21 disrupts $CD8^+$ T-cell function by rewiring cholesterol metabolism, thereby impairing T-cell effector responses and facilitating immune evasion.[28] In addition, recent data indicates that FGF21 promotes glycolytic reprogramming in HCC cells through activation of the mTOR-HIF1α signaling axis, a pathway that supports tumor growth, proliferation, and adaptation to hypoxia. Metabolic reprogramming toward glycolysis can enhance tumor aggressiveness and resistance to therapy.[29] There is emerging evidence suggesting potential anti-tumoral effects in obesity and metabolic-disorder related cancers,[9–12] and FGF21 deficiency has been associated with fatty liver disease progression, inflammation and HCC transformation.[13] Previous studies have demonstrated that FGF21 is upregulated in response to hepatic stress conditions such as hepatitis and cirrhosis,[17] and alcohol has been associated with a FGF21 response, with evidence suggesting a potential protective role against steatohepatitis.[30,31] Interestingly, patients with alcohol and smoking histories in our study demonstrated lower baseline FGF21 levels, which may reflect the potential disruption of FGF21's protective metabolic functions by chronic exposure, possibly through impaired hepatocellular synthesis or altered metabolic regulatory pathways. Patients with cirrhosis also exhibited lower FGF21 levels in our study, suggesting that severe hepatocellular disfunction may compromise the liver's capacity to produce a FGF21 response, potentially representing a loss of compensatory metabolic mechanisms in advanced liver disease. While FGF21 is upregulated during early hepatic stress, the lower FGF21 in cirrhotic patients likely reflects a threshold where severe hepatocellular dysfunction impairs biosynthetic capacity, supported by our finding that Child-Pugh B patients had higher FGF21 than class C. Similarly, lower FGF21 in patients with alcohol history may reflect chronic exposure-related dysfunction or resistance mechanisms, distinct from the acute protective FGF21 induction seen in experimental models. These observations suggest that elevated FGF21 in HCC patients with preserved hepatic function represents a tumor-associated prognostic marker, whereas loss of FGF21 response may indicate exhausted compensatory mechanisms in advanced liver disease.

Conversely, elevated FGF21 levels were significantly associated with advanced tumor characteristics, including AFP levels >400 ng/mL, multinodular disease, vascular invasion, distant metastasis and advanced stages, suggesting that FGF21 has utility not only as a prognostic marker but also in disease staging and potentially in diagnosis. The finding that patients with ECOG performance status ≥2 had higher FGF21 levels likely reflects the advanced disease stage at diagnosis in these patients. Notably, FGF21 levels were higher in Child-Pugh class B compared to class C patients, which supports that severely compromised hepatic function may impair FGF21 response, though further investigation is needed to definitively establish this relationship.

Our findings are largely consistent with the prospective study by Liu et al, which demonstrated that elevated FGF21 levels were associated with significantly worse OS,[21] with similar prognostic impact observed in our cohort. Notably, both studies identified FGF21 as an independent prognostic factor that remained significant after adjustment for established factors such as disease stage. However, to our knowledge, our study represents the largest cohort from a Western patient population, while Liu et al study represented Chinese population. Interestingly, despite notable differences in patient characteristics between our study and Liu et al's cohort, including age distribution, alcohol use history, hepatitis B prevalence, metabolic comorbidities, lymph node involvement rates, and our inclusion of Child-Pugh class C patients versus their predominantly class A-B cohort, the consistent prognostic significance of FGF21 enhances the utility of FGF21 as a biomarker across diverse HCC populations with varying etiologies and disease severities.

Recently, Kohya et al demonstrated similar findings in a Japanese multicenter cohort, where high baseline serum FGF21 levels were independently associated with significantly shorter OS and PFS in unresectable HCC patients treated with atezolizumab/bevacizumab, further validating the robustness of FGF21 as a prognostic biomarker across diverse patient populations.[32]

Beyond its prognostic implications, there is some evidence suggesting that FGF21 may also serve as a predictive biomarker. Our findings of worse survival outcomes with elevated FGF21 levels are consistent with results from the REFLECT trial,[23] which demonstrated that higher baseline FGF21 levels were associated with shorter OS in both treatment arms. Importantly, REFLECT study revealed that patients with elevated FGF21 may show superior survival when treated with lenvatinib compared to sorafenib, although authors emphasized that this finding needs confirmation. This finding is further supported by a study identifying FGF21 as a key molecule promoting sorafenib resistance, suggesting FGF21 targeting as a potential strategy to overcome treatment resistance.[25] Given the rapidly evolving landscape of HCC treatment, including novel immunotherapy combinations, additional studies are warranted to determine whether FGF21 levels can predict treatment efficacy across these modalities.

From a clinical perspective, after future independent validation studies, baseline serum FGF21 measurement could be readily incorporated into routine HCC evaluation, alongside standard prognostic biomarkers assessments such as AFP and liver function tests. Additionally, since FGF21 remained an independent prognostic factor after adjusting for established staging systems, incorporating it into clinical staging guidelines could enhance risk stratification and inform treatment decisions. Patients with elevated FGF21 levels might benefit from more aggressive therapeutic interventions, closer surveillance, or preferential enrollment in clinical trials, with equal stratification in randomized trials. Additionally, FGF21's potential predictive value for lenvatinib response, as suggested by the REFLECT trial, could guide personalized therapy selection. However, before clinical implementation, validation of optimal cutoff values in prospective cohorts, standardization of assays across laboratories, and cost-effectiveness analyses are needed to establish evidence-based guidelines for FGF21's clinical application.

The strengths of our study include evaluating a large cohort of HCC patients, providing robust statistical power. Second, we performed detailed analyses of patient subgroups including viral versus non-viral etiologies, allowing for comprehensive assessment of FGF21's prognostic value across diverse patient populations. Third, considering the limited number of clinical studies investigating the prognostic significance of FGF21 in HCC, our findings contribute valuable evidence to this field. There are also potential limitations to our study. First, we measured FGF21 levels only at baseline, which precludes assessment of temporal changes in FGF21 and their possible prognostic significance during disease progression or treatment response. Second, our study design did not account for differences in treatment modalities, as this was not the primary focus of this investigation. In addition, FGF21 demonstrated moderate diagnostic performance (AUC 0.728, sensitivity 52%), and future studies should evaluate multi-marker approaches incorporating established biomarkers such as AFP to improve diagnostic accuracy. Finally, the single-institution nature of our study design inherently carries the risk of data bias.

Conclusion

Our study demonstrates that elevated serum FGF21 levels serve as a significant independent prognostic biomarker in HCC patients, with high FGF21 levels associated with advanced disease characteristics and substantially reduced OS. The prognostic significance of FGF21 persisted even after adjustment for established prognostic factors. These findings support the potential clinical utility of FGF21 as a valuable addition to our current risk stratification models in HCC management. Future prospective studies incorporating serial FGF21 measurements and treatment-specific analyses are warranted to fully define its clinical applications and optimize personalized therapeutic strategies in HCC patients.

Disclosure

The author(s) report no conflicts of interest in this work.

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