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Original Article

Prognostic value of salt-inducible kinase 2 expression in advanced hepatocellular carcinoma treated with sorafenib or lenvatinib: a propensity score-matched cohort study

Qinghai Fu[1*], Xiaolong Wang[1*], Shiqin Zheng[1], Wei Wang[2#]

[1]Department of Gastroenterology, Sinopharm Dongfeng General Hospital, Shiyan 442008, Hubei, China; [2]Department of Gastrointestinal Surgery, Sinopharm Dongfeng General Hospital, Shiyan 442008, Hubei, China. [*]Co-first authors. [#]Corresponding author.

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Abstract: Hepatocellular carcinoma (HCC) requires reliable biomarkers to guide the use of sorafenib or lenvatinib for personalized first-line treatment. This study investigated the association between salt-inducible kinase 2 (SIK2) expression and treatment outcomes in patients with advanced HCC receiving these tyrosine kinase inhibitors (TKIs). A retrospective cohort of 120 patients who received treatment from January 2022 to December 2024 was included. The expression of SIK2 was evaluated by immunohistochemistry, and the optimal H-score cut-off value of 6 was determined by ROC analysis. After 1:1 propensity score matching, 47 patients with high SIK2 expression and 47 patients with low SIK2 expression were compared. Patients with high SIK2 expression showed a significantly superior objective response rate (36.2% vs. 12.8%, P<0.001) and disease control rate (87.2% vs. 57.4%, P<0.001), as well as prolonged median overall survival (15.4 vs. 9.5 months; HR = 0.30, P<0.001) and progression-free survival (7.8 vs. 3.7 months; HR = 0.38, P<0.001). Multivariate analysis confirmed that low SIK2 expression was an independent predictor of poor OS (adjusted HR = 2.22, P<0.05) and PFS (adjusted HR = 1.96, P<0.05). Subgroup analysis showed that the prognostic value of SIK2 was consistent in the sorafenib and lenvatinib groups, and there was no significant interaction (P for interaction >0.05). Safety analysis showed that the incidence of adverse events between the two groups was comparable, while patients with low SIK2 expression had significant increases in liver enzymes and bilirubin after treatment (all P<0.05). In conclusion, low SIK2 expression independently predicts poor therapeutic response and survival in advanced HCC patients receiving first-line sorafenib or lenvatinib, with consistent predictive value across both TKIs. SIK2 represents a promising common predictive biomarker to guide personalized first-line targeted therapy for HCC.

Keywords: Hepatocellular carcinoma, salt-inducible kinase 2, sorafenib, lenvatinib, prognosis, biomarker, propensity score matching

Introduction

Hepatocellular carcinoma (HCC) is a malignant tumor with an increasing global incidence. Due to its high incidence and mortality rate, it has brought a major burden to public health. Although advances in screening and surveillance have enabled some patients with early-stage disease can be cured by surgical resection, liver transplantation or local ablation, roughly 70% of cases are advanced upon initial diagnosis, rendering them ineligible for curative treatment. For unresectable advanced HCC, systemic therapy has evolved profoundly from single-agent targeted drugs to immune-based combinations [1-3].

The landmark targeted therapy sorafenib extended overall survival (OS) in advanced HCC and served as a first-line standard for more than ten years [4]. Thereafter, the REFLECT study demonstrated lenvatinib's non-inferiority to sorafenib in OS. Moreover, lenvatinib showed a higher objective response rate (ORR) and better progression-free survival (PFS), thus becoming another important first-line treatment option

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[5, 6]. Recent therapeutic advances have increasingly centered on immune checkpoint inhibitor-based combination strategies, such as "T + A" regimen (atezolizumab plus bevacizumab) and "Shuangda" therapy (sintilimab + a bevacizumab biosimilar), which have further improved therapeutic outcomes in advanced HCC [7, 8]. Recent research has also shown that nivolumab plus ipilimumab markedly prolongs patients' median OS compared with lenvatinib or sorafenib, providing new impetus for first-line therapy [9]. Despite the increasing number of treatment options, clinicians still face a central clinical challenge when choosing between first-line sorafenib and lenvatinib treatment: the great heterogeneity of patients' responses to these two standard targeted agents, and the lack of clinical or molecular markers that can effectively predict response and prognosis. This "one-size-fits-all" treatment mode causes some patients to suffer from unnecessary drug-related side effects without obtaining corresponding survival benefits, and may miss valuable opportunities to receive other potentially more effective treatments [10]. Therefore, finding biomarkers that can accurately predict treatment efficacy and prognosis before treatment is urgently needed to achieve individualized and precise treatment of advanced HCC and improve the overall treatment landscape.

In this context, salt-inducible kinase 2 (SIK2) has gradually emerged as a potential biomarker. SIK2 is a key kinase downstream of the liver kinase B1 signaling pathway [11, 12]. The role of SIK2 is context-dependent, exhibiting either tumor-promoting or tumor-suppressive activity in different cancers [13]. This dual effect may be due to the different modes of action of SIK2 in different cell types and environments. In some cancers, elevated SIK2 levels are associated with increased tumor invasiveness, driving malignant phenotypes, including increased proliferation, invasion and metastasis. However, the decrease or loss of SIK2 expression in other types of cancer cells may, in turn, reduce its tumor-suppressive potential. Studies have shown that SIK2 is a potential oncogene for malignant tumors, such as ovarian cancer [14], prostate cancer [15], osteosarcoma [16] and colorectal cancer [17]. In contrast, SIK2 seems to have a tumor-suppressive effect in malignant tumors such as breast cancer [18] and pancreatic ductal adenocarcinoma [19]. Increased SIK2 expression is associated with better survival in patients with HCC, indicating a favorable prognostic effect and highlighting its potential relevance in disease progression [20]. In patients receiving first-line targeted treatment for HCC, the prognostic significance of SIK2 expression has not been well established. Whether SIK2 can be used as a general predictive marker to guide clinical treatment decisions still needs to be verified in clinical research.

Unlike previous biomarker studies that mainly focused on predicting the efficacy of single agents (such as vascular endothelial growth factor (VEGF)-related markers for sorafenib or fibroblast growth factor (FGF)-related markers for lenvatinib) or immune checkpoint inhibitors, this study investigated whether SIK2 expression could be used as a common predictive biomarker for two first-line tyrosine kinase inhibitors (sorafenib and lenvatinib). This approach addresses a clinically urgent and unsolved problem: how to determine which patients may benefit from these two standard targeted therapies before treatment, so as to avoid "one-size-fits-all" strategies and achieve more personalized first-line decision-making.

Based on the above rationale, this study adopted a retrospective propensity score matching (PSM) cohort design, including patients with advanced HCC who received monotherapy with sorafenib or lenvatinib. The relationships between SIK2 expression and therapeutic effect (ORR, disease control rate (DCR)), prognosis (OS, PFS) and safety were systematically evaluated, and its independent prognostic value was further verified. We hypothesized that in patients treated with sorafenib or lenvatinib, high SIK2 expression would be associated with superior therapeutic efficacy and prolonged survival without increasing the risk of adverse events. This study aimed to provide a clinically applicable predictive tool to guide personalized first-line targeted therapy for advanced HCC and to support the clinical translation of SIK2 as a novel biomarker.

Materials and methods

Study design

A retrospective PSM cohort study was conducted to minimize confounding. Consecutive patients with unresectable advanced HCC who commenced first-line sorafenib or lenvatinib therapy at Sinopharm Dongfeng General Hospital between January 2022 and December

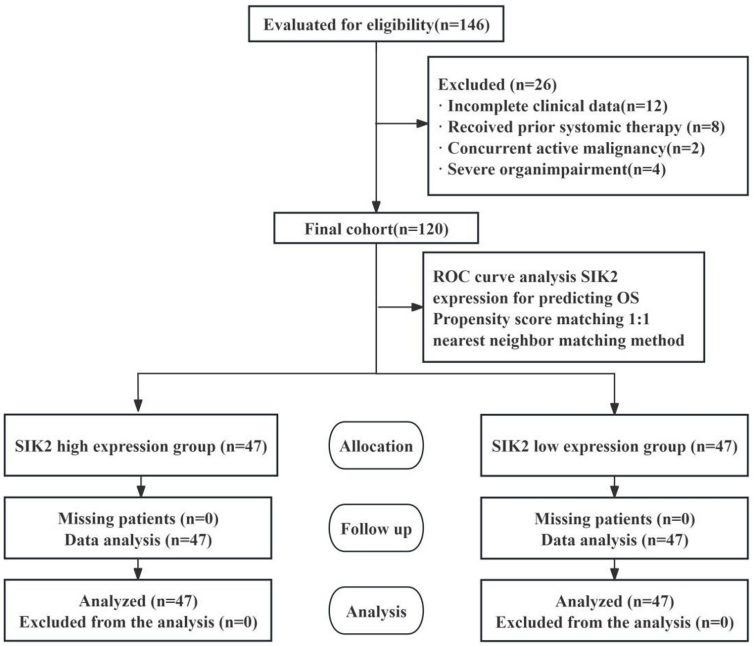

Figure 1. Design flow chart.

2024 were enrolled. Using the continuous SIK2 H-score of the entire cohort, we generated a receiver operating characteristic (ROC) curve and chose the cut-off value that best predicted 1-year survival status. This value separated patients into SIK2-high and SIK2-low groups. To improve baseline balance, we performed 1:1 nearest-neighbour PSM on baseline variables potentially linked to prognosis (treatment regimen, age, liver function, tumor burden, and other relevant factors). The matched and balanced cohort was then used for all subsequent analyses (**Figure 1**).

Ethical statement

This research was approved by the Ethics Committee of Sinopharm Dongfeng General Hospital and was conducted in accordance with the Declaration of Helsinki and the current international ethical standards for biomedical research. Due to the retrospective research design, the analysis was based on existing clinical archive data, and the ethics committee waived the requirement for informed consent. All research data were anonymized to protect the privacy and identity of the participants.

Inclusion and exclusion criteria

Inclusion criteria: (1) age 18-75 years, Eastern Cooperative Oncology Group (ECOG) performance status 0-1, expected survival time ≥3 months [21]; (2) diagnosis of HCC based on histopathology or imaging findings from contrast-enhanced CT/MRI, along with elevated serum AFP levels, in accordance with the clinical diagnostic criteria outlined in the 2019 edition of the guidelines for primary liver cancer [22]; (3) advanced, unresectable disease (Barcelona Clinic Liver Cancer stage B or C) and ineligibility for potentially curative treatments such as resection or ablation [23]; (4) confirmed receipt of first-line sorafenib/lenvatinib targeted therapy, with treatment interruption of ≤14 days; (5) complete clinicopathological data.

Exclusion criteria [24]: (1) previous systemic therapy for HCC (including but not limited to chemotherapy, targeted therapy, immunotherapy); (2) other active concurrent malignancies; (3) significant cardiac, hepatic, or renal impairment, resulting in inability to tolerate targeted therapy; (4) incomplete clinical data before or after treatment.

Treatment methods

According to the clinical medical records, all enrolled patients received standard-dose targeted drug therapy. Sorafenib (manufacturer: Bayer Healthcare Co., Ltd.; specification: 200 mg/tablet; NMPA approval number: H201732-76) was taken orally at 400 mg twice daily, within 1 h after the morning and evening meals. Lenvatinib (manufacturer: Eisai Co., Ltd., Tokyo, Japan; specification: 4 mg/tablet; NMPA approval number: H20180052) was given once daily with food: 12 mg for patients weighing ≥60 kg and 8 mg for those weighing <60 kg. All therapies were delivered per standard protocol and current guidelines [25, 26].

Observation indicators

Patient data were obtained and analyzed retrospectively from institutional electronic health records, medical imaging archives, and laboratory databases.

Main outcome indicators: OS was measured from the start of therapy until death or the last documented follow-up in June 2025.

Secondary outcome indicators: (1) PFS was defined as the time from initial treatment administration to either disease progression per RECIST 1.1 criteria [27] or death. (2) ORR was defined as the proportion of patients achieving a complete or partial response after treatment according to RECIST 1.1 [27, 28]. (3) DCR refers to the percentage of patients with the best overall response of complete response (CR), partial response (PR), or stable disease (SD) based on RECIST 1.1 [27]. (4) SIK2 expression: Archived pathology reports and whole-slide images were retrieved from the institutional digital database. SIK2 expression was evaluated via immunohistochemistry (IHC) following established methods [29, 30] with detailed modifications as described below. Formalin-fixed, paraffin-embedded (FFPE) tumor tissue sections (4 μm thick) were used. The detailed IHC procedure is as follows: after deparaffinization and rehydration, antigen retrieval was performed for 20 minutes in a citrate buffer (pH 6.0) at 95°C. Endogenous peroxidase activity was inhibited with 3% H_2O_2. The sections were then incubated overnight at 4°C with a primary mouse monoclonal anti-SIK2 antibody (clone S15G10; LifeSpan BioSciences, Seattle, Washington, USA; Catalog #LS-B1898) at an optimized dilution of 1:100. After washing, the sections were incubated with a horseradish peroxidase (HRP)-conjugated goat anti-mouse secondary antibody at room temperature for 30 minutes. Staining was visualized using 3,3'-diaminobenzidine (DAB), and the sections were counterstained with hematoxylin. For quality control, each staining batch included a positive control (human hepatocellular carcinoma tissue known to have high SIK2 expression) and a negative control (the primary antibody was replaced with isotype-matched IgG). The H-score system was then used to score each case: staining intensity (0 = none, 1 = weak, 2 = moderate, 3 = strong) was multiplied by the percentage of positive tumor cells (0-100%). Two experienced pathologists blinded to all clinical data evaluated all slides independently; the intraclass correlation coefficient for interobserver reproducibility was 0.85. (5) Safety analysis: Adverse events and changes in laboratory parameters reported during the follow-up period were monitored. Adverse events, including hypertension, hand-foot skin reaction, diarrhea, and proteinuria, were assessed and graded per CTCAE v5.0 (Common Terminology Criteria for Adverse Events) [31]. Laboratory indicators encompassed alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), albumin (ALB), and alkaline phosphatase (ALP).

External validation

To externally validate the prognostic significance of SIK2, we analyzed the independent TCGA-LIHC cohort [32], comprising 364 HCC cases with gene expression and survival data. Patients were stratified by SIK2 expression into high (n = 182) and low (n = 182) groups. Kaplan-Meier survival curves were compared using the log-rank test. Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated via univariate Cox proportional hazards models.

Sample size calculation

The sample size estimation was based on the primary outcome measure, OS. Referring to the analysis results of the subgroups with poor prognosis in phase III biomarker studies of advanced HCC, such as the METIV-HCC trial, the reported hazard ratio (HR) could reach 1.67 [33]. To ensure adequate power of the study, we used an expected HR of 2.0, two-sided α of 0.05, and power (1-β) of 80% for the estimation. The sample size was estimated using the Log-rank test formula in PASS 15.0, and at least 45 patients were required in each group. Considering a dropout rate of 10% during follow-up, we planned to screen eligible patients from the initial cohort by PSM, and finally determined the enrollment of 50 patients in each group, with a total sample size of 100, to meet the statistical power requirements.

Statistical analysis

We used SPSS 26.0 for all statistical analyses. Normally distributed continuous variables were summarized as mean ± SD, and non-normally distributed variables as median (range), with comparisons performed using t-tests or Mann-Whitney U tests, as appropriate. Categorical variables (counts and percentages) were analyzed using chi-square or Fisher's exact tests. To dichotomize SIK2 for survival analyses, we generated an ROC curve against vital status and chose the H-score that maximized the Youden index. Patients with high and low SIK2 expression were then balanced 1:1 by nearest-neighbor propensity score matching (caliper 0.2 SD) on age, sex, liver function, performance status, tumor burden, serology, drug choice,

Table 1. ROC curve analysis of SIK2 expression for predicting OS

Parameter	Value
AUC (95% CI)	0.756 (0.665-0.847)
Sensitivity (%)	77.5
Specificity (%)	70.6
Youden Index	0.481
Optimal Cut-off (H-score)	6
P-value	<0.001

and prior locoregional therapy (e.g., surgical resection, ablation, transarterial chemoembolization) [24, 34, 35]. To compare survival distributions, Kaplan-Meier curves were constructed and analyzed using the log-rank test. Independent predictors of OS and PFS were identified through sequential univariable (entry threshold: $P<0.1$) and multivariable Cox proportional hazards models. We employed a two-sided testing strategy for all analyses, where $P<0.05$ denoted statistical significance.

Results

ROC curve analysis of SIK2 expression for predicting OS

To determine the optimal cut-off value for dichotomizing SIK2 expression, we performed ROC curve analysis using 1-year survival status as the reference standard on the continuous H-scores from all 120 patients. The ROC curve demonstrated good discriminatory power (**Table 1**). The Youden index identified an H-score of 6 as the optimal cut-off value. Accordingly, patients were stratified into SIK2-high (H-score ≥6, n = 47) and SIK2-low (H-score <6, n = 47) groups for all subsequent analyses.

Comparison of baseline data

Of the 120 patients originally enrolled, 64 and 56 were assigned to the high and low SIK2 expression groups, respectively. To reduce potential confounding bias, the 1:1 PSM was applied to generate two well-matched cohorts, with 47 patients in each group for final analysis. Before matching, there were significant differences between the two groups in several baseline characteristics related to tumor invasiveness and clinical status, including ECOG performance status, tumor diameter, macrovascular invasion and treatment regimen (all P<0.05, **Table 2**). After PSM, these and all other baseline variables were well balanced, with no statistically significant difference (all P>0.05, **Table 2**). This confirms the effectiveness of the matching procedure in terms of comparability between the groups, thus enhancing the reliability of subsequent analyses of the predictive role of SIK2.

Analysis of efficacy index results

Treatment response analysis showed that there is a significant correlation between SIK2 expression and efficacy outcomes (**Table 3**). Compared with the low expression group, the ORR and DCR of the high SIK2 group were significantly higher (both P<0.05). It is worth noting that the complete response was only observed in the high-expression group. These data suggest that the high baseline SIK2 level is related to the improvement of the first-line targeted therapy response in advanced HCC.

Analysis of survival outcomes

Survival analysis revealed the clear prognostic stratification of SIK2 expression (**Table 4**). Compared with patients with low expression, the median progression-free survival and overall survival of patients with high SIK2 expression were significantly longer (both log-rank P<0.001), corresponding to an approximately 60%-70% reduction in the risk of progression or death. These findings confirm that high SIK2 expression is a powerful predictor of favorable results.

In the overall matched cohort, the median follow-up was 15.0 months, exceeding the median OS of the low SIK2 group (9.5 months) and approaching that of the high SIK2 group (15.4 months). The observed 50% OS event rate further confirms the maturity of the data for long-term survival evaluation.

Subgroup analysis by treatment regimen

In order to evaluate whether the prognostic value of SIK2 was consistent across different first-line targeted therapies, we conducted a stratified subgroup analysis according to the treatment regimen (sorafenib and lenvatinib).

In the sorafenib group (n = 48), compared with patients with high SIK2 expression, patients with low SIK2 expression had significantly worse OS (HR = 2.18, 95% CI: 1.25-3.80, P =

Table 2. Comparison of baseline characteristics by SIK2 expression level

Indicators	Before PSM				After PSM			
	High SIK2 (n = 64)	Low SIK2 (n = 56)	Statistic	*P*-value	High SIK2 (n = 47)	Low SIK2 (n = 47)	Statistic	*P*-value
Demographics								
Age, years	58.5 ± 9.7	59.8 ± 10.2	t = -0.72	0.475	59.1 ± 9.5	58.7 ± 9.9	t = 0.20	0.842
Gender (Male/Female)	50/14	45/11	χ^2 = 0.10	0.752	37/10	38/9	χ^2 = 0.07	0.792
Liver Function & Performance Status								
Child-Pugh Grade (A/B)	55/9	48/8	χ^2 = 0.01	0.94	41/6	40/7	χ^2 = 0.09	0.764
ECOG Performance Status (0/1)	46/18	31/25	χ^2 = 4.10	0.043	33/14	31/16	χ^2 = 0.21	0.65
Comorbidities								
Diabetes, n (%)	15 (23.4)	16 (28.6)	χ^2 = 0.40	0.527	11 (23.4)	13 (27.7)	χ^2 = 0.22	0.639
Hypertension, n (%)	21 (32.8)	23 (41.1)	χ^2 = 0.88	0.348	16 (34.0)	18 (38.3)	χ^2 = 0.18	0.669
Tumor Burden & Pathology								
TNM Stage (II-III/IV)	43/21	34/22	χ^2 = 0.70	0.404	34/13	31/16	χ^2 = 0.38	0.536
Maximum Tumor Diameter, cm	7.5 ± 2.4	8.4 ± 2.7	t = -2.01	0.047	7.8 ± 2.5	7.9 ± 2.6	t = -0.19	0.847
Tumor Number (<3/≥3)	31/33	27/29	χ^2 = 0.01	0.94	23/24	22/25	χ^2 = 0.04	0.835
Major Vascular Invasion, n (%)	20 (31.3)	27 (48.2)	χ^2 = 3.86	0.049	16 (34.0)	18 (38.3)	χ^2 = 0.18	0.669
Extrahepatic Metastasis, n (%)	35 (54.7)	31 (55.4)	χ^2 = 0.01	0.94	26 (55.3)	25 (53.2)	χ^2 = 0.04	0.835
Serological Markers								
AFP (<400/≥400 ng/mL)	36/28	32/24	χ^2 = 0.02	0.877	27/20	26/21	χ^2 = 0.05	0.83
ALBI Score	-2.35 ± 0.55	-2.29 ± 0.61	t = -0.57	0.572	-2.33 ± 0.57	-2.30 ± 0.59	t = -0.25	0.801
Treatment								
Sorafenib/Lenvatinib	29/35	34/22	χ^2 = 3.95	0.047	24/23	24/23	χ^2 = 0.00	1
Treatment History								
Prior Local Therapy, n (%)	31 (48.4)	29 (51.8)	χ^2 = 0.14	0.711	23 (48.9)	24 (51.1)	χ^2 = 0.04	0.835
Surgical Resection	15 (48.4)	8 (27.6)			10 (43.5)	9 (37.5)		
Ablation	10 (32.3)	13 (44.8)			8 (34.8)	9 (37.5)		
TACE	6 (19.4)	8 (27.6)			5 (21.7)	6 (25.0)		

Note: BMI: Body Mass Index; Child-Pugh: Child-Pugh classification; ECOG: Eastern Cooperative Oncology Group Performance Status; AFP: Alpha-fetoprotein; ALBI: Albumin-Bilirubin grade.

Table 3. Association between SIK2 expression and treatment response [n (%)]

Group	n	CR	PR	SD	PD	ORR (CR + PR)	DCR (CR + PR + SD)
High SIK2	47	3 (6.4%)	14 (29.8%)	24 (51.1%)	6 (12.8%)	17 (36.2%)	41 (87.2%)
Low SIK2	47	0 (0.0%)	6 (12.8%)	21 (44.7%)	20 (42.6%)	6 (12.8%)	27 (57.4%)
Statistic						χ^2 = 6.35	χ^2 = 10.08
P-value						0.012	0.001

Note: CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ORR: objective response rate; DCR: disease control rate.

Table 4. Association between SIK2 expression and survival outcomes

Survival indicators	High SIK2 (n = 47)	Low SIK2 (n = 47)	HR (95% CI)	*P*-value (Log-rank)
Median PFS	7.8 (7.4-8.2)	3.7 (3.5-3.9)	0.38 (0.27-0.53)	<0.001
Median OS	15.4 (14.8-16.0)	9.5 (9.0-10.0)	0.30 (0.20-0.45)	<0.001

Note: PFS: Median Progression-Free Survival; OS: Median Overall Survival; Intergroup survival comparisons were performed using the Log-rank test.

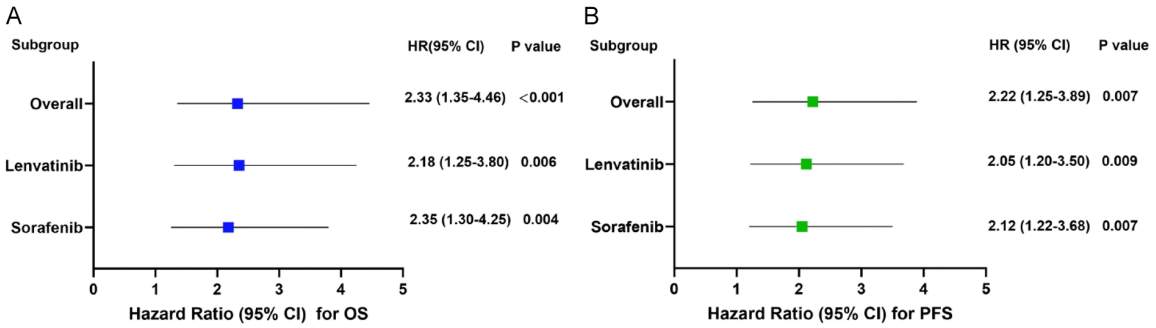

Figure 2. Subgroup analysis of survival outcomes stratified by treatment regimen. A: Overall survival; B: Progression-free survival. Squares represent hazard ratios; horizontal lines indicate 95% confidence intervals. *P* values for interaction are shown at the bottom of each panel.

0.006) and PFS (HR = 2.05, 95% CI: 1.20-3.50, P = 0.009). Similarly, in the lenvatinib group (n = 46), low SIK2 expression remained an important predictor of worse OS (HR = 2.35, 95% CI: 1.30-4.25, P = 0.004) and PFS (HR = 2.12, 95% CI: 1.22-3.68, P = 0.007).

The interaction test between SIK2 expression and treatment type was not statistically significant for OS (interaction P = 0.682) or PFS (interaction P = 0.741), indicating that there was no significant difference in the adverse prognostic effect of low SIK2 expression between patients receiving sorafenib and patients receiving lenvatinib (**Figure 2** and Supplementary Table 1).

Independent external validation of the predictive value of SIK2 expression

The survival analysis of the TCGA-LIHC cohort through the Kaplan-Meier method showed that high SIK2 expression has a significant advantage over low expression (log-rank P = 0.03). As shown in **Figure 3**, this result is closely related to our observations in the clinical cohort treated with sorafenib or lenvatinib. The consistent findings of the independent dataset support the general prognostic value of SIK2 as a biomarker in HCC.

Correlation between SIK2 expression and clinicopathological features

Table 5 shows the relationship between SIK2 expression and clinicopathological variables. High SIK2 expression was significantly associated with early TNM stage and no macrovascular invasion (P<0.05), but not with age, gender, AFP level or extrahepatic metastasis (all P> 0.05). These findings show that the increased SIK2 expression is not a marker of the general aggressiveness of tumors, but is enriched in specific subgroups characterized by earlier disease stages and absence of vascular invasion,

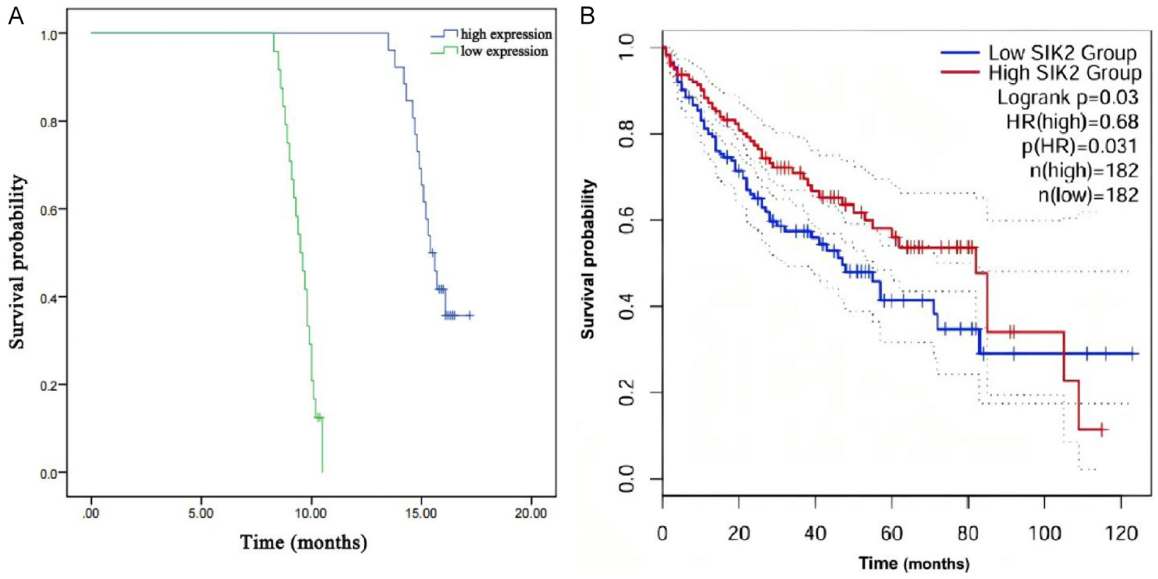

Figure 3. Kaplan-Meier survival curves. A: Overall survival (OS) in the propensity score-matched cohort stratified by high and low SIK2 expression; B: External validation of the prognostic value of SIK2 expression using the independent TCGA-LIHC cohort. The plus symbols (+) on the curves represent censored data, indicating patients who were alive at the last follow-up.

Table 5. Correlation between SIK2 expression and clinicopathological characteristics

Clinicopathological Feature	Total (n = 94)	High SIK2 [n (%)]	*P*-value
TNM Stage			0.008
II-III	70	41 (87.2%)	
IV	24	6 (12.8%)	
Vascular Invasion			0.002
Absent	53	34 (72.3%)	
Present	41	13 (27.7%)	
Extrahepatic Spread	51	26 (55.3%)	0.836
AFP (≥400 ng/mL)	42	20 (42.6%)	0.678
Age (≥60 years)	58	31 (66.0%)	0.396
Gender (Male)	75	38 (80.9%)	0.797

Note: *P* values were calculated using the Chi-square or Fisher's exact test, where applicable.

which may increase sensitivity to targeted drugs such as sorafenil and lenvatinib.

Association of SIK2 expression with tumor grade, etiology, and cirrhosis

The association between SIK2 expression and other baseline characteristics (including tumor differentiation level, potential viral hepatitis (HBV/HCV) status and the presence of cirrhosis) was evaluated. There was no statistically significant difference in the distribution of these characteristics between the high SIK2 expression group and the low SIK2 expression group (all P>0.05; see Supplementary Table 2).

Cox proportional hazards regression analysis of prognostic factors

Univariate cox proportional hazards regression analysis: Single-variable Cox regression analysis was performed on the matched cohort to identify factors associated with patient survival (**Table 6**). Low SIK2 expression emerged as the most significant factor associated with reduced overall and progression-free survival (both P<0.01). Among traditional clinicopathological factors, advanced TNM stage (IV) and the presence of vascular invasion were also significant predictors of worse prognosis (P<0.05), whereas an ECOG score of 1 showed a non-significant trend toward higher risk. The choice of treatment regimen (lenvatinib vs. sorafenib) did not show independent prognostic value in this cohort, suggesting that the observed survival differences are primarily related to tumor biological characteristics, such as SIK2 expression, rather than to the specific TKI

Table 6. Analysis of OS and PFS predictors via univariate cox proportional hazards regression

Variable	OS		PFS	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
SIK2 expression (Low vs. High)	2.38 (1.35-4.46)	0.003	2.22 (1.25-3.89)	0.007
Treatment (Lenvatinib vs. Sorafenib)	0.99 (0.62-1.58)	0.97	1.03 (0.68-1.56)	0.899
Age (≥60 vs. <60 years)	1.15 (0.64-2.17)	0.598	1.16 (0.64-2.07)	0.643
Gender (Male vs. Female)	1.14 (0.56-2.25)	0.740	1.03 (0.55-2.12)	0.823
TNM stage (IV vs. II-III)	1.90 (1.05-3.52)	0.035	1.83 (1.04-3.30)	0.038
Vascular invasion (Yes vs. No)	2.12 (1.15-3.85)	0.016	1.95 (1.11-3.55)	0.021
AFP level (≥400 vs. <400 ng/mL)	1.56 (0.74-3.04)	0.264	1.47 (0.73-2.87)	0.289
Extrahepatic metastasis (Yes vs. No)	1.36 (0.73-2.50)	0.341	1.30 (0.72-2.35)	0.382
Child-Pugh grade (B vs. A)	1.26 (0.70-2.35)	0.425	1.29 (0.70-2.23)	0.456
ECOG score (1 vs. 0)	1.72 (0.96-3.19)	0.068	1.75 (0.96-3.02)	0.070
Tumor number (≥3 vs. <3)	1.43 (0.76-2.65)	0.274	1.35 (0.76-2.52)	0.293

Table 7. Factors correlated with OS and PFS: a multivariable cox regression analysis

Variable	OS		PFS	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
SIK2 expression (Low vs. High)	2.22 (1.23-3.97)	0.008	1.96 (1.12-3.50)	0.018
TNM stage (IV vs. II-III)	1.72 (0.91-3.25)	0.098	1.66 (0.88-3.09)	0.123
Vascular invasion (Yes vs. No)	1.61 (0.87-3.05)	0.132	1.59 (0.84-2.97)	0.161
ECOG score (1 vs. 0)	1.46 (0.80-2.75)	0.214	1.47 (0.80-2.63)	0.225

Note: HR >1 denotes a risk factor. The model incorporated variables significant at $P<0.1$ in univariate testing, as well as key clinical covariates.

Table 8. Treatment-related adverse event rates [n (%)]

Adverse Event Category	High SIK2 (n = 47)	Low SIK2 (n = 47)	*P*-value
Any TRAE	43 (91.5%)	42 (89.4%)	0.723
Hypertension	27 (57.4%)	25 (53.2%)	0.671
Hand-foot skin reaction	11 (23.4%)	9 (19.1%)	0.607
Diarrhea	14 (29.8%)	12 (25.5%)	0.635
Proteinuria	8 (17.0%)	7 (14.9%)	0.776
Any Grade ≥3 TRAE	5 (10.6%)	6 (12.8%)	0.744

Note: TRAE: Treatment-Related Adverse Events.

selected. Other variables including age, gender, AFP level, extrahepatic metastasis, Child-Pugh grade, and tumor number were not significantly associated with outcomes in this analysis.

Multivariate cox proportional hazards regression analysis: In order to evaluate the independent prognostic value of low SIK2 expression, a multivariable Cox model was constructed, and variables with P<0.1 in univariate analysis (SIK2 expression, TNM stage, vascular invasion and ECOG score) were incorporated into the model (**Table 7**). After adjustment, low SIK2 expression remained an independent adverse prognostic factor of OS and PFS (P<0.05). In contrast, the statistical significance of traditional factors, including TNM stage IV and vascular invasion, was weakened in the multivariate model, and the ECOG score did not show independent prognostic value (all P>0.05). These findings show that compared with traditional clinical and pathological factors, SIK2 expression provides stronger prognostic stratification and serves as an independent biomarker for survival in HCC patients treated with sorafenib or lenvatinib.

Analysis of safety outcomes

Adverse event incidence: The evaluation of treatment-related adverse events (**Table 8**) showed that there was no significant correlation between baseline SIK2 expression and TRAE incidence. The TRAE rates, including the overall incidence rate (P = 0.723), common specific events (all P>0.05) and grade ≥3 events (P

Table 9. Changes in liver function parameters: before and after treatment

Group	Time	ALT (U/L)	AST (U/L)	TBIL (μmol/L)	ALB (g/L)	ALP (U/L)
High SIK2 (n = 47)	Before treatment	44.2 ± 10.5	48.7 ± 12.8	18.1 ± 4.3	38.8 ± 3.5	108 ± 28
	After treatment	46.8 ± 11.9	51.2 ± 13.6	18.9 ± 4.9	38.1 ± 3.7	112 ± 31
Low SIK2 (n = 47)	Before treatment	45.1 ± 11.2	49.5 ± 13.1	18.5 ± 4.6	38.5 ± 3.6	110 ± 29
	After treatment	53.7 ± 14.5*	57.4 ± 16.2*	22.3 ± 6.1*	36.8 ± 4.1*	126 ± 35*
P value (Between groups, post-treatment)		0.021	0.018	0.006	0.045	0.038

Note: Data are presented as mean ± standard deviation. * indicates *P*<0.05 versus pre-treatment within the same group (paired t-test or Wilcoxon signed-rank test). The *P* value for between-group comparisons after treatment was calculated using the independent samples t-test or Mann-Whitney U test, comparing the High SIK2 vs. Low SIK2 groups at the post-treatment time point. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; ALB, albumin; ALP, alkaline phosphatase.

= 0.744), were similar between the SIK2 expression groups. Therefore, the safety of first-line targeted treatment of advanced HCC seemed to be consistent across different levels of tumor SIK2 expression.

Changes in laboratory parameters: In order to evaluate the association between SIK2 expression and liver tolerance, key laboratory indicators before and after treatment were analyzed (**Table 9**). The results showed that the liver function parameters in the high SIK2 group remained more stable. In contrast, in the low SIK2 group, significant deterioration was observed after treatment, with increases in ALT, AST, TBIL and ALP, and a decrease in ALB (all P<0.05 vs. baseline). Crucially, direct comparison between the two groups after treatment confirmed that the liver biochemical parameters in the low SIK2 group were significantly worse than those of the high SIK2 group (all P<0.05, **Table 9**). These findings show that elevated SIK2 expression is associated with better therapeutic efficacy and improved liver tolerance.

Discussion

HCC targeted therapy has entered the phase of personalized precision medicine. However, sorafenib and lenvatinib still face the core dilemma of "large individual differences in efficacy" and "lack of accurate tools for prognostic evaluation" in clinical application. Therefore, screening predictive biomarkers with high sensitivity and specificity to achieve individualized and precise decision-making for targeted therapy in HCC has become an urgent need for clinical translational research. This retrospective cohort study evaluated the predictive role of SIK2 expression for outcomes following first-line targeted therapy in advanced HCC. High pretreatment SIK2 levels were associated with significantly better therapeutic outcomes. Low SIK2 expression was independently associated with reduced OS and PFS, yet unrelated to adverse events. These results collectively suggest that SIK2 may be a broadly applicable positive predictive biomarker for first-line TKI therapy, with potential clinical utility in guiding treatment decisions for advanced HCC.

A key finding was that the high SIK2 group demonstrated significantly higher ORR and DCR than the low SIK2 group, which was consistent with the clinical observations of targeted therapy for advanced HCC. Feng et al. [36] verified the predictive value of ACSL4 (lipid metabolism-related kinase) in the study of sorafenib in the treatment of HCC, and ACSL4 expression was inversely associated with sorafenib IC50 values (R = -0.952), reflecting greater sensitivity in high-expressing cells. Moreover, markedly elevated ORR was observed in high-expression patients from the clinical cohort. In the context of lenvatinib response prediction, Finn et al. [37] confirmed that high baseline FGF21 predicted improved OS in lenvatinib-treated patients (HR = 0.53, 95% CI: 0.33-0.85), and markedly higher disease control rates were observed in patients with increased FGF21 expression relative to the low-expression group. These findings align with our observation that high SIK2 expression confers significantly higher ORR and DCR in patients receiving either sorafenib or lenvatinib. A key strength of this study is the simultaneous validation of SIK2's predictive efficacy for both first-line TKIs, supporting its role as a common biomarker rather than an agent-specific one. Although this study did not explore the specific molecular mechanisms, our findings can be reasonably interpreted in light of existing literature [38]. As an AMPK-related kinase, SIK2 is the core regulator of cell energy metabolism and stress signals. Sorafenib and lenvatinib both induce metabolic stress and apoptosis. High SIK2 expression

can improve TKI sensitivity in the following ways: first, by optimizing cellular metabolic adaptability, tumors are more likely to be affected by TKI-induced metabolic crisis; second, by regulating cell apoptosis-related signals and lowering the cell death threshold; and third, through crosstalk with the downstream pathway (such as PI3K/Akt) of TKI targets (such as VEGFR/FGFR) thereby cooperating to inhibit pro-survival signaling. The predictive value of SIK2 for the two TKIs, although their mechanisms are different, shows that it can regulate the common stress- and death-response pathways involved in tyrosine kinase inhibition. These assumptions need to be verified in future basic research.

Importantly, subgroup analysis stratified by treatment regimen demonstrated that low SIK2 expression consistently predicted poorer OS and PFS in both the sorafenib and lenvatinib subgroups, with no significant interaction between SIK2 expression and drug type (P for interaction >0.05). These results provide strong evidence that the prognostic value of SIK2 is not related to the selected specific TKI. This finding has direct clinical significance: the SIK2 status may be used as a general biomarker to provide information for first-line treatment decision-making, whether to choose sorafenib or lenvatinib, thereby addressing a key gap in the current personalized management of advanced HCC.

Survival analysis is the core criterion for verifying the prognostic value of biomarkers. The high SIK2 group showed superior survival outcomes, which is of notable clinical significance for prolonging survival. This observation is consistent with the established model of HCC targeted treatment, in which the increase in biomarker expression is usually associated with improved survival. For example, in the study of targeted and immunotherapy, Zhang et al. [39] noted that despite the controversy, increased PD-L1 levels were associated with improved objective response and survival outcomes in trials such as CheckMate 040 and KEYNOTE-224. The prognostic ability of SIK2 observed in this study enhances the value of using tumor tissue biomarkers to provide information for prognostic evaluation. According to the TCGA database and cell experiments, Li et al. [40] confirmed that low SIK2 expression was related to poor survival ($P = 2.65 \times 10^{-6}$), and promoted HCC cell proliferation and invasion, while inhibiting apoptosis. Public database analysis and in vitro experiments also confirmed the adverse prognosis associated with low SIK2 expression, further verifying its biological relevance in the progression of HCC.

Contrary to the traditional paradigm that high expression of oncogenes is usually associated with highly aggressive characteristics, we observed that high SIK2 expression was significantly associated with lower TNM stage and absence of vascular invasion. This finding is consistent with the tumor-suppressive effect of SIK2 in HCC. In terms of mechanism, studies in other cancer types have shown that SIK2 plays an inhibitory role in cell migration and invasion by regulating epithelial-mesenchymal transition (EMT) [18]. Although this direct mechanism has not been fully clarified in HCC, SIK2 may inhibit local and vascular invasion by inhibiting the EMT program. In addition, our group has previously shown that SIK2 inactivates the Wnt/β-catenin signaling pathway in HCC cells [40]. This canonical pathway is known to promote EMT progression and metastasis. Therefore, high SIK2 expression may maintain a more differentiated and less aggressive tumor phenotype, which is less prone to angiogenesis and vascular invasion, and may inhibit Wnt/β-catenin signaling and EMT through coordinated inhibition. This biological background can also explain why these tumors are more susceptible to TKI-induced metabolic crisis and apoptosis, thus linking pathological characteristics such as absence of vascular invasion with a good therapeutic response. The association between high SIK2 expression and tumor burden reduction observed in our study is consistent with the findings of Hsu et al. [41], which further supports this explanation.

Recent efforts in HCC research have focused on developing prognostic models. For example, Wen et al. [42] developed a consensus artificial intelligence prognostic system (CAIPS) by integrating 10 machine learning algorithms (101 methods in total) and six multi-center HCC cohorts consisting of 1,110 patients. The model linked low CAIPS scores to enhanced responses to targeted therapy, TACE and immunotherapy. Our finding that low SIK2 expression is an adverse prognostic factor is consistent with these established features and suggests that SIK2 may capture the basic dimensions of HCC

biology. This study also found that SIK2 expression was not related to extrahepatic metastasis (P = 0.171), which was in stark contrast to the association of SIK2 with other aggressive characteristics (such as TNM stage and vascular invasion). This difference may indicate that SIK2 mainly affects the local invasiveness of primary tumors and has less potential impact on distant metastasis. Another explanation is that SIK2 may function by regulating specific signaling pathways more related to local growth and vascular invasion, rather than through mechanisms such as epithelial-mesenchymal transition that affects distant metastasis.

Multivariate analysis confirmed that after adjusting the established clinical pathological factors including TNM stage and vascular invasion, low SIK2 expression remained an independent predictor of OS and PFS. The robustness of this association is consistent in the entire matching cohort and the individual treatment subgroups. The robustness of this finding is similar to that of the biomarkers validated in similar studies. As shown by the sorafenib study of Llovet et al. [43], the prognostic model based on molecular characteristics such as angiogenesis reported that the HR of high-risk HCC patients was 2.0-3.0. This finding is of great clinical significance. At present, Barcelona Clinic Liver Cancer stage, liver function status and performance score are the pillars of advanced HCC treatment decision-making, but they are limited in predicting specific treatment responses.

Our study suggests that a simple immunohistochemical test for SIK2, readily implementable in routine pathology practice, could help identify patients most likely to derive substantial benefit from first-line sorafenib or lenvatinib therapy. For patients with high SIK2 expression, physicians can more confidently recommend sorafenib or lenvatinib and expect better survival outcomes. However, for patients with low SIK2 expression, other alternatives may need to be considered earlier, such as combination immunotherapy, participation in clinical trials of novel agents, or closer follow-up monitoring, so as to achieve truly individualized precision medicine and avoid the economic burden and opportunity cost of ineffective treatment.

Limitations

Although our results are important, this study has several limitations. First, despite strict adjustment, this single-center retrospective study may not be able to completely eliminate the potential confounding bias from unmeasured factors. Second, the expression data of SIK2 were based on archival immunohistochemical samples. Although the reassessment adopted a unified scoring standard, the small differences between the original staining batches cannot be completely excluded. Standardized and predefined test protocols should be incorporated into future prospective research to verify these findings. Third, the expression of SIK2 in this study was evaluated only at the protein level through IHC. Although IHC has a standardized scoring system, it has inherent semi-quantitative and subjective interpretative variability. Future research should use complementary techniques such as Western blotting, ELISA or mRNA sequencing to cross-verify expression levels, reduce potential observer bias, and explore post-transcriptional regulation. Fourth, due to the retrospective design, we lacked serial tissue samples to dynamically monitor the changes in SIK2 expression during treatment; therefore, it is not clear whether the longitudinal fluctuation of SIK2 is related to acquired drug resistance or therapeutic response. Fifth, this study did not conduct a joint or comparative analysis of SIK2 with other established (e.g., AFP) or emerging (e.g., PD-L1) biomarkers. The independent or synergistic predictive value of SIK2 relative to existing biomarkers deserves further study in the prospective cohorts. In the future, multicenter research should evaluate the predictive value of SIK2 in other HCC therapies, including immunotherapy and combination therapy, evaluate its potential as a pan-therapy predictive biomarker, and provide a unified predictive tool for the whole-course management of HCC.

Conclusion

In summary, low SIK2 expression independently correlated with poorer clinical outcomes in HCC patients receiving sorafenib or lenvatinib therapy. The predictive role of SIK2 in therapeutic response and survival was verified in multiple analytical dimensions, which is consistent with the known molecular characteristics of HCC. These results show that SIK2 may become an important tool to guide first-line targeted treatment decision-making and enable personalized precision medicine, thus improving the prognosis of advanced HCC patients.

Disclosure of conflict of interest

None.

Address correspondence to: Wei Wang, Department of Gastrointestinal Surgery, Sinopharm Dongfeng General Hospital, No. 16 Daling Road, Zhangwan District, Shiyan 442008, Hubei, China. E-mail: wang202639@hotmail.com

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Supplementary Table 1. Subgroup analysis of survival outcomes stratified by treatment regimen

Treatment	SIK2	n	Median OS (mo)	HR for OS (95% CI)	*P* value	Median PFS (mo)	HR for PFS (95% CI)	*P* value
Sorafenib	High	24	16.2	2.18 (1.25-3.80)	0.006	8.1	2.05 (1.20-3.50)	0.009
	Low	24	9.8			4.3		
Lenvatinib	High	23	15.8	2.35 (1.30-4.25)	0.004	7.9	2.12 (1.22-3.68)	0.007
	Low	23	9.2			4		

Supplementary Table 2. Association between SIK2 Expression and Tumor Grade, Etiology, and Cirrhosis

Characteristic	Category	High SIK2 (n = 47)	Low SIK2 (n = 47)	*P* Value
Tumor Differentiation	High/Moderate	28 (59.6%)	22 (46.8%)	0.214
	Poor/Undifferentiated	19 (40.4%)	25 (53.2%)	
Viral Hepatitis	HBV-positive	36 (76.6%)	38 (80.9%)	0.807
	Non-HBV (HCV/Other)	11 (23.4%)	9 (19.1%)	
Liver Cirrhosis	Present	32 (68.1%)	35 (74.5%)	0.502
	Absent	15 (31.9%)	12 (25.5%)	