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Impact of Paternal and Maternal Family History of Liver Cancer on Postoperative Prognosis in Hepatocellular Carcinoma

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ABSTRACT Family history of liver cancer (FHLC) may influence prognosis after hepatocellular carcinoma (HCC) resection, but the effect of parental origin remains unclear. This retrospective study included 2,325 patients who underwent HCC resection between 2010 and 2018. Recurrence-free survival (RFS) and overall survival (OS) were evaluated using Kaplan-Meier and multivariable Cox analyses. Maternal FHLC alone was independently associated with poorer RFS (HR 2.33, 95% CI 1.75-3.09) and OS (HR 3.02, 95% CI 2.15-4.24), whereas paternal FHLC alone was not significantly associated with either outcome. The association remained significant among patients without maternal HBV infection. Parental origin of FHLC may provide additional prognostic information after HCC resection.

Lay Summary

This study examined the impact of familial history of liver cancer (FHLC) on the postoperative prognosis of patients who underwent surgical intervention for hepatocellular carcinoma (HCC). The findings indicate that patients with a maternal FHLC exhibit poorer postoperative prognosis than those with a paternal history. Specifically, individuals with maternal FHLC demonstrated lower survival rates and a higher likelihood of cancer recurrence. The adverse association remained evident among patients without maternal HBV infection, although mother-to-child HBV transmission was not directly established in this study. These results suggest that the parental origin of FHLC, particularly maternal origin, should be considered when evaluating the prognosis and formulating treatment plans for patients with HCC following surgery.

Highlights

Maternal family history of liver cancer (FHLC) was associated with poorer postoperative recurrence-free survival (RFS) and overall survival (OS) in patients with hepatocellular carcinoma (HCC). Maternal FHLC alone remained independently associated with poorer RFS and OS after multivariable adjustment and was also associated with a recurrence pattern shifted toward earlier recurrence. Exploratory biomarker analyses showed limited differences between parental-origin groups and did not provide sufficient evidence to explain the observed survival differences. In comparison, paternal FHLC alone was not significantly associated with poorer RFS or OS. Given these differences, parental-origin FHLC warrants further evaluation as a potential prognostic factor in patients undergoing HCC resection.

INTRODUCTION

Epidemiology and Treatment of HCC

Hepatocellular carcinoma (HCC) accounts for 75 percent to 85 percent of liver cancer cases and ranks as the sixth most common cancer and the third leading cause of cancer-related mortality globally, according to the Global Cancer Statistics 2022 (Bray et al. 2024). Surgical resection is a mainstay curative therapy for well selected early stage patients, with 5 year overall survival (OS) approaching 70 percent in contemporary cohorts (Lee et al. 2024; Singal et al. 2023). However, postoperative recurrence remains the dominant barrier to long term cure: 5 year recurrence rates of 40/ percent-70 percent are consistently reported, and over 80 percent of patients experience recurrence during extended follow up (Zhang et al. 2025; Panettieri et al. 2024). Iden-

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tifying reliable preoperative prognostic markers is therefore critical for postoperative risk stratification and surveillance planning.

Family History of Liver Cancer and HCC Prognosis

Family history of liver cancer (FHLC) increases HCC susceptibility, particularly in patients with chronic viral hepatitis. While its oncogenic role is well established, FHLC exhibits inconsistent prognostic value after curative HCC resection, primarily due to heterogeneous study designs and variable clinical baselines (Panettieri et al. 2024; Lee et al. 2024). Notably, most previous prognostic studies have evaluated FHLC as a single exposure without separately examining paternal and maternal origins (Li et al. 2019). Given potential maternal-specific biological influences, including mitochondrial inheritance and maternal HBV-related transmission patterns, maternal FHLC may confer distinct prognostic impacts (Yang et al. 2018; Chattopadhyay et al. 2022; Basel et al. 2025). These considerations prompted us to investigate whether the parental origin of FHLC is associated with distinct postoperative outcomes in patients with resected HCC.

Study Objective

This study aimed to investigate whether paternal only and maternal only FHLC exert distinct effects on RFS and OS in HCC patients undergoing surgical resection. The secondary objectives were to examine the associations of parental-origin FHLC with the timing of recurrence and tumour biomarker expression patterns.

METHODOLOGY

Study Design and Patients

This retrospective study included 2,325 patients with HCC (aged 12-86 years) who underwent curative surgical resection and were pathologically confirmed at the researchers' centre between 2010 and 2018, with follow-up extending to 2022. This study was approved by the Ethics Committee of West China Hospital, Sichuan University. The requirement for a specialised informed consent form was waived, as the routine admission consent included permission for retrospective medical data analysis for scientific research. Patients with established FHLC information who could not be contacted during postoperative outcome follow-up were censored at the date of their last known follow-up.

Eligible patients were those with pathologically confirmed HCC who underwent hepatectomy between 2010 and 2018. Patients who received non-surgical treatment or had a postoperative pathological diagnosis other than HCC were excluded.

Family History Assessment

FHLC information was collected during outpatient follow-up visits using a standardised questionnaire administered by trained interviewers. Patients were asked, "Have any first-degree relatives (father, mother, brothers, or sisters) been diagnosed with liver cancer before the patient's HCC diagnosis?" Responses were recorded separately for each relative. Family histories of other cancers and hepatitis virus infection among family members were also recorded.

For patients who had died before the interview, the relationship between the respondent and the patient was confirmed before FHLC and other medical-history information was collected. If the respondent had insufficient knowledge of the patient's family history, additional relatives were contacted. Cases with undetermined family histories after these steps were resolved through medical record reviews, which clarified all initially undetermined FHLC cases.

Clinical Data Collection

Baseline patient characteristics, tumour-related parameters, and surgical variables were extracted from the medical records. Cirrhosis was confirmed through histopathological examination, and the tumour stage at diagnosis was assessed using the Barcelona Clinic Liver Cancer (BCLC) staging system. Major liver resection was defined as the removal of three or more Couinaud liver segments, whereas partial resection involved fewer than three segments.

Follow-up

HCC recurrence was primarily determined through the researchers' hospital's outpatient service system, which accurately recorded postoperative follow-up information, including details of the recurrence diagnosis. Patients were routinely advised to undergo serum alpha-fetoprotein (AFP) testing and abdominal ultrasound every 1-2 months for the first 6 months after resection, and then every 3-6 months thereafter. If recurrence was suspected, the diagnosis was confirmed using multiphasic computed tomography or magnetic resonance imaging (MRI). Early recurrence was defined as recurrence occurring within 2 years after surgery, whereas late recurrence was defined as recurrence occurring more than 2 years after surgery.

According to outpatient records, approximately 90 percent of patients adhered to regular reexaminations in the first year, 85 percent within the first two years, and 60 percent after two years of treatment. The overall follow-up rate was 86 percent, with the longest follow-up period extending to nearly 12 years after the surgery. As a supplement, telephone follow-ups were conducted every six months until August 2022.

The primary outcome was RFS, defined as the time from surgery to the first documented recurrence or death from any cause, whichever occurred first. Patients without recurrence or death were censored at the date of the last follow-up. The secondary outcome was OS, defined as the time from surgery to death from any cause; patients who were alive at the last follow-up were censored on that date. Deaths within 90 days after surgery were included as events, and the 90-day mortality rate was 1.5 percent.

Statistical Analysis

The primary aim of the statistical analysis was to investigate RFS, followed by OS, among patients with paternal or maternal FHLC alone. The Kaplan-Meier method was used to estimate RFS and OS distributions, and survival curves were compared using the log-rank test. Stratified survival analysis was also conducted, with stratifying factors including sex, Child-Pugh grade, liver cirrhosis, BCLC stage, resection range, and preexisting resection. Univariate and multivariate Cox proportional hazards models were employed to estimate hazard ratios (HRs) for recurrence-free survival and overall survival in the paternal and maternal FHLC alone groups, using the no-FHLC group as the reference. HRs were adjusted for age, sex, smoking, alcohol use, hepatitis B virus infection, AFP levels, tumour number, tumour location, maximum tumour size, microvascular invasion, BCLC stage, tumour differentiation, Child-Pugh grade, model for end-stage liver disease (MELD) score, liver cirrhosis, resection range, and preexisting resection. Each FHLC-derived variable was evaluated separately in a multivariable model together with the same set of non-FHLC covariates to avoid simultaneous inclusion of overlapping FHLC classifications. Robust sandwich variance estimates were used in the multivariable Cox regression models. The proportional hazards assumption was evaluated using Schoenfeld residuals.

In the sensitivity analysis, patients with multiple first-degree relatives with liver cancer (FRLC), which involved a paternal or maternal FHLC, were analysed separately or as a whole with FHLC alone. In addition, the potential influence of maternal HBV infection was examined by analyses stratified according to maternal HBV status (mHBV).

To investigate whether paternal or maternal FHLC was associated with early or late recurrence, multivariate logistic regression was applied to estimate the odds ratio (OR) for potential factors. Among patients who developed recurrence, late recurrence was coded as 1 and early recurrence as 0 in the logistic regression model; therefore, an OR below 1 indicated a relative shift toward early recurrence. Moreover, differences between the paternal and maternal FHLC groups in tissue biomarker expression were analysed using the chi-squared test or Fisher's exact test, as appropriate. These pathologic immunohistochemical biomarkers included glypican-3 (GPC3), hepatocyte paraffin 1 (HepPar-1), cluster of differentiation 34 (CD34), glutamine synthetase (GS), alpha-fetoprotein (AFP), arginase-1 (Arg-1), cytokeratin 7 (CK7), cytokeratin 19 (CK19), and cytokeratin 8 (CK8).

Baseline patient characteristics, tumour-related parameters, and surgical variables were summarised using frequencies and percentages for categorical covariates and mean ± standard

deviation (SD) or median with interquartile range (IQR) for continuous covariates. Categorical covariates were compared using the chi-squared test or Fisher's exact test, as appropriate, while continuous covariates were compared using the Kruskal-Wallis test, Student's t-test, or one-way ANOVA, as appropriate. No missing data were present for the variables included in the primary multivariable analyses. A two-sided P-value < 0.05 was considered statistically significant. All statistical analyses were performed using Python (version 3.8.8).

RESULTS

Patient Screening and Family History

The researchers retrospectively screened 23,778 patients with liver masses at our hospital between 2010 and 2018. After excluding patients receiving non surgical treatment (n/ =/ 17/ ,666) and those with pathologically verified non HCC after surgery (n =3,787), 2,325 pathologically confirmed HCC patients undergoing hepatectomy were included (Fig. 1). Among the final cohort, 312 patients (13.4%) had FHLC. Among these patients, 198 (8.5% of the total cohort) had one affected first-degree relative, whereas 114 (4.9%) had two or more affected first-degree relatives. Parental-origin-based classification identified 88 patients with paternal FHLC (28.2% of FHLC-positive patients), 131 with maternal FHLC (42.0%), 27 with bi-parental FHLC (8.7%), and 66 with sibling FHLC (21.2%) (Fig. 2). Further subclassification showed that 53 patients had paternal FHLC alone and 35 had paternal FHLC involving additional affected first-degree relatives; corresponding numbers were 88 and 43 for maternal FHLC, and 6 and 21 for bi-parental FHLC, respectively. Maternal FHLC was the most frequent parental-origin category, whereas bi-parental FHLC was the least frequent.

Analysis of HBV status in FRLC (Fig. S1) identified 35 patients with maternal FHLC alone whose mothers also had HBV infection.

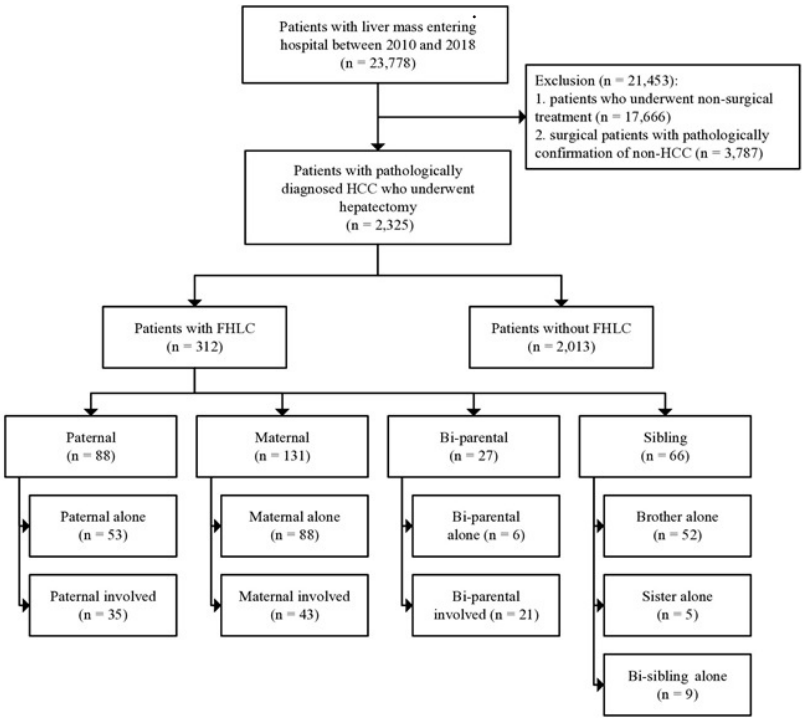


Fig. 1. Flowchart illustrating the inclusion and grouping of patients with HCC in this study
HCC: hepatocellular carcinoma; FHLC: family history of liver cancer
Source: Authors

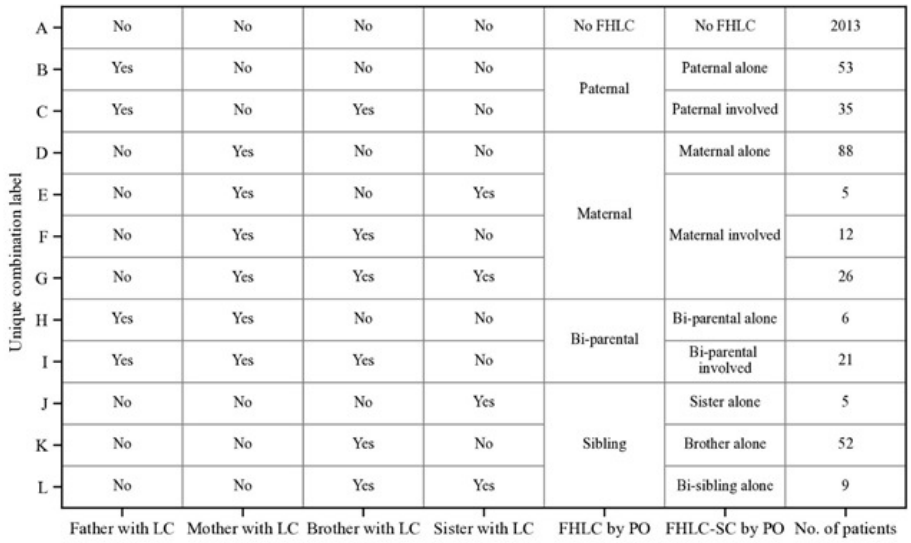


Fig. 2. Overview of FHLC based on FRLC and classified by PO
FHLC: family history of liver cancer; FRLC: first-degree relatives with liver cancer; PO: parental origin; LC: liver cancer; FHLC-SC: family history of liver cancer subclassification; No.: number

Baseline and Clinical Characteristics

The patients' baseline and clinical characteristics were compared according to FHLC by PO (Table 1). The mean age of the patients was 51.0 ± 11.5 years, and patients with bi-parental FHLC had the lowest mean age of 46.2 ± 10.3 years. The proportion of male patients differed across the parental-origin groups (P = 0.030), with the sibling-FHLC group having the lowest proportion of men. ALT and AST levels differed significantly among the parental-origin groups (P = 0.037 and P = 0.009, respectively).

Patients with bi-parental FHLC had the lowest rates of HBV infection (11/27, 40.7%) and antiviral therapy (5/27, 18.5%). Patients with sibling FHLC had more preexisting HCC resections (4/66, 6.1%). Patients with bi-parental FHLC had more early recurrence (14/27, 51.9%), and patients with paternal FHLC had more late recurrence (26/88, 29.5%).

Survival Curves

Patients with FHLC had worse RFS than those without FHLC ($p < 0.001$), and patients with two or more affected first-degree relatives showed the worst RFS ($p < 0.001$) (Fig. 3A-B). Patients with paternal FHLC alone had 1-, 3-, and 5-year RFS rates of 83.0 percent, 69.7 percent, and 59.3 percent respectively, while those with maternal FHLC alone had corresponding rates of 75.4 percent, 25.1 percent, and 14.7 percent, respectively (Fig. 3D). The median RFS was 6.1 years for patients with paternal FHLC alone and 1.53 years for those with maternal FHLC alone ($p < 0.001$). Similar RFS patterns were observed across the parental-origin classifications and after stratification by maternal HBV status (Fig. 3C, E-F). Patients with paternal FHLC alone and those with maternal FHLC alone also showed significantly different OS distributions ($P < 0.05$) (Fig. S2).

Cox Regression Analyses

Univariable Cox regression analyses of RFS and OS showed significantly higher HRs in patients with a maternal FHLC alone (Tables S1 and S2 and Figs. S3 and S4). In multivariable Cox regression analyses with a robust estimator, after adjusting for non-FHLC-derived factors, maternal FHLC alone was independently associated with worse RFS and OS after liver resection for HCC (Fig. 4 and Fig. S5). The adjusted HR of

Table 1: Baseline and clinical characteristics of patients with HCC after surgery overall and grouped by PO

	Overall (n=2325)	*No FHLC (n=2013)*	*Paternal (n=88)*	*Maternal (n=131)*	*Bi-parental (n=27)*	*Sibling (n=66)*	*P-Value*
Age (year), mean (SD)	51.0 (11.5)	51.3 (11.6)	47.4 (11.3)	49.8 (11.1)	46.2 (10.3)	52.4 (10.8)	0.002
Sex (male), n (%)	1974 (84.9)	1721 (85.5)	75 (85.2)	109 (83.2)	22 (81.5)	47 (71.2)	0.030
Smoke (yes), n (%)	1168 (50.2)	1011 (50.2)	43 (48.9)	73 (55.7)	10 (37.0)	31 (47.0)	0.433
Alcohol (yes), n (%)	747 (32.1)	653 (32.4)	25 (28.4)	42 (32.1)	11 (40.7)	16 (24.2)	0.486
FHLC (yes), n (%)	312 (13.4)		88 (100.0)	131 (100.0)	27 (100.0)	66 (100.0)	
No. of kinships in FRLC, n (%)							
1	198 (8.5)		53 (60.2)	88 (67.2)		57 (86.4)	
≥2	114 (4.9)		35 (39.8)	43 (32.8)	27 (100.0)	9 (13.6)	
FHLC-SC by PO, n (%)							
Paternal alone	53 (2.3)		53 (60.2)				
Paternal involved	35 (1.5)		35 (39.8)				
Maternal alone	88 (3.8)			88 (67.2)			
Maternal involved	43 (1.8)			43 (32.8)			
Bi-parental alone	6 (0.3)				6 (22.2)		
Bi-parental involved	21 (0.9)				21 (77.8)		
Bi-Sibling alone	9 (0.4)					9 (13.6)	
Brother alone	52 (2.2)					52 (78.8)	
Sister alone	5 (0.2)					5 (7.6)	
TB (ìmol/L), median [Q1, Q3]	14.4 [10.6,19.5]	14.4 [10.6,19.3]	16.4 [11.4,20.4]	13.9 [10.6,19.2]	13.7 [10.0,18.4]	17.2 [12.1,21.1]	0.083
ALB (g/L), median [Q1, Q3]	41.1 [37.8,43.9]	41.1 [37.7,43.9]	41.0 [38.9,44.7]	41.5 [38.3,43.8]	40.3 [35.5,44.5]	41.6 [39.0,43.9]	0.761
ALT (U/L), median [Q1, Q3]	38.0 [26.0,58.0]	38.0 [26.0,59.0]	41.5 [29.8,60.5]	40.0 [27.0,60.5]	33.0 [20.5,40.5]	34.0 [25.0,44.0]	0.037
AST (U/L), median [Q1, Q3]	38.0 [28.0,57.0]	38.0 [28.0,57.0]	42.0 [34.0,61.5]	39.0 [30.0,63.0]	34.0 [23.5,45.5]	34.0 [27.0,45.5]	0.009
PLT (10y /L), median [Q1, Q3]	127.0 [89.0,176.0]	127.0 [90.0,177.0]	121.5 [84.8,165.2]	135.0 [90.0,172.5]	98.0 [80.5,155.0]	113.5 [86.2,161.8]	0.348
HBV (yes), n (%)	1980 (85.2)	1794 (89.1)	65 (73.9)	67 (51.1)	11 (40.7)	43 (65.2)	<0.001
HBV-DNA (10^3copies/mL), median [Q1, Q3]	1.2 [1.0,55.1]	1.2 [1.0,52.3]	1.0 [1.0,41.9]	4.3 [1.0,192.5]	1.0 [1.0,13.6]	1.0 [1.0,28.2]	0.116
HCV (yes), n (%)	27 (1.2)	24 (1.2)	1 (1.1)	1 (0.8)	1 (3.7)		0.646
Antiviral therapy (yes), n (%)	1094 (47.1)	998 (49.6)	35 (39.8)	37 (28.2)	5 (18.5)	19 (28.8)	<0.001
Liver cirrhosis (yes), n (%)	1564 (67.3)	1350 (67.1)	62 (70.5)	91 (69.5)	14 (51.9)	47 (71.2)	0.391
Portal hypertension (yes), n (%)	832 (35.8)	737 (36.6)	25 (28.4)	42 (32.1)	4 (14.8)	24 (36.4)	0.070
ALBI score, median [Q1, Q3]	-2.7 [-3.0, -2.5]	-2.7 [-3.0, -2.5]	-2.7 [-3.0, -2.5]	-2.8 [-3.0, -2.5]	-2.8 [-3.0, -2.3]	-2.8 [-3.0, -2.4]	0.920
ALBI grade, n (%)							0.302
Grade 1	1471 (63.3)	1265 (62.8)	54 (61.4)	91 (69.5)	16 (59.3)	45 (68.2)	
Grade 2	829 (35.7)	728 (36.2)	34 (38.6)	38 (29.0)	10 (37.0)	19 (28.8)	
Grade 3	25 (1.1)	20 (1.0)		2 (1.5)	1 (3.7)	2 (3.0)	
Child-Pugh grade, n (%)							0.101
A	2250 (96.8)	1950 (96.9)	86 (97.7)	128 (97.7)	24 (88.9)	62 (93.9)	
B	75 (3.2)	63 (3.1)	2 (2.3)	3 (2.3)	3 (11.1)	4 (6.1)	
MELD score, median [Q1, Q3]	7.5 [6.4,8.4]	7.5 [6.4,8.4]	7.8 [7.0,8.6]	7.5[6.7,8.4]	6.7[6.4,7.5]	7.5 [6.4,8.5]	0.055
AFP (ng/mL), median [Q1, Q3]	136.4 [7.9,1210.0]	136.4 [7.9,1210.0]	164.2 [8.8,1210.0]	189.5 [12.8,1210.0]	28.9 [5.3,640.0]	61.9 [4.6,1210.0]	0.469
Tumour number, n (%)							0.623
1	1987 (85.5)	1717 (85.3)	73 (83.0)	116 (88.5)	25 (92.6)	56 (84.8)	
≥2	338 (14.5)	296 (14.7)	15 (17.0)	15 (11.5)	2 (7.4)	10 (15.2)	
Tumour location, n (%)							0.204
Left lobe	532 (22.9)	455 (22.6)	23 (26.1)	39 (29.8)	4 (14.8)	11 (16.7)	
Middle lobe	398 (17.1)	342 (17.0)	17 (19.3)	16 (12.2)	7 (25.9)	16 (24.2)	
Right lobe and caudate lobe	1395 (60.0)	1216 (60.4)	48 (54.5)	76 (58.0)	16 (59.3)	39 (59.1)	
Maximum tumour size (cm), median [Q1, Q3]	4.9[3.0,7.0]	4.9 [3.0,7.0]	4.7 [3.0,9.0]	4.5[3.0,7.0]	4.0[2.1,6.0]	4.2 [2.8,6.0]	0.744
Microvascular invasion (yes), n (%)	766 (32.9)	668 (33.2)	27 (30.7)	42 (32.1)	6 (22.2)	23 (34.8)	0.770
BCLC stage, n (%)							0.616
A	2022 (87.0)	1746 (86.7)	73 (83.0)	117 (89.3)	26 (96.3)	60 (90.9)	

Table 1: Contd...

	Overall (n=2325)	*No FHLC (n=2013)*	*Paternal (n=88)*	*Maternal (n=131)*	*Bi-parental (n=27)*	*Sibling (n=66)*	*P-Value*
B	292 (12.6)	257 (12.8)	15 (17.0)	13 (9.9)	1 (3.7)	6 (9.1)	
C	11 (0.5)	10 (0.5)		1 (0.8)			
Tumour differentiation, n (%)							0.283
High	102 (4.4)	88 (4.4)	4 (4.5)	4 (3.1)	4 (14.8)	2 (3.0)	
Intermediate	1346 (57.9)	1160 (57.6)	51 (58.0)	77 (58.8)	14 (51.9)	44 (66.7)	
Low	877 (37.7)	765 (38.0)	33 (37.5)	50 (38.2)	9 (33.3)	20 (30.3)	
Resection range, n (%)							0.069
Major resection	1517 (65.2)	1328 (66.0)	57 (64.8)	76 (58.0)	12 (44.4)	44 (66.7)	
Partial resection	808 (34.8)	685 (34.0)	31 (35.2)	55 (42.0)	15 (55.6)	22 (33.3)	
Preexisting resection (yes), n (%)	46 (2.0)	39 (1.9)	3 (3.4)			4 (6.1)	0.044
Recurrence, n (%)							<0.001
No recurrence	1039 (44.7)	907 (45.1)	28 (31.8)	65 (49.6)	9(33.3)	30 (45.5)	
Early recurrence	828 (35.6)	694 (34.5)	34 (38.6)	59 (45.0)	14 (51.9)	27 (40.9)	
Late recurrence	458 (19.7)	412 (20.5)	26 (29.5)	7 (5.3)	4(14.8)	9 (13.6)	
Death (yes), n (%)	719 (30.9)	611 (30.4)	29 (33.0)	47 (35.9)	12 (44.4)	20 (30.3)	0.366

P values were not calculated for FHLC-related classification variables because these variables were used to define the study groups. HCC: hepatocellular carcinoma; PO: parental origin; SD: standard deviation; IQR: interquartile range; No.: number; FRLC: first-degree relatives with liver cancer; FHLC-SC: family history of liver cancer subclassification; TB: total bilirubin; ALB: albumin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; PLT: platelet; HBV: hepatitis B virus; HCV: hepatitis C virus; ALBI: albumin-bilirubin; MELD: model for end-stage liver disease; AFP: alpha-fetoprotein; BCLC: Barcelona Clinic Liver Cancer

Source: Authors

maternal FHLC alone for RFS was 2.33 (95% CI: 1.75–3.09; $p < 0.001$) (Fig. 4 and Table S1) and 3.02 (95% CI: 2.15–4.24; $p < 0.001$) for OS (Fig. S5 and Table S2). Conversely, paternal FHLC alone was not significantly associated with RFS (HR = 0.95, 95% CI 0.67-1.35) (Fig. 4 and Table S1) or OS (HR = 0.66, 95% CI 0.36-1.22) (Fig. S5 and Table S2). The associations with RFS (HR = 2.99, 95% CI 2.07-4.32) and OS (HR = 3.40, 95% CI 2.21-5.23) remained significant among patients with maternal FHLC alone without mHBV infection (Fig. 4, Fig. S5, and Tables S1 and S2). Spearman correlation analyses did not identify strong monotonic correlations among the covariates included in the Cox regression models (Fig. S6).

Early and Late Recurrence

A total of 1286 (55.3%) patients experienced recurrence, including 828 patients with early recurrence and 458 patients with late recurrence. The corresponding RFS curves according to recurrence phase are presented in Figure S7. The association between parental-origin FHLC and recurrence timing was further evaluated using multivariable logistic regression. Stratified analyses of RFS according to parental-origin FHLC across clinically relevant subgroups are presented in Figures S8-S13. Multivariable logistic regression showed that maternal FHLC alone was associated with lower odds of late versus early recurrence after adjustment for non-FHLC-derived factors (OR = 0.13, 95% CI 0.05-0.36), indicating a relative shift toward early recurrence (Fig. 5). This association remained significant among patients without maternal HBV infection (OR = 0.09, 95% CI 0.02-0.33).

Tissue Biomarkers

A total of nine pathological immunohistochemical biomarkers were selected for differential analyses between the paternal and maternal FHLC alone groups. The expression levels of these biomarkers were categorised as negative, weakly positive, or strongly positive. Compared with the paternal FHLC-alone group, the maternal FHLC-alone group showed different distributions of staining intensity across several biomarkers; however, these differences were not statistically significant for GPC3, HepPar-1, CD34, GS, AFP, Arg-1, CK19, or CK8. Only CK7 reached nominal statistical significance (P = 0.027); however, no adjustment for multiple comparisons was applied (Fig. 6).

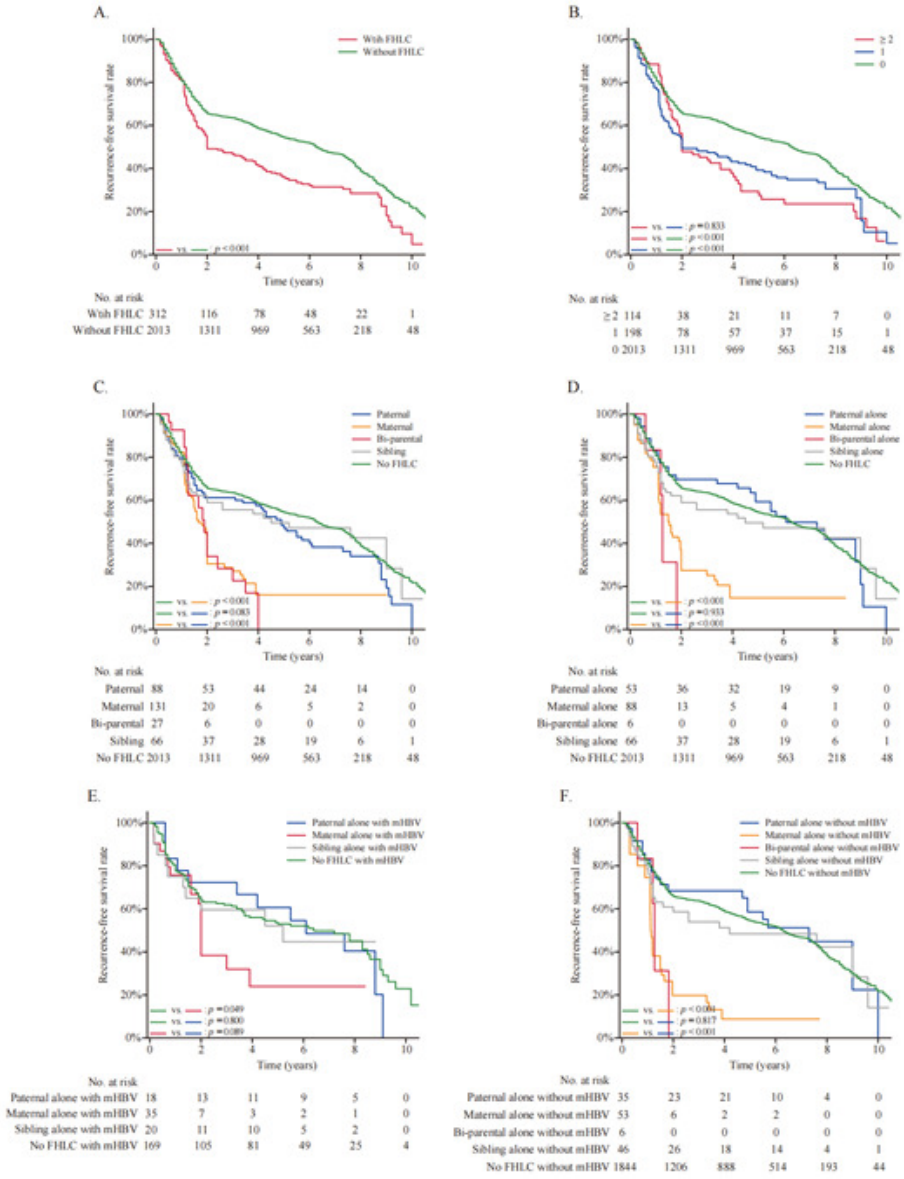


Fig. 3. Comparison of RFS curves for patients with HCC after surgery based on FHLC, number of kinships in FRLC, FHLC by PO, and FHLC-SC by PO and/or mHBV infection
(A) RFS curve comparison based on FHLC; (B) RFS curve comparison based on number of affected first-degree relatives; (C) RFS curve comparison based on FHLC by PO; (D) RFS curve comparison based on FHLC-SC by PO; (E) RFS curve comparison based on FHLC-SC by PO among patients with mHBV infection; (F) RFS curve comparison based on FHLC-SC by PO among patients without mHBV infection
RFS: recurrence-free survival; HCC: hepatocellular carcinoma; FHLC: family history of liver cancer; FRLC: first-degree relatives with liver cancer; FHLC-SC: family history of liver cancer subclassification; PO: parental origin; mHBV: maternal hepatitis B virus; No.: number
Source: Authors

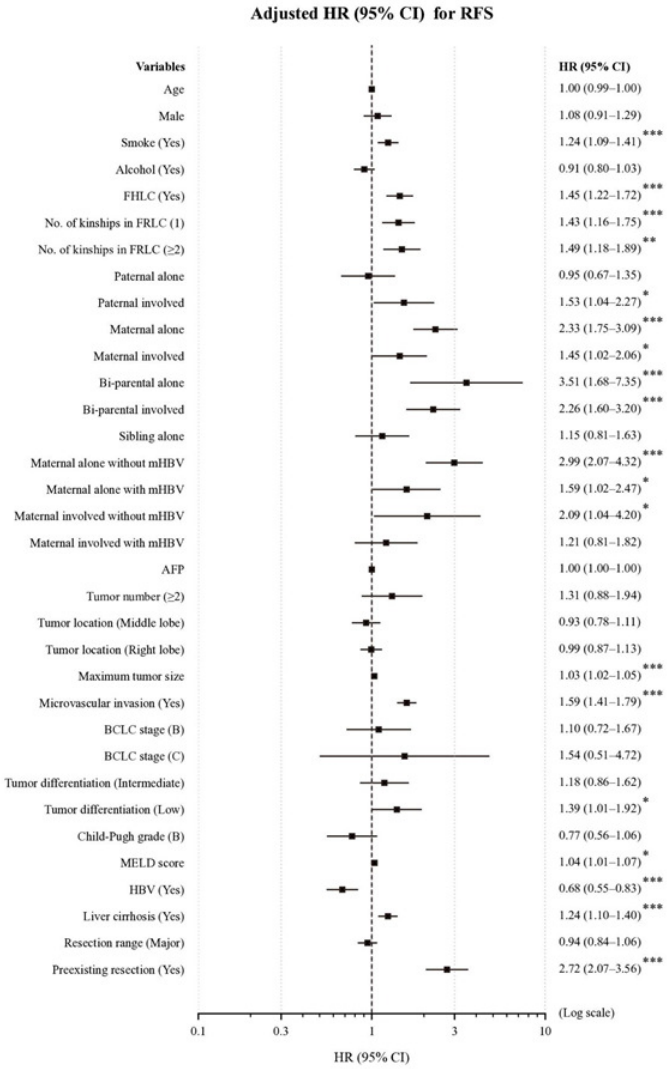


Fig. 4. Adjusted HRs of variables for RFS analysis in the multivariable Cox regression model for patients with HCC after surgery

HRs were adjusted for non-FHLC-derived variables, including age, sex, smoking, alcohol use, hepatitis B virus infection, AFP levels, tumour number, tumour location, maximum tumour size, microvascular invasion, BCLC stage, tumour differentiation, Child-Pugh grade, MELD score, liver cirrhosis, resection range and preexisting resection. The "No FHLC" group served as the reference for FHLC-derived variables in the Cox regression model

HR: hazard ratio; RFS: recurrence-free survival; HCC: hepatocellular carcinoma; CI: confidence interval; FHLC: family history of liver cancer; FRLC: first-degree relatives with liver cancer; No.: number; mHBV: maternal hepatitis B virus; AFP: alpha-fetoprotein; BCLC: Barcelona Clinic Liver Cancer; MELD: model for end-stage liver disease; HBV: hepatitis B virus

***, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$**

Source: Authors

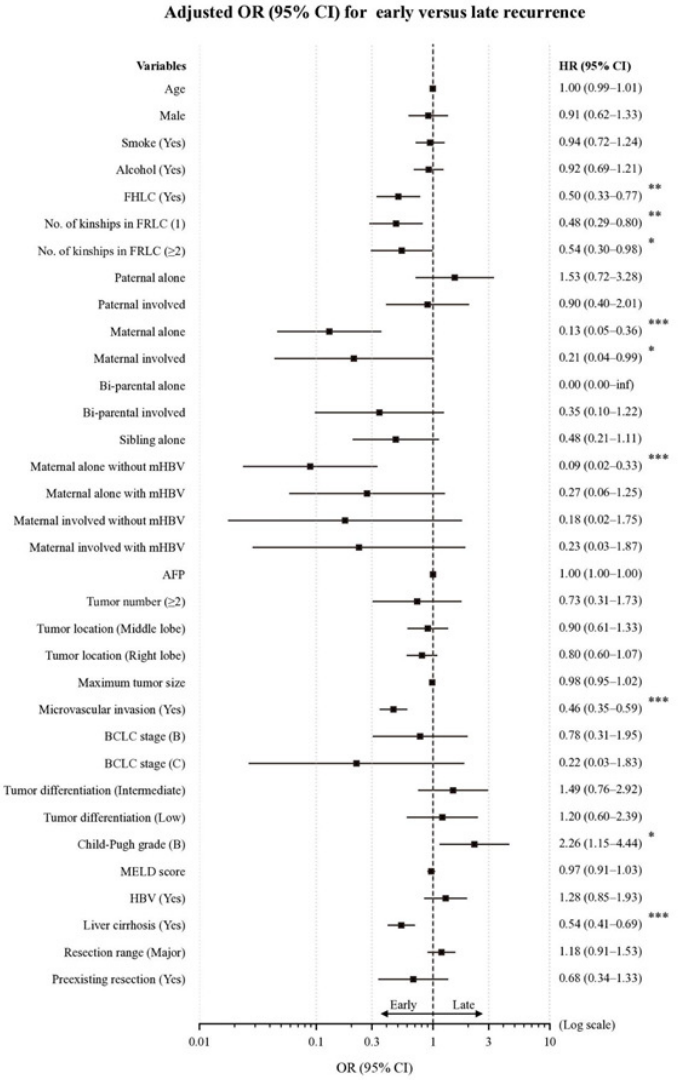


Fig. 5. Adjusted ORs for late versus early recurrence based on a multivariable logistic regression model in patients with HCC after surgery

ORs were adjusted for non-FHLC-derived variables, including age, sex, smoking, alcohol use, hepatitis B virus infection, AFP levels, tumour number, tumour location, maximum tumour size, microvascular invasion, BCLC stage, tumour differentiation, Child-Pugh grade, MELD score, liver cirrhosis, resection range, and preexisting resection. The "No FHLC" group served as the reference for FHLC-derived variables in the logistic regression model

OR: odds ratio; HCC: hepatocellular carcinoma; CI: confidence interval; FHLC: family history of liver cancer; FRLC: first-degree relatives with liver cancer; No.: number; mHBV: maternal hepatitis B virus; AFP: alpha-fetoprotein; BCLC: Barcelona Clinic Liver Cancer; MELD: model for end-stage liver disease; HBV: hepatitis B virus

*, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$

Source: Authors

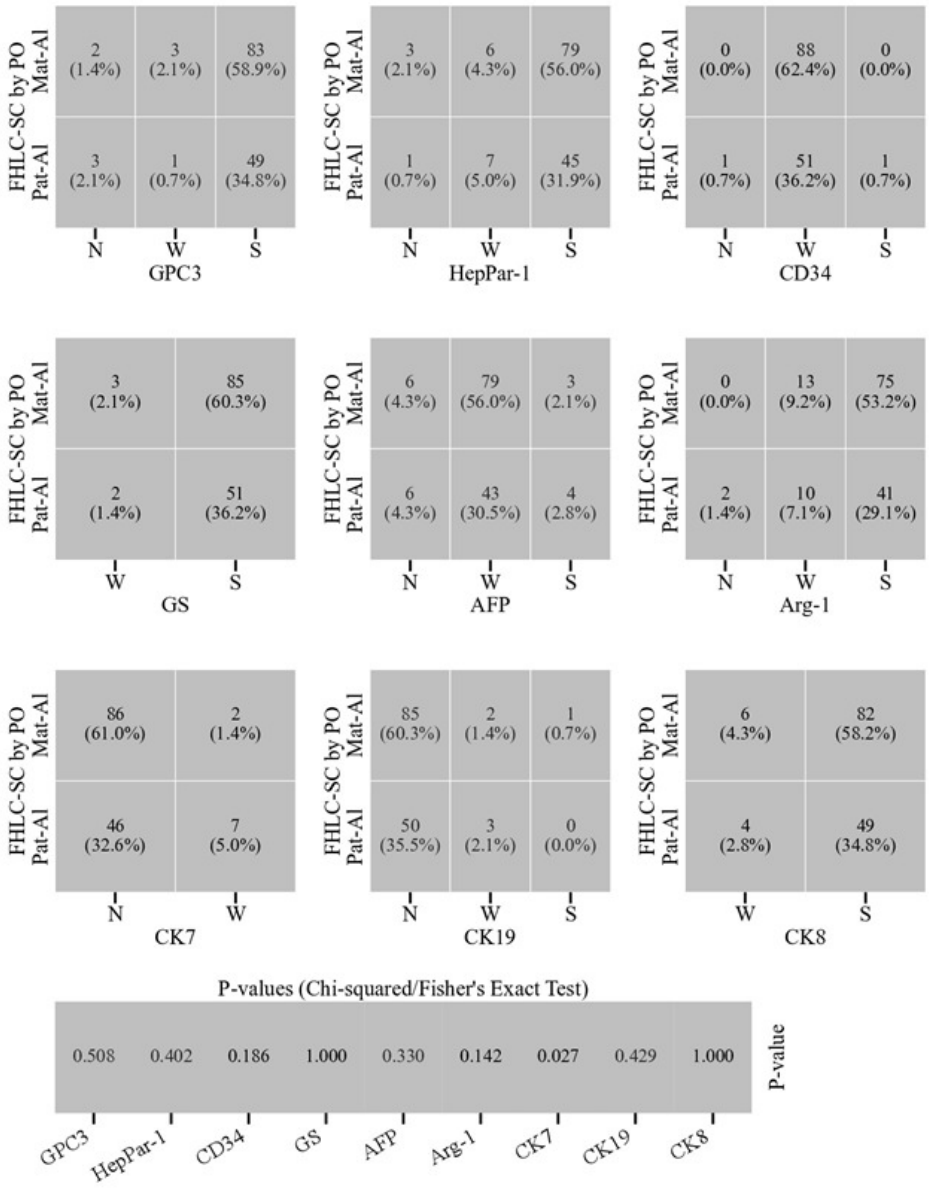


Fig. 6. Comparison of expression levels of HCC tissue biomarkers between patients with paternal FHLC alone and maternal FHLC alone

Mat-Al and Pat-Al represent maternal FHLC alone and paternal FHLC alone, respectively. N, W, and S denote negative, weakly positive, and strongly positive expression levels of biomarkers, respectively HCC: hepatocellular carcinoma; FHLC: family history of liver cancer; FHLC-SC: family history of liver cancer subclassification; PO: parental origin; GPC3: glypican-3; HepPar-1: hepatocyte paraffin 1; CD34: cluster of differentiation 34; GS: glutamine synthetase; AFP: alpha-fetoprotein; Arg-1: arginase-1; CK7: cytokeratin 7; CK19: cytokeratin 19; CK8: cytokeratin 8.

Source: **Authors.**

DISCUSSION

This study investigated the differential impact of paternal and maternal FHLC on the postoperative prognosis of HCC patients who underwent surgical resection. The findings revealed that maternal FHLC alone was independently associated with poorer RFS and OS and with a recurrence pattern relatively shifted toward earlier recurrence, whereas paternal FHLC alone was not significantly associated with poorer RFS or OS. These results support further evaluation of parental-origin FHLC as a potential prognostic factor in patients with resected HCC.

Previous studies have suggested that FHLC may be associated with postoperative outcomes in patients with HCC, although FHLC has generally been evaluated as a binary exposure without distinguishing parental origin (Li et al. 2019). More broadly, sex-related differences in HCC biology and clinical outcomes have also been reported (Toniutto et al. 2024). Compared with these earlier studies, the present analysis provides a more granular assessment by separating maternal and paternal FHLC rather than treating FHLC as a homogeneous exposure. The adverse prognostic association was concentrated in the maternal-FHLC subgroup, whereas paternal FHLC alone was not significantly associated with poorer RFS or OS. However, this contrast should be interpreted cautiously because the retrospective design and relatively small sizes of some FHLC subgroups preclude causal inference regarding maternal inheritance. Importantly, the association between maternal FHLC and adverse outcomes remained evident after accounting for the number of affected first-degree relatives and maternal HBV status.

Recent studies further emphasize that postoperative recurrence after HCC resection is multifactorial and reflects the combined influence of tumour characteristics, vascular invasion, background liver disease, and host-related factors (Malkawi et al. 2026). In parallel, recent work on hepatic sexual dimorphism has highlighted both oestrogen-dependent and oestrogen-independent mechanisms, including epigenetic regulation and immune responses, that contribute to sex-related differences in liver biology and disease (Jain and Monga 2026). Molecular studies in HBV-related HCC have also identified sex-related differences in TERT alterations and HBV integration patterns, particularly among younger patients (Kim et al. 2025). These contemporary observations provide biological context for investigating parental-origin differences in HCC outcomes; however, they do not directly establish a specific maternal-inheritance mechanism for the associations observed in this cohort.

The mechanisms underlying the differential associations of maternal and paternal FHLC remain incompletely understood and may involve genetic, mitochondrial, epigenetic, hormonal, viral, and shared environmental factors. Early animal experimental evidence shows that diethylnitrosamine exposure promotes the production of IL-6 in Kupffer cells in a manner dependent on the Toll-like receptor adaptor protein MyD88, ablation of which protects male mice from DEN-induced hepatocarcinogenesis, and estrogen-mediated inhibition of IL-6 production by Kupffer cells reduces liver cancer risk in females (Naugler et al. 2007). Several biological mechanisms may provide plausible explanations for the differential associations of maternal and paternal FHLC with postoperative outcomes, although none were directly tested in the present study. Inherited genetic variation, mitochondrial genetics, and epigenetic regulation may contribute to intergenerational differences in tumour susceptibility and behaviour. In particular, because mitochondrial DNA is maternally inherited, alterations in mitochondrial function represent one potential pathway linking maternal lineage with hepatocarcinogenesis and tumour progression (Liu et al. 2025; Rong et al. 2025). However, mitochondrial variants were not assessed in this cohort, and this mechanism therefore remains speculative. Sex-related viral, hormonal, and molecular factors may also provide relevant biological context. Sex differences in HBV integration patterns and tumour-associated genomic alterations have been reported in HBV-related HCC (Kim et al. 2025). More broadly, HBV genomic variations can influence host signalling pathways involved in hepatocarcinogenesis, providing additional evidence that viral molecular heterogeneity may contribute to differences in HBV-related HCC biology (Shoraka et al. 2023). Sex-related hormonal, epigenetic, and immune mechanisms may also contribute to differences in liver biology and hepatocarcinogenesis (Jain and Monga

2026). Sex-biased molecular signatures have also been described in HCC and may be associated with differences in tumour biology and survival (Kim et al. 2020). Nevertheless, these observations concern sex-related hepatocarcinogenesis in general and do not directly establish a mechanism for the maternal FHLC association observed in the present study.

This study's exploratory immunohistochemical analysis likewise provided limited mechanistic evidence. Although numerical differences were observed in several biomarkers between the maternal-FHLC-alone and paternal-FHLC-alone groups, only CK7 showed a statistically significant difference, with higher expression in the paternal-FHLC-alone group ($P = 0.027$). Differences in GPC3, HepPar-1, CD34, GS, AFP, Arg-1, CK19, and CK8 did not reach statistical significance. Cytokeratin expression has been associated with distinct histological and molecular phenotypes of HCC, including hepatocytic, biliary, and progenitor-like differentiation patterns (Calderaro et al. 2019). Therefore, these biomarker findings should be interpreted cautiously and cannot currently explain the poorer prognosis associated with maternal FHLC. Taken together, genetic, mitochondrial, epigenetic, viral, hormonal, and other shared familial factors may contribute to the observed parental-origin differences in HCC prognosis (Toniutto et al. 2024). However, the present findings should be interpreted as hypothesis-generating rather than evidence of a specific maternally inherited oncogenic mechanism. Further genomic, mitochondrial, epigenetic, and prospective multicentre studies are required to clarify the biological basis of these associations.

The study had several limitations. First, its retrospective design introduces the possibility of selection bias and residual confounding despite multivariable adjustment. Second, the study was conducted at a single centre, which may limit the generalisability of the findings to other centres. Third, the differential analysis of tumour markers could not undergo multivariable adjustment because of the limited sample size, and the observed biomarker differences should therefore be interpreted cautiously. In addition, FHLC was primarily ascertained through patient or family interviews and may have been subject to recall or misclassification bias. Maternal HBV infection status was evaluated, but mother-to-child HBV transmission was not directly established in individual patients. Furthermore, some FHLC subclasses contained relatively small numbers of patients, which may have reduced the precision of subgroup effect estimates. Further prospective multicentre studies with larger samples and integrated molecular analyses are needed to validate these findings and clarify the underlying biological mechanisms.

Despite these limitations, the findings have important clinical implications that warrant further investigation. Maternal FHLC may represent an easily obtainable familial factor associated with earlier recurrence and poorer postoperative outcomes after HCC resection. However, the present single-centre retrospective data are insufficient to support changes in surveillance intensity or adjuvant treatment solely on the basis of parental-origin FHLC. Future studies should evaluate whether parental origin provides incremental prognostic value beyond established clinicopathological factors and whether it can improve postoperative risk-stratification models. If externally validated, parental-origin FHLC could subsequently be considered as a low-cost clinical variable for recurrence-risk assessment and surveillance planning.

CONCLUSION

This study demonstrates that the parental origin of FHLC is associated with postoperative outcomes in patients with resected HCC, with poorer RFS and OS observed in patients with maternal FHLC alone. Paternal FHLC alone was not significantly associated with adverse survival outcomes. These findings support further evaluation of parental-origin FHLC as a potential prognostic factor and warrant prospective multicentre validation and mechanistic investigation.

RECOMMENDATIONS

This study shows that the parental origin of family history of liver cancer (FHLC) is associated with distinct postoperative outcomes in patients with resected HCC. The research's findings support further evaluation of parental-origin FHLC in postoperative risk-stratification models rather than immediate incorporation into

routine clinical practice. Future research should investigate the biological mechanisms underlying the observed differences between maternal- and paternal-origin FHLC, including potential genetic, mitochondrial, epigenetic, viral, and shared familial factors. Large-scale prospective multicentre cohorts and multi-omics investigations are also required to validate the present observations and determine whether parental-origin FHLC provides incremental prognostic value beyond established clinicopathological factors and can improve postoperative risk-stratification models.

AUTHOR CONTRIBUTIONS

LJB conceived and designed the study, ZSR analysed the data and wrote the manuscript, LT, JL, and YJ contributed to the data collection and preparation, YLN and YJY interpreted the results, and all authors contributed to the critical reading and revision of the manuscript.

ABBREVIATIONS

FHLC: family history of liver cancer
FHLC-SC: family history of liver cancer subclassification
FRLC: first-degree relatives with liver cancer
HCC: hepatocellular carcinoma
LC: liver cancer
RFS: recurrence-free survival
OS: overall survival
HR: hazard ratio
OR: odds ratio
SD: standard deviation
PO: parental origin
No.: number
TB: total bilirubin
ALB: albumin
ALT: alanine aminotransferase
AST: aspartate aminotransferase
PLT: platelet
HBV: hepatitis B virus
mHBV: maternal hepatitis B virus
HCV: hepatitis C virus
ALBI: albumin-bilirubin
MELD: model for end-stage liver disease
AFP: alpha-fetoprotein
BCLC: Barcelona Clinic Liver Cancer
GPC3: glypican-3
HepPar-1: hepatocyte paraffin 1
CD34: cluster of differentiation 34
GS: glutamine synthetase
Arg-1: arginase-1
CK7: cytokeratin 7
CK19: cytokeratin 19
CK8: cytokeratin 8

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest.

DATA AVAILABILITY STATEMENT

All raw data and code are available upon request.

FUNDING INFORMATION

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CLINICAL TRIAL REGISTRATION NUMBER

This study was approved by the Ethics Committee of West China Hospital, Sichuan University. The requirement for a specialised informed consent form was waived, as the routine admission consent included permission for retrospective medical data analysis for scientific research. The study and associated follow-up protocols were registered with the Chinese Clinical Trial Registry (ChiCTR1900022113 and ChiCTR1800016627).

ETHICS STATEMENT

The experimental protocol was established, according to the ethical guidelines of the Helsinki Declaration and was approved by the Human Ethics Committee of West China Hospital, Sichuan University(2018 Audit No. 541).

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Supplemental Tables

Table S1: Crude and adjusted HRs of variables for RFS analysis in the Cox regression models for patients with HCC after surgery

	Crude HR (95% CI)	*P value*	*Adjusted HR (95% CI)*	*P value*
Age (year)	1.00(0.99-1.00)	0.11	1.00(0.99-1.00)	0.69
Sex = male (female as ref.)	1.18(1.00-1.38)	0.04	1.08(0.91-1.29)	0.39
Smoke = yes (no as ref.)	1.23(1.10-1.37)	<0.01	1.24(1.09-1.41)	<0.01
Alcohol = yes (no as ref.)	1.01(0.89-1.13)	0.93	0.91(0.8-1.03)	0.13
FHLC = yes (no as ref.)	1.51(1.29-1.77)	<0.01	1.45(1.22-1.72)	<0.01
No. of kinships in FRLC = 1 (no FHLC as ref.)	1.45(1.20-1.76)	<0.01	1.43(1.16-1.75)	<0.01
No. of kinships in FRLC e" 2 ((no FHLC as ref.)	1.51(1.18-1.93)	<0.01	1.49(1.18-1.89)	<0.01
Paternal alone = yes (no FHLC as ref.)	0.94(0.66-1.34)	0.74	0.95(0.67-1.35)	0.79
Paternal involved = yes (no FHLC as ref.)	1.72(1.19-2.48)	<0.01	1.53(1.04-2.27)	0.03
Maternal alone = yes (no FHLC as ref.)	2.38(1.78-3.17)	<0.01	2.33(1.75-3.09)	<0.01
Maternal involved = yes (no FHLC as ref.)	1.46(0.90-2.35)	0.12	1.45(1.02-2.06)	0.04
Bi-parental alone = yes (no FHLC as ref.)	2.68(1.00-7.17)	0.05	3.51(1.68-7.35)	<0.01
Bi-parental involved = yes (no FHLC as ref.)	1.88(1.11-3.18)	0.02	2.26(1.60-3.20)	<0.01
Sibling alone = yes (no FHLC as ref.)	1.07(0.77-1.49)	0.68	1.15(0.81-1.63)	0.44
Maternal alone without mHBV = yes (no FHLC without mHBV as ref.)	3.01(2.12-4.29)	<0.01	2.99(2.07-4.32)	<0.01
Maternal alone with mHBV = yes (no FHLC with mHBV as ref.)	1.66(1.03-2.67)	0.04	1.59(1.02-2.47)	0.04
Maternal involved without mHBV = yes (no FHLC without mHBV as ref.)	2.63(1.18-5.86)	0.02	2.09(1.04-4.20)	0.04
Maternal involved with mHBV = yes (no FHLC with mHBV as ref.)	1.17(0.64-2.11)	0.61	1.21(0.81-1.82)	0.36
AFP	1.00(1.00-1.00)	0.05	1.00(1.00-1.00)	0.34
Tumor number e" 2 (1 as ref.)	1.48(1.28-1.71)	<0.01	1.31(0.88-1.94)	0.18
Tumor location = middle lobe (left lobe as ref.)	0.83(0.72-0.97)	0.02	0.93(0.78-1.11)	0.41
Tumor location = right lobe (left lobe as ref.)	1.08(0.96-1.21)	0.18	0.99(0.87-1.13)	0.92
Maximum tumor size	1.04(1.03-1.06)	<0.01	1.03(1.02-1.05)	<0.01
Microvascular invasion = yes (no as ref.)	1.73(1.55-1.93)	<0.01	1.59(1.41-1.79)	<0.01
BCLC stage =B (A as ref.)	1.51(1.29-1.76)	<0.01	1.10(0.72-1.67)	0.67
BCLC stage =C (A as ref.)	2.61(1.40-4.88)	<0.01	1.54(0.51-4.72)	0.45
Tumor differentiation = intermediate (high as ref.)	0.81(0.73-0.90)	<0.01	1.18(0.86-1.62)	0.30
Tumor differentiation = low (high as ref.)	1.33(1.19-1.49)	<0.01	1.39(1.01-1.92)	0.04
Child-Pugh grade = B (A as ref.)	0.87(0.64-1.18)	0.37	0.77(0.56-1.06)	0.11
MELD score	1.02(1.00-1.04)	0.13	1.04(1.01-1.07)	0.02
HBV = yes (no as ref.)	0.92(0.79-1.08)	0.31	0.68(0.55-0.83)	<0.01
Liver cirrhosis = yes (no as ref.)	1.23(1.09-1.38)	<0.01	1.24(1.10-1.40)	<0.01
Resection range = major (partial as ref.)	1.05(0.93-1.18)	0.44	0.94(0.84-1.06)	0.35
Preexisting resection = yes (no as ref.)	2.79(2.08-3.74)	<0.01	2.72(2.07-3.56)	<0.01

In the multivariable Cox regression model, HRs were adjusted for non-FHLC-derived variables, including age, sex, smoking, alcohol use, hepatitis B virus infection, AFP levels, tumor number, tumor location, maximum tumor size, microvascular invasion, BCLC stage, tumor differentiation, Child-Pugh grade, MELD score, liver cirrhosis, resection range and preexisting resection. Ref. refers to the reference variables in the Cox regression model. HR, hazard ratio; RFS, recurrence-free survival; HCC, hepatocellular carcinoma; CI, confidence interval; FHLC, family history of liver cancer; FRLC, first-degree relatives with liver cancer; No., number; mHBV, maternal hepatitis B virus; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; MELD, model for end-stage liver disease; HBV, hepatitis B virus

Source: Authors

Table S2: Crude and adjusted HRs of variables for OS analysis in the Cox regression models for patients with HCC after surgery

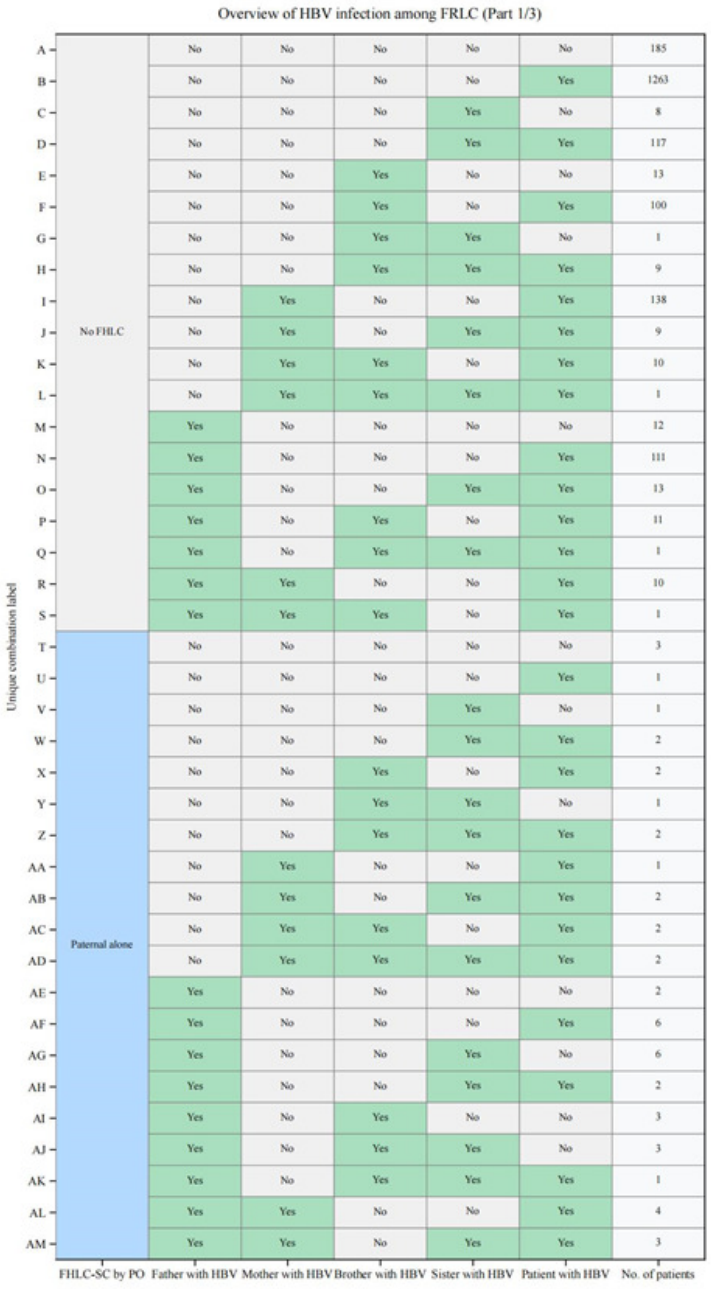
	Crude HR (95% CI)	*P value*	*Adjusted HR (95% CI)*	*P value*
Age (year)	1.00(1.00-1.01)	0.46	1.01(1.00-1.01)	0.10
Sex = male (female as ref.)	1.13(0.91-1.40)	0.26	0.95(0.75-1.21)	0.70
Smoke = yes (no as ref.)	1.36(1.17-1.58)	<0.01	1.40(1.18-1.66)	<0.01
Alcohol = yes (no as ref.)	1.03(0.88-1.20)	0.71	0.92(0.78-1.09)	0.33
FHLC = yes (no as ref.)	1.56(1.27-1.92)	<0.01	1.51(1.21-1.89)	<0.01
No. of kinships in FRLC = 1 (no FHLC as ref.)	1.40(1.09-1.81)	0.01	1.38(1.04-1.81)	0.02
No. of kinships in FRLC e" 2 ((no FHLC as ref.)	1.73(1.27-2.37)	<0.01	1.78(1.30-2.42)	<0.01
Paternal alone = yes (no FHLC as ref.)	0.62(0.35-1.10)	0.10	0.66(0.36-1.22)	0.18
Paternal involved = yes (no FHLC as ref.)	1.79(1.10-2.89)	0.02	1.73(1.07-2.82)	0.03
Maternal alone = yes (no FHLC as ref.)	2.98(2.11-4.22)	<0.01	3.02(2.15-4.24)	<0.01
Maternal involved = yes (no FHLC as ref.)	2.33(1.34-4.03)	<0.01	2.23(1.31-3.80)	<0.01
Bi-parental alone = yes (no FHLC as ref.)	1.76(0.44-7.07)	0.42	3.24(1.35-7.77)	0.01
Bi-parental involved = yes (no FHLC as ref.)	2.04(1.09-3.81)	0.03	2.70(1.72-4.24)	<0.01
Sibling alone = yes (no FHLC as ref.)	0.96(0.62-1.50)	0.86	0.98(0.62-1.55)	0.94
Maternal alone without mHBV = yes (no FHLC without mHBV as ref.)	3.27(2.16-4.97)	<0.01	3.40(2.21-5.23)	<0.01
Maternal alone with mHBV = yes (no FHLC with mHBV as ref.)	2.40(1.32-4.35)	<0.01	2.47(1.42-4.32)	<0.01
Maternal involved without mHBV = yes (no FHLC without mHBV as ref.)	3.67(1.52-8.86)	<0.01	3.32(1.34-8.27)	0.01
Maternal involved with mHBV = yes (no FHLC with mHBV as ref.)	1.88(0.93-3.77)	0.08	1.83(0.95-3.53)	0.07
AFP	1.00(1.00-1.00)	0.42	1.00(1.00-1.00)	0.07
Tumor number e" 2 (1 as ref.)	1.27(1.04-1.54)	0.02	0.94(0.57-1.56)	0.82
Tumor location = middle lobe (left lobe as ref.)	0.76(0.62-0.94)	0.01	0.80(0.62-1.02)	0.07
Tumor location = right lobe (left lobe as ref.)	1.10(0.95-1.28)	0.21	0.98(0.82-1.17)	0.79
Maximum tumor size	1.03(1.01-1.05)	<0.01	1.02(1.00-1.04)	0.02
Microvascular invasion = yes (no as ref.)	1.55(1.33-1.80)	<0.01	1.47(1.25-1.72)	<0.01
BCLC stage =B (A as ref.)	1.31(1.06-1.62)	0.01	1.35(0.78-2.31)	0.28
BCLC stage =C (A as ref.)	2.21(0.92-5.32)	0.08	1.55(0.54-4.39)	0.41
Tumor differentiation = intermediate (high as ref.)	0.94(0.81-1.09)	0.40	1.73(1.07-2.80)	0.03
Tumor differentiation = low (high as ref.)	1.18(1.02-1.37)	0.03	1.81(1.11-2.97)	0.02
Child-Pugh grade = B (A as ref.)	0.75(0.48-1.15)	0.19	0.63(0.39-1.01)	0.05
MELD score	1.02(0.99-1.05)	0.26	1.05(1.01-1.09)	0.02
HBV = yes (no as ref.)	0.92(0.74-1.13)	0.40	0.67(0.51-0.87)	<0.01
Liver cirrhosis = yes (no as ref.)	1.32(1.12-1.55)	<0.01	1.34(1.13-1.58)	<0.01
Resection range = major (partial as ref.)	1.12(0.95-1.31)	0.17	1.02(0.87-1.20)	0.77
Preexisting resection = yes (no as ref.)	1.67(1.07-2.60)	0.02	1.53(0.92-2.55)	0.10

In the multivariable Cox regression model, HRs were adjusted for non-FHLC-derived variables, including age, sex, smoking, alcohol use, hepatitis B virus infection, AFP levels, tumor number, tumor location, maximum tumor size, microvascular invasion, BCLC stage, tumor differentiation, Child-Pugh grade, MELD score, liver cirrhosis, resection range and preexisting resection. Ref. refers to the reference variables in the Cox regression model. HR, hazard ratio; OS, overall survival; HCC, hepatocellular carcinoma; CI, confidence interval; FHLC, family history of liver cancer; FRLC, first-degree relatives with liver cancer; No., number; mHBV, maternal hepatitis B virus; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; MELD, model for end-stage liver disease; HBV, hepatitis B virus

Source: Authors

Supplemental Figures and Legends

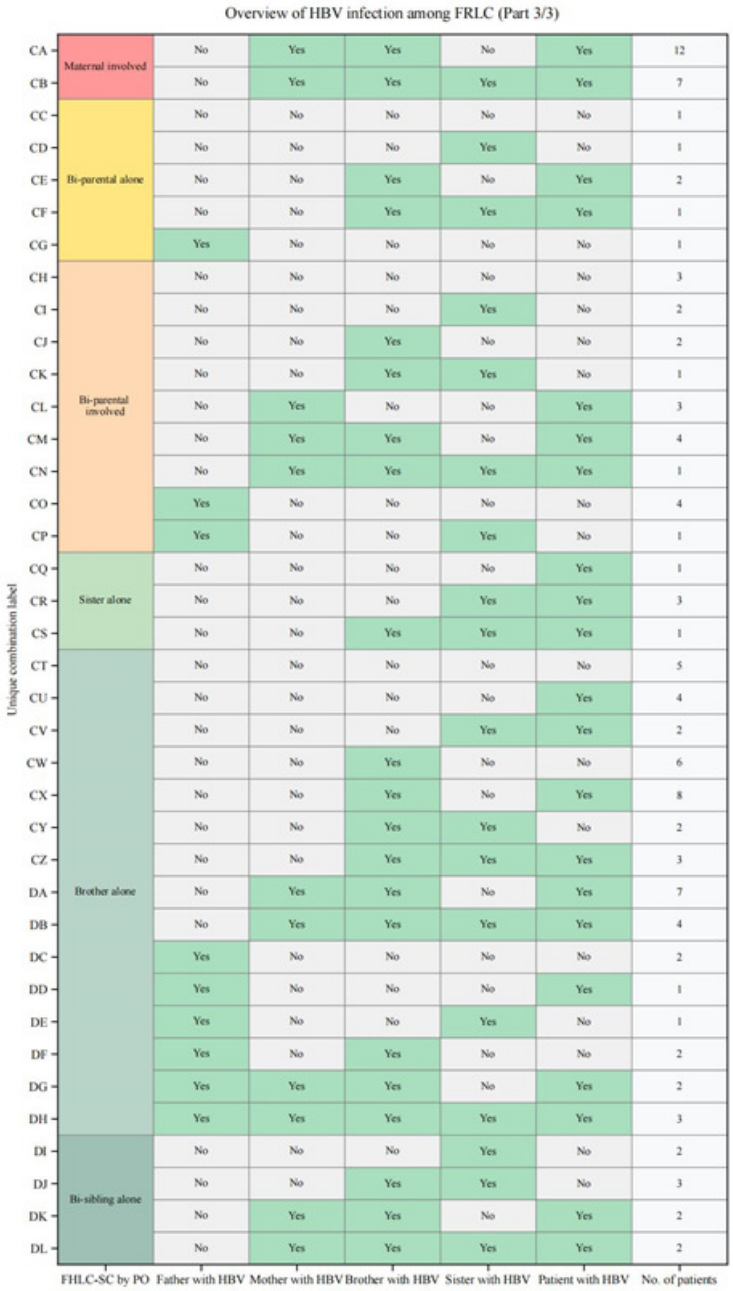
Fig. S1



	FHLC-SC by PO	Father with HBV	Mother with HBV	Brother with HBV	Sister with HBV	Patient with HBV	No. of patients
A	No FHLC	No	No	No	No	No	185
B	No FHLC	No	No	No	No	Yes	1263
C	No FHLC	No	No	No	Yes	No	8
D	No FHLC	No	No	No	Yes	Yes	117
E	No FHLC	No	No	Yes	No	No	13
F	No FHLC	No	No	Yes	No	Yes	100
G	No FHLC	No	No	Yes	Yes	No	1
H	No FHLC	No	No	Yes	Yes	Yes	9
I	No FHLC	No	Yes	No	No	Yes	138
J	No FHLC	No	Yes	No	Yes	Yes	9
K	No FHLC	No	Yes	Yes	No	Yes	10
L	No FHLC	No	Yes	Yes	Yes	Yes	1
M	No FHLC	Yes	No	No	No	No	12
N	No FHLC	Yes	No	No	No	Yes	111
O	No FHLC	Yes	No	No	Yes	Yes	13
P	No FHLC	Yes	No	Yes	No	Yes	11
Q	No FHLC	Yes	No	Yes	Yes	Yes	1
R	No FHLC	Yes	Yes	No	No	Yes	10
S	No FHLC	Yes	Yes	Yes	No	Yes	1
T	Paternal alone	No	No	No	No	No	3
U	Paternal alone	No	No	No	No	Yes	1
V	Paternal alone	No	No	No	Yes	No	1
W	Paternal alone	No	No	No	Yes	Yes	2
X	Paternal alone	No	No	Yes	No	Yes	2
Y	Paternal alone	No	No	Yes	Yes	No	1
Z	Paternal alone	No	No	Yes	Yes	Yes	2
AA	Paternal alone	No	Yes	No	No	Yes	1
AB	Paternal alone	No	Yes	No	Yes	Yes	2
AC	Paternal alone	No	Yes	Yes	No	Yes	2
AD	Paternal alone	No	Yes	Yes	Yes	Yes	2
AE	Paternal alone	Yes	No	No	No	No	2
AF	Paternal alone	Yes	No	No	No	Yes	6
AG	Paternal alone	Yes	No	No	Yes	No	6
AH	Paternal alone	Yes	No	No	Yes	Yes	2
AI	Paternal alone	Yes	No	Yes	No	No	3
AJ	Paternal alone	Yes	No	Yes	Yes	No	3
AK	Paternal alone	Yes	No	Yes	Yes	Yes	1
AL	Paternal alone	Yes	Yes	No	No	Yes	4
AM	Paternal alone	Yes	Yes	No	Yes	Yes	3

Overview of HBV infection among FRLC (Part 2/3)

Unique combination label	FHLC-SC by PO	Father with HBV	Mother with HBV	Brother with HBV	Sister with HBV	Patient with HBV	No. of patients
AN	Paternal alone	Yes	Yes	Yes	No	Yes	3
AO		Yes	Yes	Yes	Yes	Yes	1
AP	Paternal involved	No	No	Yes	No	No	1
AQ		No	Yes	No	No	Yes	3
AR		No	Yes	No	Yes	Yes	2
AS		No	Yes	Yes	No	Yes	4
AT		No	Yes	Yes	Yes	Yes	2
AU		Yes	No	Yes	No	No	2
AV		Yes	No	Yes	Yes	No	1
AW		Yes	Yes	No	No	Yes	6
AX		Yes	Yes	No	Yes	Yes	1
AY		Yes	Yes	Yes	No	Yes	10
AZ		Yes	Yes	Yes	Yes	Yes	3
BA	Maternal alone	No	No	No	No	No	21
BB		No	No	No	Yes	No	16
BC		No	No	Yes	No	No	7
BD		No	No	Yes	Yes	No	6
BE		No	Yes	No	No	Yes	12
BF		No	Yes	No	Yes	Yes	12
BG		No	Yes	Yes	No	Yes	8
BH		No	Yes	Yes	Yes	Yes	2
BI		Yes	No	No	No	No	2
BJ		Yes	No	Yes	No	No	1
BK		Yes	Yes	No	Yes	Yes	1
BL	Maternal involved	No	No	Yes	No	No	1
BM		No	Yes	No	No	Yes	1
BN		No	Yes	Yes	No	Yes	1
BO		Yes	Yes	No	No	Yes	1
BP		Yes	Yes	Yes	No	Yes	1
BQ		No	No	No	No	No	2
BR		No	No	No	Yes	No	2
BS		No	No	Yes	No	No	1
BT		No	No	Yes	Yes	No	2
BU		No	Yes	No	No	Yes	2
BV		No	Yes	Yes	No	Yes	2
BW		Yes	No	No	No	No	1
BX		No	No	Yes	No	No	2
BY		No	Yes	No	No	Yes	4
BZ		No	Yes	No	Yes	Yes	1



	FHLC-SC by PO	Father with HBV	Mother with HBV	Brother with HBV	Sister with HBV	Patient with HBV	No. of patients
CA	Maternal involved	No	Yes	Yes	No	Yes	12
CB		No	Yes	Yes	Yes	Yes	7
CC	Bi-parental alone	No	No	No	No	No	1
CD		No	No	No	Yes	No	1
CE		No	No	Yes	No	Yes	2
CF		No	No	Yes	Yes	Yes	1
CG		Yes	No	No	No	No	1
CH	Bi-parental involved	No	No	No	No	No	3
CI		No	No	No	Yes	No	2
CJ		No	No	Yes	No	No	2
CK		No	No	Yes	Yes	No	1
CL		No	Yes	No	No	Yes	3
CM		No	Yes	Yes	No	Yes	4
CN		No	Yes	Yes	Yes	Yes	1
CO		Yes	No	No	No	No	4
CP		Yes	No	No	Yes	No	1
CQ	Sister alone	No	No	No	No	Yes	1
CR		No	No	No	Yes	Yes	3
CS		No	No	Yes	Yes	Yes	1
CT	Brother alone	No	No	No	No	No	5
CU		No	No	No	No	Yes	4
CV		No	No	No	Yes	Yes	2
CW		No	No	Yes	No	No	6
CX		No	No	Yes	No	Yes	8
CY		No	No	Yes	Yes	No	2
CZ		No	No	Yes	Yes	Yes	3
DA		No	Yes	Yes	No	Yes	7
DB		No	Yes	Yes	Yes	Yes	4
DC		Yes	No	No	No	No	2
DD		Yes	No	No	No	Yes	1
DE		Yes	No	No	Yes	No	1
DF		Yes	No	Yes	No	No	2
DG		Yes	Yes	Yes	No	Yes	2
DH		Yes	Yes	Yes	Yes	Yes	3
DI	Bi-sibling alone	No	No	No	Yes	No	2
DJ		No	No	Yes	Yes	No	3
DK		No	Yes	Yes	No	Yes	2
DL		No	Yes	Yes	Yes	Yes	2

Fig. S1. Overview of HBV infection in FRLC
HBV, hepatitis B virus; FRLC, first-degree relatives with liver cancer; FHLC, family history of liver cancer; FHLC-SC, family history of liver cancer subclassification; PO, parental origin; No., number.
Source: Authors

Fig. S2

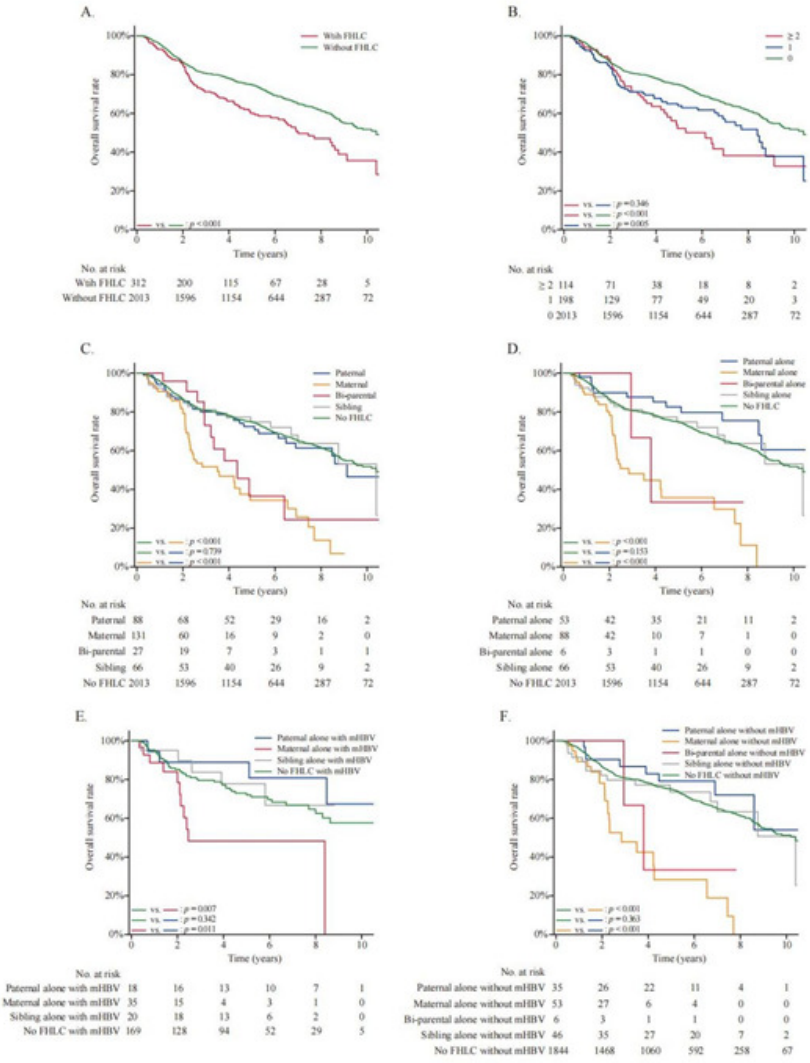


Fig. S2. Comparison of OS curves for patients with HCC after surgery based on FHLC, No. of kinships in FRLC, FHLC by PO, and FHLC-SC by PO and/or mHBV infection
(A). OS curve comparison based on FHLC; (B). OS curve comparison based on No. of kinships in FRLC; (C). OS curve comparison based on FHLC by PO; (D). OS curve comparison based on FHLC-SC by PO; (E). OS curve comparison based on FHLC-SC by PO among patients with mHBV; (F). OS curve comparison based on FHLC-SC by PO among patients without mHBV. OS, overall survival; HCC, hepatocellular carcinoma; FHLC, family history of liver cancer; FRLC, first-degree relatives with liver cancer; FHLC-SC, family history of liver cancer subclassification; PO, parental origin; mHBV, maternal hepatitis B virus; No., number
Source: Authors

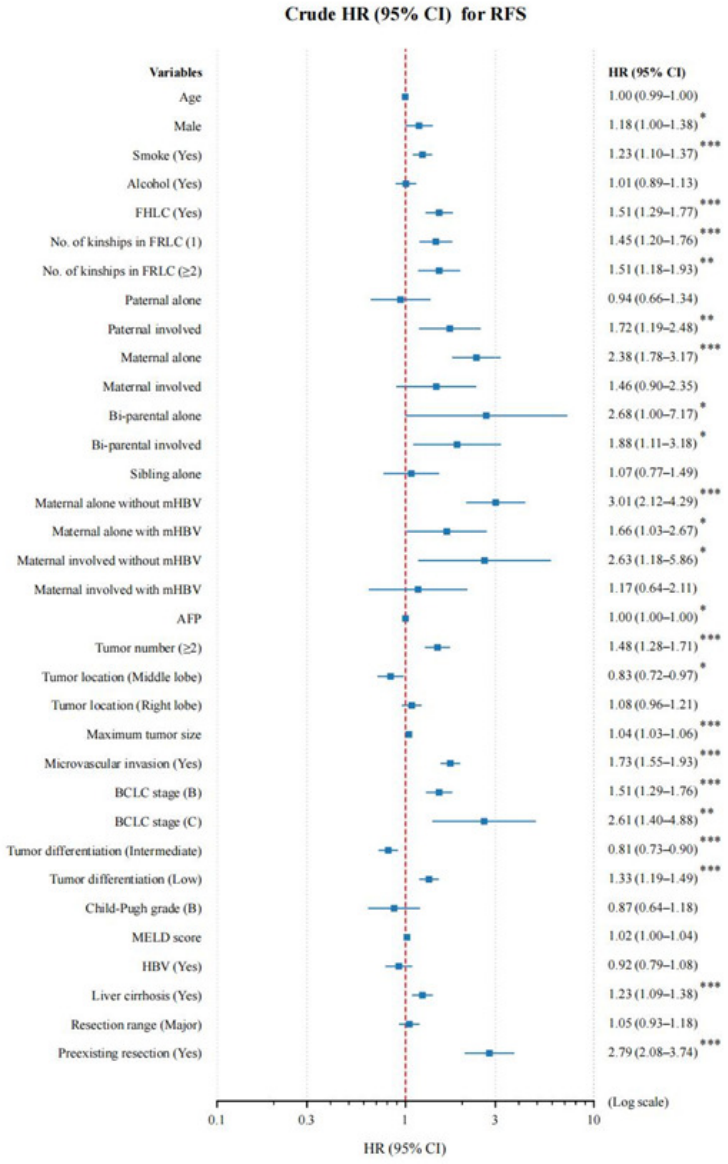


Fig. S3. Crude HRs of variables for RFS analysis in the univariate Cox regression model for patients with HCC after surgery
The "No FHLC" group served as the reference for FHLC-derived variables in the Cox regression model. HR, hazard ratio; RFS, recurrence-free survival; HCC, hepatocellular carcinoma; CI, confidence interval; FHLC, family history of liver cancer; FRLC, first-degree relatives with liver cancer; No., number; mHBV, maternal hepatitis B virus; AFP, alfa-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; MELD, model for end-stage liver disease; HBV, hepatitis B virus. *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$
Source: Authors

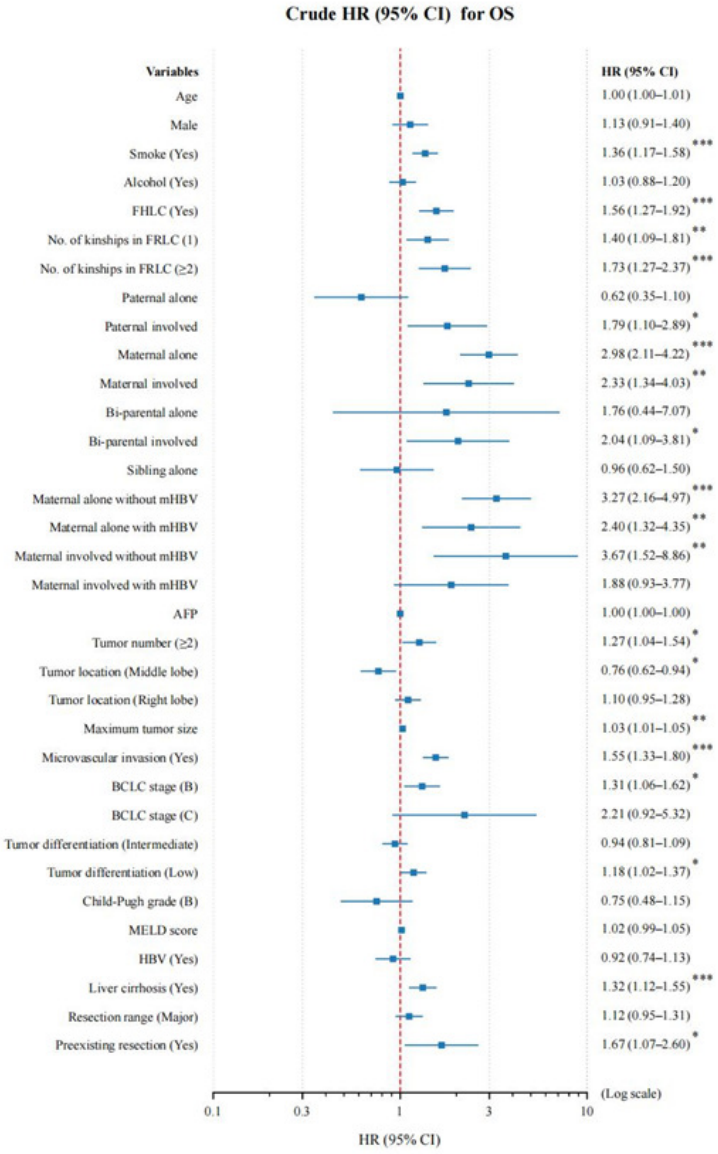


Fig. S4. Crude HRs of variables for OS analysis in the univariate Cox regression model for patients with HCC after surgery
The "No FHLC" group served as the reference for FHLC-derived variables in the Cox regression model. HR, hazard ratio; OS, overall survival; HCC, hepatocellular carcinoma; CI, confidence interval; FHLC, family history of liver cancer; FRLC, first-degree relatives with liver cancer; No., number; mHBV, maternal hepatitis B virus; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; MELD, model for end-stage liver disease; HBV, hepatitis B virus. *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$
Source: Authors

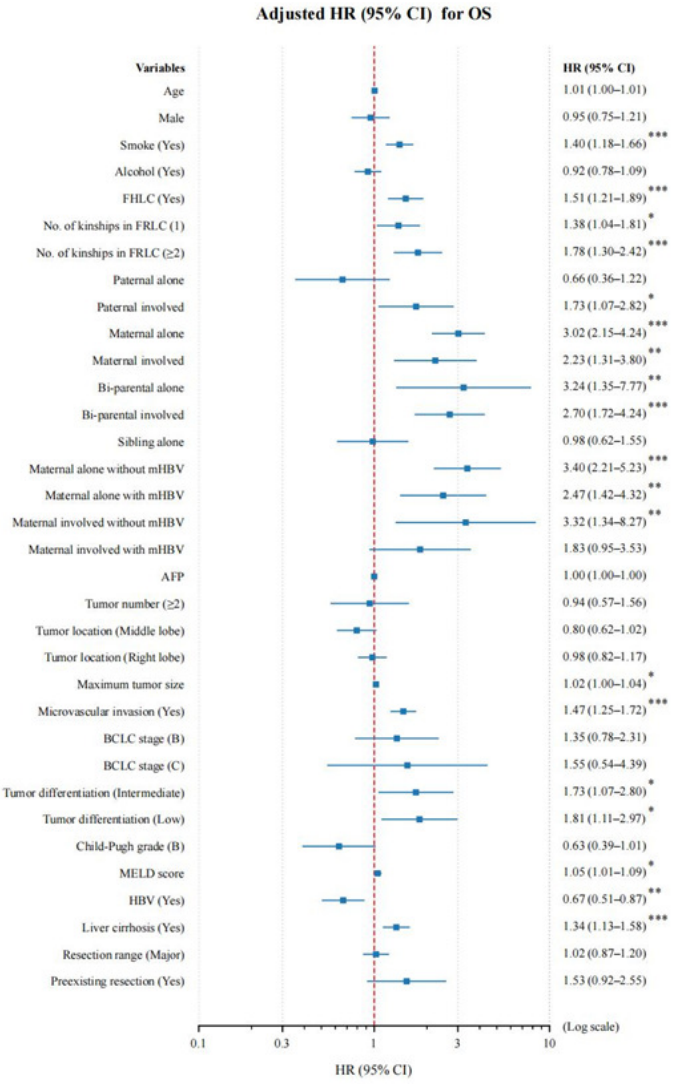


Fig. S5. Adjusted HRs of variables for OS analysis in the multivariable Cox regression model for patients with HCC after surgery
HRs were adjusted for non-FHLC-derived variables, including age, sex, smoking, alcohol use, hepatitis B virus infection, AFP levels, tumor number, tumor location, maximum tumor size, microvascular invasion, BCLC stage, tumor differentiation, Child-Pugh grade, MELD score, liver cirrhosis, resection range and preexisting resection. The "No FHLC" group served as the reference for FHLC-derived variables in the Cox regression model. HR, hazard ratio; OS, overall survival; HCC, hepatocellular carcinoma; CI, confidence interval; FHLC, family history of liver cancer; FRLC, first-degree relatives with liver cancer; No., number; mHBV, maternal hepatitis B virus; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; MELD, model for end-stage liver disease; HBV, hepatitis B virus. *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$
Source: Authors

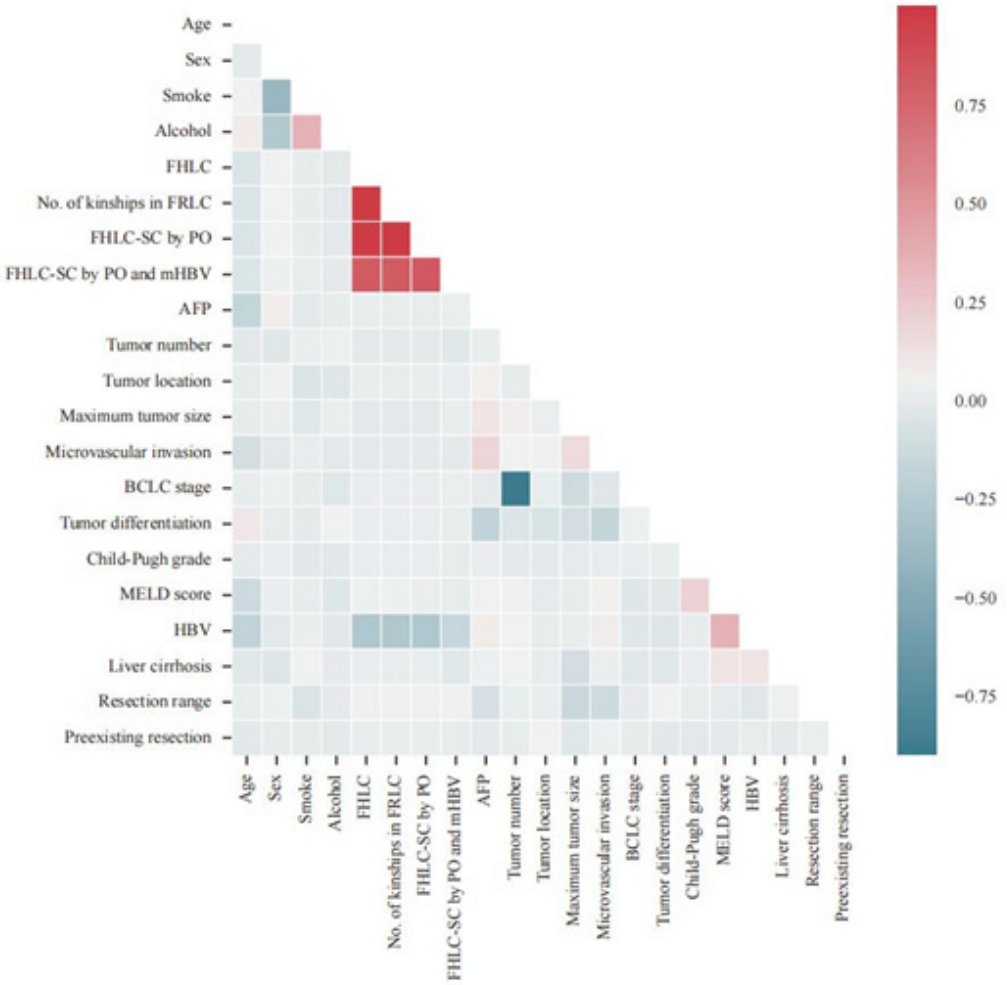


Fig. S6. Spearman correlation between variables in multivariable Cox regression models for patients with HCC after surgery
The block color intensity increases with the strength of the correlation between two intersecting variables. HCC, hepatocellular carcinoma; CI, confidence interval; FHLC, family history of liver cancer; No., number; FRLC, first-degree relatives with liver cancer; FHLC-SC, family history of liver cancer subclassification; PO, parental origin; mHBV, maternal hepatitis B virus; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; MELD, model for end-stage liver disease; HBV, hepatitis B virus

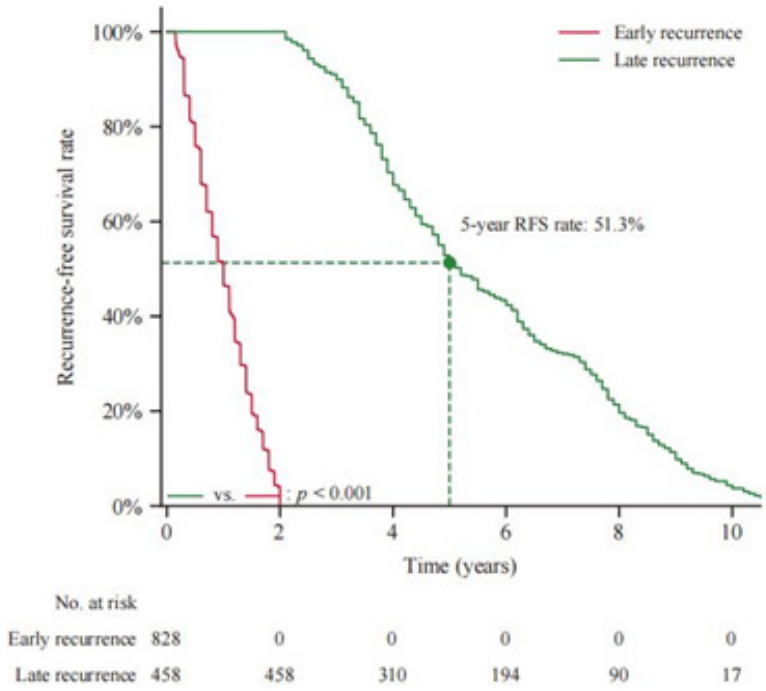


Fig. S7. Comparison of RFS curves for patients with HCC after surgery based on the recurrence phase
RFS, recurrence-free survival; HCC, hepatocellular carcinoma; No., number
Source: Authors

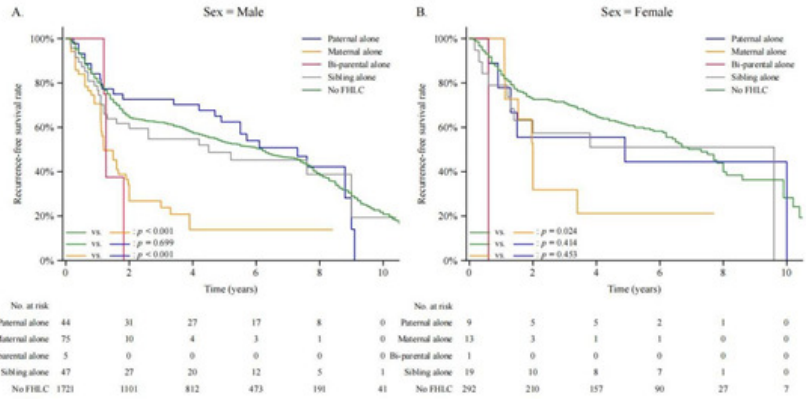


Fig. S8. Sex-stratified comparison of RFS curves in patients with HCC after surgery based on FHLC-SC according to PO
(A). RFS curve comparison in male patients; (B). RFS curve comparison in female patients. RFS, recurrence-free survival; HCC, hepatocellular carcinoma; FHLC, family history of liver cancer; FHLC-SC, family history of liver cancer subclassification; PO, parental origin; No., number
Source: Authors

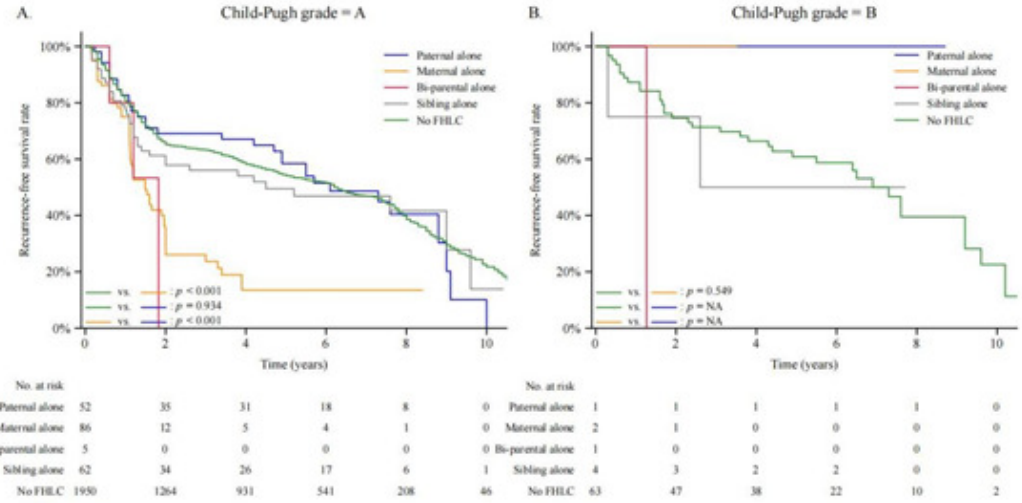


Fig. S9. Child-Pugh grade-stratified comparison of RFS curves in patients with HCC after surgery based on FHLC-SC by PO
(A). RFS curve comparison in Child-Pugh grade A patients; (B). RFS curve comparison in Child-Pugh grade B patients. RFS, recurrence-free survival; HCC, hepatocellular carcinoma; FHLC, family history of liver cancer; FHLC-SC, family history of liver cancer subclassification; PO, parental origin; No., number; NA, not available
Source: Authors

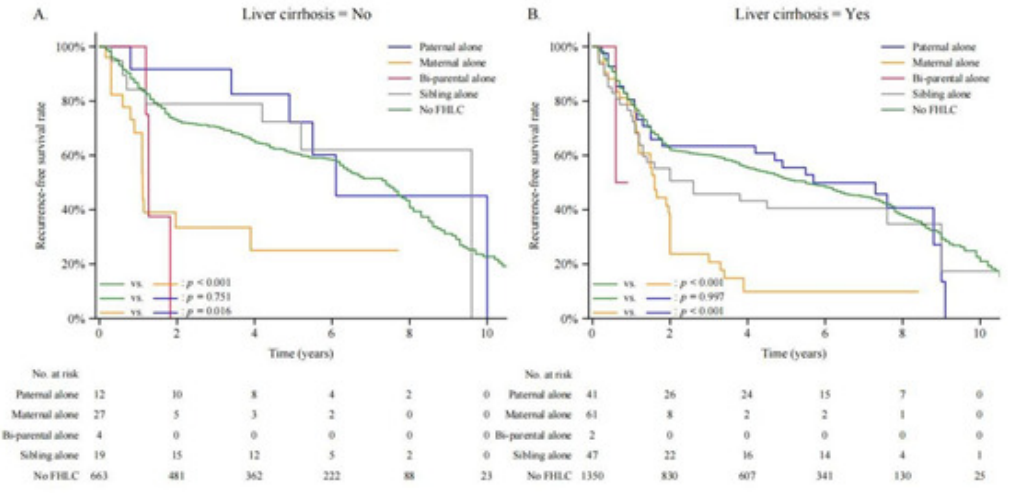


Fig. S10. Liver cirrhosis-stratified comparison of RFS curves in patients with HCC after surgery based on FHLC-SC by PO
(A). RFS curve comparison in patients without liver cirrhosis; (B). RFS curve comparison in patients with liver cirrhosis. RFS, recurrence-free survival; HCC, hepatocellular carcinoma; FHLC, family history of liver cancer; FHLC-SC, family history of liver cancer subclassification; PO, parental origin; No., number
Source: Authors

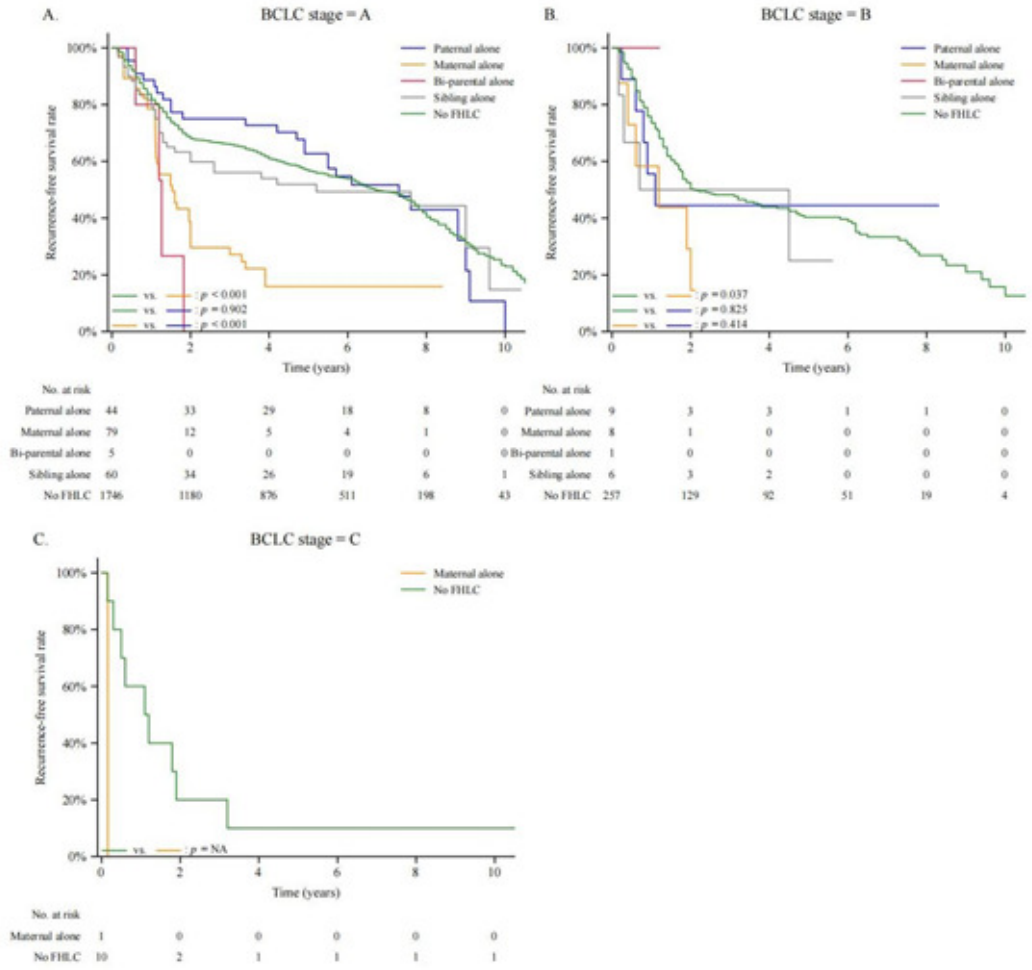


Fig. S11. BCLC stage-stratified comparison of RFS curves in patients with HCC after surgery based on FHLC-SC by PO
(A). RFS curve comparison in BCLC stage A patients; (B). RFS curve comparison in BCLC stage B patients; (C). RFS curves comparison in BCLC stage C patients. BCLC, Barcelona Clinic Liver Cancer; RFS, recurrence-free survival; HCC, hepatocellular carcinoma; FHLC, family history of liver cancer; FHLC-SC, family history of liver cancer subclassification; PO, parental origin; No., number; NA, not available
Source: Authors

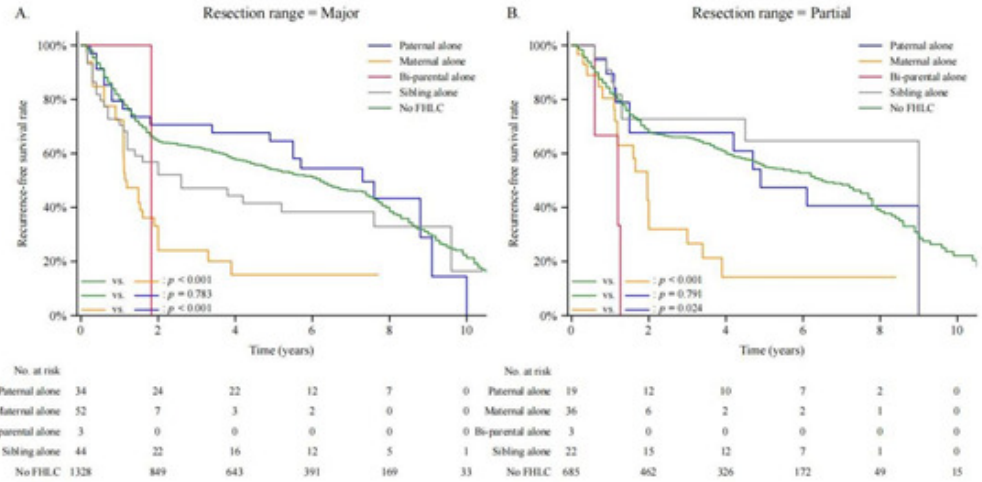


Fig. S12. Resection range-stratified comparison of RFS curves in patients with HCC after surgery based on FHLC-SC by PO
(A). RFS curve comparison in patients who underwent major liver resection; (B). RFS curve comparison in patients who underwent partial liver resection. RFS, recurrence-free survival; HCC, hepatocellular carcinoma; FHLC, family history of liver cancer; FHLC-SC, family history of liver cancer subclassification; PO, parental origin; No., number
Source: Authors

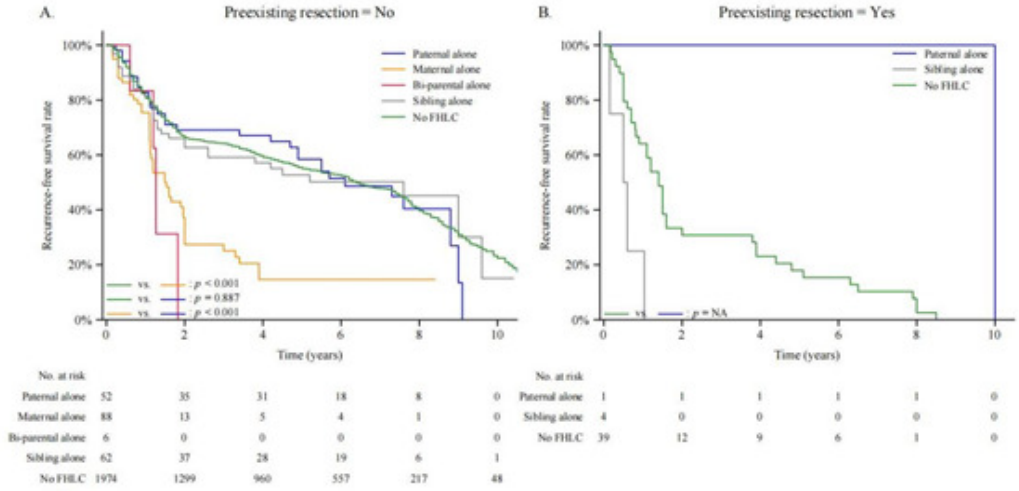


Fig. S13. Preexisting resection-stratified comparison of RFS curves in patients with HCC after surgery based on FHLC-SC by PO
(A). RFS curve comparison in patients without preexisting resection; (B). RFS curve comparison in patients with preexisting resection. RFS, recurrence-free survival; HCC, hepatocellular carcinoma; FHLC, family history of liver cancer; FHLC-SC, family history of liver cancer subclassification; PO, parental origin; No., number; NA, not available
Source: Authors