Running title: 6-month relapse in HCC after RFA

Variables Influencing 6-Month Relapse in Early-Stage Hepatocellular Carcinoma After Radiofrequency Ablation

Yumchinserchin Narangerel[1,2], Gonchigsuren Dagvasumberel[3], Enebish Sundui[4], Adilsaikhan Mendjargal[2]

[1]Department of Interventional Radiology National Cancer Center of Mongolia, Ulaanbaatar, Mongolia;

[2]Department of Radiology, Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia;

[3]Department of Oncology, Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia;

[4]Department of Anatomy, Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia.

Corresponding Author
Yumchinserchin Narangerel (M.D., M.Sc.) Department of Interventional Radiology National Cancer Center of Mongolia,
Ulaanbaatar 13270, Mongolia

Tel: +976-99017063
E-mail: yumka.dr@cancer-center.gov.mn
ORCID: https://orcid.org/0009-0002-0007-9620

Objectives: Hepatocellular carcinoma (HCC) emerged as a global health concern in 2020, ranking as the sixth most diagnosed cancer and the third leading cause of cancer-related death. This study analyzed predictors of 6-month relapse in early-stage HCC patients after Radiofrequency Ablation (RFA). **Methods:** This retrospective study, from January 1, 2018, to December 31, 2022, meticulously explored ablation methods for early-stage HCC treatment. Data collection included a 6-month relapse definition, demographic details, and tumor-related variables. **Results:** Over five years, 483 participants underwent RFA for early-stage HCC, presenting diverse demographic and tumor-related profiles. Significant associations were found between relapse and factors such as gender, smoking, alcohol use, tumor size, specific tumor locations, and pre-treatment AST levels. Notably, 6.8% of participants experienced relapse within six months. In the multivariate analysis, adjusting for confounders, smoking ($p = 0.014$), tumor size > 3cm ($p < 0.001$), tumor location S2 ($p < 0.001$), and pre-treatment AST levels ($p = 0.015$) remained significant predictors. **Conclusion:** This study sheds light on the complex dynamics of 6-month relapse in early-stage HCC patients, emphasizing the significance of predictors such as smoking, tumor size, tumor location, and pre-treatment AST levels.
Keywords: Ablation safety, Hepatic tumors, Residual tumor, Ablation techniques, Radiofrequency ablation

Introduction

In 2020, hepatocellular carcinoma (HCC) emerged as a global health concern, ranking as the sixth most diagnosed cancer and the third leading cause of cancer death with 906,000 new cases and 830,000 deaths—an alarming upward trend [1]. As the predominant form of primary liver cancers, HCC represents 75–85% of cases, exerting a profound impact on global health [2]. Despite notable progress in ablative therapeutic modalities for HCC, a substantial knowledge gap persists, particularly within the critical 6-month period, where limited data exists on relapse—whether associated with residual tumors or

aggressive reoccurrence [3-4]. This gap is noteworthy even with the widespread adoption of Radiofrequency Ablation (RFA) for treating Hepatocellular Carcinoma (HCC) [5-6]. Frequent local tumor progression (LTP) and significant recurrence rates, with reported 5-year LTP rates ranging from 3.2% to 27.0%, underscoring the imperative for a comprehensive understanding of recurrence dynamics [7]. Notably, many studies in this domain have extended over longer durations, emphasizing the urgency for focused investigations, especially in the early post-ablation period, such as the crucial 6-month timeframe [5-6, 8-9].

Mongolia bears an exceptionally high HCC burden, boasting the world's highest incidence at 86 cases per 100,000 inhabitants [1]. Remarkably, Mongolia has successfully treated HCC using ablation therapies since 2008 [10]. This study aims to contribute valuable insights into the predictors of 6-month relapse in early-stage HCC patients. Importantly, this study fills a gap in the existing literature by investigating the early 6-month post-radiofrequency ablation (RFA) period for Hepatocellular Carcinoma (HCC). While previous research has often focused on extended follow-up, our targeted approach aims to unravel the dynamics of relapse, addressing a significant knowledge gap. By examining recurrence, primarily related to residual tumors or aggressive reoccurrence in this early stage, our study provides unique and valuable insights, distinguishing it from prior efforts. The imperative to comprehend and mitigate early recurrence is underscored by its potential impact on patient prognosis and the formulation of effective treatment strategies. Therefore, this research holds added significance, particularly in regions like Mongolia, grappling with disproportionately high HCC incidence and mortality rates. Addressing these challenges is paramount for improving global outcomes in HCC management and advancing the field toward more effective and tailored interventions.

Materials and Methods

1. Study design

This retrospective study meticulously explored ablation methods for early-stage HCC treatment. Given the nature of the study, where all available cases were included due to the absence of a sampling procedure, our approach aimed to provide a comprehensive overview of treatment efficacy and complications over a specified timeframe. Furthermore, the study design incorporated a consideration of repeated measurements

to enhance the depth of our insights.

2. Study population and data collection

A comprehensive dataset was meticulously compiled from the National Cancer Center of Mongolia, a prominent tertiary healthcare institution with specialized units and dedicated cancer treatment ablation rooms. The study, conducted from January 1, 2018, to December 31, 2022, focused specifically on cases of early-stage Hepatocellular Carcinoma (HCC) treated exclusively with ablation methods. The inclusion criteria encompassed individuals with newly diagnosed HCC who had not undergone any previous treatment. Exclusion criteria were applied to cases involving combined treatments beyond ablation, encompassing those treated with Microwave Ablation (MWA).

Following established guidelines [9], our study confirmed HCC diagnosis through a comprehensive approach. This involved imaging studies (ultrasound, CT, and MRI), blood tests (AFP levels), and liver biopsy. Dynamic imaging studies, such as contrast-enhanced CT or MRI, were employed for early-stage detection by evaluating blood flow patterns within the liver. Adhering to these guidelines ensured a robust diagnostic process, facilitating timely intervention and treatment planning in line with recommended standards for HCC management [9].

Data collection for this study extended its focus to include a 6-month relapse, defined as a reoccurrence within six months of the initial RFA treatment. The gathered information encompassed various hospital-registered details, including age, gender, smoking and alcohol use, tumor-related variables, and liver function tests. We utilized the normal ranges provided by the laboratory machine for AST (1-40 U/L), ALT (5-40 U/L), and AFP (Less than ten ng/mL) The tumor-related data included the following variables: HBV, HCV, and HDV percentages (n); tumor size in millimeters with minimum and maximum values; tumor lesion number as a percentage (n); tumor location percentages (n) classified as S1 to S8; Child-Pugh class percentages (n) categorized as A, B, and C; and percentages (n) of post-RFA complications. Furthermore, the study aimed to identify predictors for 6-month relapse. Treatment complication-related information was also collected, extending beyond overall complications to specific issues like pain, bleeding, ascites, infection, pleuritis, and any other adverse events associated with the ablation procedures.

3. Statistical analysis

The study population's general characteristics were

presented as means with standard deviations (SDs) or medians with minimum to maximum ranges, depending on the variable distribution. We assessed the normality of all continuous variables using the Shapiro-Wilk test. Categorical variables were expressed as numbers with percentages (%). Group differences were evaluated using parametric tests such as the independent T-test, non-parametric tests like the Mann-Whitney U test, and the Chi-square test. P-values were calculated for pre- and post-treatment comparisons (Wilcoxon signed-rank test), and relapse differences were analyzed using mixed two-way ANOVA. We conducted a logistic regression analysis to identify factors influencing 6-month relapse, assigning univariate odds ratios (OR) for the initial evaluation of individual predictors. Significant variables from the univariate analysis were then incorporated into the multivariate analysis. Consequently, univariate OR captures the independent associations of single predictors, while multivariate OR assesses the multiple impacts of these predictors on the outcome variable. This approach offers a comprehensive insight into individual and various influences on the studied phenomenon.

All statistical analyses were conducted using IBM SPSS V.28.0 (IBM, Chicago, IL, USA), with a significance level set at p < 0.05 for all tests.

Ethical Statements

The study was approved by the Research Ethics Committee of the Mongolian National University of Medical Sciences on January 21, 2022 (Approval № 2022/3-01), aligning with the principles outlined in the Declaration of Helsinki.

Results

The study included 483 participants who underwent RFA for early-stage HCC over five years. The participants, characterized by a mean age of 61.8±10.6 years and a male preponderance of 62.5%, presented a diverse profile (Table 1).

Table 1. General characteristics of study participants stratified by 6-month relapse status

Findings	Total (n=483)	6-month relapse		P-value
		With (n=33)	Without (n=450)	
Age (year)	61.8 ± 10.6	60.1 ± 9.0	61.9 ± 10.7	0.361*
Gender: male, % (n)	37.5 (181)	54.5 (18)	36.2 (163)	0.029
Smoking, % (n)	22.6 (109)	48.5 (16)	20.7 (93)	<0.001
Alcohol use, % (n)	17.0 (82)	30.3 (10)	16.1 (72)	0.038
Hepatitis infection status				
HBV, % (n)	33.7 (163)	30.3 (10)	34.0 (153)	0.411
HCV, % (n)	52.8 (255)	57.6 (19)	52.4 (236)	0.350
HDV, % (n)	6.8 (33)	-	7.3 (33)	0.089
Tumor size (cm, min-max)	2.41 (0.8-25.0)	3.0 (1.5-15.0)	2.40 (0.8-25.0)	0.030**
Tumor lesion number, (n, min-max)	1.02 (1.0-6.0)	1.03 (1.0-4.0)	1.01 (1.0-6.0)	0.211**
Tumor location, % (n)				
S1	0.5 (3)	-	0.7 (3)	0.808
S2	8.9 (54)	48.5 (16)	8.4 (38)	<0.001
S3	6.2 (38)	3.0 (1)	8.2 (37)	0.245
S4	19.2 (117)	6.1 (2)	17.6 (79)	0.062
S5	21.8 (133)	15.2 (5)	28.4 (128)	0.069
S6	16.6 (101)	9.1 (3)	21.8 (98)	0.058
S7	22.8 (139)	42.4 (14)	27.8 (125)	0.059
S8	21.7 (132)	12.1 (4)	28.4 (128)	0.028
Child-Pugh classification, % (n)				
A	85.9 (415)	97.0 (32)	85.1 (383)	
B	12.4 (60)	3.0 (1)	13.1 (59)	
C	1.7 (8)	0 (0)	1.8 (8)	
Post RFA complication, % (n)	6.6 (32)	6.1 (2)	6.7 (30)	0.624

Data are presented as mean ± SD or median (minimum–maximum) and percentages (n). Differences were tested using the independent T–test (*), Mann–Whitney U test (**), and Chi–square test (for remaining P–values)

A subset of demographic features included 22.6% reporting smoking habits and 17.0% reported alcohol use. The HCC-related characteristics within the cohort exhibited variability, encapsulating a spectrum of tumor sizes (median of 2.4 (0.8-25.0)), lesion numbers ranging from 1 to 6, and prevalent locations primarily within segments 4 to 8. Additionally, most participants (85.9%) belonged to the favorable Child-Pugh class A category. While some cases with a tumor size > 3.0 cm might be considered for treatment exclusion, the study included 15.1% (n=73) of cases with a tumor size > 3.0 cm. Similarly, a minority of cases (1.7%, n=8) were identified with Child-Pugh class C. Complications post-RFA were reported by a limited percentage of participants, including pain (2.3%, n=11), bleeding (1.5%, n=7), ascites (1.7%, n=8), infection (1.0%, n=5), pleuritis (1.0%, n=5), and any complication (6.6%, n=32).

Among the total population, 6.8% (n=33) experienced relapse within six months. Table 1 illustrates significant gender-based differences in relapse groups (p = 0.029), with a higher proportion of males in the relapse group (45.5%). Smoking exhibited a significant association with relapse (p < 0.001), as did alcohol use, with a higher percentage of alcohol users in the relapse group (p = 0.038). Tumor characteristics, such as size (p = 0.030) and specific locations (S2, S8; p < 0.001, p = 0.028, respectively), demonstrated significant associations with relapse. Pre-treatment AST levels were also significantly different between relapse groups (p = 0.012). However, no significant differences were found in age, Hepatitis infection status, Tumor lesion number, Child-Pugh class, and complications post-RFA.

Table 2 delineates ablation parameters, indicating no significant differences in minimum and maximum ablation frequencies or ablation duration between relapse and non-relapse groups. Treatment outcomes based on laboratory findings (Table 3) unveiled substantial differences in post-treatment AST (p < 0.001) and ALT (p = 0.041) levels between relapse groups, with higher AFP levels post-treatment in the relapse group (p = 0.001). However, the difference between pre and post-AST results concerning relapse was higher in the relapse group, while other results were insignificant.

Table 2. Comparison of ablation parameters in hepatocellular carcinoma treatment

Findings	6-month relapse		P-value
	With (n=33)	Without (n=450)	
Minimum Ablation Frequency (W)	60.0 (40-80)	60.0 (12-120)	0.725
Minimum Ablation Frequency (W)	100.0 (60-150)	100.0 (8-200)	0.898
Ablation duration (minutes)	9.0 (3-15)	8.0 (2-36)	0.522

Data are presented as median (minimum–maximum). Watt is abbreviated as W. The Mann–U–Whitney test was employed to calculate P–values.

Table 3. Treatment outcomes based on laboratory findings stratified by 6-month relapse status

Findings	RFA treatment			P-value
	Pre-treatment	Post-treatment		
AST (IU/L)				
Relapse (+)	82.0 (13.9-574.3)	41.0 (21-102)	0.012	<0.001
Relapse (-)	60.0 (5-331)	39.0 (3.6-344)	<0.001	
ALT (IU/L)				
Relapse (+)	71.9 (21-313.6	42.0 (22-83.6)	0.041	0.063
Relapse (-)	58.1 (9.9-378.1)	41.0 (15.0-443.6)	<0.001	
AFP				
Relapse (+)	13.0 (1.9-271.2)	6.0 (1-14)	0.001	0.942
Relapse (-)	7.0 (0.5-2076)	4.5 (0.3-45.0)	<0.001	

Data are presented as median (minimum–maximum). The Wilcoxon signed–rank test was employed to calculate P–values between pre– and post–treatment. P–value for the difference, we used mixed two–way ANOVA

Predictors for 6-month relapse after RFA were identified in Table 4 via univariate and multivariate analyses. The univariate analysis highlighted male gender (p = 0.039) and smoking (p < 0.001) as significant predictors, along with tumor-related factors such as tumor size > 3cm (p < 0.001), tumor location S2 (p < 0.001), and pre-treatment AST levels (p = 0.002). In the multivariate analysis, adjusting for confounders, smoking (p = 0.014), tumor size > 3cm (p < 0.001), tumor location

S2 (p < 0.001), and pre-treatment AST levels (p = 0.015) remained significant predictors. Including these variables in the multivariate model provides a comprehensive understanding of

their independent contributions to predicting 6-month relapse after RFA.

Table 4. Predictors for 6-Month Relapse after RFA

Variables	Univariate OR (95% CI)	P-value	Multivariate OR (95% CI)	P - value
Gender: male	2.11 (1.04-4.31)	0.039	1.42 (0.53-3.81)	0.488
Smoking: smokers	3.60 (1.75-7.40)	<0.001	3.81 (1.31-11.1)	0.014
Alcohol use: users	2.27 (1.04-4.97)	0.040	0.83 (0.25-2.77)	0.759
Tumor size (mm)	1.13 (0.96-1.33)	0.157	-	
Tumor size > 3cm	4.23 (1.99-8.94)	<0.001	8.87 (3.43-22.9)	<0.001
Tumor lesion: number	1.35 (0.89-2.03)	0.148	-	
Tumor lesion ≥ 2	1.25 (0.59-2.62)	0.560	-	
Tumor location: S2	10.2 (4.78-21.8)	<0.001	16.1 (6.35-40.8)	<0.001
Tumor location: S8	0.35 (0.12-1.01)	0.511	-	
Pre-treatment AST (IU/L)	1.01 (1.00-1.01)	0.002	1.01 (1.01-1.02)	0.015
Post-treatment AST (IU/L)	1.00 (0.99-1.02)	0.808	-	
Treatment complication: presented	0.89 (0.21-3.96)	0.893	-	
Ablation duration (minutes)	1.00 (0.99-1.01)	0.964	-	

Data are presented as odds ratio (OR) with corresponding 95% confidence intervals (CI). Univariate OR indicates individual predictors, while multivariate OR reflects combined predictor impact on the outcome

In an additional analysis exploring interactions among significant variables, only an interaction between tumor location (S2) and smoking status emerged. Figure 1 illustrates the interaction, revealing an increased risk of 6-month relapse in smokers with S2-located tumors compared to non-smokers. Conversely, non-smokers with S2-located tumors exhibited a higher relapse rate, unveiling a nuanced interplay between smoking status and tumor location.
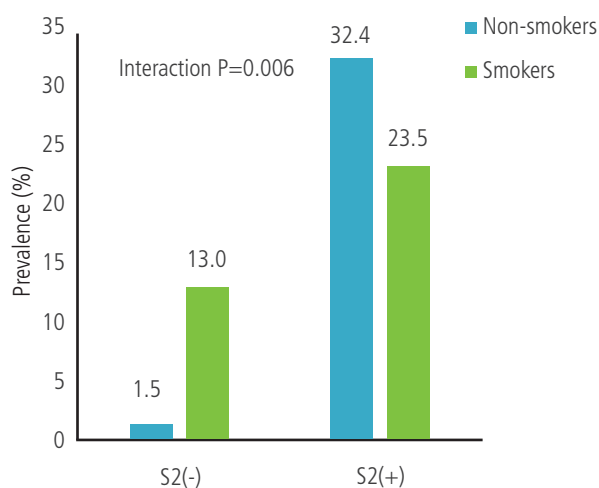

Figure 1. Interaction among significant variables from regression analysis on predictors for 6-month relapse after RFA

Discussion

Hepatocellular carcinoma imposes a significant health burden globally, and its impact is particularly pronounced in Mongolia, as evidenced by the highest incidence and mortality rates [1, 10]. Our study sought to contribute to the understanding of early-stage HCC treatment outcomes following RFA in the Mongolian population. The discussion will delve into critical findings, their implications, and potential avenues for future research.

In our study, the 6-month replacement rate was found to be 6.8%, which is lower than the rates reported in other studies, where values of 3.5 to 27%, mostly over 20%, were observed in various countries [7]. Additionally, when we compared the profiles of the study participants, our findings were consistent with those reported in the literature. The demographic profile of our study participants revealed a predominantly male population, consistent with the higher incidence of HCC among males globally [11]. The deliberate inclusion of cases with tumor sizes larger than 3.0 cm was aimed at encompassing a subset of patients frequently overlooked in research. This approach enabled us to reflect the real-world diversity of hepatocellular carcinoma (HCC) presentations in Mongolia more accurately, ensuring that our study incorporated the broader spectrum of disease manifestations observed in the population [12]. Most of

our participants belonged to the favorable Child-Pugh class A, emphasizing the potential for curative interventions in the early stages of the disease. Our analysis of treatment complications post-RFA revealed a limited percentage of adverse events, including pain, bleeding, ascites, infection, pleuritis, and any complications. These findings align with the generally favorable safety profile of RFA reported in the literature [13-14]. However, the observed complications emphasize the importance of meticulous post-procedural monitoring and management to ensure optimal patient outcomes.

This study deliberately addresses the 6-month relapse of tumors, departing from conventional categorization as residual tumor observed in most studies [15-18]. It underscores the crucial need to discern whether such recurrence should be construed as residual, thereby highlighting the importance of identifying predictors for this specific 6-month relapse [3-4]. Examining 6-month relapse rates, our study identified several significant predictors. Notably, our results indicated a higher likelihood of relapse in males, smokers, and alcohol users, emphasizing the potential influence of lifestyle factors on HCC progression. Tumor characteristics, including size and location, were also crucial determinants, echoing established knowledge regarding the impact of these factors on relapse risk. These factors have indeed been investigated in studies with longer- follow-ups [15-18]. In our multivariate analysis, smoking, tumor size > 3cm, tumor location S2, and pre-treatment AST levels emerged as independent predictors of 6-month relapse following RFA. These results underscore the multifaceted aspects contributing to HCC relapse, underscoring the necessity for a comprehensive risk stratification approach. Alternatively, these variables may imply that our results could indicate residual tumor manifesting as recurrence [3-4]. The unexpected interaction between smoking status and tumor location (S2) adds complexity to the interpretation of our results. While smokers with S2-located tumors demonstrated an increased risk of relapse, non-smokers with S2-located tumors exhibited a higher relapse rate. This intriguing finding suggests a nuanced interplay between smoking and tumor location, indicating that the impact of these factors on relapse risk may vary depending on the patient's overall profile. Moreover, smoking and the specific tumor location (S2) might have a synergistic effect, meaning that the combined impact of these factors is greater than the sum of their individual effects [19-20]. Therefore, biological mechanisms underlying this interaction could involve complex pathways that

enhance the relapse risk. Previous studies have identified patient characteristics, such as smoking, as associated with increased HCC recurrence [21]. Moreover, the segmental classification of hepatocellular carcinoma (HCC) involves dividing the liver into anatomical segments for clinical and surgical purposes. Studies on the association between specific segments, such as segment 2 (S2), and HCC recurrence are limited. However, there is speculation that specific segments, like S2, may exhibit higher rates of recurrence compared to others due to factors such as anatomical location and vascular supply [22]. Tumor location and size suggest a need for updated guidelines to address the treatment feasibility of large-sized and challenging locations with RFA. Divergent recommendations exist in global guidelines, with Asian guidelines advocating RFA for any HCC, while European guidelines refrain from recommending it for tumors larger than 3cm [22].

Several alternatives exist for treating early-stage HCC, including microwave ablation and combination therapies involving vessel clotting [7]. While limited comparative studies are available, most suggest similar efficacy and safety profiles for these modalities [23-24]. Some studies indicate that larger HCCs might benefit more from microwave ablation or a combination of treatments [25]. Consequently, certain researchers suggest that the limitations of RFA may discourage its recommendation for more significant HCC cases [26-27].

Although this study has inherent limitations, such as the inability to collect all possible predictors and the absence of data on tumor characteristics at 6-month relapse, its robustness stems from the utilization of nationwide data from the National Cancer Center over five years. We must also acknowledge the limitation regarding the comparison of operators in this study. Due to the challenges in collecting comprehensive data on each operator and a lack of comparative analysis of their outcomes, such comparisons were not feasible. However, it's important to note that the RFA procedure is protocol-driven, with all operators adhering to established guidelines.

In light of our findings, future research in early-stage HCC treatment holds promise for advancing our understanding and improving patient outcomes. Extended follow-up studies are warranted to track the long-term consequences of patients undergoing RFA for early-stage HCC, providing a more comprehensive understanding of treatment efficacy and relapse over time. Validation studies on larger cohorts are essential to confirm the identified predictors of 6-month relapse, ensuring the

generalizability of our results to diverse populations. Additionally, exploring additional biomarkers and dynamic changes in liver function could enhance the accuracy of predicting relapse risk, potentially identifying novel indicators for early recurrence. Further investigation into the impact of lifestyle factors, such as smoking and alcohol use, on HCC progression and relapse is crucial, with an emphasis on potential interventions to mitigate their influence. Mechanistic studies are also warranted to elucidate the biological pathways underlying the observed interactions between smoking status and tumor location, contributing to a deeper understanding of the factors influencing relapse. These future research directions collectively aim to build upon our current findings, fostering advancements in managing early-stage HCC and ultimately improving patient outcomes.

Furthermore, in parallel investigations, a comparative study assessing the adverse events associated with selective internal radiation therapy (SIRT) and sorafenib in treating locally advanced HCC found comparable safety profiles in both treatments [28]. These findings align with our emphasis on the need for meticulous post-procedural monitoring in the context of RFA, reinforcing the importance of tailoring treatment approaches to the specificities of the Mongolian patient population. Additionally, an analysis comparing the clinical characteristics of HBV and HCV-related HCC patients in Mongolia sheds light on demographic and prognostic differences [29]. While our study primarily focused on predictors of 6-month relapse post-RFA, these comparative findings highlight the multifaceted nature of HCC in Mongolia, emphasizing the need to consider not only the treatment modality, as in our study, but also the unique clinical and viral characteristics influencing outcomes, as revealed in these parallel investigations. Moreover, a recent molecular characterization study of Mongolian HCCs compared with Western HCCs unveiled distinct genomic and transcriptomic features associated with environmental factors in the Mongolian population [30]. This study identified a high mutational burden and a novel mutational signature associated with genotoxic ecological factors, providing valuable insights into the unique molecular traits of Mongolian HCC.

Conclusions

In conclusion, our study contributes valuable insights into the treatment outcomes and prognostic factors of early-stage HCC following RFA in the high-incidence context of Mongolia.

The identified predictors of relapse underscore the importance of personalized risk assessment and surveillance strategies in managing HCC. Future research could explore the long-term outcomes and the impact of emerging therapeutic modalities and validate our findings in larger cohorts to enhance the generalizability of our results.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgements

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