

The Impact of Spatiotemporal Patterns of Tumor Recurrence on Prognosis in Hepatocellular Carcinoma Patients Undergoing Surgery After Conversion Therapy

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Purpose: To characterize the spatiotemporal patterns of recurrence and assess their impact on survival in hepatocellular carcinoma (HCC) patients undergoing curative resection after conversion therapy.

Methods: We retrospectively analyzed 80 HCC patients who achieved successful conversion and underwent resection between January 2019 and February 2025. Recurrence was classified by timing (early ≤ 10.5 months vs. late > 10.5 months, determined by maximally selected log-rank statistics) and location (intrahepatic vs. extrahepatic) of the first recurrence. Exploratory analyses were also conducted using a 12-month cutoff to align with clinical practice. Post-recurrence survival (PRS), overall survival, and recurrence-free survival were evaluated using Kaplan-Meier analysis. The multivariable Cox models were used to calculate the adjusted hazard ratio and 95% confidence interval for PRS.

Results: Recurrence occurred in 52.5% of patients. Early recurrence was associated with significantly worse PRS than late recurrence ($P = 0.04$). Although no significant difference in PRS was observed between subgroups when using a 12-month cutoff ($P = 0.1$) for the small sample size, this factor still showed a trend toward significance. Extrahepatic recurrence conferred poorer survival than intrahepatic recurrence ($P < 0.0001$). Combined spatiotemporal analysis revealed that early extrahepatic recurrence had the worst prognosis, while all late recurrences showed favorable outcomes. Multivariable Cox regression analysis confirmed that the later time recurrence was independently associated with better PRS.

Conclusion: In this cohort, time to recurrence is the dominant prognostic factor, with recurrence site providing additional stratification. These findings support the use of spatiotemporal recurrence patterns for risk-adapted surveillance and adjuvant strategies.

Keywords: hepatocellular carcinoma, conversion therapy, surgical resection, patterns of recurrence, survival prognosis

Introduction

Hepatocellular carcinoma (HCC) remains the third leading cause of cancer-related mortality worldwide and typically arises in the context of chronic liver disease, such as hepatitis B or C, metabolic dysfunction-associated steatohepatitis, or alcohol-related liver disease.¹ The pathogenesis of HCC is complex and not yet fully understood.^{2,3} Moreover, a large proportion of patients present with unresectable advanced HCC at initial diagnosis. For these patients, conversion therapy, comprising systemic therapies including tyrosine kinase inhibitors and immune checkpoint inhibitors, as well as locoregional interventions such as transarterial chemoembolization or hepatic artery infusion chemotherapy, has emerged as a promising strategy to downstage tumors and enable salvage liver resection.⁴⁻⁶

Despite achieving R0 resection, nearly 50–70% of patients experience tumor recurrence within two years, which substantially diminishes the survival benefit of conversion therapy.⁷ Multiple factors critically influence the risk of post-operative HCC recurrence. Persistent replication of hepatitis B virus (HBV) or hepatitis C virus (HCV), along with the associated chronic liver inflammation, can promote tumor development.⁸ Consequently, standardized antiviral therapy plays a significant role in reducing recurrence risk.⁹ Elevated preoperative alpha-fetoprotein (AFP) levels have been widely confirmed as a strong predictor of poor prognosis and early recurrence.^{10,11} Further studies have demonstrated that both baseline and recurrent AFP levels, as well as their dynamic changes, are important prognostic indicators for overall survival (OS) and post-recurrence survival (PRS) in patients undergoing repeat liver resection.¹² Additionally, the tumor burden score (TBS), a comprehensive assessment tool, has proven effective in predicting clinical outcomes after HCC resection.^{13,14} A high TBS is not only associated with higher recurrence rates and poorer OS but also correlates with more aggressive recurrence patterns, including early recurrence, multifocal intrahepatic recurrence, and extrahepatic metastasis.¹⁵

Importantly, recurrence is heterogeneous in both its biological underpinnings and clinical presentation. Accumulating evidence indicates that the timing (early vs. late) and location (intrahepatic vs. extrahepatic) of recurrence reflect distinct underlying tumor biology. Early recurrence is typically driven by invasive micro metastasis or intrahepatic dissemination, whereas late recurrence more often results from de novo tumor development in the setting of chronic liver disease. Notably, early extrahepatic recurrence after surgical resection is associated with particularly poor prognosis.¹⁶

Although multiple predictive models have been developed to guide risk stratification and adjuvant therapy for HCC recurrence, these models are predominantly derived from cohorts undergoing direct surgical resection and thus do not fully capture the unique invasive biology of initially unresectable HCC.^{17–20} Moreover, existing studies have largely examined the timing or location of recurrence in isolation, without systematically characterizing their combined spatiotemporal patterns, particularly in patients undergoing resection after conversion therapy.^{21,22} Consequently, the prognostic significance of specific spatiotemporal recurrence phenotypes in this population remains unclear.

In this study, we aim to describe the spatiotemporal heterogeneity of tumor recurrence and evaluate its impact on the PRS of HCC patients who undergo curative resection following successful conversion therapy. By depicting high-risk recurrence patterns, our findings can provide information for risk stratification and monitoring strategies.

Materials and Methods

Patient Selection and Data Collection

This study is a single-center, retrospective, real-world exploratory analysis of patients diagnosed with HCC who underwent conversion surgery at Peking Union Medical College Hospital between January 2019 and February 2025. The data, including demographic characteristics, clinicopathological features, recurrence patterns, and survival outcomes, were collected through a comprehensive review of medical records and subsequent follow-up assessments. The study protocol was approved by the Ethics Committee of Peking Union Medical College Hospital, Chinese Academy of Medical Sciences (research ethics number: I-25PJ1846) and conducted in accordance with the Declaration of Helsinki. Due to the retrospective and observational nature of the study, the requirement for individual informed consent was waived. To protect patient privacy, the data were anonymized and de-identified.

The inclusion criteria are as follows: 1) age ≥ 18 years; 2) HCC confirmed by histopathology; 3) China Liver Cancer Stage (CNLC) Ib to IIIa; 4) initial diagnosis of unresectable HCC; 5) receiving systemic therapy alone or in combination with local treatment, followed by radiological and clinical evidence of successful conversion, and underwent curative-intent hepatectomy; 6) preoperative imaging or postoperative pathology confirmed no extrahepatic metastasis. The exclusion criteria are as follows: 1) history of other malignant tumor; 2) reoperation for recurrent or residual HCC; 3) previous liver transplantation; 4) the surgical method is associating liver partition and portal vein ligation for staged hepatectomy (ALPPS); 5) history of HCC rupture; 6) key clinical data is missing or postoperative follow-up is insufficient (<1 month).

Follow-Up and Endpoints

The patients were followed up for the first time one month after surgery, then every three months during the first two years, and every six months thereafter. Follow-up assessments included examination of tumor markers, liver function

test, and imaging studies (contrast-enhanced computed tomography [CT] or magnetic resonance imaging [MRI]). In addition to outpatient follow-up, survival status and tumor recurrence were also obtained through telephone follow-up. The decision for adjuvant therapy was based on pathological evaluation of the resected specimen, including the presence of microvascular invasion (MVI), multifocal tumors, large tumor size (>5 cm), or inadequate surgical margins (<1 cm). HCC recurrence was defined according to the appearance of new suspected intrahepatic or extrahepatic lesions on CT, MRI, bone scan, or positron emission tomography computed tomography with or without elevated tumor markers. After confirming recurrence, the optimal treatment strategy should be selected based on the patients' clinical status and disease characteristics.

The primary endpoint was PRS, defined as the interval from first recurrence to death from any cause or last follow-up. The secondary endpoints were OS and recurrence-free survival (RFS), defined as the interval from surgery to death from any cause or last follow-up and the interval from surgery to the first diagnosis of tumor recurrence or last follow-up, respectively. To avoid immortal time bias, we primarily investigated the impact of tumor recurrence patterns on patients' PRS.²³

To investigate the potential association between time to tumor recurrence (TTR) and PRS, TTR was modeled using restricted cubic splines (RCSs). RCS curves were constructed within a Cox regression framework. The RCS model used three knots at the 10th, 50th, and 90th percentiles of the TTR distribution to capture potential nonlinear effects. A Wald test formally assessed the nonlinearity of the relationship between TTR and the hazard ratio (HR) for post-recurrence mortality. The HR for post-recurrence mortality per unit increase in TTR, along with its 95% confidence interval (CI), was estimated to clarify the quantitative relationship. Trends in multivariable-adjusted HRs (including 95% CIs) for post-recurrence mortality across TTR values were also plotted.

The optimal cutoff value for TTR was determined using maximally selected log-rank statistics, as implemented in the maxstat R package.²⁴ This analysis identified 10.5 months as the statistically optimal threshold. To align with clinical practicality and facilitate interpretation, a rounded value of 12 months was subsequently adopted for additional exploratory analyses. These analyses were considered exploratory and hypothesis-generating.

Statistical Analysis

Categorical variables are presented as numbers and percentages, and compared using the chi-square test or Fisher's exact test. Continuous variables are reported as median and interquartile range, and compared using the Mann-Whitney *U*-test or Kruskal-Wallis rank sum test. Survival outcomes were evaluated using the Kaplan-Meier method, and prognostic differences between subgroups were assessed with the Log-rank test. All statistical analyses were performed using RStudio (version 4.4.0), and a two-sided *P*-value < 0.05 was considered statistically significant.

Results

As shown in Figure 1, a total of 189 patients with HCC who underwent conversion surgery were initially identified. After applying the inclusion and exclusion criteria, 109 patients were excluded due to the following reasons: repeat hepatectomy ($n = 34$), distant metastasis ($n = 29$), tumor rupture ($n = 15$), concurrent malignancy ($n = 14$), ALPPS surgery ($n = 5$), combined hepatocellular and intrahepatic cholangiocarcinoma (cHCC-ICC; $n = 4$), follow-up duration <1 month ($n = 4$), lack of data ($n = 3$), or age <18 years ($n = 1$). The final study population comprised 80 patients, with a median follow-up of 21.50 months (interquartile range [IQR], 13.75–31.30 months). During follow-up, HCC recurrence occurred in 42 patients (52.5%). Recurrence was classified as early (≤ 10.5 months after surgery) or late (>10.5 months after surgery). Early recurrence was observed in 26 patients (median follow-up: 18.70 months; IQR, 12.10–31.48 months), while late recurrence developed in 16 patients (median follow-up: 33.10 months; IQR, 27.25–40.93 months).

The Kaplan-Meier curves for OS and RFS in the overall cohort are shown in Figure 2. The 6-, 12-, 24-, and 36-months OS rates were 98.7%, 94.7%, 85.0%, and 76.8%, respectively (Figure 2A). The median OS was not reached during the follow-up period. The RFS rate was 78.5% at 6 months, 60.8% at 12 months, 37.4% at 24 months, and 25.1% at 36 months (Figure 2B). The median RFS was 17.8 months (95% CI: 12.4–26.5). The PRS rate was 91.9% at 6 months, 88.8% at 12 months, 78.5% at 24 months, and 61.1% at 36 months (Figure 2C). Figure 2D shows the cumulative recurrence rate of HCC after curative resection in the entire cohort, with cumulative incidences of 21.5%, 38.2%, 57.2%, and 71.2% at 6, 12, 24, and 36 months, respectively.

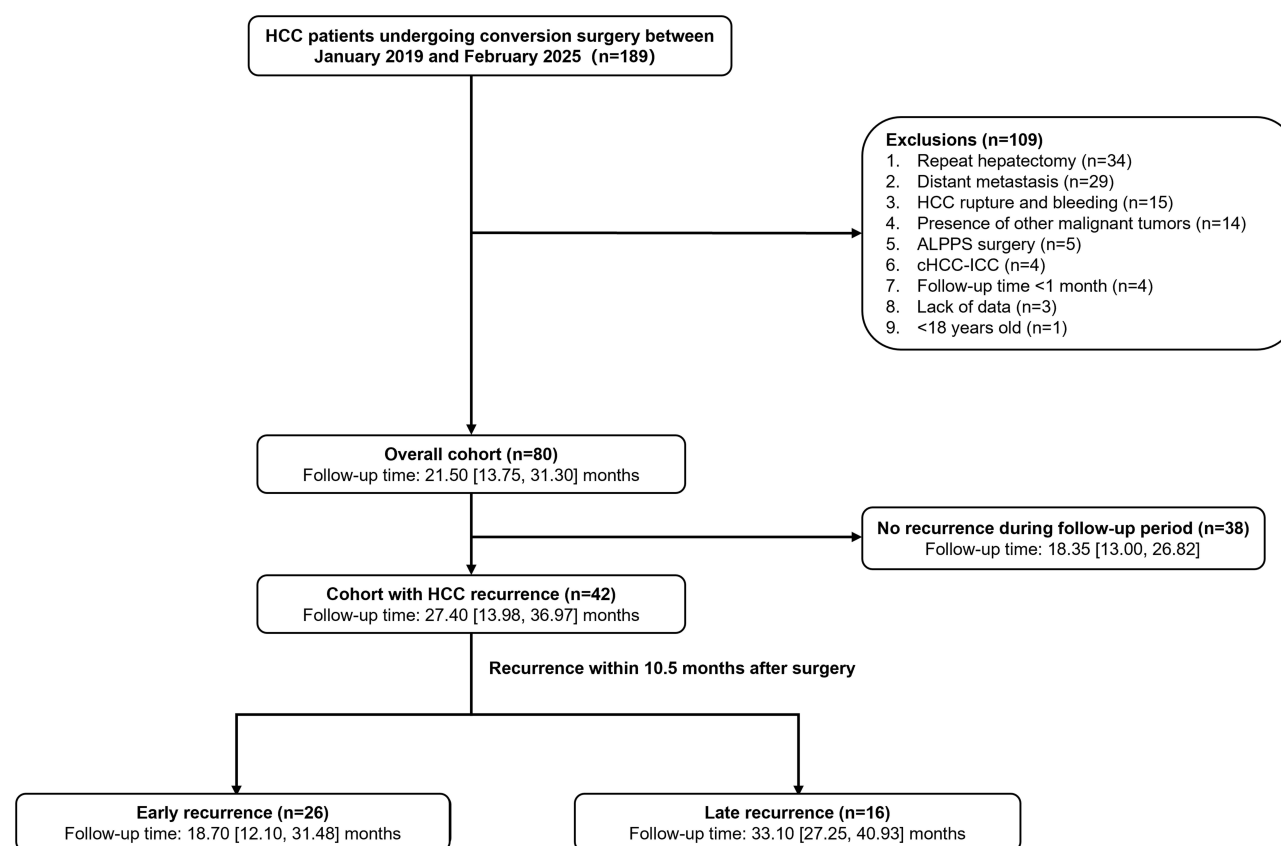


Figure 1 Flowchart of patient selection and cohort stratification.

Abbreviations: HCC, hepatocellular carcinoma; ALPPS, associating liver partition and portal vein ligation for staged hepatectomy; cHCC-ICC, combined hepatocellular and intrahepatic cholangiocarcinoma.

A total of 80 patients were divided into two groups based on their recurrence status. Thirty-eight patients (47.5%) remained recurrence-free, while 42 (52.5%) experienced tumor recurrence. Significant differences in baseline characteristics were observed between the groups (Table 1).

Of the 80 patients, 75 (93.75%) received combination systemic therapy, predominantly targeted therapy and immunotherapy (76.25%). Locoregional interventions were administered to 93.75% of patients, with TACE alone being the most frequent modality (53.75%). Statistical analysis indicated no significant differences in the distribution of systemic ($P = 0.874$) or locoregional ($P = 0.408$) therapies between recurrence and non-recurrence subgroups, confirming baseline comparability.

Patients in the non-recurrence group were more likely to present with solitary tumors (65.79% vs. 30.95%), whereas multiple tumors were markedly more prevalent in the recurrence group (69.05% vs. 34.21%) ($P = 0.0038$). Interestingly, the median maximum tumor diameter in the non-recurrence group was larger (8.30 [5.45, 10.90] cm vs. 6.55 [3.78, 8.8] cm) ($P = 0.0477$). Early-stage disease (China Liver Cancer (CNLC) stage Ib) was more common in the non-recurrence group (50.00% vs. 19.05%), while advanced stages (CNLC stage IIb/IIIa: 61.90% vs. 35.84%) predominated among the recurrence group ($P = 0.0016$). The pathological complete response (pCR) rate was significantly higher in the non-recurrence group (39.47% vs. 4.76%) ($P = 0.0007$). MVI (33.33% vs. 10.53%) ($P = 0.0299$) and poorly differentiated or undifferentiated histology (23.81% vs. 5.26%) ($P = 0.0013$) were more frequent in the recurrence group. There were no significant differences between the two groups in terms of age, gender, liver function, viral hepatitis status, surgical approach, extent of resection, or incidence of severe postoperative complications (all $P > 0.05$).

To evaluate the impact of TTR on PRS, we employed restricted cubic splines within a Cox proportional hazards framework to model the hazard of death after recurrence as a continuous function of TTR. In the unadjusted analysis, although the HR appeared highest for early recurrences and declined with prolonged TTR, no statistically significant linear

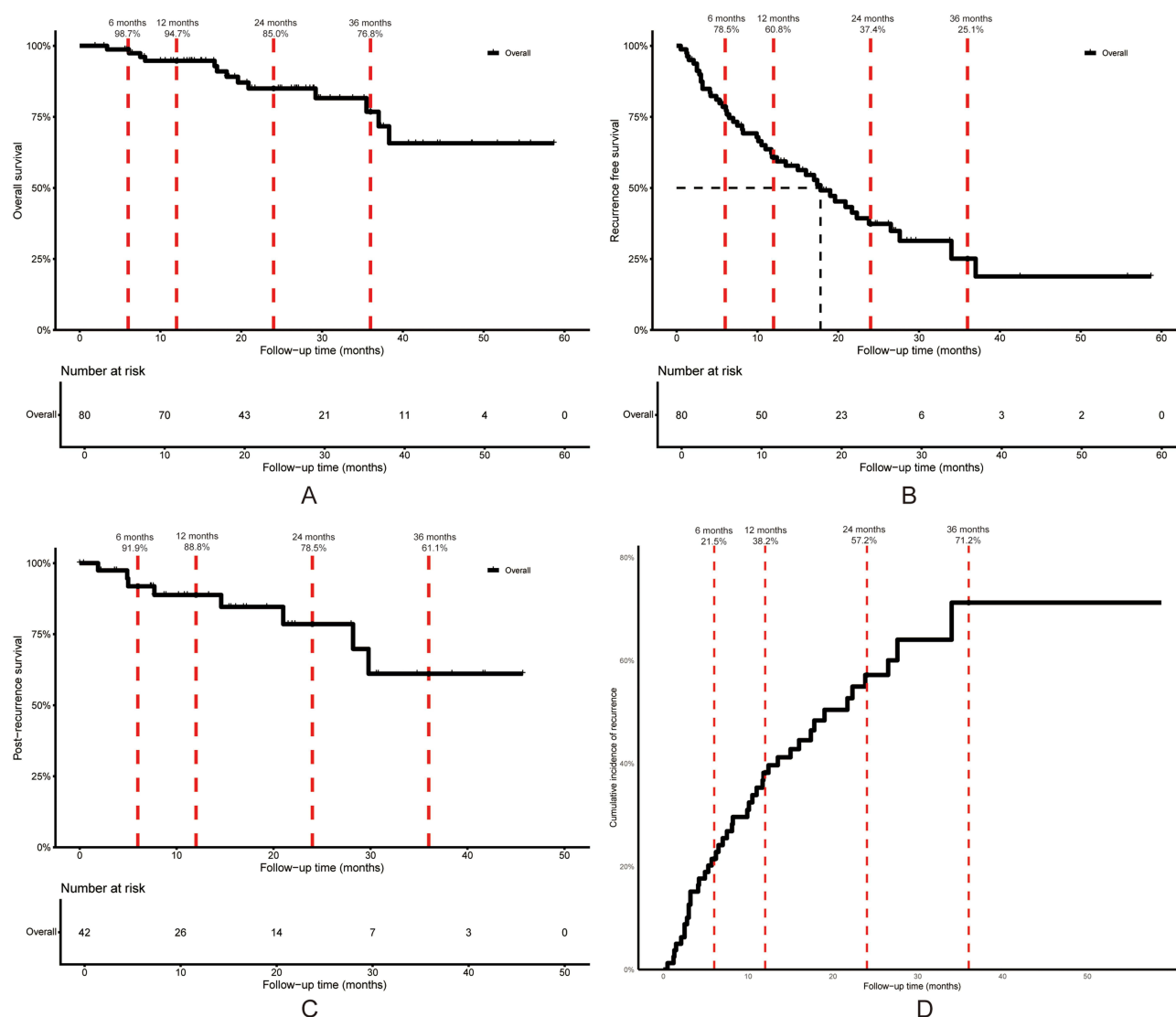


Figure 2 Kaplan-Meier curves and cumulative occurrence curves for survival outcomes in the overall cohort. **(A)** Overall survival; **(B)** Recurrence-free survival. The dashed horizontal line denotes the 50% threshold. Numbers at risk at selected time points are displayed below each panel. **(C)** Post-recurrence survival. **(D)** Cumulative recurrence rate of tumors.

or nonlinear association was observed. However, after adjusting for potential confounders, including age, sex, CNLC stage, conversion therapy regimens, and adjuvant therapy, the multivariable model revealed a significant inverse association: a longer TTR was independently associated with a reduced risk of post-recurrence mortality (adjusted HR < 1; $P < 0.05$), indicating a protective effect of delayed recurrence (Figure S1).

Maximally selected rank statistics identified 10.5 months as the optimal cutoff for TTR (Figure S2). Among the 42 patients who experienced tumor recurrence, 26 (61.90%) developed early recurrence (≤ 10.5 months after surgery) and 16 (38.10%) had late recurrence (> 10.5 months). Baseline demographic and clinicopathological characteristics stratified by timing of recurrence are summarized in Table 2. No statistically significant differences were observed between early and late recurrence groups for the majority of variables, including age, sex, liver function (Child-Pugh class, ALBI grade), viral hepatitis status, CNLC stage, surgical details (approach, range, and margin), or pathological features such as MVI, tumor differentiation, and pathological response to conversion therapy (all $P > 0.05$).

Among the 41 patients with evaluable recurrence sites, 33 (80.49%) experienced intrahepatic recurrence, and 8 (19.51%) had extrahepatic recurrence as their first site of disease relapse. Baseline characteristics stratified by recurrence site are summarized in Table 3. No statistically significant differences were observed between groups for most

Table 1 Baseline Demographic and Clinicopathological Characteristics Stratified by Tumor Recurrence Status

Variable	No Recurrence (n=38)	Recurrence (n=42)	P value
Conversion therapy			0.4183
Combination therapy	1 (2.63)	4 (9.52)	
Systemic therapy alone	37 (97.37)	38 (90.48)	
Systemic therapy			0.874
Targeted therapy	9 (23.68)	8 (19.05)	
Targeted therapy + immunotherapy	28 (73.68)	33 (78.57)	
Chemotherapy + targeted therapy + immunotherapy	1 (2.63)	1 (2.38)	
Locoregional therapy			0.4078
No	1 (2.63)	4 (9.52)	
TACE	22 (57.89)	21 (50.00)	
Radiotherapy	2 (5.26)	0 (0.00)	
Ablation	1 (2.63)	0 (0.00)	
TACE + HAIC	3 (7.89)	6 (14.29)	
TACE + ablation	3 (7.89)	5 (11.90)	
TACE + HAIC + radiotherapy	6 (15.79)	6 (14.29)	
mRECIST			0.6499
SD	12 (31.58)	13 (30.95)	
PR	25 (65.79)	26 (61.90)	
CR	1 (2.63)	3 (7.14)	
Gender			0.2361
Female	7 (18.42)	3 (7.14)	
Male	31 (81.58)	39 (92.86)	
Age (year)	58.00 [50.25, 66.00]	55.00 [48.50, 64.00]	0.4966
BMI (kg/m ²)	24.20 [21.92, 26.73]	23.40 [22.50, 26.48]	0.8851
ASA			0.9428
I/II	25 (65.79)	29 (69.05)	
III	13 (34.21)	13 (30.95)	
CCI			0.8581
<5	32 (84.21)	37 (88.10)	
≥5	6 (15.79)	5 (11.90)	
HBsAg			0.7761
Negative	12 (31.58)	11 (26.19)	
Positive	26 (68.42)	31 (73.81)	
Anti-HCV			0.3519
Negative	33 (86.84)	40 (95.24)	
Positive	5 (13.16)	2 (4.76)	
AFP level (ng/mL)	6.35 [1.90, 38.50]	7.65 [2.50, 126.72]	0.3938
Child-Pugh			1
A	36 (94.74)	40 (95.24)	
B	2 (5.26)	2 (4.76)	
ALBI			0.8741
1	21 (55.26)	25 (59.52)	
2	17 (44.74)	17 (40.48)	
ECOG-PS			1
0	35 (92.11)	39 (92.86)	
1	3 (7.89)	3 (7.14)	
Baseline tumor number			0.0038
Solitary	25 (65.79)	13 (30.95)	
Multiple	13 (34.21)	29 (69.05)	

(Continued)

Table 1 (Continued).

Variable	No Recurrence (n=38)	Recurrence (n=42)	P value
Baseline maximum tumor diameter (cm)	8.30 [5.45, 10.90]	6.55 [3.78, 8.80]	0.0477
Tumor location			0.1916
Left lobe	3 (7.89)	3 (7.14)	
Right lobe	29 (76.32)	25 (59.52)	
Both	6 (15.79)	14 (33.33)	
Macrovascular invasion			0.9428
No	25 (65.79)	29 (69.05)	
Yes	13 (34.21)	13 (30.95)	
CNLC stage			0.0016
Ib	19 (50.00)	8 (19.05)	
IIa	5 (13.16)	8 (19.05)	
IIb	1 (2.63)	13 (30.95)	
IIIa	13 (34.21)	13 (30.95)	
Surgical approach			0.304
Laparoscopic	25 (65.79)	33 (78.57)	
Open	13 (34.21)	9 (21.43)	
Extension of hepatectomy			0.6293
Minor	22 (57.89)	21 (50.00)	
Major	16 (42.11)	21 (50.00)	
Severe surgical complications (CD $\geq$ 3)			0.8656
No	34 (89.47)	36 (85.71)	
Yes	4 (10.53)	6 (14.29)	
Surgical margin			0.2046
$\leq$ 1cm	32 (84.21)	40 (95.24)	
$>$ 1cm	6 (15.79)	2 (4.76)	
WHO tumor differentiation			0.0013
Poor/undifferentiated	2 (5.26)	10 (23.81)	
Moderate	17 (44.74)	25 (59.52)	
Well	3 (7.89)	4 (9.52)	
Unknown	16 (42.11)	3 (7.14)	
MVI			0.0299
No	34 (89.47)	28 (66.67)	
Yes	4 (10.53)	14 (33.33)	
Satellite nodule			0.1321
No	34 (89.47)	31 (73.81)	
Yes	4 (10.53)	11 (26.19)	
Capsular invasion			0.3519
No	33 (86.84)	40 (95.24)	
Yes	5 (13.16)	2 (4.76)	
Cirrhosis			0.1887
No	28 (73.68)	24 (57.14)	
Yes	10 (26.32)	18 (42.86)	
Pathologic response			0.0007
pNR	4 (10.53)	6 (14.29)	
pPR	19 (50.00)	34 (80.95)	
pCR	15 (39.47)	2 (4.76)	
Adjuvant therapy			0.0223
No	8 (21.05)	1 (2.38)	
Yes	30 (78.95)	41 (97.62)	

(Continued)

Table 1 (Continued).

Variable	No Recurrence (n=38)	Recurrence (n=42)	P value
Adjuvant treatment regimen			0.0628
No	8 (21.05)	1 (2.38)	
Local therapy	4 (10.53)	4 (9.52)	
Systemic therapy	20 (52.63)	27 (64.29)	
Local therapy + systemic therapy	6 (15.79)	10 (23.81)	

Abbreviations: TACE, transcatheter arterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy; mRECIST, modified Response Evaluation Criteria in Solid Tumors; SD, stable disease; PR, partial response; CR, complete response; BMI, body mass index; ASA, American Society of Anesthesiologists physical status classification; CCI, Charlson Comorbidity Index; HBsAg, hepatitis B surface antigen; anti-HCV, antibody to hepatitis C virus; Child-Pugh, Child-Turcotte-Pugh score; ALBI, albumin-bilirubin grade; ECOG-PS, Eastern Cooperative Oncology Group performance status; AFP, alpha-fetoprotein; CNLC, China Liver Cancer Stage; CD, Clavien-Dindo classification; MVI, microvascular invasion; pCR, pathological complete response; pPR, pathological partial response; pNR, pathological non-response.

Table 2 Baseline Demographic and Clinicopathological Characteristics Stratified by the Time of Tumor Recurrence (10.5 Months)

Variable	Late Recurrence (n=16)	Early Recurrence (n=26)	P-value
Therapy			0.979
Systemic therapy alone	1 (6.25)	3 (11.54)	
Combination therapy	15 (93.75)	23 (88.46)	
mRECIST			0.771
SD	6 (37.50)	7 (26.92)	
PR	9 (56.25)	17 (65.38)	
CR	1 (6.25)	2 (7.69)	
Gender			0.659
Female	2 (12.50)	1 (3.85)	
Male	14 (87.50)	25 (96.15)	
Age (year)	59.50 [50.75, 64.50]	53.50 [48.00, 62.75]	0.468
BMI (kg/m ²)	23.55 [21.98, 25.27]	23.25 [22.55, 26.80]	0.836
ASA			0.756
I/II	12 (75.00)	17 (65.38)	
III	4 (25.00)	9 (34.62)	
CCI			0.691
≤5	15 (93.75)	22 (84.62)	
>5	1 (6.25)	4 (15.38)	
HBsAg			0.823
Negative	5 (31.25)	6 (23.08)	
Positive	11 (68.75)	20 (76.92)	
Anti-HCV			1
Negative	15 (93.75)	25 (96.15)	
Positive	1 (6.25)	1 (3.85)	
AFP			0.887
Negative	11 (68.75)	16 (61.54)	
Positive	5 (31.25)	10 (38.46)	
AFP level (ng/mL)	3.20 [2.15, 42.50]	9.70 [3.62, 144.00]	0.3
Child-Pugh			0.696
A	16 (100.00)	24 (92.31)	
B	0 (0.00)	2 (7.69)	
ALBI			0.527
I	11 (68.75)	14 (53.85)	
2	5 (31.25)	12 (46.15)	

(Continued)

Table 2 (Continued).

Variable	Late Recurrence (n=16)	Early Recurrence (n=26)	P-value
ECOG-PS			0.659
0	14 (87.50)	25 (96.15)	
I	2 (12.50)	1 (3.85)	
Baseline tumor number			0.19
Solitary	7 (43.75)	18 (69.23)	
Multiple	9 (56.25)	8 (30.77)	
Baseline maximum tumor diameter (cm)	5.20 [3.68, 7.90]	7.00 [4.45, 9.00]	0.407
Tumor location			0.572
Left lobe	2 (12.50)	1 (3.85)	
Right lobe	9 (56.25)	16 (61.54)	
Both	5 (31.25)	9 (34.62)	
Macrovascular invasion			0.756
No	12 (75.00)	17 (65.38)	
Yes	4 (25.00)	9 (34.62)	
CNLC stage			0.883
Ib	3 (18.75)	5 (19.23)	
Ila	3 (18.75)	5 (19.23)	
Ilb	6 (37.50)	7 (26.92)	
IIla	4 (25.00)	9 (34.62)	
Surgical approach			0.956
Laparoscopic	12 (75.00)	21 (80.77)	
Open	4 (25.00)	5 (19.23)	
Extension of hepatectomy			0.751
Minor	9 (56.25)	12 (46.15)	
Major	7 (43.75)	14 (53.85)	
Severe surgical complications (CD $\geq$ 3)			0.476
No	15 (93.75)	21 (80.77)	
Yes	1 (6.25)	5 (19.23)	
Surgical margin			0.271
$\leq$ 1cm	14 (87.50)	26 (100.00)	
$>$ 1cm	2 (12.50)	0 (0.00)	
WHO tumor differentiation			0.434
Poor/undifferentiated	5 (31.25)	5 (19.23)	
Moderate	9 (56.25)	16 (61.54)	
Well	2 (12.50)	2 (7.69)	
Unknown	0 (0.00)	3 (11.54)	
MVI			0.574
No	12 (75.00)	16 (61.54)	
Yes	4 (25.00)	10 (38.46)	
Satellite nodule			0.052
No	15 (93.75)	16 (61.54)	
Yes	1 (6.25)	10 (38.46)	
Capsular invasion			1
No	15 (93.75)	25 (96.15)	
Yes	1 (6.25)	1 (3.85)	
Pathologic response			0.181
pNR	4 (25.00)	2 (7.69)	
pPR	12 (75.00)	22 (84.62)	
pCR	0 (0.00)	2 (7.69)	

(Continued)

Table 2 (Continued).

Variable	Late Recurrence (n=16)	Early Recurrence (n=26)	P-value
Adjuvant therapy			0.147
No	0 (0.00)	1 (3.85)	
Yes	16 (100.00)	25 (96.15)	
Treatment after first recurrence			
Palliative systemic	2 (12.50)	10 (38.46)	
Palliative local	12 (75.00)	15 (57.69)	
Curative	2 (12.50)	1 (3.85)	

Abbreviations: mRECIST, modified Response Evaluation Criteria in Solid Tumors; SD, stable disease; PR, partial response; CR, complete response; BMI, body mass index; ASA, American Society of Anesthesiologists physical status classification; CCI, Charlson Comorbidity Index; HBsAg, hepatitis B surface antigen; anti-HCV, antibody to hepatitis C virus; Child-Pugh, Child-Turcotte-Pugh score; ALBI, albumin-bilirubin grade; ECOG-PS, Eastern Cooperative Oncology Group performance status; AFP, alpha-fetoprotein; CNLC, China Liver Cancer Stage; CD, Clavien-Dindo classification; MVI, microvascular invasion; pCR, pathological complete response; pPR, pathological partial response; pNR, pathological non-response.

Table 3 Baseline Demographic and Clinicopathological Characteristics Stratified by the First Site of Tumor Recurrence

Variable	Intrahepatic Recurrence (n=33)	Extrahepatic Recurrence (n=8)	P-value
Therapy			0.0971
Systemic therapy alone	3 (9.09)	1 (12.50)	
Combination therapy	30 (90.91)	7 (87.50)	
mRECIST			0.7269
SD	13 (39.39)	0 (0.00)	
PR	18 (54.55)	7 (87.50)	
CR	2 (6.06)	1 (12.50)	
Gender			0.8305
Female	20 (60.61)	6 (75.00)	
Male	13 (39.39)	2 (25.00)	0.0964
Age (year)	55.00 [50.00, 64.00]	54.50 [47.25, 61.00]	
BMI (kg/m ²)	23.40 [22.50, 26.50]	24.10 [22.72, 25.85]	0.5668
ASA			
I/II	25 (75.76)	3 (37.50)	0.8409
III	8 (24.24)	5 (62.50)	
CCI			0.8051
≤5	28 (84.85)	8 (100.00)	
>5	5 (15.15)	0 (0.00)	0.8409
HBsAg			
Negative	9 (27.27)	2 (25.00)	0.76
Positive	24 (72.73)	6 (75.00)	
Anti-HCV			0.8051
Negative	32 (96.97)	7 (87.50)	
Positive	1 (3.03)	1 (12.50)	0.8409
AFP level (ng/mL)	6.20 [2.40, 92.90]	10.10 [3.03, 45.08]	
Child-Pugh			0.76
A	32 (96.97)	7 (87.50)	
B	1 (3.03)	1 (12.50)	0.76
ALBI			
1	21 (63.64)	4 (50.00)	
2	12 (36.36)	4 (50.00)	

(Continued)

Table 3 (Continued).

Variable	Intrahepatic Recurrence (n=33)	Extrahepatic Recurrence (n=8)	P-value
ECOG-PS			0.8972
0	30 (90.91)	8 (100.00)	I
I	3 (9.09)	0 (0.00)	
Baseline tumor number			I
Solitary	19 (57.58)	5 (62.50)	0.6808
Multiple	14 (42.42)	3 (37.50)	
Baseline maximum tumor diameter (cm)	6.00 [3.60, 8.90]	7.35 [4.90, 8.62]	0.1724
Tumor location			I
Left lobe	3 (9.09)	0 (0.00)	
Right lobe	17 (51.52)	7 (87.50)	
Both	13 (39.39)	1 (12.50)	
Macrovascular invasion			I
No	23 (69.70)	6 (75.00)	0.6567
Yes	10 (30.30)	2 (25.00)	
CNLC stage			0.2914
Ib	7 (21.21)	1 (12.50)	
IIa	7 (21.21)	1 (12.50)	
IIb	9 (27.27)	4 (50.00)	
IIIa	10 (30.30)	2 (25.00)	
Surgical approach			0.6376
Laparoscopic	25 (75.76)	8 (100.00)	
Open	8 (24.24)	0 (0.00)	I
Extension of hepatectomy			
Minor	15 (45.45)	5 (62.50)	0.8409
Major	18 (54.55)	3 (37.50)	
Severe surgical complications (CD $\geq$ 3)			0.4872
No	28 (84.85)	7 (87.50)	
Yes	5 (15.15)	1 (12.50)	0.9753
Surgical margin			
$\leq$ 1cm	32 (96.97)	7 (87.50)	0.2286
$>$ 1cm	1 (3.03)	1 (12.50)	
WHO tumor differentiation			0.8409
Poor/undifferentiated	6 (18.18)	3 (37.50)	
Moderate	22 (66.67)	3 (37.50)	
Well	3 (9.09)	1 (12.50)	
Unknown	2 (6.06)	1 (12.50)	0.5348
MVI			
No	22 (66.67)	6 (75.00)	0.8409
Yes	11 (33.33)	2 (25.00)	
Satellite nodule			0.8409
No	26 (78.79)	4 (50.00)	
Yes	7 (21.21)	4 (50.00)	0.5348
Capsular invasion			
No	32 (96.97)	7 (87.50)	0.5348
Yes	1 (3.03)	1 (12.50)	
Pathologic response			0.5348
pNR	5 (15.15)	1 (12.50)	
pPR	27 (81.82)	6 (75.00)	
pCR	1 (3.03)	1 (12.50)	

(Continued)

Table 3 (Continued).

Variable	Intrahepatic Recurrence (n=33)	Extrahepatic Recurrence (n=8)	P-value
Adjuvant therapy			0.5582
No	1 (3.03)	0 (0.00)	
Yes	32 (96.97)	8 (100.00)	
Treatment after first recurrence			
Palliative systemic	8 (24.24)	3 (37.50)	
Palliative local	22 (66.67)	5 (62.50)	
Curative	3 (9.09)	0 (0.00)	

Abbreviations: mRECIST, modified Response Evaluation Criteria in Solid Tumors; SD, stable disease; PR, partial response; CR, complete response; BMI, body mass index; ASA, American Society of Anesthesiologists physical status classification; CCI, Charlson Comorbidity Index; HBsAg, hepatitis B surface antigen; anti-HCV, antibody to hepatitis C virus; Child-Pugh, Child-Turcotte-Pugh score; ALBI, albumin-bilirubin grade; ECOG-PS, Eastern Cooperative Oncology Group performance status; AFP, alpha-fetoprotein; CNLC, China Liver Cancer Stage; CD, Clavien-Dindo classification; MVI, microvascular invasion; pCR, pathological complete response; pPR, pathological partial response; pNR, pathological non-response.

demographic, clinical, or pathological variables, including age, sex, liver function (Child-Pugh class, ALBI grade), tumor burden (baseline number and size), CNLC stage, surgical details, or pathological features (all $P > 0.05$).

PRS varied significantly according to both the timing and site of tumor recurrence. One patient with simultaneous intrahepatic and extrahepatic recurrence was excluded from the subgroup analysis stratified by the site of first recurrence due to ambiguous classification and limited sample size. Patients with early recurrence had markedly worse OS than those with late recurrence, respectively ($P = 0.04$) (Figure 3A). Patients with intrahepatic recurrence exhibited a favorable survival prognosis, compared to those with extrahepatic recurrence ($P < 0.0001$) (Figure 3B).

When combined, four distinct prognostic patterns emerged (early intrahepatic, early extrahepatic, late intrahepatic, and late extrahepatic recurrence). Compared with early intrahepatic recurrence, the survival rate of early extrahepatic recurrence was significantly reduced ($P = 0.0024$), which is consistent with the overall trend of poor prognosis caused by extrahepatic diffusion (Figure 3C). Both late intrahepatic and late extrahepatic recurrence have shown excellent survival outcomes, supporting its classification as a “late recurrence” with good prognosis. However, due to the small number of patients with late intrahepatic metastasis, it is statistically indistinguishable (all paired $P > 0.05$). There is a significant difference between early extrahepatic recurrence and late intrahepatic recurrence ($P = 0.0024$), which further confirms the prognostic impact of time on the site of recurrence.

In further exploratory analyses, we dichotomized recurrence time at the clinically conventional threshold of 12 months to enhance clinical utility. The early recurrence group included 29 patients (69.05%), while the late recurrence group comprised 13 patients (30.95%). No significant differences were observed between the two groups in terms of

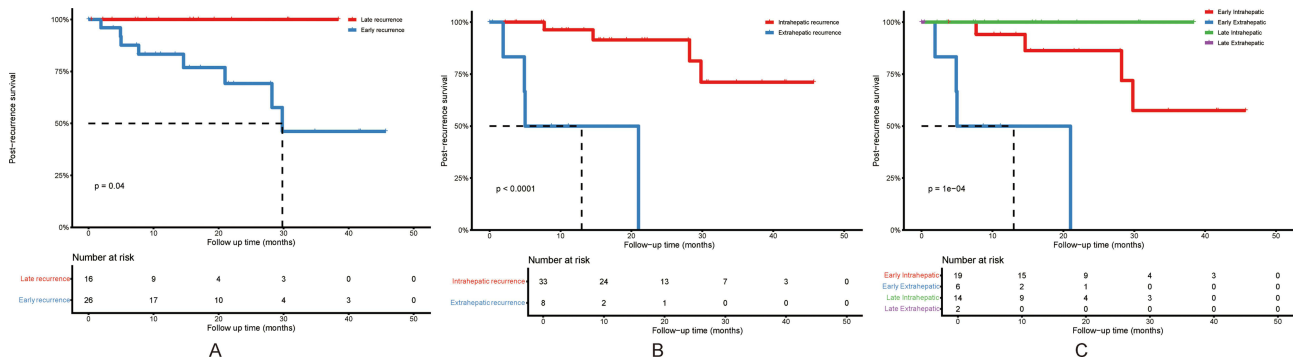


Figure 3 Post-recurrence survival curves stratified by recurrence pattern. (A) Comparison between early recurrence (≤ 10.5 months, $n = 26$) and late recurrence (> 10.5 months, $n = 16$); Log rank test $P = 0.04$. (B) Intrahepatic recurrence ($n = 33$) vs. extrahepatic recurrence ($n = 8$); $P < 0.0001$. (C) Combined analysis of early and late recurrence by location: early intrahepatic ($n = 19$), early extrahepatic ($n = 6$), late intrahepatic ($n = 14$), and late extrahepatic ($n = 2$); $P < 0.0001$. Numbers at risk are shown below each panel.

baseline clinical or pathological characteristics (all $P > 0.05$) (Table S1). In PRS analyses, the prognostic associations of the first recurrence site and combined recurrence pattern were consistent with those derived using the optimal TTR cutoff identified in our study (10.5 months). Although the survival curves for early versus late recurrence appeared visually distinct, the difference did not reach statistical significance ($P > 0.05$), due to limited statistical power resulting from the small sample size (Figure S3).

Discussion

In this retrospective cohort of 80 patients with HCC who underwent curative resection after successful conversion therapy, over half still experienced postoperative tumor recurrence. The combination of systemic and locoregional treatment has become the mainstream approach for the downstaging treatment of advanced HCC patients. Previous studies on HCC recurrence after resection mainly focused on the timing or location in upfront resection cohorts. However, patients who undergo resection after conversion therapy represent a biologically distinct population, initially unresectable, typically with larger tumors, vascular invasion, or advanced CNLC stage, and may therefore exhibit different recurrence dynamics. Our study is among the first to systematically characterize integrated spatiotemporal recurrence phenotypes in this emerging clinical scenario.

Our comparative analysis suggested that preoperative tumor burden, reflected by tumor number, size, and CNLC stage, was associated with an increased risk of postoperative recurrence. Additionally, key pathological features, including MVI, poor tumor differentiation, and suboptimal pathological response to conversion therapy, were also linked to higher recurrence rates. Notably, most patients who experienced recurrence had received adjuvant therapy due to these high-risk features, yet their outcomes remained suboptimal. A similar pattern was observed in the IMBrave050 study.²⁵ Future studies should employ multivariable regression models to identify independent predictors of recurrence, enabling risk-adapted surveillance and personalized adjuvant strategies in patients undergoing curative resection following conversion therapy.

Previous studies have demonstrated that liver resection following downstaging therapy can significantly improve OS and PFS in patients with HCC, irrespective of whether the tumor was initially resectable or unresectable.^{26–28} To avoid the immortality time bias caused by using tumor recurrence as a prognostic factor, a limitation in prior studies, we used PRS as the outcome measure. Comparison of subgroup differences across recurrence patterns suggests that baseline characteristics were well balanced. In this context, we demonstrate that the spatiotemporal pattern of tumor recurrence, integrating both timing and location, is a critical determinant of PRS. Notably, TTR becomes the dominant prognostic factor, outweighing the site of recurrence. Specifically, late recurrences (>10.5 months) were associated with favorable PRS regardless of location, whereas early recurrences (≤ 10.5 months) conferred poor outcomes, with extrahepatic spread further worsening prognosis. These findings are consistent with the prognosis reported for upfront resectable HCC.^{29,30}

Our finding that TTR is important in prognostic stratification aligns with the prevailing biological paradigm of HCC recurrence. Early recurrence likely reflects occult micrometastases or aggressive intrahepatic dissemination present at the time of surgery, hallmarks of intrinsically high-risk disease resistant to conversion therapy.^{31,32} A previous study has shown that in patients with early recurrence (≤ 6 months) following R0 resection, tumor progression to intermediate or advanced stages is associated with limited benefit from curative-intent therapies.³³ In contrast, late recurrence often arises from de novo carcinogenesis in a cirrhotic liver, representing another carcinogenic process with inherently better prognosis.³⁴ Consistent with these biological distinctions, the decreasing risk of death after tumor recurrence associated with delayed TTR in our study further supports a biological threshold for distinguishing systemic micrometastasis from metachronous carcinogenesis.

These findings offer direct implications for clinical practice. First, recurrence within 10.5 months after surgery may serve as an evidence-based risk stratification threshold, warranting intensified surveillance during this critical window. Although many studies define early HCC recurrence as occurring within 2 years after surgery, the optimal timing varies across studies due to HCC heterogeneity.^{35–37} Our data suggest a sharper inflection point at 10.5 months for this specific population. Second, considering the high systemic disease burden of early recurrence patients, particularly those with extrahepatic recurrence, in addition to active local intervention, systemic treatment should be considered. Third, in future studies related to adjuvant therapy for patients after conversion surgery, stratification of patients based on tumor recurrence phenotype should be considered, as it more accurately captures potential tumor biology than binary recurrence

status alone. In addition, emerging technologies such as multi-omics biomarkers (genomics, transcriptomics, proteomics, metabolomics), liquid biopsy, and artificial intelligence (AI)-driven imaging and pathological analysis may provide new avenues for optimizing recurrence risk stratification.^{38,39}

Several limitations warrant acknowledgment. First, this was a single-center retrospective study with a small sample size (n=80), limiting statistical power for subgroup analyses, particularly for rare events like late extrahepatic recurrence (n=2). Second, while we used standardized imaging criteria for recurrence diagnosis, pathological confirmation was not available for all cases. Third, we only focused on the first tumor recurrence and did not include subsequent recurrences in the analysis. Finally, heterogeneity in conversion regimens (systemic ± locoregional) may introduce confounding, although multivariate adjustment partially mitigated this issue.

Conclusion

In summary, the spatiotemporal pattern of recurrence provides a biological framework for the prognosis of HCC patients who undergo resection after conversion therapy. Time to recurrence is the primary determinant of survival, while the site of first recurrence provides additional prognostic refinement. Future multicenter prospective studies are needed to validate these phenotypes and explore whether tailored adjuvant strategies guided by early recurrence risk can improve the long-term prognosis of this high-risk population.

Data Sharing Statement

Based on patient privacy and ethical considerations, de-identified data may be made available upon reasonable request through the corresponding author under controlled access.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

There is no funding to report.

Disclosure

The authors report no conflicts of interest in this work.

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