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ORIGINAL RESEARCH

Risk Factors of Non-Classic Radiation-Induced Liver Disease (ncRILD) After Intensity-Modulated Radiotherapy in Hepatocellular Carcinoma

You-Qin Du[1,2], Su-Ping Tao[3], Jian-Xu Li[1], Yin-Nong Zhao[2]

[1]Department of Radiation Oncology, Guangxi Medical University Cancer Hospital, Nanning, Guangxi, 530021, People's Republic of China; [2]Department of Hepatobiliary Surgery, Guangxi Medical University Cancer Hospital, Nanning, Guangxi, 530021, People's Republic of China; [3]Department of Oncology, Guiping People's Hospital, Guiping, People's Republic of China

Correspondence: Yin-Nong Zhao, Department of Hepatobiliary Surgery, Guangxi Medical University Cancer Hospital, Nanning, Guangxi, 530021, People's Republic of China, Tel +86 18977783542, Email zhaoyinnong@gxmu.edu.cn

Purpose: This study aimed to identify independent risk factors for non-classic radiation-induced liver disease (ncRILD) in hepatocellular carcinoma (HCC) patients treated with intensity-modulated radiation therapy (IMRT) and to construct a predictive nomogram.

Patients and Methods: We retrospectively analyzed 177 primary HCC patients treated with IMRT between 2013 and 2021. Univariate and multivariate analyses were conducted to identify risk factors for ncRILD. A nomogram was developed based on significant variables. Dosimetric parameters were also assessed across different fractionation doses.

Results: Multivariate analysis identified tumor number ≥ 2, mean liver dose ≥ 1371.4 cGy, and normal liver volume < 700 mL as independent risk factors for ncRILD. A nomogram was established using logistic regression. In patients receiving ≥ 4 Gy per fraction, ncRILD was significantly associated with Vs5–Vs40 ($p < 0.05$), but not with V5–V40. No such associations were found for 2 Gy and 3 Gy groups.

Conclusion: Patients with multifocal tumor, lower normal liver volume and higher mean liver dose are at increased risk of developing radiation-induced liver injury. These findings suggest that dosimetric parameters, especially at higher fraction doses, may play a critical role in the occurrence of ncRILD.

Keywords: hepatocellular carcinoma, ncRILD, IMRT, liver toxicity, child-Pugh score

Introduction

With advancements in radiation techniques, such as intensity-modulated radiation therapy (IMRT) and stereotactic body radiotherapy (SBRT), radiotherapy has increasingly played a significant role in the local treatment of hepatocellular carcinoma (HCC). Meanwhile, significant progress has been made in systemic therapies for HCC in recent years. Targeted therapies, including Lenvatinib,[1] cabozantinib,[2] ramucirumab,[3] donafenib,[4] and apatinib,[5] have shown promising results. However, these systemic treatments generally exhibit low objective response rates. Similarly, monotherapy with immune checkpoint inhibitors has demonstrated some efficacy as second-line therapy for HCC, but the objective response rate remains low, at only 15%-20%.[6] In 2020, the landmark IMbrave 150 trial ushered in a new era of combined targeted and immune therapy for HCC, with the combination of atezolizumab and bevacizumab showing a higher objective response rate of 27.3%.[7] The HIMALAYA study marked the beginning of dual immunotherapy for HCC.[8,9] However, the highly anticipated LEAP-002 trial did not meet the prespecified threshold for statistical significance in overall survival (OS).[10] This result further underscores the high heterogeneity in response to systemic therapy in HCC. Whether adding local therapies to this combined systemic therapy can further improve efficacy has garnered significant attention.[11] Moreover, whether combined treatments will lead to greater liver function damage remains a critical concern.

Previous reports have indicated that liver radiotherapy can achieve local control rates exceeding 80% for intrahepatic lesions.[12] In the era of conventional two-dimensional radiotherapy, whole liver irradiation was often necessary to manage local tumors, frequently resulting in radiation-induced liver disease (RILD). RILD is classified into classic RILD (cRILD) and non-classic RILD (ncRILD). cRILD is characterized by the onset of ascites, liver enlargement, and alkaline phosphatase (ALP) levels rising more than twice the upper limit of normal within 2 weeks to 3 months after radiotherapy, without

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the presence of jaundice and excluding tumor progression. ncRILD is defined by an elevation of transaminases to more than five times the upper limit of normal or five times the pre-radiotherapy levels.[13] Hepatic injury has traditionally been attributed to veno-occlusive disease resulting from radiation-induced fibrosis. Established risk factors for cRILD include elevated mean liver dose, presence of primary liver tumors, male sex, and prior hepatic intra-arterial chemotherapy. The veno-occlusive pattern of classic RILD is reflected by reduced hepatic arterial and portal venous perfusion on magnetic resonance imaging (MRI). In contrast, the underlying mechanisms of ncRILD remain unclear but may be related to impaired hepatic regeneration and possible reactivation of underlying hepatitis.[14] With advancements in radiotherapy and imaging technology, partial liver irradiation and precise radiotherapy for intrahepatic lesions have become viable, making cRILD rare in clinical practice. However, ncRILD continues to be a significant concern. The definition of ncRILD has evolved in line with changes in treatment methods, and currently, there is no standardized definition. Recent studies have predominantly used increases in Child-Pugh (CP) score or alterations in Albumin-Bilirubin (ALBI) score to define ncRILD, with the most common criterion being a CP score increase of ≥2 points within 3 months post-radiotherapy.[14] Some researchers suggest that this score is a strong predictor of OS.[15]

Current research on radiation-induced liver injury mainly focuses on SBRT, which is primarily applicable to small liver tumors. A meta-analysis indicated that IMRT provides similar survival outcomes.[16] Unlike SBRT, IMRT uses more subfields to ensure sufficient dose coverage and conformity to the target area, resulting in a greater amount of normal liver tissue being exposed to radiation. As a result, the low-dose radiation exposure in the liver is significantly higher compared to SBRT, and the incidence of radiation-induced liver injury is relatively greater.[17–19] There are various reports on the high-risk factors and dosimetric parameters that can predict avoidable ncRILD in patients undergoing IMRT, most of which are based on retrospective analyses with small sample sizes.[20,21]

The Lyman model is among the most commonly utilized tools for estimating the probability of complications in normal tissues (NTCP). Effective volume (Veff) of normal liver irradiated has played a significant role in modeling RILD, especially in early efforts to account for the heterogeneous distribution of liver dose.[22,23] Vx (the percentage of normal liver volume receiving x Gy or more) and Vsx (the absolute liver volume (mL) spared from at least x Gy) are also commonly used clinical indicators.[19,24,25]

The liver consists of many functional subunits arranged in a parallel structure, enabling it to withstand considerable localized damage without immediate clinical consequences. This functional redundancy permits high-dose irradiation to portions of the liver, provided that a sufficient volume of healthy liver tissue is preserved.[26] In a Phase I dose-escalation study on liver SBRT, Schefter et al implemented a "critical volume" constraint, requiring that at least 700 mL of normal liver tissue receive no more than 15 Gy over three fractions.[27] Another study found that liver function decline at 3 months post-SBRT was closely linked to baseline CP scores and elevated liver radiation exposures, including metrics such as mean liver dose, effective volume, and doses delivered to 700–900 cc of liver tissue.[28] In addition, several other studies have also confirmed the importance of functional liver sparing in the context of liver irradiation.[25,29]

Given the potential adverse effects of ncRILD on prognosis and subsequent systemic therapies, ncRILD caused by IMRT warrants further investigation.

Methods

Patients

A retrospective study was conducted on 177 hCC patients who underwent IMRT for intrahepatic lesions, either alone or in combination with portal vein thrombosis or metastatic lymph nodes, at Guangxi Medical University Cancer Hospital between July 2013 and December 2021. The inclusion criteria were as follows: (1) hepatocellular carcinoma (HCC) diagnosed by either histopathology or characteristic imaging features; (2) Child-Pugh class A or B liver function; (3) an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; (4) unresectable, locally advanced disease not amenable to radical treatments such as surgical resection or local ablation; (5) with available dosimetric data; (6) a follow-up period of at least 3 months when possible; and (7) complete clinical and follow-up data. Patients without available imaging review data, liver function test results, or complete dose-volume histogram (DVH) information, along with those who experienced tumor progression within 3 months after radiotherapy, were excluded. The study flowchart is shown in Figure 1. The biologically

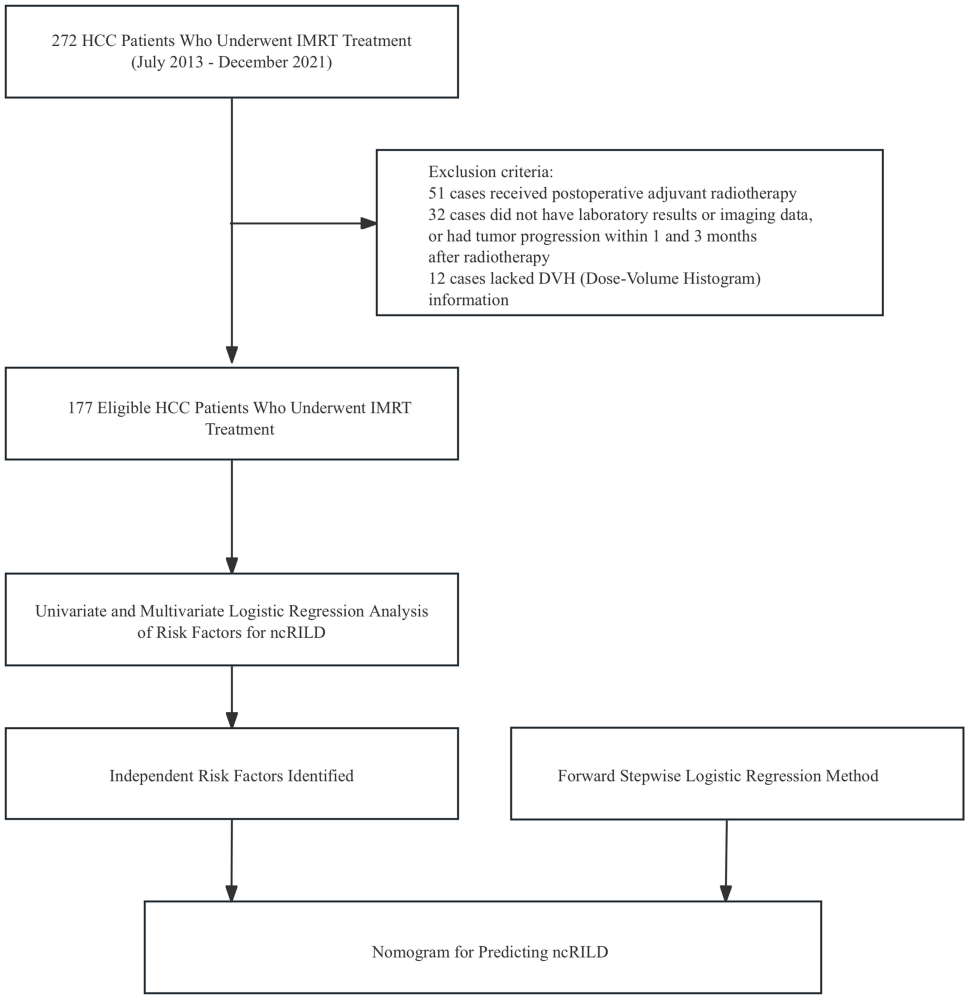

Figure 1 Study flowchart.
Abbreviations: HCC, hepatocellular carcinoma; IMRT, Intensity-Modulated Radiotherapy; ncRILD, Non-classic Radiation-Induced Liver Disease.

effective dose (BED) was calculated using the linear quadratic (LQ) model, assuming an α/β ratio of 10. This study was approved by the Ethics Committee of Guangxi Medical University Cancer Hospital (LW2023075).

All patients received IMRT with either vacuum cushion or thermoplastic body mask fixation. CT scans with a 5 mm slice thickness were obtained during normal breathing. The Gross Tumor Volume (GTV) was defined as the tumor visible during the arterial phase of enhanced CT and was outlined using PET-CT or MRI fusion when available. The Clinical Target Volume (CTV) included the GTV along with a 5 to 10 mm margin expansion. The Planning Target Volume (PTV) extended outward from the GTV or CTV by 10 mm in the cephalocaudal direction and 5 mm in other directions. The normal liver volume (NLV) was defined as the total liver volume minus the GTV. The mean liver dose (MLD) was calculated based on the NLV. We referred to dose constraints such as preserving residual liver ≥700 mL and limiting the MLD to <21Gy, preserving residual liver ≥600-700 mL and limiting the MLD to <15Gy depending on baseline liver function. Treatment planning was performed using the Monaco 5.1 or Pinnacle 3 system, and 6-MV X-ray radiotherapy was administered via an ELEKTA Synergy or Versa-HD linear accelerator, with daily Cone Beam Computed Tomography (CBCT) for the first five fractions, followed by weekly CBCT.

ncRILD Definition

In this study, ncRILD was defined as an increase in the CP score by ≥2 points within 3 months post-radiotherapy, excluding tumor progression.

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Follow-Up

All patients were monitored at one month and three months after radiotherapy. During each visit, physical examinations, laboratory tests (including blood counts, liver and kidney function, and coagulation tests), and imaging tests (including chest and abdominal CT scans, liver MRI, and liver ultrasound) were performed. Patients lacking laboratory results or imaging data within three months post-radiotherapy were excluded from the analysis. OS was defined as the time from the initiation of radiotherapy to the occurrence of death from any cause or the date of the last follow-up.

Statistical Analysis

All statistical analyses were conducted using SPSS (version 26.0) and R (version 3.6.3). Normality tests were applied to continuous variables. Normally distributed data are presented as mean ± standard deviation, whereas non-normally distributed data are reported as median (interquartile range). Categorical variables are shown as frequency and percentage. Differences in continuous variables are evaluated using independent sample *T*-tests or Mann-Whitney *U*-tests, while differences in categorical variables are analyzed with Chi-square tests or Fisher's exact tests. Univariate logistic regression analysis was performed on factors with $P < 0.05$ from the baseline data, as well as on factors potentially related to ncRILD based on previous literature, such as hepatitis B carrier status, portal vein tumor thrombosis, baseline Child-Pugh score, prescription dose fractionation, mean normal liver dose, cirrhosis, platelet count.[26,28,30] Additionally, factors of interest such as single fraction mean dose to normal liver and liver function-related factors like AST, ALT, and total bilirubin are also considered. The optimal cutoff values are determined using the Youden index derived from receiver operating characteristic (ROC) curves. Univariate and multivariate analyses are performed using logistic regression. The above statistical analyses were performed using SPSS. We used R for survival analysis, specific modeling and validation steps, including the construction and ROC comparison of the nomogram. The nomogram was constructed based on independent risk factors identified through multivariate analysis. A medical statistician was involved throughout the process, from the initial model construction to the selection of appropriate statistical methods. A p-value < 0.05 was considered statistically significant.

Results

Baseline Characteristics

A total of 177 patients met the inclusion criteria. Detailed baseline characteristics are presented in Table 1. The total radiotherapy dose ranged from 30 to 66 Gy, with a median dose of 51 Gy, administered in fractions ranging from 9 to 33. The dose per fraction varied from 2 to 6 Gy, with 3 patients receiving more than 4 Gy per fraction (2 patients received 5

Table 1 Baseline Characteristics of Patients

Characteristics	ncRILD		χ^2/Z	p
	No (N=128)	Yes (N=49)		
Gender			0.261[§]	0.834
Male	118(92.2%)	44(89.8%)		
Female	10(7.8%)	5(10.2%)		
Age (years)	55(48–62.8)	54(50.5–63.5)	−0.5	0.617
BMI	21.8(19.9–24.2)	22.5(20.2–24.0)	−0.943	0.346
Prothrombin time (s)	12.5(12–13.6)	12.9(12.1–13.9)	−1.028	0.304
Total bilirubin (μmol/L)	14.65(10.6–22.8)	18.5(10.9–24.2)	−1.295	0.195
Albumin (g/L)	35.5(32.9–38.6)	35.5(32.8–37.9)	−0.336	0.737
AST (U/L)	42(30–79)	51(39–74)	−1.243	0.214
ALT (U/L)	38(26–66)	38(23.5–54)	−0.898	0.369
Alkaline phosphatase (U/L)	112.5(80–185)	107(88.5–157)	−0.238	0.812
Platelet (×10^9/L)	158.5(112.2–238.5)	152(114.5–204.1)	−0.483	0.630

(*Continued*)

Table 1 (Continued).

Characteristics	ncRILD		χ^2/Z	*p*
	No (N=128)	Yes (N=49)		
HBsAg			0.205§	0.651
Positive	117(91.4%)	43(87.8%)		
Negative	11(8.6%)	6(12.2%)		
HBV DNA			1.967§	0.374
<2×10^3 IU/mL	96(75.0%)	32(65.3%)		
≥2×10^3 IU/mL	23(18.0%)	11(22.4%)		
Unknown	9(7.0%)	6(12.2%)		
Imaging-diagnosed cirrhosis			0.146§	0.703
Yes	56(43.8%)	23(46.9%)		
No	72(56.2%)	26(52.1%)		
AFP			4.128§	0.042*
≥400 ng/mL	44(34.4%)	25(51.0%)		
<400 ng/mL	84(65.6%)	24(49.0%)		
Ascites			0.05§	0.824
Yes	37(28.9%)	15(30.6%)		
No	91(71.1%)	34(69.4%)		
Previous liver tumor surgery			9.546§	0.002*
Yes	75(58.6%)	16(32.7%)		
No	53(41.4%)	33(67.3%)		
Primary tumor diameter (cm)	5.95(2.8–9.6)	7.8(5.8–11.2)	−3.033	0.002*
Tumor number			6.426§	0.011*
Single	58(45.3%)	12(24.5%)		
Multifocal	70(54.7%)	37(75.5%)		
Extrahepatic metastasis			1.154§	0.561
None	82 (64.1%)	35 (71.4%)		
Lymph node	29(22.7%)	10(20.4%)		
Distant metastasis	17(13.3%)	4(8.2%)		
Child-Pugh grade			0.748§	0.387
Grade A	91(71.7%)	38(77.6%)		
Grade B	37(28.9%)	11(22.4%)		
Cheng's classification of portal vein invasion			6.461§	0.143
None	65(50.8%)	21(42.9%)		
I	16(12.5%)	2(4.1%)		
II	23(18.0%)	15(30.6%)		
III	23(18.0%)	10(20.4%)		
IV	1(0.8%)	1(2.0%)		
Pre-radiotherapy ALBI grade			3.069§	0.216
Grade 1	30(23.4%)	6(12.2%)		
Grade 2	91(71.1%)	41(83.7%)		
Grade 3	7(5.5%)	2(4.1%)		
Pre-radiotherapy local treatment			4.578§	0.175
None	55(43.0%)	19(38.8%)		
TACE	59(46.1%)	28(57.1%)		
RFA	5(3.9%)	2(4.1%)		
TACE+RFA	9(7.0%)	0(%)		
Pre-radiotherapy systemic treatment			4.479§	0.171
None	104(81.3%)	45(91.8%)		
Immunotherapy	5(3.9%)	2(4.1%)		
Targeted therapy	4(3.1%)	1(2.0%)		

(*Continued*)

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Table 1 (Continued).

Characteristics	ncRILD		χ^2/Z	*p*
	No (N=128)	Yes (N=49)		
Targeted + Immunotherapy	15(11.7%)	1(2.0%)		
Concurrent systemic therapy during radiotherapy			6.925§	0.056
None	92(71.9%)	43(87.8%)		
Immunotherapy	23(18.0%)	2(4.1%)		
Targeted therapy	2(1.6%)	1(2.0%)		
Targeted + Immunotherapy	11(8.6%)	3(6.1%)		
Systemic therapy within 3 months post-radiotherapy			7.592§	0.049*
None	95(74.2%)	39(79.6%)		
Immunotherapy	14(10.9%)	2(4.1%)		
Targeted therapy	7(5.5%)	7(14.3%)		
Targeted + Immunotherapy	12(9.4%)	1(2.0%)		
TACE within 3 months post-radiotherapy			0.711§	0.399
Yes	11 (8.6%)	7 (14.3%)		
No	117 (91.4%)	42(85.7%)		
BED(Gy)	66.3(60–78)	67.2(60.8–78)	−1.028	0.304
EQD2(Gy)	55.3(50–65)	56(50–65)	−1.044	0.296
Total GTV radiotherapy dose (Gy)	51(48.5–59.3)	55(49–60)	−1.561	0.119
Fraction number	18(13.3–25)	20(15–25)	−1.558	0.119
Dose per fraction (Gy)	3(2.24–4)	3(2.18–3.5)	−1.006	0.314
GTV volume (mL)	194.9 (94.0–616.4)	451.6 (161.6–867.8)	−2.459	0.014*
Normal liver volume (mL)	1024(862.3–1185.3)	867.6(696.1–1216.8)	−1.882	0.060
Mean liver dose (cGy)	1688(1245.9–2153.8)	1945.7(1487.6–2304.0)	−2.038	0.042*
Single fraction mean liver dose (cGy)	94.4(72.3–122.0)	91.9(73.0–124.0)	−0.226	0.821

Notes: §indicates Chi-square or Fisher's exact test; *indicates $p < 0.05$, statistically significant difference.
Abbreviations: AFP, Alpha-fetoprotein; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; TACE, Transarterial chemoembolization; RFA, Radiofrequency ablation; BED, Biologically effective dose; EQD2, Equivalent dose in 2 Gy fractions; GTV, Gross tumor volume.

Gy per fraction, and 1 received 6 Gy per fraction). Among the patients, 35 (19.8%) received fractional doses below 3 Gy. The BED ranged from 39 to 90 Gy, and the equivalent dose in 2 Gy fractions (EQD2) ranged from 32.5 to 75 Gy. Normal liver volumes ranged from 376.2 to 2438.1 mL, with 23 patients (13%) having a normal liver volume below 700 mL. Immunotherapy agents included, but were not limited to, tislelizumab, sintilimab, and camrelizumab. Targeted therapies included sorafenib, lenvatinib, apatinib, among others. These agents were administered either as monotherapy or in combination, based on clinical judgment.

Non-Classic RILD and Its Association with Poor Prognosis Following Radiotherapy

By the end of follow-up on October 9, 2022, a total of 126 out of 177 patients had died, with a median overall survival (OS) of 17.4 months and a median follow-up duration of 39.6 months. As shown in Table 1, 49 patients (27.7%) developed ncRILD within 3 months after radiotherapy. CP scores and ALBI grades before and after radiotherapy are detailed in Table 2.

Due to irregular follow-up in some cases, liver function data beyond 6 months post-treatment were incomplete. As a result, long-term progression analysis of ncRILD could not be conducted. Therefore, only overall survival was assessed in relation to ncRILD status, as depicted in Figure 2.

Patients with ncRILD had a significantly shorter median OS of 10.6 months, compared to 19.7 months in those without ncRILD.

Table 2 Child-Pugh Scores and ALBI Grades Before and After Radiotherapy

Characteristics	ncRILD	
	No (N=128)	Yes (N=49)
Pre-radiotherapy CP score		
5	53	22
6	38	16
7	28	8
8	8	3
9	1	
Post-radiotherapy CP score		
5	33	
6	50	
7	29	22
8	14	16
9	2	8
10		3
Pre-radiotherapy ALBI grade		
1	30	6
2	91	41
3	7	2
Post-radiotherapy ALBI grade		
1	16	
2	106	26
3	6	23

ROC Curve Analysis

Using the Youden index, we established the optimal cutoff values for primary tumor diameter, GTV volume, and mean liver dose in predicting ncRILD. The optimal cutoff for primary tumor diameter was 5.6 cm, with an AUC of 0.647 (95% CI: 0.5588–0.7362); for GTV volume, the optimal cutoff was 196.5 mL, with an AUC of 0.620 (95% CI:

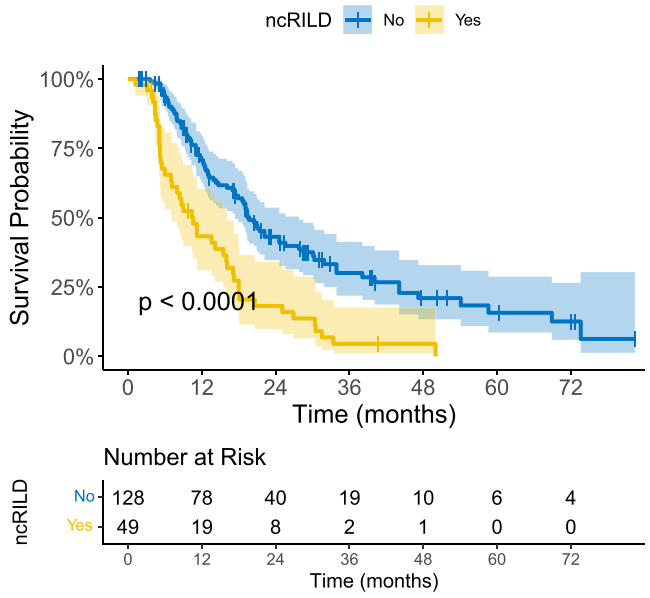

Figure 2 Survival Outcomes in Patients with and Without Non-Classic Radiation-Induced Liver Disease Post-Radiotherapy.

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0.5288–0.7115); and for mean liver dose, the optimal cutoff was 1371.4 cGy, with an AUC of 0.599 (95% CI: 0.5081–0.6901). These results are depicted in Figures 3.

Univariate and Multivariate Analyses of ncRILD

The analysis identified AFP ≥ 400 ng/mL, tumor number ≥ 2, primary tumor diameter ≥ 5.6 cm, portal vein thrombosis, mean liver dose ≥ 1371.4 cGy, tumor volume > 196.5 mL, normal liver volume < 700 mL, and AST ≥ 40 U/L as risk factors for ncRILD. Multivariate analysis indicated that tumor number ≥ 2, mean liver dose ≥ 1371.4 cGy, and normal liver volume < 700 mL were independent risk factors for ncRILD (Table 3).

Nomogram Construction

Based on the results of the multivariate analysis and by employing forward stepwise logistic regression, the optimal regression equation included three parameters: tumor numbers, MLD and NLV. A nomogram was developed using these three parameters to predict the risk of ncRILD in HCC patients undergoing IMRT (Figure 4). For the validation of the nomogram, we compared the AUC of the Nomogram model with that of MLD and NLV. The results are shown in Figure 5. The results show that the AUC of the nomogram is superior to that of the independent risk factors, MLD and NLV.

Dosimetric Analysis of Different Fractional Doses

The most common fractional doses among the analyzed patients were 2 Gy, 3 Gy, and 4 Gy. Although doses of 2 Gy and 3 Gy were relatively common, there were few consistent cases; therefore, we conducted univariate analyses only on patients receiving fractional doses of 2 Gy, 3 Gy, and 4 Gy. The results indicated that for patients receiving 2 Gy or 3 Gy, no significant correlation existed between ncRILD and dosimetric parameters such as V5-V40 or Vs5-Vs40 ($p > 0.05$). However, for those receiving 4 Gy, a significant correlation was found between ncRILD and Vs5-Vs40 ($p < 0.05$), but not with V5-V40 ($p > 0.05$) (Table 4).

Discussion

Recent advancements in systemic therapies have steadily improved the median OS of patients with advanced HCC. Various combination regimens, including targeted therapy paired with immunotherapy, immunotherapy combined with radiotherapy, and combinations involving transarterial chemoembolization (TACE), are being investigated to improve OS.[11,31–34] Due to

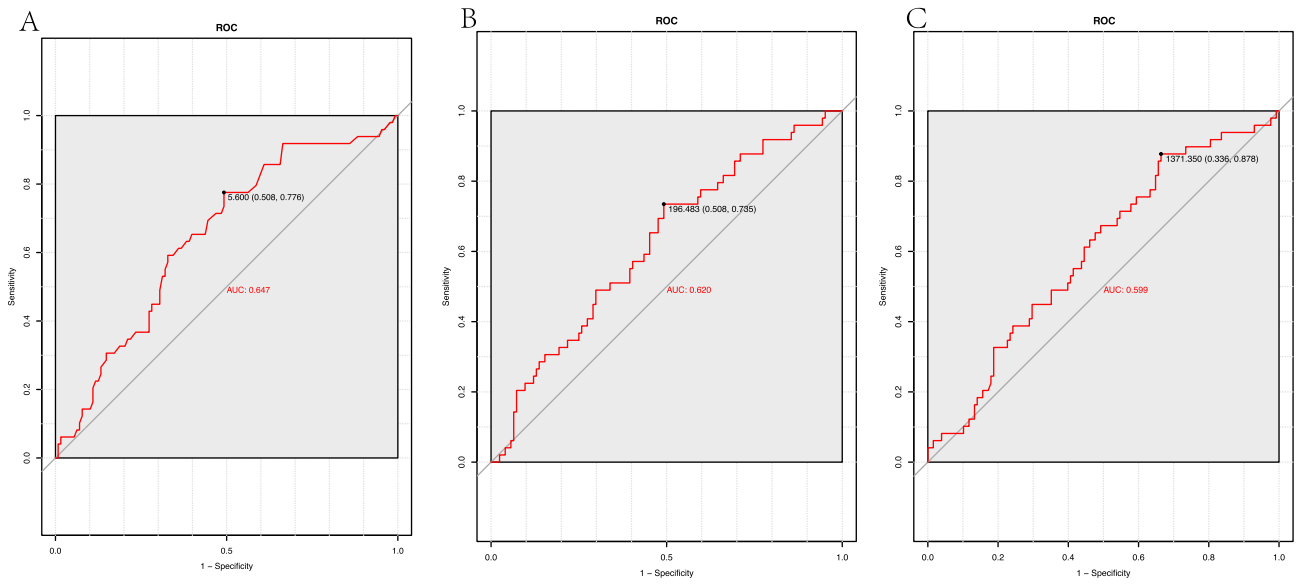

Figure 3 ROC curves. (**A**) ROC curve of major tumor diameter when ncRILD as the end point. (**B**) ROC curve of GTV volume when ncRILD as the end point. (**C**) ROC curve of normal liver mean dose when ncRILD as the end point.
Abbreviations: ROC, Receiver Operating Characteristic; ncRILD, Non-classic Radiation-Induced Liver Disease.

Table 3 Univariate and Multivariate Analyses of ncRILD

Variables	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Platelet<150×10^9/L	0.883 (0.380–2.048)	0.771		
ALT>40U/L	0.923 (0.477–1.789)	0.813		
AST>40U/L	2.138 (1.050–4.351)	0.036*	1.208(0.531–2.750)	0.652
Total Bilirubin ≥ 34umol/L	0.925 (0.315–2.721)	0.888		
Albumin ≤ 35g/L	0.718 (0.367–1.405)	0.333		
Alkaline Phosphatase ≥ 150U/L	0.17 (0.022–1.326)	0.091		
Ascites	1.085 (0.529–2.224)	0.824		
AFP ≥ 400ng/mL	1.989 (1.019–3.88)	0.044*	1.27(0.581–2.776)	0.548
HBsAg Positive	0.674 (0.235–1.934)	0.463		
HBV DNA				
<2×10^3IU/mL	Reference	0.380		
≥2×10^3 IU/mL	1.435 (0.630–3.265)	0.390		
Unknown	2.0 (0.661–6.055)	0.220		
Imaging Cirrhosis	1.137 (0.587–2.202)	0.703		
Pre-RT Child-Pugh Grade A	0.712 (0.329–1.541)	0.389		
Child-Pugh Score				
5	Reference	0.855		
6	1.014(0.471–2.184)	0.971		
7	0.688(0.272–1.744)	0.431		
≥8	0.803(0.198–3.250)	0.758		
Number of Tumors ≥ 2	2.555 (1.221–5.345)	0.013*	2.296(1.030–5.119)	0.042*
Main Tumor Diameter ≥ 5.6 cm	3.564(1.675–7.585)	0.001*	1.693(0.668–4.290)	0.267
Portal Vein Tumor Thrombus	2.154 (1.044–4.443)	0.038*	1.114(0.477–2.600)	0.803
Extrahepatic Metastasis	0.713 (0.348–1.461)	0.355		
History of Liver Tumor Surgery	0.343 (0.171–0.685)	0.002*	0.588(0.253–1.366)	0.217
Post-RT Systemic Therapy				
None	Reference	0.070		
Immunotherapy	0.348(0.076–1.603)	0.176		
Targeted Therapy	2.436(0.801–7.406)	0.117		
Immunotherapy + Targeted Therapy	0.203(0.026–1.615)	0.132		
Post-RT TACE within 3 Months	1.773 (0.645–4.873)	0.267		
Tumor Volume>196.5mL	3.042 (1.476–6.267)	0.003*	1.558(0.663–3.658)	0.309
Normal Liver Volume<700mL	3.45 (1.406–8.466)	0.007*	3.054(1.114–8.375)	0.03*
BED	1.015(0.981–1.050)	0.389		
Fractional Dose ≥4Gy/fraction	0.829 (0.389–1.766)	0.627		
Mean Dose to Normal Liver ≥13714cGy	3.625 (1.431–9.815)	0.007*	3.384(1.211–9.451)	0.02*
Single Fraction Mean Dose to Normal Liver	1.003(0.996–1.010)	0.418		

Note: *$p < 0.05$.

Abbreviations: AFP, Alpha-Fetoprotein, HBsAg, Hepatitis B Surface Antigen; RT, Radiotherapy; TACE, Transarterial Chemoembolization; BED, Biological Effective Dose; OR, Odds Ratio.

underlying chronic liver disease or cirrhosis, HCC patients often show poorer liver function compared to those with other malignancies, and many succumb to liver failure rather than tumor progression. Therefore, it is crucial to balance tumor treatment with liver function protection to prolong survival. RILD can be fatal in HCC patients with chronic viral hepatitis, with mortality rates ranging from 10% to 76%.[30] This emphasizes the importance of protecting liver function after radiotherapy. Given the favorable local control rates of radiotherapy,[17,18,35] combining local treatment with systemic therapies is expected to further enhance OS. This highlights the importance of predicting liver damage and protecting liver function during local therapies. Currently, there is no universally accepted definition of ncRILD. Definitions vary across studies. Scholars have defined RILD as CTCAE grade 3 or 4 hepatotoxicity.[36] El Naqa et al indicated that ALBI and CP scores are more sensitive

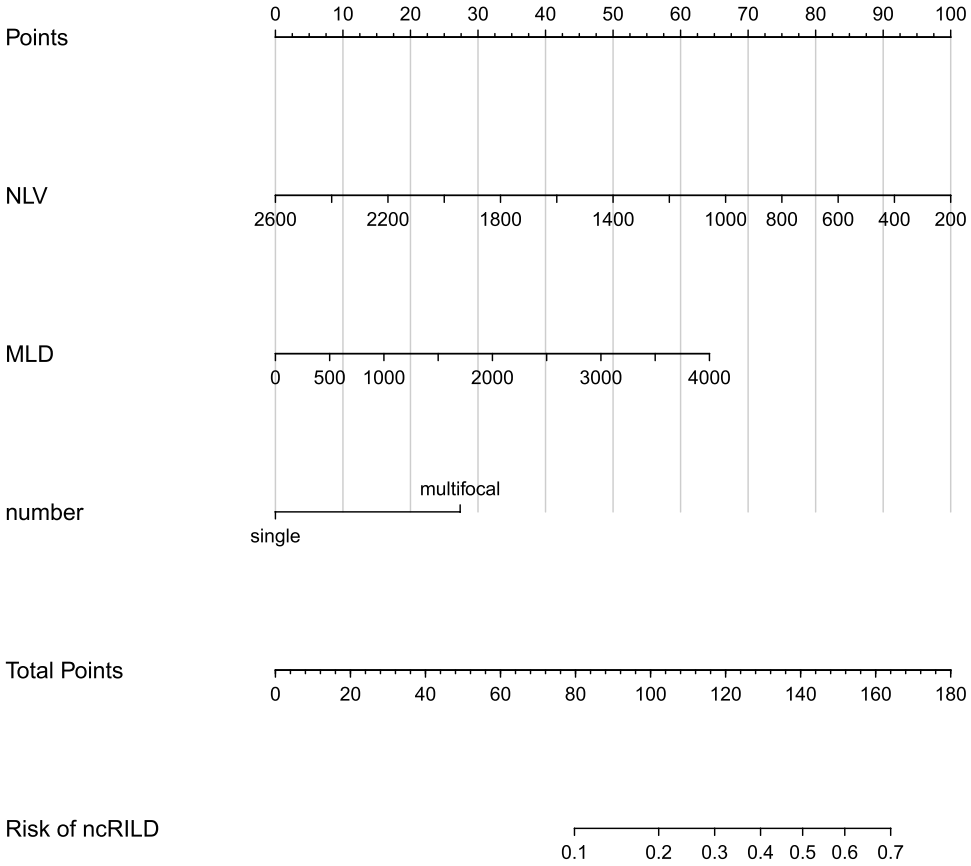

Figure 4 Nomogram based on mean liver dose, normal liver volume, and tumor numbers for ncRILD prediction.
Abbreviations: MLD, Mean Liver Dose; ncRILD, Non-classic Radiation-Induced Liver Disease; NLV, Normal Liver Volume.

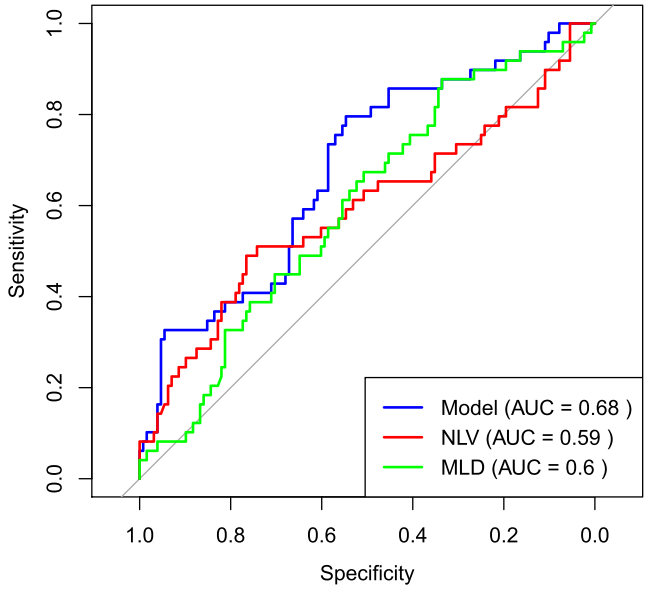

Figure 5 Comparison of Predictive Performance: Nomogram vs NLV and MLD.
Abbreviations: MLD, Mean Liver Dose; NLV, Normal Liver Volume.

Table 4 Univariate Analysis of Different Fractional Doses

Variable	Fractional Dose 2Gy (N=36)	Fractional Dose 3Gy (N=66)	Fractional Dose 4Gy (N=42)	
	p	*p*	*p*	*OR (95CI%)*
V5	0.348	0.375	0.084	
V10	0.123	0.684	0.125	
V15	0.102	0.721	0.081	
V20	0.234	0.751	0.058	
V25	0.338	0.851	0.113	
V30	0.320	0.825	0.075	
V35	0.481	0.858	0.082	
V40	0.732	0.762	0.070	
Vs5	0.420	0.435	0.033*	0.995(0.989–1.0)
Vs10	0.265	0.872	0.022*	0.995(0.990–0.999)
Vs15	0.283	0.902	0.013*	0.994(0.989–0.999)
Vs20	0.454	0.822	0.011*	0.994(0.989–0.999)
Vs25	0.531	0.755	0.020*	0.995(0.992–0.999)
Vs30	0.531	0.772	0.017*	0.995(0.991–0.999)
Vs35	0.618	0.754	0.017*	0.995(0.992–0.999)
Vs40	0.704	0.817	0.016*	0.995(0.992–0.999)

Notes: V5 represents the percentage volume of the normal liver receiving more than 5Gy, and similarly, V10-40 represents the percentage volumes of the normal liver receiving more than 10–40Gy, respectively; Vs5 represents the absolute volume of the normal liver spared from receiving more than 5Gy (in mL), and similarly, Vs10-40 represent the absolute volumes spared from receiving more than 10–40Gy, respectively. *indicates $p < 0.05$.
Abbreviation: OR, Odds Ratio.

than grade 3 liver enzyme increases in reflecting liver function injury.[37] A recent meta-analysis of SBRT for HCC highlighted varying incidences of severe hepatic toxicity and differing definitions of ncRILD across studies.[38]

Some researchers have investigated the development of individualized radiotherapy plans to protect liver function. Jackson et al conducted a study on 178 patients with HCC who received personalized SBRT treatments over 3 to 5 fractions. Of these, 84 patients took a one-month break during radiotherapy after the third or fourth session. Among the entire cohort, 54 patients experienced a CP score increase of ≥ 2 points within six months of radiotherapy. After adjusting for the number of intrahepatic treatments and mean liver dose, the one-year local control rate for patients with a treatment break was comparable to that of patients without a break. Furthermore, treatment-related toxicity was reduced.[39] This study suggests that by applying modern radiotherapy techniques, treatment plans can be adjusted based on the patient's liver function and treatment response during radiotherapy. This approach may decrease the risk of RILD without compromising local control rates. It is noteworthy that 36% of patients underwent only three fractions of SBRT due to treatment-related liver function deterioration in this study. These patients had a higher prevalence of cirrhosis, elevated CP scores, and more frequent local treatments (all $p < 0.05$), indicating that baseline liver function significantly influences a patient's tolerance to radiotherapy.

Currently, the primary factors predicting RILD are the liver function status before treatment and dosimetric factors such as mean liver volume and V30. Additionally, other factors, including tumor stage, HBV infection, pre-radiotherapy TACE, concurrent chemotherapy, portal vein thrombosis, and male gender, may also elevate the risk of liver damage. The types and cutoff values of dosimetric parameters linked to RILD vary significantly across studies.[40]

Some researchers suggest that RILD may be related to the fractional dose delivered to the normal liver. The radiation tolerance dose of the liver depends on the patient's liver function and the dose per fraction, with normal liver volume also being an influencing factor. However, conventional dosimetric parameters and NTCP models did not sufficiently predict the risk of fatal RILD.[41] Liang et al proposed that V20 is a suitable dosimetric indicator for predicting RILD in cirrhotic Child-Pugh A patients receiving fractional doses of 4–6 Gy. Tumor volume was similarly associated with RILD in their univariate analysis.[42] In our study, we found no significant correlation between ncRILD and common dosimetric

parameters in patients receiving fraction doses ≤3 Gy. In patients receiving fraction doses of 4 Gy, ncRILD significantly correlated with Vs5-Vs40 but not V5-V40. The V5-V40 parameter only represents the percentage of liver volume receiving 5–40 Gy but does not consider the absolute liver volume. In contrast, the Vs parameter indicates the absolute volume of normal liver tissue spared from a specified dose, which may better assess liver damage than V5-V40. However, standardizing this across different fractionation schemes requires further investigation.

IMRT planning, including the arrangement of subfields, varies according to the shape of the target area. The actual fractional dose received by different parts of the normal liver surrounding the tumor can vary significantly, complicating calculations using conventional equivalent doses. It is also uncertain whether different functional areas of the liver have varying sensitivities to radiation. The mean liver dose is a commonly used dosimetric factor,[43] but fractionation should be considered since the same mean liver dose across different fractionation schemes implies different per-fraction doses, particularly with high-dose fractions. Our study focused on mean liver dose per fraction, but no significant correlation was found with ncRILD, either in the total cohort or among patients receiving fraction doses of 4 Gy. Therefore, further exploration of relevant dosimetric parameters is essential.

In SBRT, fractional doses often exceed 10 Gy. Early SBRT studies on liver metastases suggested that as long as 700 mL of normal liver receives less than 15 Gy, a dose of 60 Gy in 3 fractions is safe for patients with normal liver function.[44] However, IMRT encompasses more low-dose areas around the tumor than SBRT, and reports on whether this dose limit is appropriate are scarce. In our study, a liver volume of less than 700 mL was identified as an independent risk factor for ncRILD after IMRT, confirming the significance of liver volume. However, in our study, only the mean liver dose was found to be associated with ncRILD, showing no correlation between the mean liver dose per fraction and ncRILD. Further research is needed to determine whether higher per-fraction doses and the location of the irradiated area influence RILD risk.

Clinical characteristics, such as baseline liver function and other liver-damaging treatments like chemotherapy, targeted therapy, and immunotherapy, should also be taken into account. Liang et al found that the severity of cirrhosis significantly affects the occurrence of RILD, and certain dosimetric parameters may help predict the risk of liver injury. Different fractional doses and previous treatments, such as TACE, may also pose varying risks and should be considered.[24] In our study, neither cirrhosis nor prior treatments increased the incidence of ncRILD. Cirrhosis was diagnosed based on imaging reports, without comparison to pathological diagnoses or analysis of the severity. Many studies have indicated that cirrhosis is associated with RILD, but the question of whether patients with decompensated cirrhosis have a significantly elevated risk of liver injury or the extent to which cirrhosis increases the risk of RILD still demands further evidence.

Some studies have shown that systemic therapies combined with radiotherapy exhibit strong anti-tumor activity in unresectable advanced HCC, with acceptable toxicity and no unexpected adverse events.[11,31,32,34,45–47] In our study, the incidence of ncRILD was not significantly different between patients who received immunotherapy combined with radiotherapy and those who did not. This suggests that immunotherapy may not worsen liver function damage. Through multivariate analysis, our study identified independent risk factors for ncRILD: a tumor number of ≥2, a mean liver dose of ≥1371.4 cGy, and a normal liver volume of <700 mL. Our conclusions are generally consistent with the study findings.[28] A nomogram was developed using these three parameters to predict the risk of ncRILD in HCC patients undergoing IMRT. We also compared the AUC of the Nomogram model with that of MLD and NLV used an internal validation. The results show that the AUC of the nomogram is superior to that of the independent risk factors, MLD and NLV. However, the predictive performance of the nomogram was only moderate. However, the predictive performance of the nomogram was only moderate. This suggests that additional predictive parameters and studies with larger sample sizes may be necessary to develop a more robust model for clinical application. Furthermore, external validation in independent cohorts is essential to confirm the utility and generalizability of the model. Nonetheless, our study reinforces the complexity of ncRILD, highlighting the need for further research to better understand its multifactorial nature and improve risk prediction strategies.

Conclusions

Patients with multifocal tumor, lower normal liver volume and higher mean liver dose are at increased risk of developing radiation-induced liver injury. These findings suggest that dosimetric parameters, especially at higher fraction doses, may play a critical role in the occurrence of ncRILD.

Abbreviations

AFP, Alpha-Fetoprotein; ALBI, Albumin-Bilirubin (score); ALP, Alkaline Phosphatase; AST, Aspartate Aminotransferase; BED, Biologically Effective Dose; CBCT, Cone Beam Computed Tomography; CI, Confidence Interval; CP, Child-Pugh (score); cRILD, Classic Radiation-Induced Liver Disease; CTV, Clinical Target Volume; DVH, Dose-Volume Histogram; EQD2, Equivalent Dose in 2 Gy Fractions; GTV, Gross Tumor Volume; HCC, Hepatocellular Carcinoma; HR, Hazard Ratio; IMRT, Intensity-Modulated Radiation Therapy; MLD, Mean Liver Dose; ncRILD, Non-classic Radiation-Induced Liver Disease; NLV, Normal Liver Volume; NTCP, Normal Tissue Complication Probability; OR, Odds Ratio; OS, Overall Survival; PTV, Planning Target Volume; RILD, Radiation-Induced Liver Disease; ROC, Receiver Operating Characteristic; SBRT, Stereotactic Body Radiotherapy; TACE, Transarterial Chemoembolization.

Data Sharing Statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

The requirement for ethics approval was approved by the ethics committee/ Institutional Review Board of Guangxi Medical University Cancer Hospital (number LW2023075). The requirement for informed consent was waived by the ethics committee/ Institutional Review Board of Guangxi Medical University Cancer Hospital due to the retrospective nature of the study. The data were anonymously analysed, and all the participants' personal information is confidential. All methods were performed in accordance with the guidelines of the Helsinki Declaration.

Consent for Publication

We confirm that the manuscript submitted for publication does not contain any personal data or sensitive information that could identify individual patients or research participants. All authors have provided their consent for the publication of this manuscript.

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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; DU YQ took part in drafting, All authors revising or critically reviewing the article; All authors gave final approval of the version to be published; All authors have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

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