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ORIGINAL RESEARCH

Dynamic Neutrophil-to-Lymphocyte Ratio at 3-4 weeks of Intensity-Modulated Radiotherapy Combined with Normal Liver Volume Predicts Radiation-Induced Hepatic Toxicity in Hepatocellular Carcinoma: A Retrospective Study

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Purpose: This study aimed to investigate whether early dynamic variation in circulating neutrophil-to-lymphocyte ratio(NLR) during intensity-modulated radiotherapy (IMRT) can predict radiation-induced hepatic toxicity (RIHT) in patients with hepatocellular carcinoma(HCC).

Patients and methods: Neutrophil and lymphocyte counts of 103 HCC patients were measured every 2 weeks before, during and after completion of IMRT.Generalized estimating equations analyses was used to analyze the dynamic changes of neutrophil and lymphocyte counts. The prognostic significant factors were assessed through logistic regression analyses. Statistical power was assessed using power analysis, and the model was adjusted for multiple comparisons via the Bonferroni correction. Receiver operating characteristic (ROC) curves and calibration curves were used to evaluate the prediction accuracy.The predictive model was internally validated using 5-fold cross-validation.

Results: Radiation-induced liver disease(RILD) is a type of RIHT and is a relatively severe phenomenon of hepatic toxicity.Overall, 23 patients (22%) developed RILD. In RILD group, NLR were significantly changed in the first 3 to 4 weeks during IMRT (p=0.006). In multivariate analysis, NLR in first 3–4 weeks(NLR 4), the ratio of NLR in first 3–4 weeks to 1–2 weeks(NLR 4/2),and normal liver volume(NLV) were independent predictive factors for RILD. The area under the curve(AUC) was 0.860 (95% CI, 0.783–0.937).Larger NLV correlated with a lower likelihood of developing RILD(p = 0.041).The mean AUC values was 0.86 in the training set and 0.81 in the test sets across 5-fold cross-validation (p=0.41).

Conclusion: Circulating NLR in first 3 to 4 weeks and its relatively change during IMRT were significantly associated with RIHT.The model based on early dynamic variation of NLR and dosimetric factors NLV can predict RIHT with high accuracy in HCC patients.It can timely assist clinician to take preventive measures and adjusting treatment plans.

Keywords: neutrophils, lymphocytes, neutrophil-to-lymphocyte ratio, hepatocellular carcinoma, radiation-induced hepatic toxicity

Background

Radiation therapy (RT) has been increasingly utilized in patients with hepatocellular carcinoma (HCC), as it offers effective local control and survival benefits for those with medically inoperable or unresectable HCC.[1–4] Radiation-induced hepatic toxicity (RIHT), which is one of the most severe side effects of RT in the liver, remains a challenge.[5] Treatment-related classic radiation-induced liver disease (RILD) is a life-threatening RIHT. Given the advancements in modern radiation delivery systems, many patients can now safely receive RT to limited liver volumes.However, the

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relatively mild radiation-induced liver injury, non-classic RILD, remains a major challenge.[6] Classic RILD defined as a serum alkaline phosphatase (ALP) level greater than twice the upper limit of baseline or normal values. Non-classic RILD defined as an increase in CP score of two or more, or an elevation in the liver transaminase levels of at least five times the upper limit of baseline or normal value.

Furthermore, the specific molecular mechanisms underlying radioactive liver damage are poorly understood. Ionizing radiation induces damage to deoxyribonucleic acid (DNA) molecules. The event leads to the activation of downstream signaling molecules and cascades, triggering oxidative stress as well as immune, inflammatory, and metabolic alterations. These changes maybe result in the recruitment of neutrophils to the liver, where they release a variety of inflammatory mediators and proteases. Meanwhile, the reduction in lymphocytes weakens the body's ability to regulate inflammation. Consequently, hepatocyte apoptosis and acute inflammatory responses occur in the irradiated regions. The increase in neutrophils and the decrease in lymphocytes lead to an elevated neutrophil-to-lymphocyte ratio (NLR).[7,8]

Inflammation can influence how a tumor responds to RT and radiation-induced injury.[9,10] Neutrophils and lymphocytes in circulating peripheral blood are the most common indicators of immune-inflammation in patients with HCC. Several studies have demonstrated that HCC patients with a high pre-/post-RT NLR are more susceptible to liver injury.[11–13]

Currently, several metrics and models can be used to predict the onset of RIHT. These include the Normal Tissue Complication Probability (NTCP) model based on the average liver dose, as well as the Child-Pugh (CP) score, Indocyanine Green (ICG) clearance. These metrics and models have been used to predict the onset of RIHT.[14–16] However, their accuracy and timeliness remain unsatisfactory. The NTCP model dose not take volume thresholds into consideration for RILD. When the irradiated liver volume is kept below a threshold volume, the risk of RILD is estimated to be rather low, regardless of the radiation dose delivered.[14] Some studies have demonstrated that even minor errors in the NTCP model may lead to incorrect plan ranking.[17] The CP score is more subjective based on ascites. Moreover, it is not easy to evaluate during RT period, for it needs repeated imaging examinations. Therefore, the timeliness and effectiveness of detecting hepatic toxicity is relatively poor.

These indicators can be used to assess the occurrence of RIHT in HCC patients that treated with RT. So as to guide physicians to adjust the treatment regimen. However, existing models were usually built using indicators before and after radiotherapy, neglecting the dynamic changes of these indicators during RT.At present, only few studies have evaluated the changes in such indicators during IMRT that can dynamically predict RIHT to guide physicians' decisions in selecting the most suitable RT strategies. In this study, we collected readily accessible blood data from the clinic before, during, and after intensity-modulated RT (IMRT), aimed to investigate the correlation between early dynamic changes in lymphocyte and neutrophil counts during IMRT and to early predict the risk of RIHT in patients with HCC.

Methods

Patient Eligibility

This retrospective study included 103 consecutive patients from Guangxi Medical University Cancer Hospital between September 2017 and November 2023. Patients 1) with pathologically or clinically confirmed HCC diagnosis, 2) with a liver function CP grade A or B before RT and an Eastern Cooperative Oncology Group physical status score of 0–2, and 3) whose treatment involved irradiation of intrahepatic lesions in HCC and who completed the RT program on schedule were included in the study. Conversely, patients 1) who underwent interventional or radiofrequency ablation (RAF) within 1 month before RT or within 3 months after RT completion, 2) who received granulocyte colony-stimulating factor within 1 week prior to the first fraction of IMRT or within 8 weeks from the first fraction of IMRT, 3) with incomplete laboratory and imaging data, and 4) who experienced disease progression during or within 3 months after completion of RT or development of other immune system or infectious diseases. Both an independent protocol review committee and an ethics committee authorized the protocol procedures. Using standard phlebotomy techniques, the lymphocyte and neutrophil counts were measured in the peripheral blood samples obtained from each patient at six different time points: (1) The −2-week timeframe spanned from the second week to the first week before IMRT initiation. (2) The 0-week period commenced on the day of IMRT initiation. (3) The 2-week timeframe covered the first week to the second week

after IMRT initiation. (4) The 4-week timeframe encompassed the third week to the fourth week after IMRT initiation. (5) The 6-week timeframe spanned from the fifth week to the sixth week after IMRT initiation. (6) The 8-week timeframe encompassed the seventh week to the eighth week after IMRT initiation. The ethics committee approved this retrospective study.

Radiotherapy Technique

For RT planning, contrast-enhanced computed tomography (CT) was conducted with a slice thickness of 2.5–5 mm, with the patient placed in the supine position and breathing spontaneously. To determine the clinical target volume (CTV), a 4–5-mm margin was set outside Gross tumor volume (GTV). GTV was programmed to include size of the intrahepatic tumor enhanced on contrast-enhanced computed tomography (CT) and CT-magnetic resonance imaging fusion. The CTV and 5–10-mm buffer were included in the planned target volume to reduce the positioning uncertainty and the impact of breathing movement. The Pinnacle 3 system (Philips, Netherlands) or the MIM 6.8 system (MIM, USA) was used to delineate all the target areas and organs at risk (OARs).

The IMRT total dose was 55 to 66 Gy, per fraction does was 2 to 5 Gy. Patients received a median total dose of 58.0 Gy (57.0, 63.0Gy) and a median fraction does of 3.0 Gy (3.0, 3.3Gy). Radiation was administered over five consecutive days each week. Among these patients, 87 (84.47%) finished radiotherapy between weeks 4 and 5, and 16 (15.53%) concluded radiotherapy within weeks 5 and 6. All patients received IMRT with a 6-MV X-ray machine using a linear accelerator and none of patients treated with SBRT. A dose-volume histogram analysis was conducted to evaluate the radiation plan, which determined that the OARs were adequately protected.The OARs evaluation criteria was as follows. The mean dose to normal liver is less than 23–28Gy, with V20≤48%. For the kidneys, V15 < 1/3 of the volume. For the spinal cord, the maximum dose is less than 40Gy.For the stomach, small intestine and duodenum, the maximum dose is less than 40–45Gy.

Follow-up and RIHT Assessment

Within 1 month after IMRT initiation and every 2–3 months thereafter, contrast-enhanced CT and/or MRI were used to assess the patients. Two types of RILD have been identified: non-classic RILD (ncRILD) and classic RILD (cRILD). RILD is frequently assessed within less than 3 months after completion of RT, assuming the absence of tumor growth or hepatitis B virus (HBV) reactivation, which is defined as a 10-fold or higher increase in HBV DNA levels. Anicteric hepatomegaly and ascites are associated with cRILD, defined as a serum alkaline phosphatase (ALP) level greater than twice the upper limit of baseline or normal values. An increase in CP score of two or more, or an elevation in the liver transaminase levels of at least five times the upper limit of baseline or normal value, is associated with ncRILD.

Statistical Analyses

Statistical analyses were performed using SPSS version 26.0 and R version 4.3.2. First, the data were subjected to descriptive statistical analysis. Quantitative variables were evaluated for normality of distribution using histograms and the Kolmogorov–Smirnov test. If the data followed a normal distribution, the means and standard deviations were used. If the data were not normally distributed, the median and interquartile ranges were used. Categorical variables are presented as frequencies and percentages. Analysis of variance was conducted to analyze normally distributed quantitative data. An independent sample Student's *t*-test was used to compare two sets of data. If the data followed an abnormal distribution, The Mann–Whitney *U*-test was performed to compare the two groups.

If the repeated measurement data demonstrated a normal distribution, the Repeated Measures ANOVA was used to compare the two groups. If the data were not normally distributed, the Generalized Estimating Equations were used to compare the two groups. Categorical variables were compared between the two groups using Pearson's chi-square test, Yates-corrected chi-square test, or Fisher's exact test. Univariate and multivariate logistic regression analyses were conducted for variables that showed significant differences ($p < 0.05$). The correlation between variables included in the logistic regression analyses was examined using the Pearson's correlation coefficient, while highly correlated variables were eliminated based on clinical experience ($r > 0.6$). Linear correlations were analyzed using the Box-Tidwell method. Statistical power was assessed using power analysis, and the model was adjusted for multiple comparisons via the

Bonferroni correction. The receiver operating characteristic (ROC) curve and Youden index were used to calculate the optimal cut-off values. The area under the curve (AUC) and calibration curves were calculated to evaluate the precision of the logistic regression analyses. The generalizability of the model was assessed via 5-fold cross-validation with random data partitioning (training set: test set ratio=4:1).Performance metrics were averaged across all folds, with all preprocessing steps strictly confined to training data to eliminate leakage effects.

Results

Patient Characteristics

The patients' baseline characteristics, including clinical features, liver function factors before RT, and dosimetry factors, are shown in Table 1. More than 90% of the patients in the non-RILD and RILD groups were men (91.25% vs 91.30%), more than 80% of the patients contracted HBV infection (85.00% vs 95.65%), and more than half of the patients developed cirrhosis (58.75% vs 56.52%). Approximately 60% and 80% of the patients had tumors exceeding 5 cm, while 58.75% and 65.22% had more than four intrahepatic tumors. Moreover, most patients exhibited macrovascular invasion and had a Barcelona Clinic Liver Cancer (BCLC) stage B or C. Most of the patients had a liver function CP grade A before RT. Some patients underwent surgery, transarterial chemoembolization, or RAF before RT, while approximately half were treated with targeted therapy or immunotherapy. In the analysis of differences between the no-RILD and RILD groups, only NLV was significant ($p<0.001$).

Table 1 Baseline Characteristics of the Patients in This Study

Characters	Total (n = 103)	Non-RILD (n =80)	RILD (n=23)	Z	P
Sex				−0.008	0.994
Male	94(91.26%)	73(91.25%)	21(91.3%)		
Female	9(8.74%)	7(8.75%)	2(8.7%)		
Age				−0.190	0.849
>50	43(41.75%)	33(41.25%)	10(43.48%)		
≤50	60(58.25%)	47(58.75%)	13(56.52%)		
HBV				−1.349	0.177
Yes	90(87.38%)	68(85%)	22(95.65%)		
No	13(12.62%)	12(15%)	1(4.35%)		
Cirrhosis				−0.190	0.849
Yes	60(58.25%)	47(58.75%)	13(56.52%)		
No	43(41.75%)	33(41.25%)	10(43.48%)		
ECOG PS				−0.075	0.940
1	62(60.19%)	48(60%)	14(60.87%)		
0	41(39.81%)	32(40%)	9(39.13%)		
Maximum tumor size (cm)				−1.500	0.134
>5	72(69.9%)	47(58.75%)	19(82.61%)		
≤5	31(30.1%)	33(41.25%)	4(17.39%)		
Tumor number				−0.556	0.578
≥4	62(60.19%)	47(58.75%)	15(65.22%)		
<4	41(39.81%)	33(41.25%)	8(34.78%)		
MVI				−0.473	0.636
Yes	72(69.9%)	55(68.75%)	17(73.91%)		
No	31(30.1%)	25(31.25%)	6(26.09%)		
Metastasis				−1.328	0.184
Yes	33(31.04%)	23(28.75%)	10(43.48%)		
No	70(67.96%)	57(71.25%)	13(56.52%)		

(*Continued*)

Table 1 (Continued).

Characters	Total (n = 103)	Non-RILD (n =80)	RILD (n=23)	Z	P
BCLC stage				−0.255	0.799
A/B	26(25.24%)	21(26.25%)	5(21.74%)		
C	77(74.76%)	59(73.75%)	18(78.26%)		
AFP				−1.112	0.266
≥400	39(37.86%)	28(35%)	11(47.83%)		
<400	64(62.14%)	52(65%)	12(52.17%)		
CP grade				−0.274	0.784
A	74(71.84%)	58(72.5%)	16(69.57%)		
B	29(28.16%)	22(27.5%)	7(30.43%)		
TACE				−0.074	0.941
Yes	71(68.93%)	55(68.75%)	16(69.57%)		
No	32(31.07%)	25(31.25%)	7(30.43%)		
Hepatectomy				−1.447	0.148
Yes	45(43.69%)	38(47.5%)	7(30.43%)		
No	58(56.31%)	42(52.5%)	16(69.57%)		
RAF				−0.632	0.527
Yes	18(17.48%)	15(18.75%)	3(13.04%)		
No	85(82.52%)	65(81.25%)	20(86.96%)		
Systemic therapy Yes	51(49.51%)	40(50%)	11(47.83%)	−0.183	0.855
No	52(50.49%)	40(50%)	12(52.17%)		
ALT(U/L)	37(21.5, 58)	37(21, 56)	36(22, 65)	−0.590	0.555
ALP(U/L)	115(86, 166)	115.5(86.5, 162.5)	112(86.5, 169)	−0.028	0.978
PT(sec)	12.4(12, 13.6)	12.35(11.75, 13.6)	12.8(12.1, 13.8)	−1.185	0.236
ALBI score	−2.13±0.43	−2.16±0.41	−2.04±0.49	0.602	0.862
GTV (cc)	277(100.95, 689.14)	270(104, 660.5)	294(100.45, 743.23)	−0.550	0.582
NLV (cc)	1028.64±272.28	1068.32±242.54	890.61±326.88	1.966	<0.001
Dmean (cGy)	1618.3(1302.3, 1966.4)	1588.5(1324, 1966.4)	1758(1291.5, 1949)	−0.143	0.887
$EQD2^2$ (Gy)	63.75(60,75)	63.75(56.28,75)	63.75(60,72.56)	-0.064	0.895
V25(%)	24.4(18.39,37.7)	24.4(17.9,37.8)	24.8(19.64,36.75)	−0.068	0.946
Group 1	59(57.28%)	57(71.25%)	2(8.69%)	−0.226	0.821
Group 2.	26(25.24%)	17(21.25%)	9(39.13%)		
Group 3	18(17.47%)	6(7.50%)	12(52.17%)		

Notes: V25, the percentage of normal liver volume receiving>25 Gy radiation; Group 1 (NLR 4 ≤ 13.5 and NLR 4/2 ≤ 1.93); Group 2 (NLR 4 > 13.5 or NLR 4/2 > 1.93); Group 3 (NLR 4 > 13.5 and NLR 4/2 > 1.93).

Abbreviations: HBV, Hepatitis B virus; ALBI, albumin–bilirubin; ALP, alkaline phosphatase; AFP, alpha fetoprotein; ALT, alanine aminotransferase; BCLC, Barcelona Clinic Liver Cancer; Dmean, mean dose to the normal liver; ECOG PS, Eastern Cooperative Oncology Group-performance status; MVI, Macrovascular invasion; CP, Child-Pugh; $EQD2^2$, equivalent dose in 2-Gy fractions; GTV, gross tumor volume; NLV, normal liver volume; PT, prothrombin time; RFA, radiofrequency ablation; TACE, transcatheter chemoembolization; RILD, radiation-induced liver disease; IMRT, intensity-modulated radiotherapy; M: Median, Q□: 1st Quartile, Q□: 3st Quartile.

Evaluation of RIHT

The results of the RIHT assessment within 3 months post-IMRT are shown in Table 2. None of the patients experienced classic RILD. Overall, 23 patients developed non-classic RILD. Forty-one patients exhibited a CP score increase of 1 point. Eighteen patients had a CP score of 2. Five and two patients experienced grade 3 aspartate transaminase and alanine transaminase elevations, respectively. However, none of the patients showed grade 3 ALP elevation.

Table 2 Patients Evaluated for RIHT within 3 months Post-IMRT

Variables	Number of Patients	Percentage (%)
Liver function metrics		
CP Score+1 or more	41	39.80
CP Score+2 or more	18	17.47
CTCAE 5.0 laboratory toxicities		
AST≥G1	62	60.19
AST≥G2	14	13.59
AST G3	5	4.85
ALT≥G1	42	40.77
ALT≥G2	13	12.62
ALT G3	2	1.94
ALP≥G1	29	28.15
ALP≥G2	4	3.88
ALP G3	0	0
RILD	23	22.33

Abbreviations: ALP, alkaline phosphatase; RILD, radiation-induced liver disease; ALT, alanine aminotransferase; G1, grade1; G2, grade2; AST, aspartate aminotransferase; G3, grade3; CTCAE 5.0, the Common Terminology Criteria for Adverse Events of the National Cancer Institute v5.0; CP, Child–Pugh.

Neutrophil and Lymphocyte Counts at Different Time Points and Their Association with RILD

The neutrophil and lymphocyte counts throughout the IMRT course are shown in Figure 1. In general, both neutrophil and lymphocyte counts initially decreased and then increased during RT. The changes in lymphocyte count were more pronounced, reaching their lowest values within the 4-week timeframe. Table 3 presents a comparison of neutrophil and lymphocyte counts between patients with and without RILD, as well as within the RILD and non-RILD groups at different time intervals during IMRT. For patients who did not develop RILD within 3 months post-IMRT, the mean neutrophil count at 4-week timeframe was 2.72 × 109/L. The mean neutrophil count in patients with RILD was 3.42 × 109/L, and the difference was significant (p = 0.020). Meanwhile, the lymphocyte count in patients with RILD was lower both before and during RT and was strongly linked to the occurrence of RILD, with the most significant difference observed at 4-week timeframe ($p < 0.001$). Moreover, the trends of changes in neutrophil counts (p=0.004) and lymphocyte counts (p=0.029) are different among various groups of RILD (Table 3). This finding indicates that patients

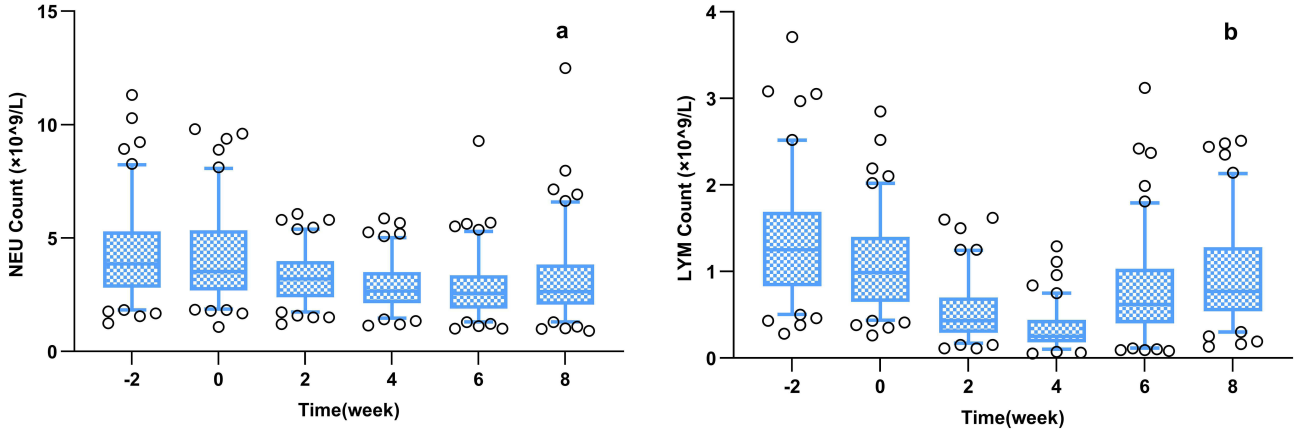

Figure 1 Neutrophil and lymphocyte distributions over time during IMRT. (**a**) neutrophil; (**b**) lymphocyte. Central horizontal lines represent the median. The upper edge of a box represents the 95th percentile, while the lower edge indicates the 5th percentile. Central boxes represent 50% of the distribution of the values. The small circles represent distant values (ie, beyond 5%-95% range).
Abbreviation: NEU, neutrophil; LYM, lymphocyte.

with a low lymphocyte count may be at a higher risk of RILD within 3 months after IMRT. In patients who developed RILD, the neutrophil counts were significantly higher at 4-week timeframe (the first 3–4 weeks of IMRT).

Profile of Covariations and Relative Changes During IMRT and Their Association with RILD

At 4-week timeframe, a significant difference was observed in the neutrophil count between patients who developed RILD and those who did not, with a peak in neutrophil counts demonstrating significance (Figure 2). Similarly, the lymphocyte count decreased to its lowest point, and the disparity between patients with RILD and those without RILD became increasingly significant. Meanwhile, the differences in neutrophil-to-lymphocyte ratio (NLR) among different RILD groups have become quite pronounced. It has been observed that patients with elevated NLR were at a higher risk of developing RILD (P=0.002), with significant differences in NLR observed between the fourth and sixth weeks of IMRT (P=0.006, P=0.029) (Table 3). In addition, in the RILD group, the relative changes of NLR between weeks 2–4 (P<0.001) and 4–6 (P=0.424) is greater than that in the non-RILD group (Table 4).

Table 3 Comparison of Neutrophil Counts, Lymphocyte Counts and NLR Between or within Patients with and without RILD Throughout the IMRT Course

Variables(10^9/L)	Total (n=103)	Non-RILD (n=80)	RILD (n=23)	Wald X^2	P
LYM −2-week, Mean ± SD	1.34±0.65	1.42±0.66	1.03 ± 0.47	10.64	0.001
LYM 0-week, M (Q_1, Q_3)	0.99 (0.66, 1.39)	1.10 (0.68, 1.45)a	0.71 (0.53, 0.96)	6.71	0.010
LYM 2-week, M (Q_1, Q_3)	0.43 (0.30, 0.70)	0.48 (0.32, 0.73)ab	0.36 (0.20, 0.49)ab	3.56	0.059
LYM 4-week, M (Q_1, Q_3)	0.25 (0.18, 0.44)	0.30 (0.21, 0.48)abc	0.16 (0.13, 0.21)abc	11.81	0.001
LYM 6-week, M (Q_1, Q_3)	0.62 (0.40, 1.03)	0.70 (0.43, 1.15)abcd	0.46 (0.15, 0.65)abd	12.32	0.000
LYM 8-week, M (Q_1, Q_3)	0.77 (0.55, 1.27)	0.93 (0.59, 1.30) acde	0.57 (0.48, 0.73)acde	5.16	0.023
NEU −2-week, Mean ± SD	4.28 ± 2.00	4.23 ± 1.97	4.22 ± 2.13	0.15	0.697
NEU 0-week, M (Q_1, Q_3)	3.52 (2.72, 5.34)	3.58 (2.81, 5.34)	3.33 (2.47, 5.26)	0.17	0.681
NEU 2-week, M (Q_1, Q_3)	3.20 (2.45, 3.98)	3.12 (2.39, 3.98)ab	3.23 (2.69, 3.71)ab	0.28	0.598
NEU 4-week, Mean ± SD	2.88 ± 1.04	2.72 ± 0.91abc	3.42 ± 1.28	6.36	0.012
NEU 6-week, M (Q_1, Q_3)	2.56 (1.90, 3.34)	2.59 (1.92, 3.36)abc	2.29 (1.76, 3.29)abcd	0.52	0.470
NEU 8-week, M (Q_1, Q_3)	2.64 (2.06, 3.83)	2.75 (2.06, 3.83)abd	2.59 (2.07, 4.31)	0.22	0.636
NLR −2-week, M (Q_1, Q_3)	3.07 (1.93, 5.01)	3.05 (1.83, 4.5)	3.19 (2.58, 6.19)	3.08	0.079
NLR 0-week, M (Q_1, Q_3)	3.90 (2.23, 6.04)	3.67 (2.43, 5.50)	4.44 (3.54, 7.82)	1.64	0.201
NLR 2-week, M (Q_1, Q_3)	6.81 (4.53, 11.63)	6.60(4.24, 10.94)ab	8.83 (6.03, 14.40)ab	1.86	0.172
NLR 4-week, M (Q_1, Q_3)	9.76 (6.26, 16.07)	9.13 (5.52, 12.53)abc	18.00 (14.60,25.08)abc	7.61	0.006
NLR 6-week, M (Q_1, Q_3)	4.33 (2.04, 7.38)	3.91 (1.90, 6.83)acd	5.51 (2.99, 17.29)abd	4.79	0.029
NLR 8-week, M (Q_1, Q_3)	3.18 (2.12, 5.73)	2.92 (2.08, 5.62)cd	3.64 (2.63, 8.06)cd	1.32	0.250
Overall Test					
LYM Between-Subjects Effects (W, P)	(17.88, 0.000)				
Time-LYM (W, P)	(496.47, 0.000)				
LYM interaction effect (W, P)	(12.47, 0.029)				
NEU Between-Subjects Effects (W, P)	(0.22, 0.638)				
Time-NEU (W, P)	(43.05, 0.000)				
NEU interaction effect (W, P)	(17.26, 0.004)				
NLR Between-Subjects Effects (W, P)	(9.41, 0.002)				
Time-MLR (W, P)	(42.88, 0.000)				
NLR interaction effect (W, P)	(7.95, 0.159)				

Notes: a indicates a comparison with −2-week, P<0.05; b indicates a comparison with 0-week, P<0.05;c indicates a comparison with 2-week, P<0.05; d indicates a comparison with 4-week, P<0.05; e indicates a comparison with 6-week, P<0.05.

Abbreviations: NEU, neutrophil; LYM, lymphocyte; NLR, neutrophil-to-lymphocyte ratio; M, Median; Q_1, 1st Quartile; Q_3, 3st Quartile.

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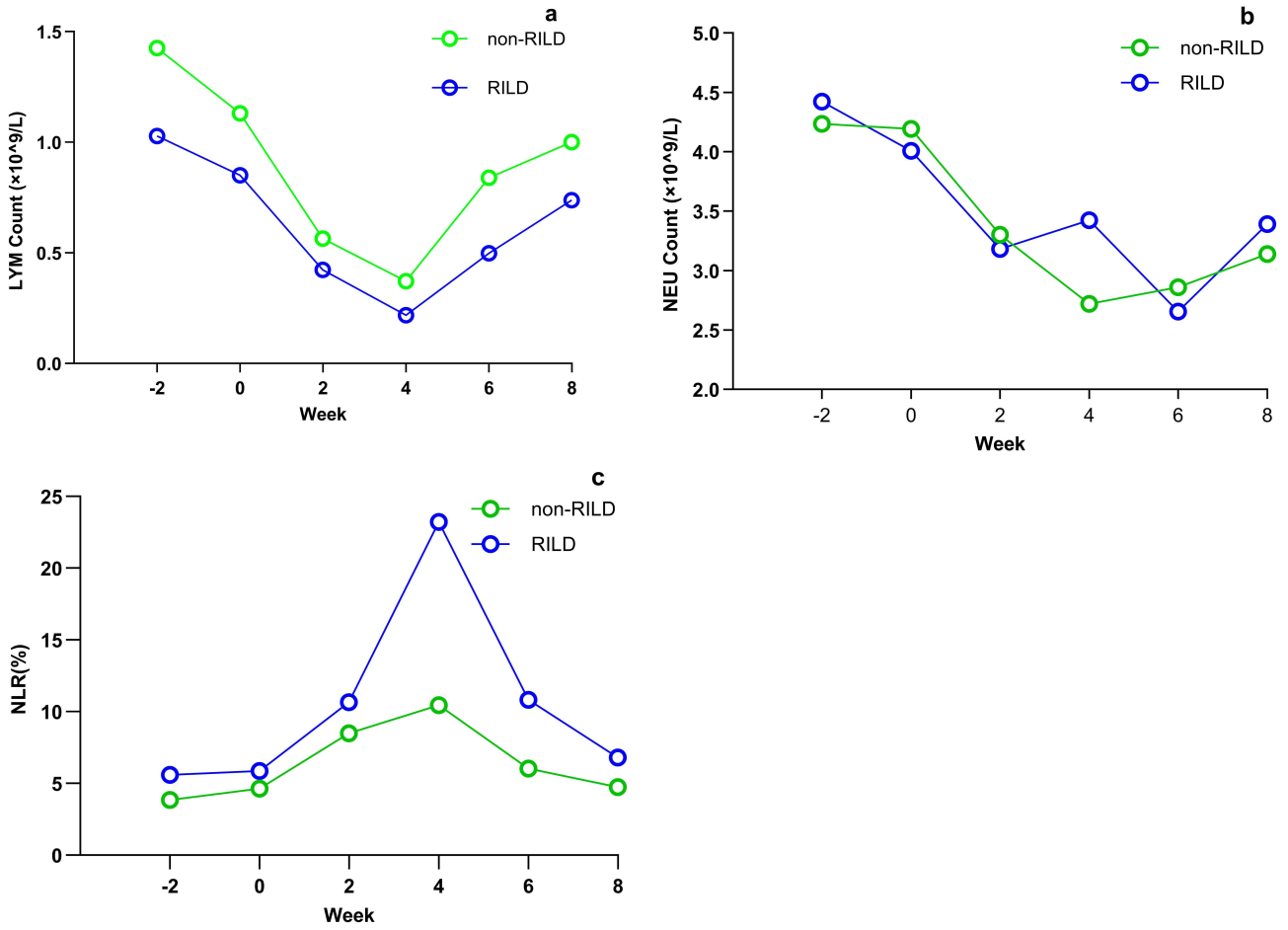

Figure 2 Variations of lymphocyte counts, neutrophil counts and neutrophil-to-lymphocyte ratio over time in patients with and without RILD within 3 months of IMRT. (**a**) lymphocyte; (**b**) neutrophil; (**c**) neutrophil-to-lymphocyte ratio.

Univariate and Multivariate Logistic Analyses

Based on the optimal cut-off values of NLR 4 and NLR 4/2, we divided the patients into Group 1 (NLR 4 ≤ 13.5 and NLR 4/2 ≤ 1.93), Group 2 (NLR 4 > 13.5 or NLR 4/2 > 1.93), and Group 3 (NLR 4 > 13.5 and NLR 4/2 > 1.93) (Table 1).The clinical, dosimetry, and functional factors; neutrophil and lymphocyte counts; and NLR were analyzed as predictive factors, and Pearson's correlation coefficient was calculated for each variable. Table 5 presents univariate analyses of risk factors for RILD within 3 months post-IMRT. Variables with strong correlations (r > 0.6) were extracted from the univariate logistic regression analysis, and the factors considered significant in the univariate analysis and the Generalized Estimating Equations were included in the multivariate analysis ($p < 0.05$). A collinearity analysis of the variables included in the logistic regression analysis was conducted to exclude collinearity between the quantitative

Table 4 Comparison of Relative Changes in NLR Between Patients with and without RILD When Receiving IMRT During weeks 3–4 Versus 1–2, and weeks 4–6 Versus 3–4

Variables	Total (n = 103)	No RILD (n = 80)	RILD (n = 23)	Statistic	p
NLR 4/2, M (Q_1, Q_3)	1.34 (1.02, 1.86)	1.27 (0.96, 1.66)	2.34 (1.27, 2.94)	Z=−3.30	<0.001
NLR 6/4, M (Q_1, Q_3)	0.53 (0.20, 0.82)	0.53 (0.22, 0.84)	0.45 (0.18, 0.80)	Z=−0.80	=0.424

Abbreviations: NLR 4/2=NLR level at 4-week timeframe/NLR level at 2-week timeframe; NLR 6/4=NLR level at 6-week timeframe/NLR level at 4-week timeframe; NLR, neutrophil-to-lymphocyte ratio; RILD, radiation-induced liver disease. Z: Mann–Whitney test, M: Median, Q□: 1st Quartile, Q_3: 3st Quartile.

Table 5 Univariate Analyses of Risk Factors for RILD Within 3 months Post-IMRT

Variables	β	S.E	Z	*p*	OR (95% CI)
Sex,male vs.female	0.01	0.84	0.01	0.994	1.01 (0.19 ~ 5.21)
Age,>50 vs.≤ 50	0.09	0.48	0.19	0.849	1.10 (0.43 ~ 2.80)
HBV, yes vs.no	1.36	1.07	1.27	0.205	3.88 (0.48 ~ 31.57)
Cirrhosis, yes vs no	−0.09	0.48	−0.19	0.849	0.91 (0.36 ~ 2.33)
ECOG PS, 1 vs.0	0.04	0.48	0.08	0.940	1.04 (0.40 ~ 2.68)
Maximum tumor size(cm),>5 vs.≤ 5	0.88	0.60	1.48	0.140	2.42 (0.75 ~ 7.82)
Tumor number,≥4 vs.<4	0.27	0.49	0.56	0.577	1.32 (0.50 ~ 3.46)
MVI, yes vs no	0.25	0.53	0.48	0.635	1.29 (0.45 ~ 3.66)
Extrahepatic metastasis, yes vs no	0.65	0.49	1.32	0.186	1.91 (0.73 ~ 4.96)
BCLC stage,C vs B	0.31	1.01	0.31	0.759	1.36 (0.19 ~ 9.91)
AFP, ≥400 vs <400	0.53	0.48	1.11	0.266	1.70 (0.67 ~ 4.35)
ALT(U/L)	0.00	0.01	0.57	0.568	1.00 (0.99 ~ 1.02)
ALP(U/L)	−0.00	0.00	−0.67	0.504	1.00 (0.99 ~ 1.00)
PT(sec)	0.16	0.17	0.94	0.349	1.17 (0.84 ~ 1.64)
ALBI score	0.63	0.54	1.17	0.243	1.87 (0.65 ~ 5.38)
CP grade, B vs A	0.14	0.52	0.28	0.783	1.15 (0.42 ~ 3.18)
GTV(cc)	0.00	0.00	0.36	0.719	1.00 (1.00 ~ 1.00)
NLV(cc)	−0.01	0.00	−2.68	0.007	0.99 (0.99 ~ 0.99)
Dmean (cGy)	−0.00	0.00	−0.15	0.879	1.00 (1.00 ~ 1.00)
$EQD2^2$(Gy)	−0.00	0.02	−0.14	0.887	1.00 (0.96 ~ 1.04)
V25(%)	0.00	0.02	0.20	0.843	1.00 (0.97 ~ 1.03)
TACE, yes vs no	0.04	0.51	0.07	0.941	1.04 (0.38 ~ 2.84)
Hepatectomy, yes vs no	−0.73	0.51	−1.44	0.151	0.48 (0.18 ~ 1.30)
RAF, yes vs no	−0.43	0.68	−0.63	0.528	0.65 (0.17 ~ 2.48)
Systemic therapy, yes vs no	−0.09	0.47	−0.18	0.854	0.92 (0.36 ~ 2.32)
Group					
2 vs.1	2.71	0.83	3.27	0.001	15.09 (2.97 ~ 76.63)
3 vs.1	4.04	0.88	4.61	<0.001	57.00 (10.24 ~ 317.40)

Abbreviations: HBV, Hepatitis B virus; ALBI, albumin–bilirubin; ALP, alkaline phosphatase; AFP, alpha fetoprotein; ALT, alanine aminotransferase; BCLC, Barcelona Clinic Liver Cancer; Dmean, mean dose to the normal liver; ECOG PS, Eastern Cooperative Oncology Group-performance status; MVI, Macrovascular invasion; CP, Child-Pugh; EQD22, equivalent dose in 2-Gy fractions; GTV, gross tumor volume; NLV, normal liver volume; PT, prothrombin time; RFA, radiofrequency ablation; TACE, transcatheter chemoembolization; RILD, radiation-induced liver disease; IMRT, intensity-modulated radiotherapy; V25, the percentage of normal liver volume receiving>25 Gy radiation; Group 1 (NLR 4 ≤ 13.5 and NLR 4/2 ≤ 1.93); Group 2 (NLR 4 > 13.5 or NLR 4/2 > 1.93); Group 3 (NLR 4 > 13.5 and NLR 4/2 > 1.93); M: Median, Q□: 1st Quartile, Q□: 3st Quartile. OR: Odds Ratio, CI: Confidence Interval.

variables. The analysis of the linear relationship between the quantitative variable and logit (p) showed a linear association between the quantitative variable and logit (p). LYM at −2-week, 0-week, 4-week, 6-week and 8-week timeframe, NEU at 4-week timeframe, NLR 4, NLR 6 and NLR 4/2 were included in the multivariate analysis. Based on multivariate analysis, the NLR 4-week (HR, 1.09; 95% CI, 1.02–1.16; P=0.008), NLR 4/2 (HR, 2.60; 95% CI, 1.39–4.88; P=0.003, NLV (normal liver volume; HR, 0.998; 95% CI, 0.996–1.00; P=0.041) were independent risk factors for RILD (Table 6). The model was adjusted for multiple comparisons via the Bonferroni correction (α=0.05/3). Although Vliver showed significance without correction (p=0.041), its significance disappeared after multiple testing correction, suggesting a possible false positive. In contrast, both NLR4/2 and NLR4 maintained robust significance. Statistical power was assessed using power analysis. The current sample size provides adequate power to detect the effect of NLR4/2 (Power=92%), The AUC for the joint diagnostic ROC was 0.860 (95% CI, 0.783–0.937). The calibration curve demonstrated strong predictive ability for RILD within 3 months post-IMRT (P=0.988) (Figure 3). Univariate logistic analyses indicates that Group 3 (NLR 4 > 13.5 and NLR 4/2 > 1.93) demonstrated a 57-fold increased risk of developing RILD within 3 months post-IMRT(P<0.001). By contrast, Group 2 (NLR 4 > 13.5 or NLR 4/2 > 1.93) exhibited an 15.1-fold increased risk of developing RILD.(P=0.001) (Table 5). The model demonstrated consistent discriminative ability,

Table 6 Multivariate Analyses of Risk Factors for RILD Within 3 months Post-IMRT

Variables	β	S.E	Z	*p*	OR (95% CI)
LYM −2-week	−1.47	0.91	2.63	0.105	0.229 (0.04~1.36)
LYM 0-week	0.95	1.01	0.88	0.348	2.59 (0.36~18.85)
LYM 4-week	0.54	3.37	0.03	0.873	1.72 (0.002~1270.40)
LYM 6-week	−1.82	1.28	2.02	0.156	0.16 (0.01~2.00)
LYM 8-week	−0.15	0.72	0.05	0.832	0.86 (0.21~3.54)
NEU 4-week	0.49	0.46	1.15	0.284	1.63 (0.67~3.99)
NLR 4-week	0.09	0.03	7.00	0.008	1.09 (1.02~1.16)
NLR 6-week	−0.02	0.06	0.18	0.669	0.98 (0.87~1.09)
NLR 4/2	0.96	0.32	8.93	0.003	2.60 (1.39~4.88)
NLV	−0.002	1.34	2.08	0.041	0.998 (0.996~1.00)

Abbreviations: NEU, neutrophil; LYM, lymphocyte; NLR, neutrophil-to-lymphocyte ratio; NLV,normal liver volume; NLR 4/2=NLR level at 4-week timeframe/NLR level at 2-week timeframe.

with mean AUC values of 0.86 in the training set and 0.81 in the test sets. The sensitivity and specificity were 0.46 and 0.94 in the training set,0.38 and 0.94 in the test sets across 5-fold cross-validation(P=0.41) (Table 7).

Discussion

Our study demonstrates the significant predictive value of neutrophil and lymphocyte counts, neutrophil-to-lymphocyte ratio and normal liver volume for RILD during IMRT in patients with HCC. Lower lymphocyte levels increase the risk of developing RILD. Additionally, a more rapid decline in lymphocyte count during early RT may be associated with the development of RILD within 3 months post-IMRT. Moreover, from the third to the fourth week of RT, neutrophil counts exhibited contrasting trends between RILD and non-RILD group and RILD group has significantly higher neutrophil counts than non-RILD group. A higher neutrophil-to-lymphocyte ratio during weeks 3–6 of RT is linked to an increased risk of RILD. ALSO, rapid changes in NLR between weeks 3–4 of RT often indicate the occurrence of RILD. We also observed that a smaller volume of normal liver tissue correlates with a higher likelihood of developing RILD. A retrospective study by Liang et al showed, the tolerable mean dose to normal liver in patients with CP-A is less than 23 Gy.[18] The recommended formula for calculating the mean dose to normal liver is: mean dose to normal liver = −1.686

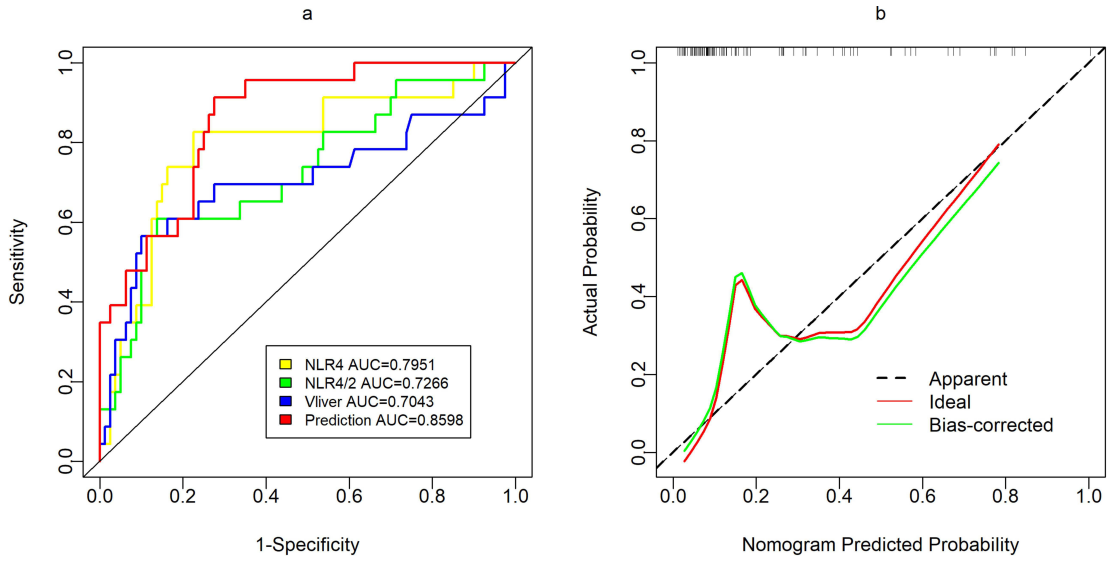

Figure 3 ROC (**a**) and calibration curves (**b**) for logistic analysis predicting the probability of RILD within 3 months post-IMRT.

Table 7 Model Performance Across 5-Fold Cross-Validation

Fold	Training Set			Test Set			t	P
	AUC(95% CI)	Sensitivity	Specificity	AUC(95% CI)	Sensitivity	Specificity		
1	0.86(0.74~0.93)	0.47	0.92	0.81(0.5~0.97)	0.25	1		
2	0.86(0.70~0.94)	0.56	0.95	0.74(0.37~0.95)	0.4	0.875		
3	0.84(0.71~0.92)	0.47	0.95	0.80(0.34~1)	0.25	1		
4	0.88(0.78~0.94)	0.44	0.95	0.74(0.41~0.95)	0.4	0.875		
5	0.84(0.72~0.92)	0.33	0.93	0.98(0.81~1)	0.6	0.9375		
Mean	0.86(0.85~0.57)	0.46	0.94	0.81(0.75~0.91)	0.38	0.94	0.93	0.41

Abbreviations: AUC, area under the ROC curve; CI: Confidence Interval; t: Student's *t* test.

+0.023× NLV (mL).Li et al found that the mean dose to normal liver in patients with CP-B was less than 15.1 Gy.These studies illustrated the importance of NLV in the design of radiotherapy plans optimization for HCC.[19]

Collectively, these factors predicted the development of RILD within 3 months post-IMRT. The AUC reached 0.860, suggesting that dynamic changes in neutrophil and lymphocyte counts and neutrophil-to-lymphocyte ratio in the early stages of IMRT are reliable predictors of RILD.

Patients who developed RILD at a later stage may experience changes in inflammation and immune levels that have already begun between days 15 and 22 after the initiation of IMRT. Inflammation and immunity are closely associated with the development, treatment, and prognosis of HCC.[20,21] A high systemic immune-inflammation index is associated with poor outcomes in HCC after surgery.[22] Alterations in the inflammatory immune microenvironment in hepatocytes may help combat hepatocarcinogenesis and its treatment.[23] RILD commonly arises in patients receiving RT for HCC, viral infections, and cirrhosis. The specific molecular mechanism of RILD remains unclear owing to the challenges associated with animal modeling and the limited number of studies examining the mechanism of RILD. RILD development is closely linked to inflammation and the immune system response. Animal experiments have demonstrated that radiation-induced breaks in double-stranded DNAs (dsDNA) through the cyclic guanosine monophosphate-adenosine monophosphate (cGAMP) synthase (cGAS)-cytoplasmic DNA sensors activate innate immune and inflammatory responses through the production of the second messenger cGAMP. Radiation-induced hepatocellular cell death releases large amounts of DNA deposits. Moreover, the phagocytosis of dsDNA by non-parenchymal cells triggers the activation of cGAS-stimulator of interferon genes and increases the production of oxidative stress acting on hepatocytes, resulting in hepatic injury.[7,24]

Neutrophil and lymphocyte count determination is a cost-effective routine blood test that is commonly utilized in clinical practice. This test is easy to monitor and perform. Lymphocytes are highly sensitive to radioactivity, and the occurrence of lymphopenia after RT influences the long-term prognosis of malignant tumors.[25] A reduction in lymphocyte count following transarterial RT embolization for HCC has been associated with a worse prognosis.[26] Neutrophils are key contributors to aseptic hepatic inflammation and serve as mediators of abnormal inflammation in T-cell immunotherapy-induced hepatotoxicity.[27,28] The complex interactions between neutrophils and macrophages also play a crucial role in liver repair by promoting the phenotypic transformation of macrophages.[29] The findings of these studies underscore the significance of neutrophils in hepatic inflammatory injury and repair and warrant further investigation. Previous studies have reported that high baseline NLR is associated with poor survival outcomes in various solid tumors.[30,31] The NLR values before RT are a valuable prognostic marker of RT toxicity in patients with HCC.[12] The NLR values, in combination with immune inflammation, can predict the toxic effects of HCC.

In this study, we analyzed early dynamic changes in neutrophil and lymphocyte counts during IMRT. We identified the time points at which both these counts showed significant changes and combined the dynamic changes of the two indices to predict the occurrence of RILD. The changes in neutrophil and lymphocyte counts were most pronounced at first 3–4 weeks during IMRT in patients with RILD. We calculated the NLR values at this time point, along with the NLR ratio of NLR at 3–4 weeks and NLR at 1–2 weeks. Based on the optimal cut-off values of these two parameters, we divided the patients into three groups. The group of NLR at 3–4 weeks > 13.5 and NLR at 3–4 weeks/NLR at 1–2 weeks

> 1.93 was associated with a high risk of RILD. The predictive performance for RILD of different groups was exceptional. Our findings hold potential significance for physicians in promptly recognizing patients at risk of RILD and making timely decisions regarding RT strategies during IMRT.

This study has some limitations. First, this is a single-center retrospective study and the model lacks external validation. However, we are conducting a prospective validation of the model established in this study. Second, the analysis of changes in platelet count, another important inflammatory parameter, was not included owing to the high proportion of patients with HCC who demonstrated low platelet levels at baseline and during RT. Drugs that stimulate platelet production can affect platelet count. Third, although we selected patients who received the same RT dose, split dose, and the number of splits, the RT was initiated and completed at different time points.

Conclusion

Our study identified that circulating NLR at first 3 to 4 weeks and its relatively change compared to NLR at first 1 to 2 weeks during IMRT were significantly associated with RIHT.It implies that neutrophils and lymphocytes may change the liver immune microenvironment and play an important role in the mechanism research of RIHT.The model based on early dynamic variation of NLR and dosimetric factors NLV can predict RIHT with high accuracy in HCC patients.But it still requires validation by external cohorts or prospective cohorts.It can be used as a supplement to other predictive models, which are helpful for clinicians to predict the occurrence of RIHT earlier and more accurately.

Abbreviations

AFP, alpha fetoprotein; ALBI, Albumin-Bilirubin Score; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AUC, area under the curve; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; cGAMP, cyclic guanosine monophosphate-adenosine monophosphate; cGAS, cyclic guanosine monophosphate-adenosine monophosphate synthase; CI, confidence interval; CP, Child-Pugh; cRILD, classic radiation-induced liver disease; CT, computed tomography; CTV, clinical target volume; DNA, deoxyribonucleic acid; dsDNA, double-stranded DNA; ECOG PS, Eastern Cooperative Oncology Group-performance status; GTV, gross tumor volume; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; ICG, Indocyanine Green; IMRT, intensity-modulated radiotherapy; ncRILD, non-classic radiation-induced liver disease; NLR, neutrophil-to-lymphocyte ratio; NLV, normal liver volume; NTCP, Normal Tissue Complication Probability; OARs, organs at risk; OR, odds ratio; RAF, radiofrequency ablation; RILD, radiation-induced liver disease; ROC, receiver operating characteristic; RT, radiation therapy.

Human Ethics and Consent to Participate declarations

This study was approved by the ethical review committee of Guangxi Medical University Cancer Hospital (approval no. KY2025592). Since the patients' datas could not be recognized, the informed consent requirement was dropped.We will strictly keep patients' medical data confidential. The Declaration of Helsinki was followed in the execution of this study plan.

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.

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Disclosure

The authors report no conflicts of interest in this work.

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