Novel Radiomic Signature as a Prognostic Biomarker for Locally Advanced Rectal Cancer

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Background: Locally advanced rectal cancer (LARC) patient stratification by clinicoradiologic factors may yield variable results. Therefore, more efficient prognostic biomarkers are needed for improved risk stratification of LARC patients, personalized treatment, and prognostication.
Purpose/Hypothesis: To compare the ability of a radiomic signature to predict disease-free survival (DFS) with that of a clinicoradiologic risk model in individual patients with LARC.
Study Type: Retrospective study.
Population: In all, 108 consecutive patients (allocated to a training and validation set with a 1:1 ratio) with LARC treated with neoadjuvant chemoradiotherapy (nCRT) followed by total mesorectal excision (TME).
Field Strength/Sequence: Axial 3D LAVA multienhanced MR sequence at 3T.
Assessment: ITK-SNAP software was used for manual segmentation of 3D pre-nCRT MR images. All manual tumor segmentations were performed by a gastrointestinal tract radiologist, and validated by a senior radiologist. The clinicoradiologic risk factors with potential prognostic outcomes were identified in univariate analysis based on the Cox regression model for the whole set. The results showed that ypT, ypN, EMVI, and MRF were potential clinicoradiologic risk factors. Interestingly, only ypN and MRF were identified as independent predictors in multivariate analysis based on the Cox regression model.
Statistical Tests: A radiomic signature based on 485 3D features was generated using the least absolute shrinkage and selection operator (LASSO) Cox regression model. The association of the radiomic signature with DFS was investigated by Kaplan–Meier survival curves. Survival curves were compared by the log-rank test. Three models were built and assessed for their predictive values, using the Harrell concordance index and integrated time-dependent area under the curve.
Results: The novel radiomic signature stratified patients into low- and high-risk groups for DFS in the training set (hazard ratio [HR] = 6.83; $P < 0.001$), and was successfully validated in the validation set (HR = 2.92; $P < 0.001$). The model combining the radiomic signature and clinicoradiologic findings had the best performance (C index = 0.788, 95% confidence interval [CI] 0.72–0.86; integrated time-dependent area under the curve of 0.837 at 3 years).
Data Conclusion: The novel radiomic signature could be used to predict DFS in patients with LARC. Furthermore, combining this radiomic signature with clinicoradiologic features significantly improved the ability to estimate DFS ($P = 0.001$, 0.005 in training set and in validation set, respectively), and may help guide individualized treatment in such patients.
Level of Evidence: 3
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Additional supporting information may be found in the online version of this article.

Neoadjuvant chemoradiotherapy (nCRT) followed by total mesorectal excision (TME) is currently considered the standard combined modality treatment for patients with locally advanced rectal cancer (LARC).[1] This therapeutic strategy improves local control of the disease, but does not notably increase overall survival (OS) or disease-free survival (DFS).[1–4] The reported 3- and 5-year cumulative incidence rates of distant metastasis after nCRT are 22% and 25%, respectively.[5,6] Meanwhile, distant metastasis is the main cause of treatment failure in patients with LARC who undergo nCRT. In individuals at high risk for an adverse outcome after nCRT, additional systemic therapy may reduce the risk of distant relapse, conferring a survival benefit. Therefore, identifying adverse prognostic features that affect survival and preoperative risk stratification could help select individualized management strategies and improve the prognosis of patients with LARC.

Currently, clinicoradiologic prognostic factors are used to identify patients with rectal cancer who would benefit from nCRT, based on risk stratification. Preoperative higher-resolution magnetic resonance imaging (MRI) assessment of mesorectal fascia (MRF) involvement is considered a strong independent predictor of poor outcome in patients with LARC who undergo nCRT followed by curative TME.[7,8] Extramural venous invasion (EMVI) detected on MRI preoperatively is also an index of poor prognosis in patients with rectal cancer.[9–11] Post-nCRT EMVI positivity also indicates reduced survival.[12] The depth of invasion of a malignant tumor beyond the outer border of the muscularis propria (pT3) is considered an important prognostic factor in rectal carcinoma,[13–16] with a pT3 depth above 5 mm representing an adverse prognostic factor for DFS (hazard ratio [HR] 2.13, 95% confidence interval [CI] 1.16–3.89).[15] Studies have also shown that the pathologic T category (ypT) and N stage (ypN) after nCRT are relevant independent prognostic factors for survival.[17–19] However, patient stratification by these clinicoradiologic factors leads to overt differences in outcomes among studies, suggesting heterogeneity in survival outcomes. Therefore, more efficient prognostic biomarkers are needed for improved risk stratification of LARC patients, personalized treatment, and prognostication.

Radiomics characterizes tumor phenotypes by extracting multiple quantitative features from radiologic images, and provides a comprehensive view of the entire intratumor heterogeneity. Studies have shown that radiomics has potential for predicting survival outcomes.[20] In addition, several studies have integrated radiologic and clinicopathologic features with radiomic signatures, and it is currently considered that a signature composed of multiple biomarkers is superior to a single biomarker counterpart for prognostic purposes.[21] However, studies evaluating radiomic signatures for DFS prediction in patients with LARC are scarce.

The aim of this study was to compare a radiomic signature and a clinicoradiologic risk model for their abilities in predicting 3-year DFS in patients with LARC.

Materials and Methods

Patients

The analysis workflow is shown in Fig. 1.

This retrospective study was approved by our Institutional Review Board, with a waiver of informed consent. From October 2010 to December 2013, we enrolled 108 consecutive patients with locally advanced rectal adenocarcinoma ($\geq$T3 and lymph node positive or negative on initial MRI) originating within 15 cm of the anal verge, treated with nCRT before TME at our institution. Pelvic MRI and chest, abdominal, and pelvic computed tomography (CT) were performed for tumor staging before nCRT. All tumors were staged by our multidisciplinary team according to the Union for International Cancer Control/American Joint Committee on Cancer TNM staging system (7^{th} edition). Patients with a history of malignancy, previous radiotherapy to the pelvis, a contraindication to MRI, and images of insufficient quality for analysis were excluded. The patients were randomly divided into training and validation sets (1:1 ratio).

Treatment Protocol and Reference Standard for Pathology

All patients underwent radiation therapy to the whole pelvis at a dose of 50 Gy (25 daily fractions of 2 Gy), with an overall treatment time of 35 days. The chemotherapy consisted of an infusion of oxaliplatin (50 mg/m^2) on the first day of each week of radiation therapy and oral administration of the 5-fluorouracil precursor capecitabine (1650 mg/m^2) twice daily from the first to last day of nCRT. Dose reduction of oxaliplatin and capecitabine was not planned.

Subsequent treatment in patients who completed nCRT was decided by a multidisciplinary team. All patients underwent standard TME surgery performed by experienced surgeons specialized in colorectal oncology. The surgical approach was based on tumor location and post-nCRT MRI restaging results. TME was performed within 6–8 weeks of nCRT.

The resected gross specimens were processed and evaluated by a single pathologist with 15 years of experience in rectal cancer pathology, blinded to the clinical and MRI findings. The specimens were examined according to the Union for International Cancer Control/American Joint Committee on Cancer TNM staging system (7^{th} edition) criteria. The ypT0N0 stage was defined as the absence of any residual tumor cells in the surgical specimen (pathologic complete response).

Follow-up

According to our routine protocols, all patients were followed up for at least 5 years after surgery: 3-month intervals in the first 2 years; every 6 months in the following 2 years; annually thereafter. The primary study endpoint was DFS, defined as the interval between the TME surgery and disease progression, including local tumor recurrence, distant metastasis, and death from any cause, or the date of the last follow-up visit (censored). Local recurrence was defined as recurrence in the pelvis, and distant metastasis as

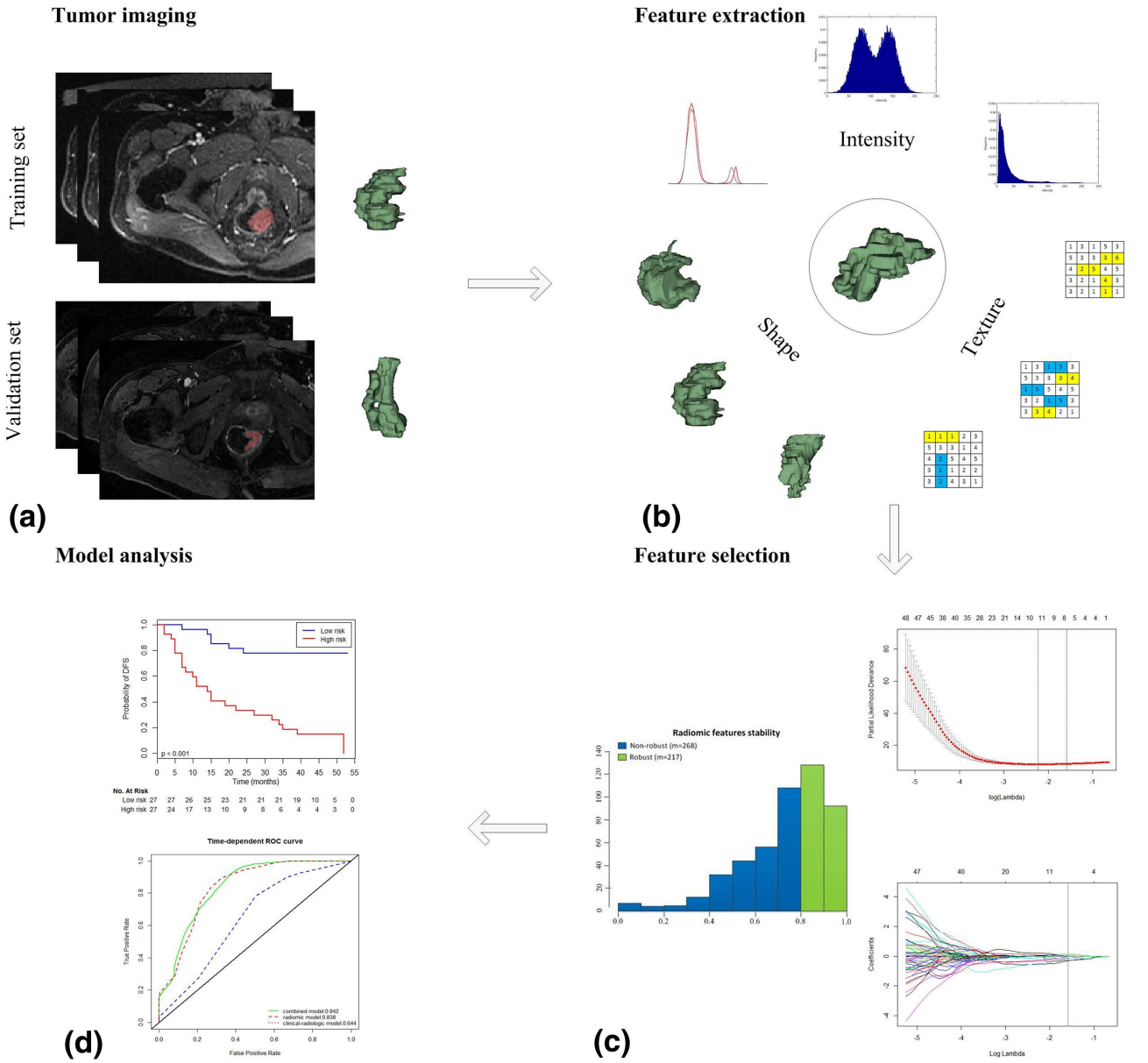

FIGURE 1: Workflow analysis. A: Examples of tumors in the training and validation sets with MRI (left) and 3D segmentation (right). B: Multiple radiomic features were extracted from 3D segmented tumor regions in patients with locally advanced rectal cancer, including density, shape, and textural features. In addition, eight wavelet decompositions were performed on original images. The most useful prognostic features were selected by the intraclass coefficient and LASSO Cox model (C), and analyzed by KM curves and modeling (for details see text) (D).

recurrence at sites different from the pelvis. All local recurrence and distant metastatic cases were diagnosed by a multidisciplinary team based on clinical examination, serum carcinoembryonic antigen levels, chest and abdominopelvic CT, and/or abdominopelvic MRI, endoscopy, and biopsy. Follow-up information was recorded in the database. A minimum follow-up of 36 months was required to confirm the 3-year DFS status of the patients. The minimum postoperative follow-up period was 2 months, for a maximum of 54 (median 30) months.

Image Acquisition and Analysis

MRI was performed on a 3T scanner (SignaHDx, General Electric, Milwaukee, WI) equipped with a phased array body coil. A routine clinical imaging protocol was carried out as follows. First, axial 3D LAVA multienhanced MR images were acquired. A bolus of gadolinium-based contrast agent (gadopentetate dimeglumine; Bayer, Leverkeusen, Germany) at 0.1 mmol/kg body weight was administered at 2 mL/s with a power injector. The patients underwent bowel preparation with antispasmodic medications before the MRI examinations.

Axial, sagittal, and oblique coronal (parallel to the long axis of the rectum) T_2-weighted spin-echo sequences were acquired. Subsequently, a small field of view (16 × 16 cm), high-resolution, oblique axial (perpendicular to the long axis of the tumor) T_2-weighted image sequence (repetition time [TR]/ echo time [TE] 5160/151 msec; flip angle, 90°; echo train length, 19; slice

thickness, 3 mm; matrix, 512 × 512) was performed. An axial spin-echo, diffusion-weighted echo-planar imaging sequence, with background body signal suppression, was then acquired at b values between 0 and 800 s/mm^2.

One phase of imaging before contrast agent injection and nine phases thereafter were carried out (acquisition time per phase, 15 sec; TR, 3 msec; TE, 1.4 msec; flip angle, 15°; matrix, 320 × 192; field of view, 40 × 40 mm; slice thickness, 3 mm; no thickness spacing). All sequences were obtained during free breathing.

MRI analysis (T category, N stage, and EMVI and MRF status) was randomly performed by a gastrointestinal tract radiologist with 20 years of experience in interpreting rectal MR images, blinded to histology and outcomes.

T3 rectal cancer was clinically subclassified based on MR images from the outer edge of the low signal-intensity longitudinal muscularis propria to the outermost edge of the tumor (T3a, T3b, T3c, and T3d reflecting tumors extending <1 mm, 1–5 mm, >6–15 mm, and >15 mm beyond the muscularis propria, respectively). This subclassification correlates with survival in patients with rectal cancer. Patients with T3a and T3b disease stages were classified as the low-risk subgroup, and those with T3c and T3d disease stages as the high-risk subgroup.

EMVI was assessed according to radiologic features using a 0–4 scoring system[9]: EMVI 0, pattern of tumor extension through the muscle coat not nodular, with no vessels adjacent to areas of tumor penetration; EMVI 1, minimal extramural stranding/nodular extension, but not in the vicinity of any vascular structure; EMVI 2, tumor stranding in the vicinity of extramural vessels (of normal caliber), with no definite tumor signal within the vessels; EMVI 3, overt intermediate signal intensity within the vessels, whose contour and caliber are only slightly expanded; EMVI 4, overt irregular vessel contour or nodular expansion by a definite tumor signal. EMVI 0, 1, or 2 was classified as negativity, and EMVI 3 or 4 as positivity.

MRF positivity was defined as a primary tumor, tumor deposit, or positive lymph node abutting or extending through or within 1 mm of the MRF.[22]

Image Segmentation and Texture Analysis

Segmentation is required before extraction of quantitative radiomic features. ITK-SNAP software (open source, www.itk-snap.org) was used only for manual segmentation of 3D pre-nCRT MR images. All manual tumor segmentations were performed by a gastrointestinal tract radiologist (Y.K.M.) with 15 years of experience in interpreting rectal MR images, and validated by a senior radiologist (H.M.Z.) with 20 years of experience (mainly in colorectal cancer). The fifth phase (60 sec after contrast agent injection) image from multienhanced MRI was selected for segmentation, with the region of interest covering the whole tumor.

In this study, the radiomic features selected could capture the characteristics of tumor intensity and shape, as well as texture patterns. Intensity normalization was performed to transform the original image to standardized inputs and the MR images transformed have similar intensity distribution.[23] It can reduce the data variability and is easy to calculate the quantitative radiomic feature. In our study, we used two-step process for intensity normalization: 1) bicubic resampling was used to standardize the image scale; and 2) the histogram matching was used to minimize the discrepancy of intensity distributions among patients' MR images. The radiomic features used in the current study contained 485 3D descriptors, including 440 features described by Aerts et al[24] and 45 additional modified phenotypic descriptors. These features were extracted using MatLab v. R2015b (MathWorks, Natick, MA). All radiomic features are provided in Supplementary Methods S2.

The intraclass correlation coefficient (ICC) was calculated to assess the stability of radiomic features from 25 randomly selected patients, which were segmented twice by the same experienced radiologist with 15 years of experience (Y.K.M.). Forty-five percent of the 485 radiomic features derived from the region of interest with ICC >0.8 were included in the analysis, and used in the follow-up study (Supplementary Fig. S1). All radiomic features were normalized by z-score transformation.

Statistical Analysis

Statistical analyses were performed using R software v. 3.3.1 (http://www.R-project.org). The R packages used in this study are described in Supplementary Methods 1. Differences between the training and validation sets were assessed by the chi-square and log-rank tests. Survival curves were compared by the log-rank test. $P < 0.05$ was considered statistically significant.

Results

The training and validation sets were balanced for survival (median DFS of 34.5 months and 22.5 months for the training and validation sets, respectively; $P = 0.847$, log-rank test) as well as clinical endoplasmic reticulum and radiologic characteristics ($P = 0.182$–0.993). The clinical characteristics of the training and validation cohorts are summarized in Table 1.

Construction of the Novel Radiomic Signature

The most useful prognostic features were selected by the least absolute shrinkage and selection operator (LASSO) Cox regression model in the training set. This technique is suitable for regression analysis of high-dimensional data, and patient features can be selected based on their associations with survival endpoints and time.[25,26] Using a 10-fold crossvalidation, the LASSO Cox model identified three intensity features and five textural parameters that were most important for predicting treatment outcome (Supplementary Fig. S2), including X1_fos_energy, X1_fos_maximum, X6_fos_kurtosis, X6_GLCM_correlation, X1_GLRLM_LRE, X1_GLRLM_SRLGLE, X1_GLRLM_LRLGLE, and X7_GLRLM_mean. Nonzero coefficients of the Cox model for each selected imaging feature were computed and combined into a radiomic signature. A radiomic score was then determined for each patient using a weighted linear combination of selected features. Radiomic score = 0.217*X1_fos_energy – 0.005*X1_fos_maximum + 0.157*X6_fos_kurtosis – 0.211*X6_GLCM_correlation + 0.230* X1_GLRLM_LRE + 0.259* X1_GLRLM_SRLGLE + 0.021* X1_GLRLM_LRLGLE + 0.182 *X7_GLRLM_mean.

Performance Validation of the Radiomic Signature

The LASSO Cox model generated in the training set was used to predict the radiomic risk group of each patient. The optimal cut-off (−0.14) was the median radiomic risk score in the training set, and also used in the validation set.[27] The patients were classified into low- (score < −0.14) and high- (score ≥ −0.14) risk groups. Patients' radiomic score were calculated ranging from −0.83 to −0.15 for the low-risk group (median −0.44) and −0.13 to 1.89 for the high-risk group (median 0.16) in the training set. Patients' radiomic score were calculated ranging from −1.05 to −0.15 for the low-risk group (median −0.47) and −0.13 to 2.38 for the high-risk group (median 0.17) in the training set. Kaplan–Meier survival curves were generated for both the training and validation sets. There was a significant correlation between the radiomic signature and DFS in patients with LARC in the training set (HR = 6.83, 95% CI 3.65–12.79, $P < 0.001$), which was confirmed in the validation set (HR = 2.92, 95% CI 1.91–4.47, $P < 0.001$). The association of the radiomic signature with DFS is shown by Kaplan–Meier survival curves in Fig. 2. Survival rates in the radiomic risk groups were compared by the log-rank test.

The clinicoradiologic risk factors with potential prognostic outcomes were identified in univariate analysis based on the Cox regression model for the whole set. The results showed that ypT (HR = 1.37, 95% CI 1.07–1.74, $P = 0.009$), ypN (HR = 1.27, 95% CI 1.10–1.46, $P < 0.001$), EMVI (HR = 1.33, 95% CI 1.06–1.68, $P = 0.013$), and MRF (HR = 1.53, 95% CI 1.24–1.90, $P < 0.001$) were potential clinicoradiologic risk factors for recurrence and metastasis in rectal cancer. Multivariate analysis based on the Cox regression model was then performed using the identified risk factors and the radiomic signature. Interestingly, ypN ($P = 0.027$), MRF ($P = 0.032$), and radiomic signature ($P < 0.001$) were identified as independent predictors. Using the nine clinicoradiologic risk factors, stratified analyses were

TABLE 1. Patient and Tumor Characteristics in the Training and Validation Sets

	Training set ($n = 54$)	Validation set ($n = 54$)
Gender		
Male	29 (53.7%)	42 (77.8%)
Female	25 (46.3%)	12 (22.2%)
Age (years)	53.9 ± 11.5	55.7 ± 10.5
Stage		
IIA	8 (14.8%)	8 (14.8%)
IIIB	20 (37.0%)	33 (61.1%)
IIIC	26 (48.2%)	13 (24.1%)
Clinical T stage		
T3	36 (66.7%)	38 (70.4%)
T4	18 (33.3%)	16 (29.6%)
Clinical N stage		
N0	8 (14.8%)	10 (18.5%)
N1	24 (44.4%)	17 (31.5%)
N2	22 (40.7%)	27 (50.0%)
Pre-nCRT CEA level (median) (ng/ml)		
<4.75	28 (51.9%)	25 (46.3%)
≥4.75	26 (48.1%)	29 (53.7%)
Post-nCRT CEA level (median) (ng/ml)		
<2.11	29 (53.7%)	24 (44.4%)
≥2.11	25 (46.3%)	30 (55.6%)
EMVI		
Negativity	31 (57.4%)	34 (63.0%)
Positivity	23 (42.6%)	20 (37.0%)
MRF		
Positivity	17 (31.5%)	10 (18.5%)
Negativity	37 (68.5%)	44 (81.5%)
ypTN stage		
ypT0N0	8 (14.8%)	9 (16.7%)
non ypT0N0	46 (85.2%)	45 (83.3%)
Local recurrence		
	3 (5.6%)	3 (5.6%)
Distant metastasis		
Lung	13 (24.0%)	18 (33.3%)
Live	9 (16.7%)	6 (11.1%)
Lymph node	3 (5.6%)	3 (5.6%)
Other[a]	2 (3.7%)	0 (0%)
Follow-up time (months)		
Median (IQR)	34.5 (11, 45)	22.5 (11, 47)

The data are shown as *n* (%) unless otherwise indicated. No significant differences were found between the training and validation cohorts.
[a]One case of subscalp metastasis and one of metastasis to psoas major.
CEA, carcinoembryonic antigen; EMVI, extramural venous invasion; IQR, interquartile range; MRF, mesorectal fascia; nCRT, neoadjuvant chemoradiotherapy; ypTN, the pathologic classification after nCRT.

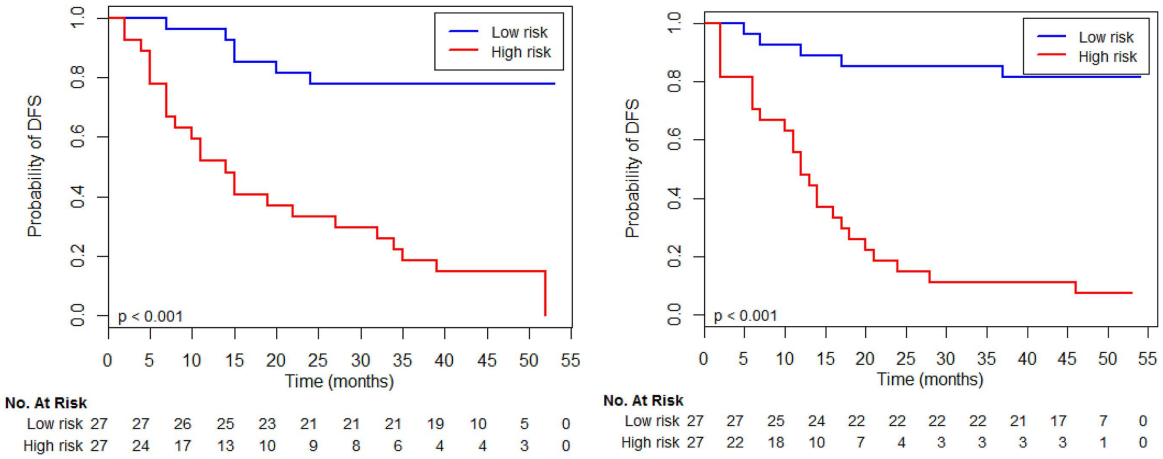

FIGURE 2: Kaplan–Meier curves for disease-free survival in the training (left) and validation (right) sets stratified by risk group, as identified by the LASSO Cox model.

performed for the whole set to evaluate the association of the radiomic signature with DFS. As shown in Fig. 3 and Supplementary Fig. S3, the radiomic signature was significantly associated with DFS in all subgroups. In stratified subgroup analysis according to ypT0N0, EMVI, and MRF status, the low-risk group had longer DFS than the high-risk group, which is significant in terms of individualized treatment. Multivariate analysis showed that MRF ($P = 0.032$), ypN ($P = 0.027$), and radiomic signature ($P < 0.001$) were independent prognostic risk factors.

Assessment of Models for DFS Estimation

Three models were assessed in the training set, ie, the radiomic model with the radiomic signature, clinicoradiologic Cox model with clinical and radiologic parameters (ypN, MRF), and a combined model. Then the predictive ability of each model was assessed in the validation set by determining the Harrell concordance (C) index and integrated time-dependent area under the curve (iAUC) at 3 years[28]; C index values range from 0.5 to 1.0, with 0.7 considered to be good for outcome discrimination.

The predictive accuracy of the combined model (C index = 0.788, 95% CI 0.72–0.86; iAUC of 0.837 at 3 years) was higher than that of the clinicoradiologic (C index = 0.644, 95% CI 0.53–0.76; iAUC of 0.467 at 3 years) or radiomic (C index = 0.767, 95% CI 0.72–0.86; iAUC of 0.827 at 3 years) model. The iAUC curves and nomogram for the combined model are presented in Fig. 4. The performances of all three models are shown in Table 2. Although most clinicoradiologic parameters were not independent prognostic risk factors in this study, they increased the predictive power of the radiomic model, and positively contributed to the combined model.

Discussion

Radiomics uses a large number of medical imaging features, and reveals voxelwise intratumor heterogeneity. In this study we identified a combined model as an effective biomarker for individualized evaluation of 3-year DFS before nCRT in patients with LARC. To the best of our knowledge, Wang et al[29] and Lovinfosse et al[30] described the prognostic values of CT and PET/CT radiomics features in rectal cancer. In their pioneering study, they developed robust models and strong independent prognostic factors for survival outcomes in LARC patients. Our study assessed the prognostic value of a combined model and explored the predictive value of a radiomic model based on MRI in patients with LARC who undergo nCRT. The combined model had superior prognostic performance in terms of predicting DFS compared with either the radiomic or clinicoradiologic model alone.

In this study the radiomic signature was extracted from the fifth-phase images (acquired 60 sec after contrast agent administration) of the multiphase enhancement sequence, as reported for rectal and breast cancers by Nie et al[31] and Ahmed et al,[32] respectively. Unlike the unenhancement scan, postcontrast images at 60 seconds provided improved tissue contrast for tumor segmentation, and contained more information on intratumor heterogeneity for predicting prognosis voxelwise. The LASSO Cox model identified eight features, including three intensity and five textural features. Nie et al[31] reported that intensity and voxelwise textural features extracted from enhanced images show promise in terms of their ability to predict response to treatment. Furthermore, a review by Alobaidli et al[33] discussed the relationships between textural features of tumors and outcome prediction.

Combining clinicoradiologic risk factors and the radiomic model achieved higher prognostic performance than the radiomic or clinicoradiologic model alone; however, only prediction accuracy significantly differed between the combined model and clinicoradiologic model. Furthermore, the combined model was superior to previously reported clinicoradiologic biomarkers in terms of prognostic accuracy.[34,35] Therefore, the combined model appears to be very robust

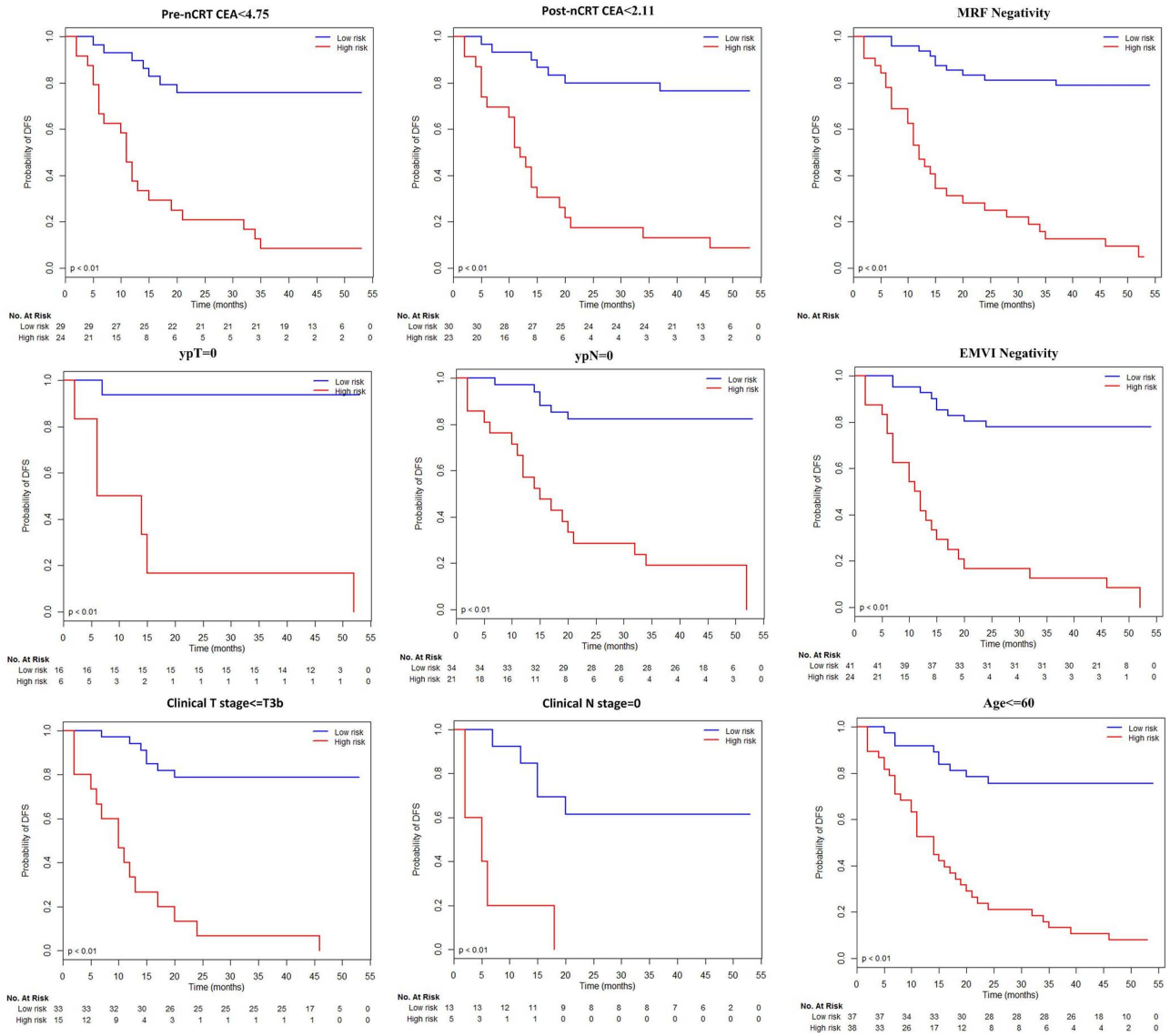

FIGURE 3: Disease-free survival curves for the low- and high-risk groups classified according to the radiomic signature in various subgroups ($P < 0.01$ in different subgroups). The remaining clinicoradiologic risk factors are presented in Supplementary Fig. S3.

compared to the clinicoradiologic model, and could serve as an effective noninvasive biomarker for predicting prognosis before treatment in patients with LARC. Intratumor heterogeneity is significantly correlated with oncologic prognosis, and therefore considered a potential prognostic factor. Thus, our present findings could be attributed to the fact that malignant tumors consist of heterogeneous cell populations with distinct molecular and microenvironmental differences. In the combined model, prognostic radiomic features could be extracted by voxelwise imaging, while clinicoradiologic data characterize the macroscopic features of the tumor. Thus, the combined model reflects tumor diversity and overcomes the potential shortcomings of a single-sided model.

As shown above, the radiomic signature successfully stratified patients into high- and low-risk groups based on the median radiomic risk score. The two groups had significantly different 3-year DFS. Meanwhile, the radiomic signature was an independent predictive biomarker, allowing noninvasive risk stratification of patients with LARC, providing an avenue for identifying patients who may potentially obtain the most benefit from nCRT. MRI is routinely performed in patients with rectal cancer before nCRT. Radiomic profiling is therefore a complementary perspective that could unmask previously hidden imaging characteristics for prognostic purposes.

There was no statistically significant accuracy difference in the prediction of 3-year DFS between the combined and radiomic models, or between the radiomic and clinicoradiologic models in either the training or validation cohort in this study (Table 2). This finding might be explained by three reasons. First, there are relatively few known clinicoradiologic predictors of 3-year DFS in patients with LARC, and multivariate Cox regression analysis identified only two

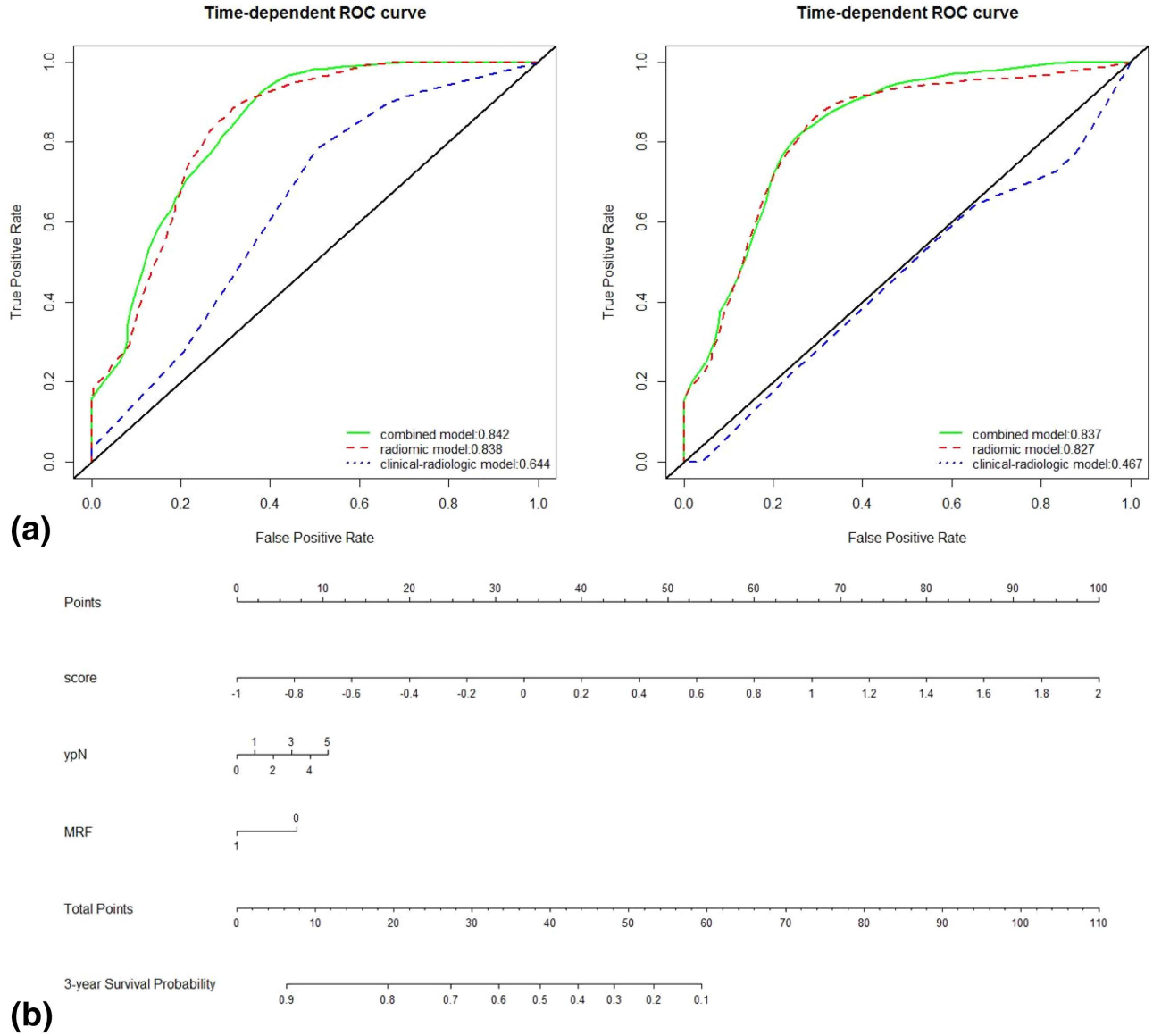

FIGURE 4: A: Time-dependent receiver-operating characteristic curves at 3 years in the training (left) and validation (right) sets. B: The nomogram was developed in the training set, with the radiomic signature (score), N stage, and mesorectal fascia incorporated.

independent predictors (ypN and MRF), as shown above. Second, relative to the radiomic signature, the two other factors selected had less powerful predictive performance.[3] Third, the actual imaging characteristics extracted from the training cohort may have been inadequate because of the relatively small sample size ($n = 54$). In an upcoming

TABLE 2. Performance of the Three Models for Prediction of Outcomes

	Training set		Validation set	
Model	**C index (95% CI)**	***P*-value**	**C index (95% CI)**	***P*-value**
1	0.804 (0.736–0.873)	0.001[a]	0.788 (0.718–0.857)	0.005[b]
2	0.831 (0.772–0.897)	0.999	0.767 (0.718–0.859)	0.992
3	0.661 (0.556–0.767)	0.979	0.644 (0.531–0.757)	0.563

Model 1 is the combined model; model 2 is the radiomic model; model 3 is the clinicoradiologic model.
[a,b]Statistically significant difference between the combined model and the clinicoradiologic model in the training set and validation set, respectively.

follow-up study, more data will be incorporated to assess further significant clinicoradiologic factors and improve the predictive ability of the combined model.

We also established an effective prognostic nomogram to predict survival outcome in LARC following nCRT. A nomogram is a useful tool for predicting individualized outcomes, and has been successfully utilized in many malignancies. By deriving total scores, a vertical line could be drawn downwards from the total point scale to obtain the probability of 3-year DFS. Thus, the nomogram of the combined model may act as a tool for selecting high-risk patients in whom individualized treatment and follow-up can be planned.

Furthermore, analysis of clinicoradiologic subgroups identified a significant difference in survival based on the radiomic signature. Studies have recommended a watch-and-wait strategy with strict follow-up rather than surgery in patients with ypT0N0 post-nCRT,[36,37] suggesting that MRF and EMVI status have an impact on survival preoperatively and may determine clinical management. However, effective clinicoradiologic markers allowing further outcome stratification in patients with low-risk prognostic factors were not found. Our results showed that the radiomic signature could successfully predict better survival in patient subgroups with EMVI negativity, clear MRF, ypT0N0, low carcinoembryonic antigen levels, and low-risk T and N stages pre-nCRT. In contrast with the conventional management, the radiomic signature may be used, thanks to its discriminatory performance, in low-risk patients to guide treatment selection and clinical follow-up, which would lead to reduced risk of relapse, improved prognostic accuracy, and optimized outcome in rectal cancer.

In this study the correlations of ypT and EMVI positivity with prognosis were not consistent with previous findings.[38,39] Such a discrepancy possibly stems from a selection bias introduced by the enrolment of patients with stage II or III rectal cancer, known to constitute a heterogeneous cohort.[38] However, multivariate regression analysis showed that MRF positivity was an independent factor for poor prognosis, as reported by Taylor et al.[7] The predictive accuracy of the clinicoradiologic model for DFS in this study was similar to that of previous clinical prediction models[6,34,35]; in addition, the clinicoradiologic model also enhanced the predictive accuracy of the radiomic model and contributed to building the combined model.

This study has some limitations to be acknowledged. First, it was a retrospective design and was performed and validated in a single hospital; therefore, external validation is required. Second, the relatively small sample size in both the training and validation sets may have led to a relatively low predictive performance. Studies with larger sample sizes and longer follow-up durations are required in the future. Third, radiomic features were extracted only from pre-nCRT MRI enhancement sequences, and other radiomic features extracted using different imaging modalities to build predictive survival models should be further investigated. Finally, only the predictive accuracy of the above models was assessed, in terms of DFS without inclusion of other prognostic endpoints.

In conclusion, the combined model significantly improved the ability to estimate 3-year DFS compared with the radiomic or clinicoradiologic model alone, and could help guide individualized treatment in patients with LARC.

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