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Research article

Preoperative prediction of pelvic lymph nodes metastasis in early-stage cervical cancer using radiomics nomogram developed based on T2-weighted MRI and diffusion-weighted imaging

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ABSTRACT

Objective: To explore an MRI-based radiomics nomogram for preoperatively predicting of pelvic lymph node (PLN) metastasis in patients with early-stage cervical cancer (ECC).

Methods: Ninety-six patients with ECC were enrolled in this study. All patients underwent T2WI and DWI scans before radical hysterectomy with PLN dissection surgery. Radiomics features extracted from T2WI and DWI were selected by least absolute shrinkage and selection operation regression for further radimoics signature calculation. The discrimination of this radiomics signature for PLN metastasis was then assessed using a support vector machine (SVM) model. Subsequently, a radiomics nomogram was constructed based on the radiomics signature and clinicopathologic risk factors using a multivariable logistic regression method. The performance of the radiomics nomogram for the preoperative prediction of PLN metastasis was evaluated for discrimination and calibration.

Results: The radiomics signatures demonstrated a good discrimination for PLN metastasis. A radiomics signature derived from joint T2WI and DWI yielded higher AUC than the signatures derived from T2WI or DWI alone. The radiomics nomogram integrating the radiomics signature with clinicopathologic risk factors showed a significant improvement over the nomogram based only on clinicopathologic risk factors in the primary cohort(C-index, 0.893 vs. 0.616; P = 4.311×10^{-5}) and validation cohort(C-index, 0.922 vs. 0.799; P = 3.412×10^{-2}).The calibration curves also showed good agreement.

Conclusions: The radiomics nomogram based on joint T2WI and DWI demonstrated an improved prediction ability for PLN metastasis in ECC. This noninvasive and convenient tool may be used to facilitate preoperative identification of PLN metastasis in patients with ECC.

1. Introduction

Cervical cancer is the fourth most common malignancy diagnosed in women worldwide, with 87% of cases occurring in underdeveloped countries [1]. Pelvic lymph node (PLN) metastasis is one of the most significant prognostic factors in cervical cancer [2]. The 5-year survival rate of patients without lymph-node metastases in early-stage cervical cancer (ECC) is 90%, but it is only 65% in patients with lymph-node metastases in ECC [2]. Although lymph node status is not included in the FIGO (International Federation of Gynecology and Obstetrics) staging system, it is critical for determining the individualized treatment of patients with ECC. Knowing the accurate status of PLN metastasis preoperatively can help clinicians determine whether to perform a pelvic lymph node dissection (PLND), as well as which postoperative adjuvant therapy to use. However, it is difficult to detect the PLN metastasis status efficiently and reliably using the FIGO staging system.

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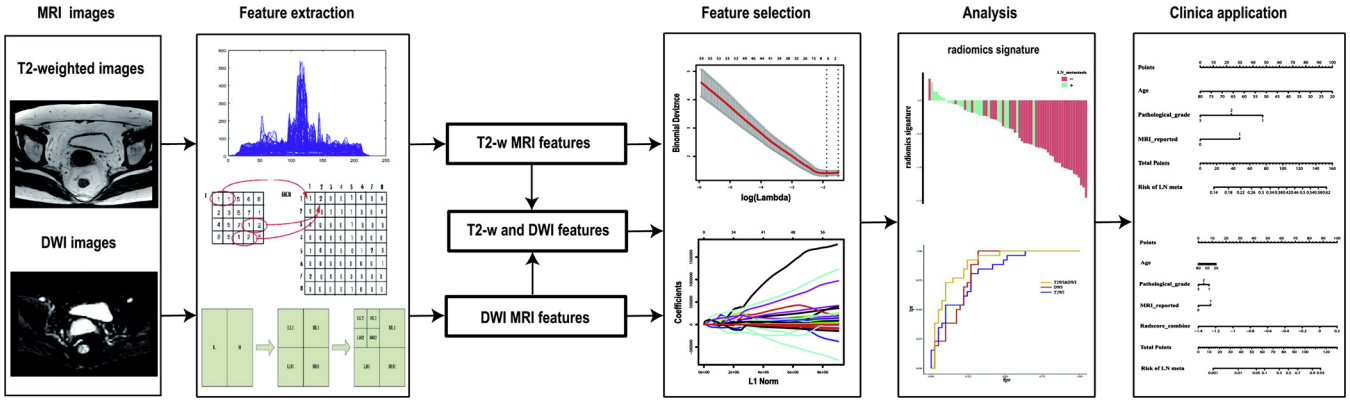

Fig. 1. Flowchart of the study. With manually segmented ROI of tumor, 1046 features were first extracted from T2WI and DWI respectively and then were combined. Next the least absolute shrinkage and selection operator (LASSO) was used to select features from these three groups of features respectively. Thereafter, the radiomics signatures were calculated via a linear combination of the selected features and were assessed using the linear kernel support vector machine model. Finally, the nomogram for individual evaluation was constructed incorporated with the radiomics signature based on joint T2WI and DWI features and clinicpathological factors.

Currently, the PLN metastasis status can be evaluated accurately by histopathological examination either during surgery or after surgery. The FIGO guidelines recommend a pelvic lymph node dissection (PLND) for patients with early-stage (FIGO IA2, IB1, IIA) cervical cancer [1]. However, the incidence of lymph node involvement in patients with ECC is estimated to be 15–20% [3]. Therefore, a large proportion of patients may have to accept an unnecessary PLND which is accompanied by a series of risks of severe complications and a decreased quality of life [3,4]. Although pelvic sentinel lymph node (SLN) biopsy, an alternative approach for detecting PLN metastasis, is less invasive than PLND, its accuracy of PLN metastasis status detection depends on both the detection rate and the diagnostic accuracy during the SLN procedure [5]. In addition, the SLN biopsy is still an invasive method that requires general anesthesia. Therefore, there is an urgent need to explore a noninvasive and reliable method for assessing PLN metastasis in patients with ECC.

In recent years, radiomics has drawn increasing attention in oncology to aid in disease detection, diagnosis, evaluation of prognosis, and prediction of treatment response due to its robust use. By extracting a large number of quantitative features from digital medical data, radiomics analysis can provide decision support noninvasively for oncology at a low cost [6,7]. This method has been successfully applied to preoperatively predict lymph node metastasis of colorectal cancer, bladder cancer and breast cancer [8–10]. T2-weighted MRI (T2WI) and diffusion-weighted imaging (DWI), which has been widely for the local staging evaluation of cervical cancer, could provide important anatomical and functional information on the tumour as well as better tissue contrast. To date, most previous works based on MRI are focused only on texture analysis [11,12], their studies only indicated that the texture analysis in MRI may provide potentially predictive information for tumour prognostic but did not mention that how to use these texture features to obtain a prediction result in a tumour prognostic problem. There are few studies assessing the utility of radiomics analysis in the prediction of PLN metastasis in patients with ECC and we could extract more features to explore more potential information from MRI and obtain a multi-direction and multi-levels description of tumours through radiomics analysis. Moreover, we attempted to apply radiomics method with multiparametric analysis to prediction of the PLN metastasis status in patients with ECC. To our knowledge, there is no published study on whether a radiomics model based on T2WI and DWI could provide a preoperative prediction of the PLN metastasis status in patients with ECC.

In this study, we aim to develop and validate a noninvasive radiomics model based on T2WI and DWI for preoperatively predicting of PLN metastasis in patients with ECC.

2. Methods

2.1. Patients

This retrospective study was approved by our institutional review board and the informed consent requirement was waved. A total of 96 consecutive patients with histopathologically confirmed ECC between February 2012 and April 2018 were involved. The inclusion and exclusion criterias are introduced in Supplementary. Patients were randomly allocated to the primary and validation cohort by a ratio of 7 to 3 and then 67 and 29 patients were assigned to each cohort respectively. Clinicopathologic characteristics of all patients were obtained from the medical records, including age, histopathology grade, and MRI-reported PLN status.

2.2. MRI acquisition and segmentation

All patients underwent pretreatment 3.0 T MRI scans (Ingenia, Philips Healthcare, Best, The Netherlands), using a 16-channel matrix torso coil. The detailed information for MRI scan parameters is introduced in Supplementary. Before examination, patients had to fast 6 h.

Before the feature selection, segmentation was required. Tumors of all patients were manually segmented by a radiologist with 8 years of experience in gynecological imaging by using the 3D slicer software (version 4.8.1; https://www.slicer.org) and all tumor segmentations were confirmed by a senior radiologist with 15 years of experience in gynecological imaging. The region of interest (ROI) of the tumour was delineated along the largest tumour's diameter in an axial orientation on the slice of the T2WI and DWI.

2.3. Radiomics feature extraction

The feature extraction was implemented with MATLAB (2016b; https://www.mathworks.cn) (Fig.1) All detailed information of feature extraction is introduced in the Supplementary.

2.4. Feature selection and radiomics signature construction

We used the least absolute shrinkage and selection operator (LASSO) method to obtain the most significant features for PLN metastasis prediction in the primary cohort. This method will compress some coefficients of features to zero and the features with nonzero coefficients, which indict a strong association with the PLN metastasis status, were selected. Then, their linear combination was calculated as a

radiomics signature for each patient.

2.5. Performance of radiomics signature

To assess the potential association of the radiomics signature with the PLN metastasis, a support vector machine (SVM) model with a linear kernel was trained based on the radiomics signature in the primary cohort and then validated in the validation cohort. The receiver operating curve (ROC) for the SVM model was drawn and the area under the receiver operating curve (AUC) was calculated along with a 95% confidence interval (CI) to quantify the discrimination of the SVM model. All steps above have been performed on radiomics signatures extracted from T2WI and DWI alone, as well as on joint T2WI and DWI.

2.6. Development of the radiomics and clinical nomogram

A multivariable logistic regression analysis was applied to build radiomics and clinical models in the primary cohort for predicting the PLN metastasis. The radiomics model was built integrating the radiomics signature with the clinicopathologic factors while the clinical model was built based only on clinicopathologic factors. Both models were tested in the validation cohort. To provide a visualized and individual tool for predicting probability of PLN metastasis, the radiomics and clinical nomograms were constructed based on the radiomics and clinical models respectively.

2.7. Performance of the radiomics and clinical nomograms

The C-index was calculated to assess the discrimination performance of the nomograms. To evaluate the calibration performance, which measures how close the predictions generated by the model are to the observed outcome, calibration curves were plotted accompanied with the Hosmer-Lemeshow (H–L)test and a significant test statistic implies that the models' prediction does not match the observed outcome perfectly [13].

3. Results

3.1. Patients'clinicopathologic characteristics

The patients'clinicopathologic characteristics are shown in Table 1. There are no significant differences between the primary and validation cohorts in the clinicopathologic characteristics and in PLN metastasis prevalence (38.81% and 24.17% in the primary and validation cohort, P = 0.165).

3.2. Feature extraction and selection

2092 radiomics features were extracted from T2WI and DWI, of which 1046 features were from T2WI and the remaining 1046 were from DWI. We selected features according to their coefficients in the LASSO logistic regression model (Fig.2). The result of feature selection is summarized in the Supplementary Table S1.

3.3. Performance of the radiomics signature

The radiomics signature calculation formula and histograms are shown in the Supplementary (Fig.S1A–S1B). There is a significant difference in radiomics signatures between PLN-positive and PLN-negative patients in the primary cohort ($p < 0.01$) and validation cohort ($p < 0.01$) (Table S2), which indicates the radiomics signatures are related to the PLN metastasis status.

The SVM model was constructed using the radiomics signature in the primary cohort. For T2WI, DWI and joint T2WI and DWI, the radiomics signature yielded an AUC of 0.816(95% CI, 0.716-0.916), 0.830(95% CI, 0.732-0.928) and 0.893(95% CI, 0.817-0.970) respectively in the primary cohort, and 0.844(95% CI, 0.702-0.987), 0.870(95% CI, 0.733–1) and 0.909(95% CI, 0.801–1) respectively in the validation cohort. This shows that the radiomics signature derived from the joint T2WI and DWI has a greater performance than did the radiomics signatures from T2WI or DWI alone. The ROC curves are shown in Fig.3.

3.4. Performance of the nomograms

We developed a radiomics nomogram integrating the optimal radiomics signature from the joint T2WI and DWI with the following clinicopathologic information: age, histopathological grade and MRI-reported PLN status in the primary cohort. For comparison, a clinical nomogram based on clinicopathologic predictors was also built.

The radiomics and clinical nomograms yielded a C-index of 0.893(95% CI, 0.817-0.969) and 0.616(95% CI, 0.468-0.764) respectively in the primary cohort, 0.922(95% CI, 0.825–1) and 0.799(95% CI, 0.599-0.998) respectively in the validation cohort. The nomograms and calibration curves are shown in Fig.4 and Fig.5. The radiomics nomogram shows a significant improvement over the clinical

Table 1
Patients' characteristics in the primary and validation cohorts.

Characteristic	PLN Metastasis(+)		P	PLN Metastasis(-)		P
	Primary Cohort	Validation Cohort		Primary Cohort	Validation Cohort	
Age(years)			0.165			0.539
Mean±SD	48.73±10.20	42.29 ± 12.30		51.49±9.21	49.77±12.62	
≤45	11(33.33%)	4(12.12%)		11(17.46%)	8 (12.70%)	
>45	15(45.45%)	3(9.09%)		30(47.62%)	14 (22.22%)	
Pathological grade			0.568			0.102
I	9 (27.27%)	3(9.09%)		10 (15.87%)	4 (6.35%)	
II	15 (45.45%)	3(9.09%)		25 (39.68%)	18 (28.57%)	
III	2 (6.06%)	1(3.03%)		6(9.52%)	0	
MRI-reported PLN metastasis			0.642			0.966
LN negative	8(24.24%)	1(3.03%)		17(26.98%)	9 (14.29%)	
LN positive	18(54.55%)	6(18.18%)		24(38.91%)	13 (20.63%)	
Radiomics Signature(mean(SD))						
T2WI	0.004 (0.370)	0.023(0.423)	0.537	−0.805(0.470)	−0.677(0.521)	0.491
DWI	−0.246 (0.169)	−0.225(0.185)	0.758	−0.607(0.311)	−0.622(0.326)	0.812
T2WI&DWI	−0.220(0.155)	−0.206(0.187)	0.837	−0.625(0.308)	−0.625(0.301)	0.965

NOTE: Age: patient's age when they the diagnosis of ECC was confirmed by radiologist. Pathological grade: patients' tumor differentiated grade (I represents poorly differentiated tumor, II represents moderate differentiated tumor, III represents high differentiated tumor). MRI-reported PLN metastasis status: diagnosed by a radiologist according to patient's MRI manifestations.

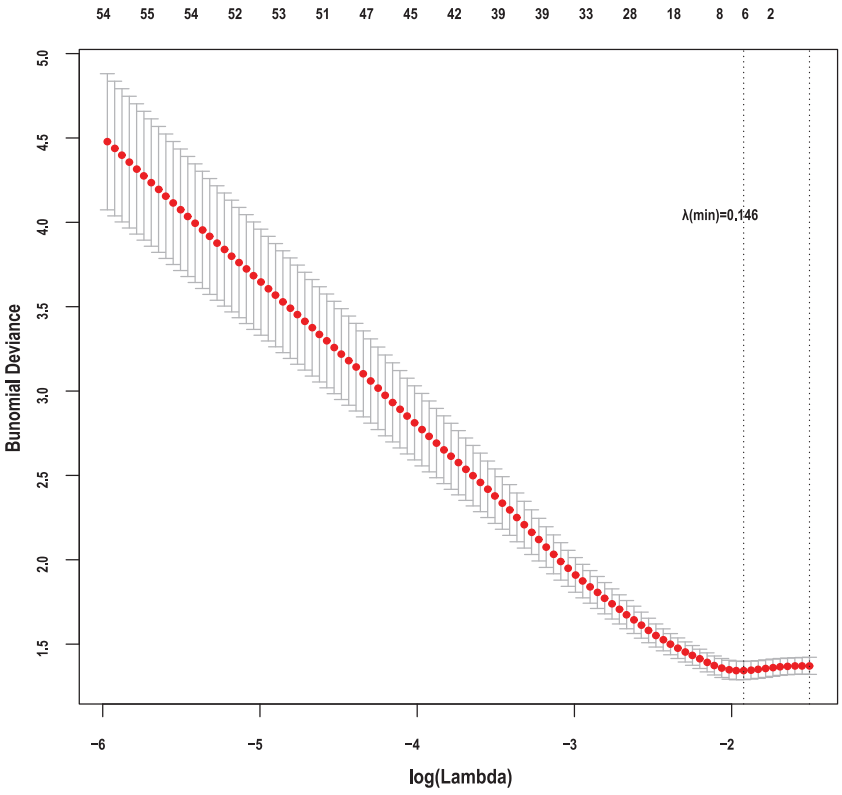

Fig. 2. Radiomics features selection using the least absolute shrinkage and selection operator (LASSO) regression method. Identification of the optimal penalization coefficient lambda (λ) in the LASSO model used 10-fold cross-validation and the minimum criterion. As a result, a λ value of 0.146, with log (λ) = -0.836 was selected.

nomogram and also shows a better agreement between the prediction and observation than the clinical nomogram does. The H–L test showed a nonsignificant statistic (P = 0.680 and P = 0.089 for radiomics nomogram and clinical nomogram, respectively). This demonstrates that there is no significant deviation between the calibration curve and a perfect fit for predicting PLN metastasis.

4. Discussion

In this study, a noninvasive radiomics model based on the clinicopathologic factors and radiomics signature that reflects primary tumour characteristics information was proposed for preoperatively predicting PLN metastasis in ECC. Our results demonstrated that the radiomics signature from the combined T2WI and DWI outperformed the radiomics signature from either the T2WI or DWI alone. Meanwhile, the radiomics nomogram integrating the radiomics signature and the clinicopathological factors improved significantly in predicting the PLN metastasis when compared with the clinical nomogram based only on clincopathological factors.

The performance of a radiomics signature for PLN metastasis prediction was assessed by the AUC of the SVM model. Our results showed that the radiomics signature from the joint T2WI and DWI performed better than did the radiomics signatures from T2WI or DWI alone in predicting the PLN metastasis status. First, T2WI can provide more detailed tumour anatomical characteristics because of its excellent contrast resolution in soft tissue. Then, as a functional imaging technique, DWI enables the noninvasive characterization of biological tissues based on the random translational molecular motion of water molecules [14–16]. Textural features from DWI have been proven to be useful for predicting lymph node metastasis in cervical cancer [12]. Therefore, the features extracted from the combination of T2WI and DWI could take full advantages of one another and reflect much more detailed and comprehensive information about the tumours. Accordingly, the radiomics signature based on the joint T2WI and DWI could provide a more accurate prediction of PLN metastasis.

To develop a visualized and quantitative tool that is convenient for clinical use, we constructed nomograms based on the models built by the multivariate logistic regression method. A radiomics nomogram was constructed by integrating the radiomics signature derived from joint T2WI and DWI which showed the best performance for PLN metastasis prediction in the clinical nomogram incorporating only clinicopathological factors. Age, histopathological grade and MRI-reported PLN metastasis status were chosen as the clinicopathological factors for nomograms. Kim et al. constructed a nomogram based on a multivariate logistic model incorporating age, tumour size assessed by MRI, and PLN metastases reported by PET/CT which exhibited a robust prediction of PLN metastases in early-stage cervical cancer [17]. Although their nomogram demonstrated a good discrimination (C-index: 0.878; 95% CI: 0.833-0.917 in the primary cohort and a C-index of 0.825, 95% CI, 0.736-0.895 in the validation cohort), PET/CT was not widely used due to its high cost and radiation. In our study, the clinical nomogram yielded a C-index of 0.616 (95% CI, 0.468-0.764) and 0.799 (95% CI, 0.599-0.998) in the primary and validation cohort, whereas the radiomics nomogram yielded a C-index of 0.893 (95% CI, 0.817-0.969) and 0.922 (95% CI, 0.825–1) in the primary and validation cohort. Obviously the radiomics nomogram exhibits a significant improvement in performance for predicting PLN metastasis compared with the clinical nomogram. Moreover, the radiomics nomogram we proposed can also achieve a comparable discrimination performance with the nomogram constructed by Kim et al. One reason might be that clinicopathological characteristics reflect the qualitative and rough features of tumours and inevitably involves the subjective judgement of the clinician to patients, whereas radiomics features comprise the quantitative and detailed information in multi-dimension and could reflect the heterogeneity and biological behaviour of tumours, thus the evaluation obtained based on radiomics features would be more objective and accurate.

Risk factors for lymph node metastasis include lymphovascular invasion, depth of invasion, parametrial involvement, and age [2]. However, lymphovascular invasion, depth of invasion, and parametrial involvement can only be acquired from postoperative pathohistological examination, they cannot be used as guidance for preoperative decision-making [18]. Additionally, all clinicopathological factors we used

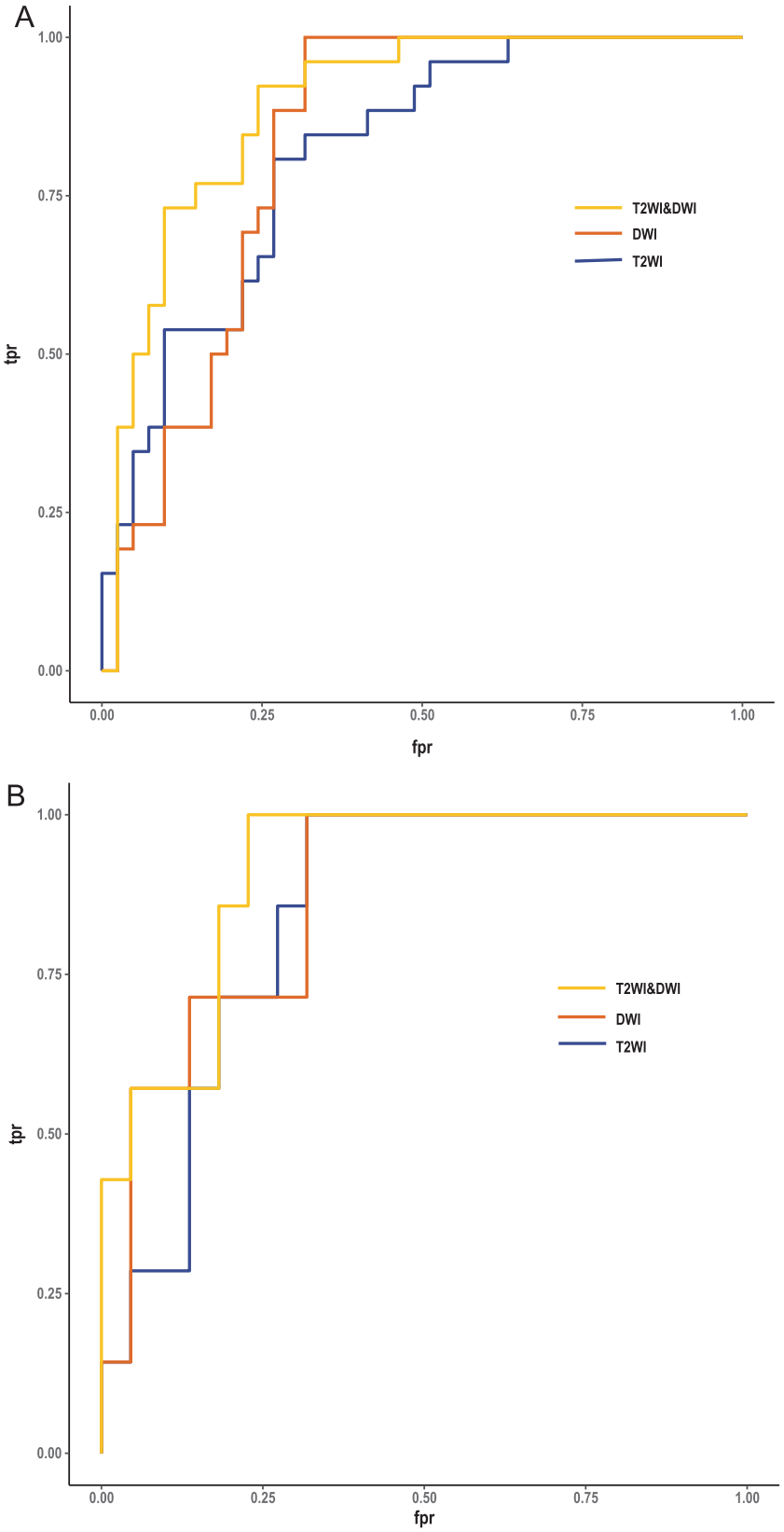

Fig. 3. ROC curves of SVM models for radiomics signatures from T2WI, DWI, joint of T2WI and DWI, respectively.
A. ROC curves in the primary cohort.
B. ROC curves in the validation cohort.

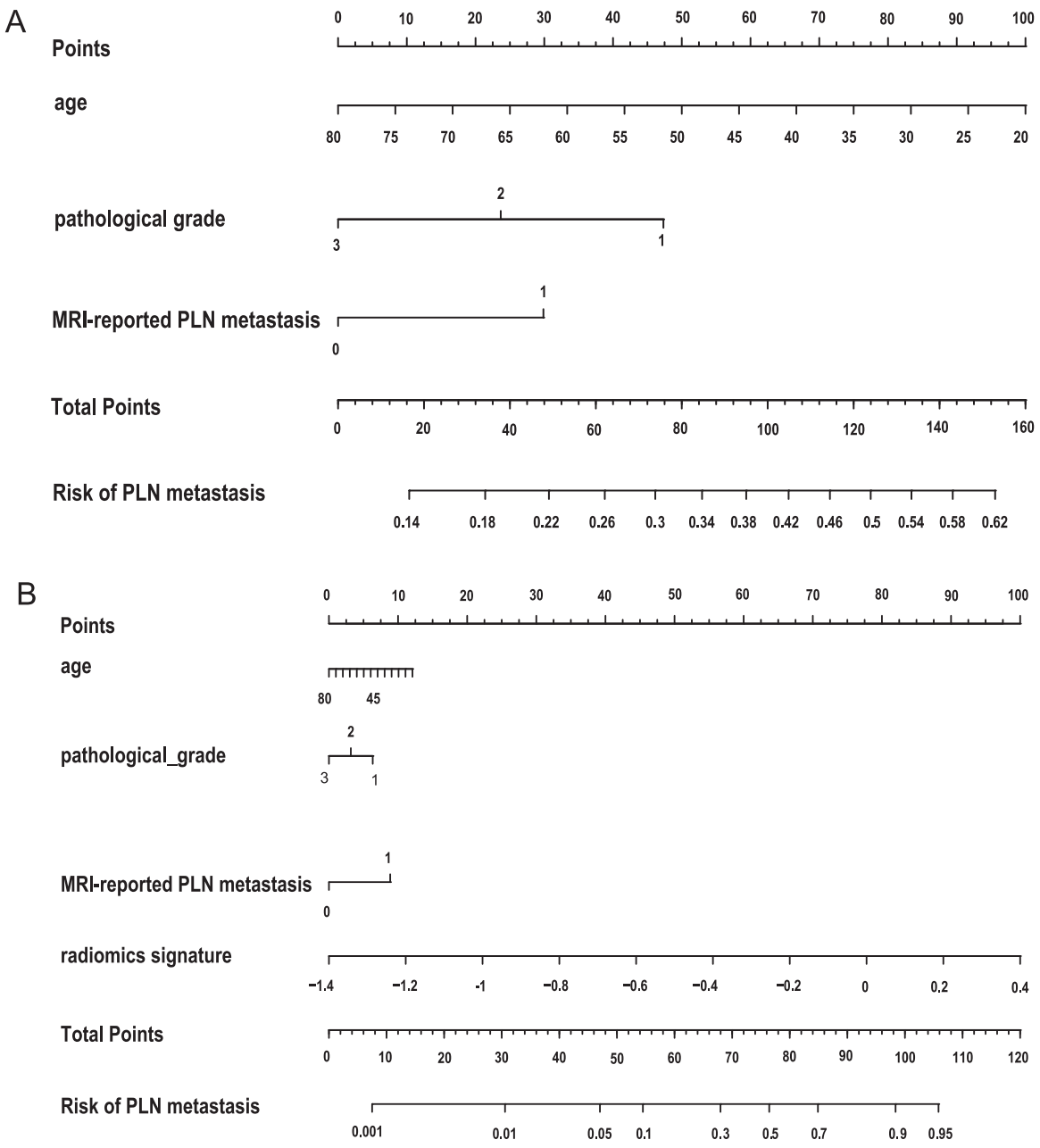

Fig. 4. Nomograms developed based on the clinical and radiomics model.
A. The clinical nomogram integrated only clinicopathological factors.
B. The radiomics nomogram integrated clinicopathological factors with the radiomics signature from joint T2WI and DWI.

for radiomics model construction can be conveniently collected preoperatively. The histopathological grade is also an important risk factor for the PLN metastasis of cervical cancer [12]. A previous study suggested that high PLN metastasis risk was correlated with a poorly differentiated tumour, and this relationship is also shown in our nomograms.

Currently, PLND is the standard criterion that evaluates the lymph nodal status of cervical cancer. Nonetheless, PLND would lead to an increase in operation time and it is also associated with some severe short- and long-term complications [19]. Thus, many clinicians consider whether PLND should be performed for patients with a low risk of PLN metastasis [17–19]. In addition, SLN biopsy as an alternative and a less invasive approach for detecting PLN metastasis is not routinely performed, because it is an intra-operative approach dependent on pathological evaluation and its operation procedure standard and performances are still full of controversy, such as whether to perform a bilateral or per pelvis side detection should depend on the actual condition of the patients. Recently, Gabriella et al. provided an answer to the question of whether the risk of lymph node metastasis in early-stage cervical cancer patients could be defined to enable these patients to avoid any lymph nodal procedure, including SLN biopsy. Their conclusion was to define the precise risk of lymph node metastasis [3].

In recent years, radiomics has been proven to be able to predict the lymph node metastasis for the patients with cancer on the basis of quantitative image features derived from routine medical imaging [8–10]. Recently, Kan et al. has published an article about using radiomics method for prediction of lymph node metastasis in ECC and obtained a good result [20]. Though their article investigated the same topic as our study did, there are still many differences in details between their study and ours. Firstly, we used different MRI sequences to extract the radiomics features and our radiomics signature based on joint T2WI and DWI yielded a higher AUC in both primary (0.893 vs

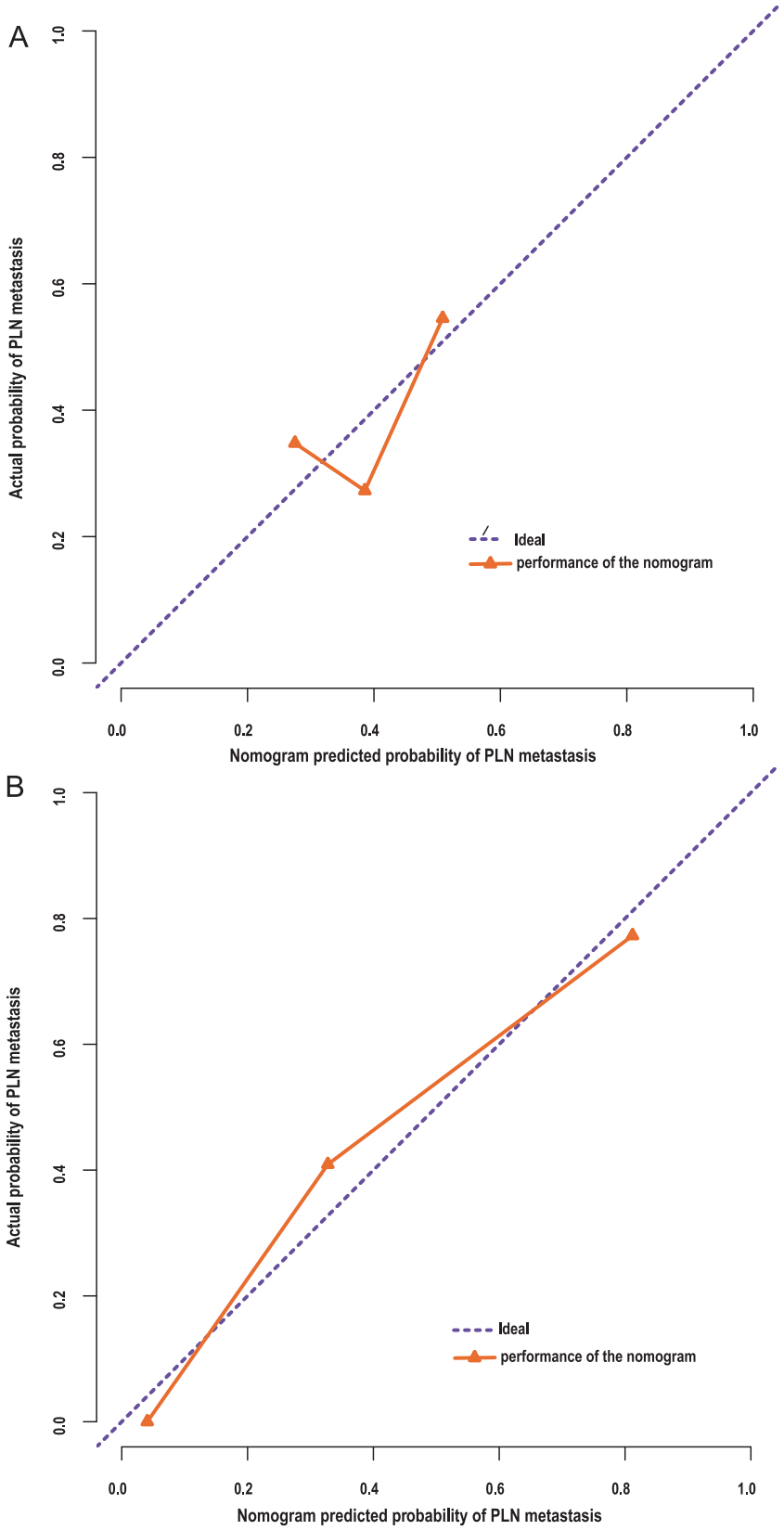

Fig. 5. Calibration curves of nomograms in the primary cohort. The y axis reflects the actual probability of PLN metastasis. The x axis reflects the predicted probability of PLN metastasis generated from nomogram. The diagonal blue dotted line represents a perfect prediction generated by an ideal model. The red solid line represents the actual prediction derived from our model.
A. The calibration curve of clinical nomogram based on the clinical model.
B. The calibration curve of radiomics nomogram based on the radiomics model.

0.753) and validation (0.909 vs 0.754) cohorts than their radiomics signature based on joint T1 contract-enhanced and T2 MRI did. Secondly, we not only built radiomics signatures based on different MRI sequences and their combination but also compared their performance for PLN metastasis prediction and found that a mixing radiomics signature would have a better performance. Thirdly, the clinicopathological factors we collected in our study are more relative to the PLN metastasis. Furthermore, we also constructed a radiomics nomogram comprised of high-dimensional MRI features and clinicopathological risk factors which demonstrated a good discrimination and calibration for predicting PLN metastasis in patients with ECC. This radiomics nomogram provided an individualized and easy-to-use tool for the preoperative prediction of PLN metastasis.

Differing from traditional methods, radiomics nomogram offers a noninvasive and low-cost method for the clinical use of assessing the risk of lymph node metastasis before surgery and helping clinicians make optimal surgery decisions for patients. In addition, accurate preoperative detection of PLN metastasis using conventional imaging (such as CT or MRI scans) is still a challenge for clinical devices. CT and MRI have the same limitation in detecting lymph node metastasis; the only recognized criterion for diagnosing lymph node metastasis is that the shortest axis of the lymph node is greater than 1 cm, and this limitation can easily lead to some missed diagnosis of lymph node micrometastasis. With the radiomics method, we could do away with this limitation by extracting information of the lymph node metastasis from the tumour imaging analysis.

This study has several limitations. Obviously, this is a retrospective study with a small sample size, so there is still a need for more patients to provide more reliable evidence for clinical application. Additionally, the data of the radiomics model established and validated in our study were all from the same hospital in China, so an external validation is required for the model. Finally, the association between features we extracted from the MRIs and some important proteins and genes biomarkers for lymph node metastasis of cervical cancer were not considered [21,22].

In conclusion, we developed and validated an effective and easy-to-use radiomics model based on T2WI and DWI for the preoperative prediction of PLN metastasis in patients with early-stage cervical cancer. This new approach provides a noninvasive and reliable tool to help make individualized treatment planning in patients with early-stage cervical cancer.

Conflict-of-interest disclosure

All authors declare no competing financial interests related to the present work

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejrad.2019.01.003.

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