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ORIGINAL RESEARCH

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Prediction of parametrial invasion of early cervical squamous cell carcinoma: combining apparent diffusion coefficient and greatest primary lesion dimension with hematological variables

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Abstract

Background: Cervical cancer is the fourth most common malignant tumor in women, with cervical squamous cell carcinoma (CSCA) being the most prevalent subtype. Parametrial invasion (PMI) significantly impacts treatment decisions for CSCA patients. Current methods for predicting PMI rely on postoperative histopathological evaluation, which may delay optimal therapy. Combining imaging and hematological markers could improve preoperative risk stratification. **Methods**: This retrospective study included 134 patients with early stage CSCA who underwent 3.0 T magnetic resonance imaging (MRI) and preoperative hematological examination. We assessed the apparent diffusion coefficient (ADC) value, greatest tumor dimension, squamous cell carcinoma antigen (SCC-Ag) level, neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR). Patients were categorized into PMI-positive (n = 22) and PMI-negative (n = 112) groups based on postoperative findings. Receiver operating characteristic (ROC) curves evaluated individual and combined parameters for predicting PMI. **Results**: Among the 134 patients, PMI was detected in 22 cases, which represented 16.42% of the total population. The ADC value in the PMI-positive group was lower than that in the PMI-negative group, while the greatest dimension and the median SCC-Ag values were higher in the PMI-positive group than in the PMI-negative group. However, there was no significant difference in NLR or PLR between the two groups. The areas under the curve for ADC, greatest dimension, SCC-Ag level, and all three parameters combined were 0.787, 0.765, 0.673 and 0.880, respectively, for predicting PMI. **Conclusions**: Combining ADC, greatest dimension, and SCC-Ag provides superior accuracy for predicting PMI in early CSCA. This multimodal approach may enable preoperative risk assessment, potentially guiding individualized treatment strategies and reducing unnecessary costs.

Keywords

Cervical squamous cell carcinoma; Greatest dimension; Diffusion-weighted imaging; Apparent diffusion coefficient; Parametrial invasion; Squamous cell carcinoma antigen

1. Introduction

Cervical cancer is the fourth most common malignant tumor in women and poses a serious threat to the life and health of women worldwide [1]. Cervical squamous cell carcinoma (CSCA) is the most common type of cervical cancer [2]. The prognosis of CSCA is related to tumor stage, and parametrial invasion (PMI) is one of the most important factors considered in the pretreatment evaluation of patients with CSCA. PMI is usually associated with the recurrence and poor prognosis of CSCA [3, 4]. Patients who do not have PMI can opt for less radical surgery and avoid the related perioperative and postoperative complications, while those with evidence of PMI are usually treated with primary chemoradiotherapy or adjuvant treatment after surgery [5, 6]. The staging system of the International Federation of Gynecology and Obstetrics (FIGO) is used for clinical staging of cervical cancer before treatment decisions are made, but in some early cases, PMI may be detected in postoperative pathological examinations. Therefore, it is important to accurately determine the presence of PMI before surgery for making appropriate treatment decisions [7].

Magnetic resonance imaging (MRI) has the advantages of high soft tissue resolution and multi-directional, multi-sequence imaging. In recent years, it has become the main imaging method for preoperative pelvic examination of

cervical cancer. Routine MRI is the most widely used MRI technique, but its ability to evaluate PMI is limited [8]. Diffusion weighted imaging (DWI) is currently the only functional imaging technology that can be used to noninvasively examine living tissues. Its quantitative parameter apparent diffusion coefficient (ADC) provides a measure of the diffusion limitation of water molecules, and previous studies have shown that the ADC value can predict and be used to evaluate the degree of tumor differentiation, invasiveness and even staging of malignant tumors [9–11]. Further, several studies [12, 13] have shown that patients with cervical cancer who are positive for PMI have lower ADC values than those without PMI. Previous studies [14, 15] have also shown that the length and diameter of cervical tumors are related to PMI and the prognosis of cervical cancer. Further, the greatest lesion dimension was found to be an independent predictor of PMI [16]. Therefore, the greatest tumor dimension could act as an indirect marker of the potential risk of PMI in cervical cancer [17]. The greatest tumor dimension can be easily determined by routine MRI and DWI for more accurate evaluation of PMI [18]. In addition to these imaging parameters, squamous cell carcinoma antigen (SCC-Ag) and routine blood parameters can also reflect tumor characteristics, and these parameters are assessed through routine hematological examinations performed before surgery for CSCA. In particular, SCC-Ag is a type of antigen detected in CSCA that is related to the occurrence and development of squamous cell carcinoma [19, 20]. The SCC-Ag level reflects the invasiveness of squamous cell carcinoma, to a certain extent, and is related to the prognosis of cervical cancer. Moreover, it is considered to be valuable for auxiliary diagnosis, clinical efficacy evaluation, and prediction of the recurrence and metastasis of CSCA [21]. Many studies have reported reference values of SCC-Ag for the early diagnosis, PMI, lymph node metastasis and prognostic evaluation of CSCA [22, 23]. In addition, studies have found that inflammatory indicators, such as the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR), can also reflect the invasive characteristics of tumors [24, 25]. While there is some research on indicators of PMI in CSCA, there are few studies that combine routine MRI and DWI with hematological indicators for the preoperative evaluation of CSCA, especially for the prediction of PMI [5, 26]. Therefore, the present study sought to contribute to the research on topic by combining routine MRI and DWI with hematological indicators and evaluating their ability, when applied alone and in combination, to predict PMI in early-stage CSCA.

2. Materials and methods

2.1 Patient selection

MRI examination and clinical data from patients with early-stage CSCA who underwent surgery at our hospital between August 2014 and September 2022 were retrospectively analyzed. The inclusion criteria of this study were: (1) routine MRI and DWI performed within 2 weeks before surgery, (2) radical hysterectomy with complete surgical and pathological results indicative of squamous cell carcinoma, and (3) complete preoperative SCC-Ag and routine blood examination data. The exclusion criteria were (1) history of treatment before MRI examination, (2) postoperative pathological findings that were not indicative of CSCA, (3) preoperative history of blood transfusion or infection, and (4) the presence of image artifacts that affected observation and measurement, including an extremely small lesion with a maximum area of <0.5 cm^2, or the inability to accurately delineate a region of interest (ROI). The patients were divided into PMI-positive and PMI-negative groups on the basis of the presence or absence of PMI after surgery.

2.2 MRI protocol

MRI was performed using a 3.0 T scanner (Ingenia 3.0 T, Philips Healthcare) with a 16-channel pelvic phased-array coil. The sequences included axial T_1WI, sagittal T_2WI, coronal T_2WI, axial T_2WI, and axial DWI (b-values: 0, 800/mm^2). The main scanning parameter was a repetition time/echo time ratio (TR/TE) of 645 ms/17 ms for T_1WI, 4420–4730 ms/70–90 ms for T_2WI, and 2750 ms/80 ms for DWI. Scanning or reconstruction was performed at a slice thickness of 4 mm and an interval of 1 mm (intersection gap).

All patients were required to fast for at least 6 h before imaging and keep their bladder moderately filled before the examination. Intestinal preparation was performed as required, and drugs for the inhibition of intestinal peristalsis were injected intramuscularly 30 min before scanning. During the examination, the patients were placed in the supine position and asked to maintain a normal, calm breathing rhythm.

2.3 Image analysis

All images were imported into the random built-in Intellispace Portal workstation, and ADC maps were acquired using DWI images. Two observers with 10 and 6 years of experience in pelvic MRI, who were blinded to the pathological and clinical information of the patients, delineated ROIs on the ADC maps in accordance with the following principles. (1) The largest three slices of the lesion were selected for establishing the ROIs, and the lesion was delineated carefully by referring to the T_2WI scans (Fig. 1A,B) and high b-value DWI scans (Fig. 1C). (2) The ROIs were placed as close as possible to the center of the lesion, with uniform signals in each sequence, and for small lesions, the ROI was drawn 5 mm along the medial edge of the lesion to avoid the partial volume effect (Fig. 1D). (3) ROI delineation was performed with careful visualization of multiple sequences and complete avoidance or rejection of residual normal cervical tissue, cervical canal mucosa within the lesion, and areas of intralesional hemorrhage, necrosis or cystic change. (4) ROI delineation was performed while avoiding artifacts related to various causes. Measurements for each enrolled case were determined three times, and the average value was considered the final ADC value for that lesion (Fig. 1D). The greatest dimension of the lesion was obtained by measuring the diameter after coronal, sagittal and axial multi-directional and multisequence observation, and the mean value calculated after three consecutive measurements was considered the final result (Fig. 1A,B).

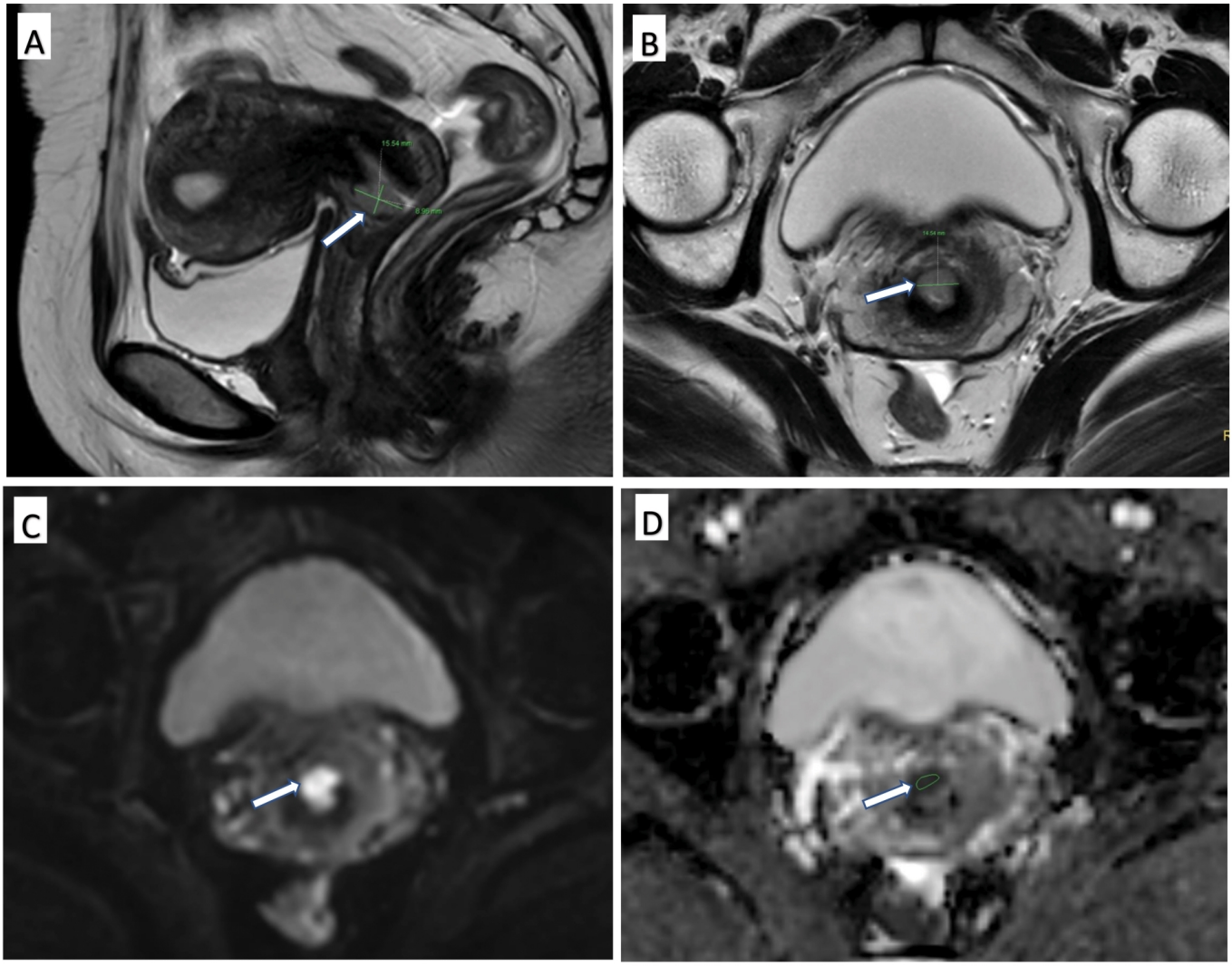

FIGURE 1. Delineation of ROIs and measurement of the greatest dimension. MRI scans of a 58-year-old woman showing moderately differentiated squamous cell carcinoma negative for PMI. The tumor (white arrow) showed a slightly hyperintense signal on sagittal T_2WI (A) and axial T_2WI (B), and the corresponding axial DWI (C) and ADC maps (D) showed high- and low-intensity signals, respectively. The green lines indicate the tumor diameters in different planes, and the largest value in each plane was recorded as the greatest dimension. ROIs were drawn with reference to DWI and other sequences and on ADC maps (D) (ROI: region of interest).

2.4 Acquisition of the results of hematological examination

Peripheral venous blood samples in the fasting state were routinely collected before surgery from all the enrolled patients, and the hematological specimens were sent to the laboratory center of our hospital for SCC-Ag and routine blood examination. The SCC-Ag level was calculated according to the final test results (unit: ng/mL). NLR and PLR, the inflammatory indicators derived from routine blood examination, were calculated using the following formulae.

NLR = absolute value of neutrophils (N)/absolute value of lymphocytes (L).

PLR = absolute value of platelets (P)/absolute value of lymphocytes (L).

2.5 Statistical analysis

SPSS (version 19.0; IBM SPSS, Chicago, IL, USA) and MedCalc (version 19.0.4; MedCalc Software Ltd., Ostend, Belgium) were used for data analysis. The intra-group correlation coefficient (ICC) value was used to test the consistency of the ADC values and the greatest dimension measured by the two observers, and data with ICC >0.75 were averaged. The Kolmogorov-Smirnov test was used to compare data between the PMI-negative and PMI-positive groups. The data for age, body mass index (BMI), ADC and greatest dimension of the tumor were normally distributed and were, therefore, presented as the mean and standard deviation. An independent samples *t*-test was used for comparison of these normally distributed variables between the two groups. The SCC-Ag level, NLR and PLR data were not normally distributed and were, therefore, presented as median values. Accordingly, the Mann-Whitney U-test was used to compare these variables between the two groups. Qualitative variables, such as degree of

differentiation, family history of tumor, menstrual status, depth of interstitial invasion, lymph node metastasis, and vaginal resection margin, were compared between the PMI-positive and PMI-negative groups using the chi-squared test. Logistic regression analysis was used to build a combined diagnostic model comprising ADC, the greatest lesion dimension, and SCC-Ag level. Logistic regression was used for multivariate analysis of predictive factors. A receiver operating characteristic (ROC) curve was used to analyze the performance of these different parameters, and the DeLong test was used to assess differences in the predictive performance of the ROC curves of the parameters (based on the area under the curve (AUC)). $p < 0.05$ was considered to indicate statistical significance.

3. Results

3.1 Participant characteristics

This study initially included 284 patients, but 150 were excluded based on the inclusion and exclusion criteria. Fig. 2 presents a flowchart depicting the selection of participants for this study. The study ultimately included 134 patients. Their average age was 50.76 ± 10.73 years, and it ranged from 23 to 78 years. According to the FIGO 2018 staging system, the patients were divided into the following preoperative clinical stages: IB1, 24 cases; IB2, 45 cases; IB3, 21 cases; IIA1, 24 cases; and IIA2, 20 cases. Surgical specimens were routinely obtained after surgery and confirmed by pathological evaluation. Among the 134 cases, PMI was detected in 22 cases, which corresponded to 16.42% of the study population.

3.2 Inter-observer agreement

The ICCs of the ADC values and greatest dimensions measured by the two observers indicated excellent inter-observer agreement ($p < 0.001$), as the ICC values were above 0.75 for both ADC (ICC = 0.857) and greatest lesion dimension (ICC = 0.977). Therefore, the average of the values measured by the two observers was used for further analysis, as shown in Table 1.

3.3 Comparison of quantitative data

Statistical analysis of differences in the normally distributed variables ADC, greatest lesion dimension, age and BMI between the PMI-positive and PMI-negative groups revealed significant differences in ADC and greatest lesion dimension but not in age or BMI (first four rows of Table 2). Further, statistical analysis of differences in the non-normally distributed parameters SCC-Ag, NLR and PLR demonstrated that there were significant differences only in SCC-Ag, but not in NLR or PLR, between the two groups (last three rows of Table 2).

3.4 Comparison of qualitative data

The chi-squared test showed that there were no significant differences in family history of tumor or menstrual status between the PMI-positive and PMI-negative groups, but the degree of differentiation, stromal invasion depth, PMI and vaginal margin differed significantly between the two groups (Table 3).

3.5 Comparison of predictive ability based on AUC

AUC values were determined from the ROC curve for each of the significant parameters (that is, ACD, greatest lesion dimension, and SCC-Ag), individually and in combination, in order to determine their ability to predict PMI. The AUC value was the highest when all three significant parameters were combined (Fig. 3). The results of the DeLong test showed that the AUC of the combination of parameters for predicting PMI was significantly different from the AUC of ADC, the greatest tumor dimension, and SCC-Ag alone (AUC_{ADC} *vs.* $AUC_{combined\ diagnosis}$: $p = 0.0076$, $z = 2.669$; $AUC_{greatest\ dimension}$ *vs.* $AUC_{combined\ diagnosis}$: $p = 0.0258$, $z = 2.229$; AUC_{SCC-Ag} *vs.* $AUC_{combined\ diagnosis}$: $p = 0.0024$, $z = 3.034$).

4. Discussion

In this study, we have designed a diagnostic model for detecting PMI in CSCA that is easy to implement and cost-effective. This model combines imaging measurements of ADC and the greatest dimension of the primary lesion with SCC-Ag levels determined via hematological examination, and it significantly improves the possibility of diagnosing PMI preoperatively. While ADC, greatest lesion dimension, and SCC-Ag level were significantly different between the PMI-positive and PMI-negative groups, the inflammatory indices NLR and PLR were not significantly different (although they showed some degree of difference). In addition, this study found that PMI was not related to age, BMI, family history of tumor, or menstrual status, but it may be related to histological grade, lymph node metastasis, depth of cervical stromal invasion, and vaginal resection margin, as also reported in previous studies [27, 28]. However, most of these indicators are related to pathological evaluation, which is usually difficult to perform before surgery. Therefore, their application for the preoperative diagnosis of PMI is limited. This limitation can be overcome by using the tool presented in this study, as it is a noninvasive method that includes routinely performed imaging and laboratory tests.

We used 3.0 T MR to explore the diagnostic value of DWI in evaluating PMI of CSCA. The results are consistent with previous research results [12, 13] and confirm the value of ADC for the prediction of PMI. In addition, the results for the association of the greatest lesion dimension with PMI of cervical cancer were also consistent with previous findings [16], and the greatest dimension was found to have diagnostic value for the detection of PMI. Zhang *et al.* [29] demonstrated that tumor volume can be used as a marker of high-risk patients and could be an indication for initial chemotherapy for early malignant cancer [18]. However, from the viewpoint of practical application, it is easier to measure the greatest dimension of the tumor than to measure tumor volume. Moreover, greatest dimension measurements have better consistency and repeatability. Apart from these imaging factors, SCC-Ag was also found to be related to PMI in CSCA, as significant differences in the SCC-Ag level were found between PMI-positive and PMI-negative patients.

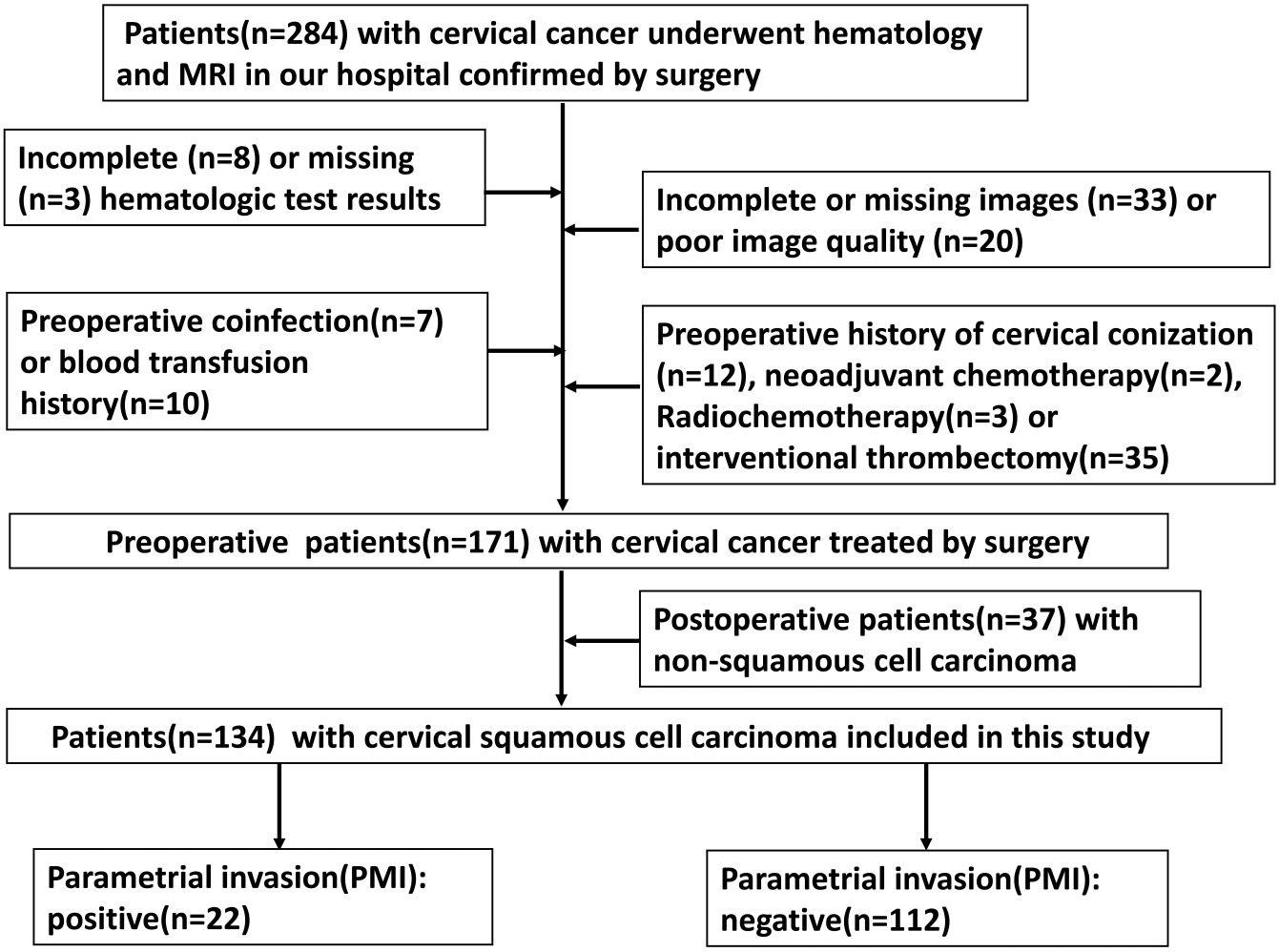

FIGURE 2. Flow chart depicting the participant selection process.

TABLE 1. ICC values indicating inter-observer reproducibility.

	Observer 1	Observer 2	ICC	95% CI
ADC ($\times 10^{-6}$ mm^2/s)	847.94 ± 94.00	848.02 ± 107.00	0.857	0.805–0.897
Greatest dimension (cm)	3.50 ± 1.49	3.51 ± 1.48	0.977	0.967–0.983

ADC: apparent diffusion coefficient; ICC: intra-group correlation coefficient; CI: confidence interval.

TABLE 2. Comparison of quantitative data between PMI-positive and PMI-negative patients.

Parameter	PMI-negative patients (n = 112)	PMI-positive patients (n = 22)	*t*/*z* value*	*p*
Age (yr)	50.07 ± 10.80	52.41 ± 10.36	0.934	0.352
BMI	23.21 ± 3.11	24.32 ± 2.59	1.562	0.121
ADC ($\times 10^{-6}$ mm^2/s)	862.46 ± 96.00	771.05 ± 73.00	−4.210	<0.001
Greatest dimension (cm)	3.27 ± 1.35	4.69 ± 1.56	4.387	<0.001
SCC-Ag (ng/mL)	2.43	6.65	−2.559	0.010
NLR	2.55	3.00	−1.309	0.190
PLR	144.31	158.81	−1.237	0.216

**Note: The first four rows contain t values, while the last three rows contain z values. PMI: Parametrial invasion; BMI: body mass index; ADC: apparent diffusion coefficient; SCC-Ag: squamous cell carcinoma antigen; NLR: neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio.*

TABLE 3. Comparison of qualitative data between PMI-positive and PMI-negative patients.

Parameters	PMI-negative patients (n = 112)	PMI-positive patients (n = 22)	χ^2	*p*
Degree of differentiation				
G1	9	1		
G2	81	10	9.136	0.010
G3	22	11		
Family history of tumor				
Yes	14	0	3.071	0.080
No	98	22		
Menstrual status				
Yes	57	10	0.218	0.641
No	55	12		
Stromal invasion depth				
<1/2	39	0	10.806	0.001
≥1/2	73	22		
Lymph node metastasis				
Positive	34	12	4.772	0.029
Negative	78	10		
Vaginal margin				
Positive	5	4	5.523	0.019
Negative	107	18		

PMI: Parametrial invasion.

A

Parameters	AUC	95% CI	Sensitivity	Specificity
ADC	0.787	0.708 - 0.853	86.36%	66.07%
Greatest dimension	0.765	0.684 - 0.834	95.45%	48.21%
SCC-Ag	0.673	0.587 - 0.751	63.64%	76.79%
Combined diagnosis	0.880	0.812 - 0.930	72.73%	91.96%

B

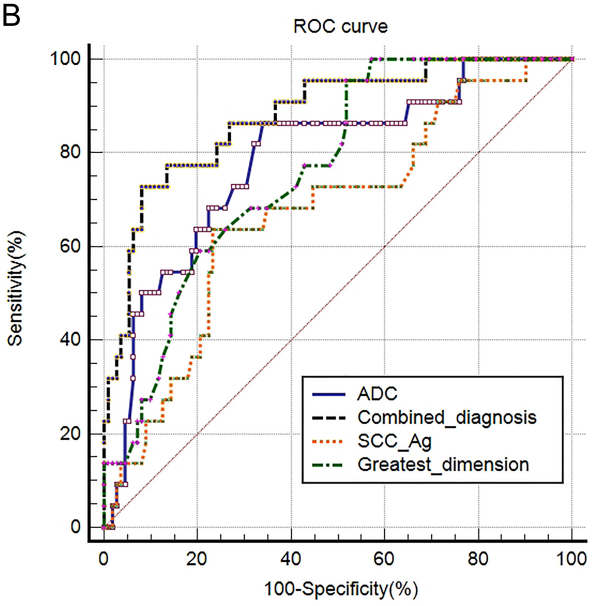

FIGURE 3. Analysis of the predictive ability of ADC, greatest tumor dimension, and SCC-Ag, alone and in combination, for the diagnosis of PMI. (A) AUC, 95% CI, sensitivity and specificity; (B) ROC curves of ADC, greatest dimension, SCC-Ag, and all three parameters combined. AUC: area under curve; ROC: receiver operating characteristic; ADC: apparent diffusion coefficient; SCC-Ag: squamous cell carcinoma antigen; CI: confidence interval.

These findings were also in agreement with previous findings on SCC-Ag and PMI [22, 23]. In addition to these three parameters, abnormalities in NLR and PLR [24, 30] have also been reported in patients with CSCA. However, in contrast to these previous findings, the present study did not find any obvious differences in NLR or PLR between PMI-positive and PMI-negative patients. A possible explanation could be that all the patients included in this study had early-stage CSCA. In addition, other differences in patient populations and research methodologies could also explain the differences in the results.

Plain MRI, DWI and hematological examination of SCC-Ag and routine blood parameters have become the standard preoperative measurements in patients with CSCA, and it is easy to obtain data on these parameters [31, 32]. Accordingly, given the ease of obtaining data on these parameters, we designed a model with known imaging and laboratory indicators of PMI in order to improve the preoperative prediction of PMI without the need for any additional examinations. Specifically, we selected three meaningful and significant indicators—ADC, greatest dimension, and SCC-Ag—to establish a prediction model that is relatively simple to operate in practice and does not significantly increase the workload of statistical analysis. We found that the AUC reached 0.880 when all three parameters were combined, and this value was higher than that of individual parameters. The preoperative prediction and evaluation of PMI in patients with early cervical cancer will enable more accurate determination of the preoperative stage and, thereby, better treatment decisions. In addition, this preoperative assessment method will reduce the economic burden on patients and the public healthcare system, help avoid unnecessary examinations, prevent drug side effects or damage, and significantly improve the efficiency of patient examination in hospitals [33, 34].

Our study has a few limitations that need to be mentioned. First, this was a single-center retrospective analysis, and the sample size was relatively small; in particular, only 22 patients had PMI, and this might not be adequate for detection of PMI predictors. Second, this study only included patients with CSCA, so it may not be suitable for patients with adenocarcinoma and other rare histological types of cervical cancer. Third, there are no standard ADC measurement methods, and the ADC value in this study was determined based on measurements of selected areas comprising the largest three layers that had uniform lesion signal. However, this approach may have led to one-sided evaluation of the overall lesion, so future studies should consider measuring the ADC value of the entire tumor volume. Despite these limitations, the diagnostic model proposed here has some advantages that need to be reiterated. Routine MRI and DWI imaging can be used to easily obtain the ADC value and the greatest dimension of the lesion, and they do not require the administration of contrast agents or additional sequences. Moreover, hematological examinations are also routinely conducted in hospitalized patients and are, therefore, easily available at many centers without additional investment or cost to patients. Thus, the integration and combined application of these easily obtained parameters have high value for clinical diagnosis, and in the future, these routine easily obtained parameters can be combined to conduct comprehensive preoperative evaluation of patients with cervical cancer, as well as related research on advanced cervical cancer.

5. Conclusions

The ADC value and greatest dimension of the primary lesion combined with hematological SCC-Ag measurements have high clinical value for the preoperative evaluation of early PMI in CSCA, but the diagnostic value of inflammatory indicators (NLR and PLR) is relatively limited. Importantly, using routine preoperative imaging methods, such as MRI and DWI, combined with SCC-Ag measurements, to evaluate PMI can reduce the economic burden on patients while improving diagnostic efficiency.

AVAILABILITY OF DATA AND MATERIALS

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

AUTHOR CONTRIBUTIONS

QQY and ZQM—established the study design, analyzed the data, and wrote the paper; BL and LHC—collected clinical data; QQY and JZ—participated in MRI data measurement and analysis; XYL—performed the statistical analysis. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Institutional Review Committee of Shaanxi Provincial People's Hospital reviewed and approved this study involving human participants (Approval Number: XYYJSLS2022043) and waived informed consent. The study was conducted in accordance with the principles of the Declaration of Helsinki.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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