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Original Research

Peripheral Blood Inflammation Indicators as Predictive Factors for Treatment Response Assessed by MRI in Cervical Cancer Patients Referred for Radiotherapy

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Abstract

Backgroud: Radiotherapy (RT) with or without concurrent chemotherapy is regarded as the standard therapy for locally advanced cervical cancer (International Federation of Gynecology and Obstetrics [FIGO] stage IB2 and above). However, markedly different responses to RT are seen among patients with similar FIGO stages.The study aimed to evaluate the peripheral blood inflammation indicators that may have predictive value for treatment response in cervical cancer patients referred for RT. **Methods**: This was a retrospective study that enrolled 75 patients who had stages IB2 to IVA cervical cancer, and who underwent RT alone or concurrent chemoradiation therapy (CCRT). All patients were treated at the department of Clinical Oncology of the University of Hong Kong-Shenzhen hospital between November 2015 and April 2020. The endpoint was treatment response assessed by magnetic resonance imaging (MRI) according to the Response EvaluationCriteria in Solid Tumors (RECIST). Multivariate logistic regression models were used to identify predicting values of peripheral blood inflammation indicators, including the systemic immune-inflammation index (SII), neutrophil/lymphocyte ratio (NLR), tumor-related leukocytosis (TRL), platelet/lymphocyte ratio (PLR) and monocyte/lymphocyte ratio (MLR). **Results**: The percentage of complete response (CR) was significantly different between different groups of peripheral blood inflammation indicators. The percentage of CR was 64.3%, 57.9%, 81.8% and 48.3% respectively in low SII, NLR, PLR and MLR groups, which was significantly higher than in the high SII group (34.0%), high NLR group (32.4%), high PLR group (30.2%) and high MLR group (35.3%). Multivariate logistic regression revealed that the TRL and PLR were significant prognostic factors for treatment response with an odds ratio of 0.18 (95% confidence interval [95% CI] 0.04–0.77) for TRL and 16.36 (95% CI 3.67–73.04) for PLR. **Conclusions**: The result revealed that a TRL-negative or lower PLR tumor was associated with radiosensitivity, which may provide important information for the prediction of treatment response in cervical cancer patients referred for RT.

Keywords: cervical cancer; radiotherapy; tumor-related leukocytosis; platelet/lymphocyte ratio; magnetic resonance imaging

1. Introduction

Worldwide, cervical cancer is the second most common cancer and third lethal cause of malignancy among women [1]. Radiotherapy (RT) with or without concurrent chemotherapy is regarded as the standard therapy for locally advanced cervical cancer (International Federation of Gynecology and Obstetrics [FIGO] stage IB2 and above) [2]. However, markedly different responses to RT are seen among patients with similar FIGO stages. After RT, the cervical mass in some patients markedly decreased disappeared. However, in other patients, the mass either did not shrink or increase in bulk suggesting resistance to RT. Thus, factors that can predict treatment response after RT are highly desired.

A number of studies [3–5] have reported that peripheral blood inflammation indicators are related to the treatment outcome and survival for a variety tumors including gastric, prostate, and non-small cell lung cancer. The peripheral blood inflammation indicators include the systemic immune-inflammation index (SII), neutrophil/lymphocyte ratio (NLR), tumor-related leukocytosis (TRL), platelet/lymphocyte ratio (PLR) and monocyte/lymphocyte ratio (MLR). As for locally advanced cervical cancer, there were reports that overall survival (OS) and progression-free survival (PFS) were significantly shorter in patients with higher SII or higher NLR, revealing a negative impact of high SII or high NLR on prognosis [6,7]. Takai *et al.* [8] reported that a low NLR demonstrated significant association with a complete response (CR) to RT alone or concurrent chemoradiation therapy (CCRT) at every stage of cervical cancer, indicting a positive impact of low NLR on treatment outcome after RT. There are two main defects in this study. First is that the therapeutic response to RT was assessed by computed tomography (CT). Although magnetic resonance imaging (MRI) is superior to CT in evaluating morphological characteristics of cervical cancer as well as pelvic lymph node status. An appropriate correlation has been seen between preoperative MRI and

post-operative pathological results [9]. The MRI findings, including stage, tumor diameter, vaginal involvement, and uterine body involvement have been confirmed as important prognostic factors for cervical cancer patients [10,11]. Second, except for NLR, the correlation between other peripheral blood inflammation indicators and treatment outcome after RT in cervical cancer patients has not been evaluated. Thus, further research on peripheral blood inflammation indicators predicting treatment outcome in cervical cancer patients after RT is warranted.

In our study, we retrospectively evaluated the value of peripheral blood inflammation indicators, including SII, NLR, TRL, PLR and MLR, in predicting the treatment response in cervical cancer patients referred for RT. Treatment response was assessed by MRI in our study on account of the superiority of MRI over CT. The purpose of our observations was to establish the personalized choice of therapeutic strategies for cervical cancer patients.

2. Materials and Methods

2.1 Patients

This retrospective study enrolled 75 stage IB2 to IVA cervical cancer patients. All patients had biopsy-proven squamous cell carcinoma (SCC) of the cervix and underwent RT or CCRT at the department of Clinical Oncology of the University of Hong Kong-Shenzhen hospital between November 2015 and April 2020. The median age was 56 years of age (33–78 years). All of the 75 patients under went blood sampling within one week before the beginning of treatment. This study was approved by the University of Hong Kong-Shenzhen hospital's Ethics Committee.

2.2 Treatment

Total of 13 patients underwent RT alone and 62 patients were treated with CCRT, with 40 mg/m^2 weekly cisplatin for six cycles. Cisplatin was replaced by carboplatin if creatinine clearance $\leq$50 mL/min. External beam radiation therapy (EBRT) including RapidArc or three-dimensional conformal radiotherapy (3DCRT) was delivered to all patients. Dose for RapidArc was 45 Gy/25 Fr to the entire pelvis including cervix, uterus, portions of vagina, parametrium, and regional lymphatics with a 55.0–57.5 Gy simultaneous integrated boost to pelvic or metastatic lymph nodes. As to 3DCRT, two sequential phases included 45 Gy in 25 fractions boosting to pelvis for phase I and FIGO IIIB 16 Gy in 8 fractions, other stage 10 Gy in 5 fractions to pelvic wall for phase II. The EBRT was delivered daily with five 5 fractions per week. After initiation of EBRT, high dose rate (HDR) brachytherapy was performed once a week for 4 weeks. Cumulative equivalent of cervical cancer was set >90 Gy (Equivalent Dose in 2 Gy/f, EQD2) for $\geq$ stage IIIB and >84 Gy (EQD2) for stage IB~IIIA.

2.3 Definition of Peripheral Blood Inflammation Indicators

Baseline routine complete blood counts (CBCs) were obtained within one week prior to the start of treatment. The NLR, PLR and MLR were defined as the ratio between absolute neutrophil count, platelet count and monocyte count, to absolute lymphocyte count. TRL (+) was determined as the leukocytes exceeding 9000/μL without any infection.The SII was defined as follows: SII = absolute platelet count $\times$ absolute neutrophil count/absolute lymphocyte count. According to previous literature [6] and clinical practice, the optimal cut-off values are listed as 475 for SII, 2.4 for NLR, 118 for PLR and 0.26 for MLR.

2.4 Definition of Treatment Response

The statistical endpoint was treatment outcome assessed by MRI according to the Response Evaluation Criteria in Solid Tumors (RECIST). All of the 75 patients underwent abdomenal or pelvis MRI, before RT and about 2 months after completion of RT. Patients was scanned with a 1.5T MRI machine (Magnetom Avanto; Siemens, Erlangen, Germany). Axial, sagittal and coronal T1-weighted spin echo (SE) sequences, T2-weighted SE images, axial diffusion-weighted images and apparent diffusion coefficient (ADC) map of the whole pelvis were acquired. Following injection of gadolinium chelate, axial and sagittal contrast-enhanced dynamic MRI images were examined. MRI images were analyzed by two senior radiologists. On the basis of RECIST [12], complete response was determined by having the cervical tumor and enlarged lymph nodes (short diameter $\geq$10 mm) being completely invisible in MRI. A partial remission (PR) was determined as having the diameter of the cervical tumor decrease by at least 30%, compared with the measurements acquired prior to treatment. Progressive disease (PD) was determined when the diameter of the cervical tumor increased by at least 20%. Stable disease (SD) was determined when neither PR nor PD was noted.

2.5 Statistical Analysis

SPSS 26.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism software (Version 9.0.0, GraphPad Prism, Inc., San Diego, CA, USA) were used for data analysis. Statistically significance was determined when $p < 0.05$. Student's t test was used for comparation of continuous variables, whereas chi-square test was used for comparation of categorical variables. Ordinal logistic regression models were used to identify prediction value of peripheral blood inflammation indicators for treatment response. Factors included in logistic regression models were as follows: age, FIGO stage, tumor size, baseline SII, NLR, TRL, PLR and MLR.

3. Results

3.1 Clinical Characteristics and Treatment Outcomes

The present study investigated data from 75 cervical cancer patients with stage IB2 to IVA according to the 2018 FIGO staging system. The treatment response was evaluated according to RECIST. After treatment, 34 (45.3%) patients experienced a CR, 27 (36.0%) patients a PR, 10 (13.3%) patients with SD, and 4 (5.3%) patients experienced PD. Clinical details and treatment outcomes of all patients these cases are presented in Table 1. Treatment response of several patients assessed by MRI are presented in Fig. 1.

Table 1. Characteristics of 75 patients with cervical cancer.

Variables	*n* (%), or mean (range)
Number of patients	75
Age (y)	56 (33–78)
FIGO stage (%)	
IB–IIB	16 (21.3)
IIIA–IIIB	8 (10.7)
IIIC–IVA	51 (68.0)
Tumor size before RT (cm)	4.3 (1.0–8.5)
Tumor size after RT (cm)	1.5 (0–7.9)
Treatment (%)	
RT alone	13 (17.3)
CCRT	62 (82.7)
Treatment response	
CR	34 (45.3)
PR	27 (36.0)
SD	10 (13.3)
PD	4 (5.3)

FIGO, International Federation of Gynecology and Obstetrics; RT, radiation therapy; CCRT, concurrent chemoradiation therapy; CR, complete response; PR, partial remission; SD, stable disease; PD, progressive disease.

3.2 Comparison of Treatment Response between Different Groups by Peripheral Blood Inflammation Indicators

As to treatment response to RT, total short-term efficacy (PR plus CR) was 81.3%. The percentage of CR were significantly different between different groups of peripheral blood inflammation indicators, including SII, NLR, PLR and MLR ($p = 0.011$, 0.027, <0.001, 0.048, respectively). The percentage of CR in low SII group (SII $\leq$475) was 64.3%, which was higher than in high SII group (34.0%). The percentage of CR was 57.9%, 81.8%, and 48.3% respectively in low NLR, low PLR and low MLR groups, which was statistically higher than in the high NLR (32.4%), high PLR (30.2%) and high MLR groups (35.3%). In the different TRL groups, treatment response was not significantly different ($p > 0.05$) (Table 2 and Fig. 2).

3.3 Predicting Value of Peripheral Blood Inflammation Indicators for Treatment Response

The following factors were included in multivariate logistic regression models: age, FIGO stage, tumor size, baseline SII, TRL, NLR, PLR and MLR in order to identify the predicting value of peripheral blood inflammation indicators for treatment response. As shown in Table 3, multivariate logistic regression revealed that the TRL and PLR were significant predictive factors of treatment response with an odds ratio of 0.18 (95% CI 0.04–0.77) for TRL and 16.36 (95% CI 3.67–73.04) for PLR.

4. Discussion

Response to treatment is often used as a surrogate for prognosis or survival in cervical cancer patients treated with RT. However, it is critical to be able to discriminate between responders and non-responders using clinical information prior to treatment. Recently, cancer-related inflammation has been recognized as a prognostic biomarker as well as an indicator for treatment response. Systemic inflammation, which is reflected by peripheral leukocytes, lymphocytes, neutrophils, monocytes and platelets are proved to play a major role in cancer progression and development [13]. A variety of studies have reported that peripheral blood inflammation indicators are related to the treatment outcome of a number of tumors including rectal adenocarcinomas, gastric cancer, and non-small cell lung cancer. For example, in a study conducted by Sun *et al.* [14], 100 patients with rectal mucinous adenocarcinomas (MACs) undergoing neoadjuvant chemoradiotherapy (NCRT) and curative resection were included. Inflammation-based indexes such as SII, NLR, PLR, and prognostic nutritional index (PNI) were calculated. Logistic regression analysis showed that smaller tumor size, lower pre-treatment NLR level and PLR level, higher pre-treatment PNI level were independent predictors of good response to NCRT. In another study conducted by Graziano *et al.* [15], 373 patients affected by breast cancer and candidates to neoadjuvant chemotherapy (NACT) were investigated, in order to reveal a possible relationship between pathological complete response (pCR) and two peripheral indicators of immunity, including NLR and PLR. The results showed NLR and PLR were not significantly associated with pCR if analyzed separately. However, when analyzed together, patients with a NLR^{low}/PLR^{low} profile achieved a significantly higher rate of pCR compared to those with NLR^{high} and/or PLR^{high}. This study indicated low levels of both NLR and PLR may thus suggest a status of immune system activation that may predict pCR in breast cancer patients treated with NACT.

The present study demonstrated that treatment responses (CR, PR, SD) were significantly different between different groups of peripheral blood inflammation indicators, including SII, NLR, PLR and MLR. Our study revealed that TRL-negative and lower PLR were significant

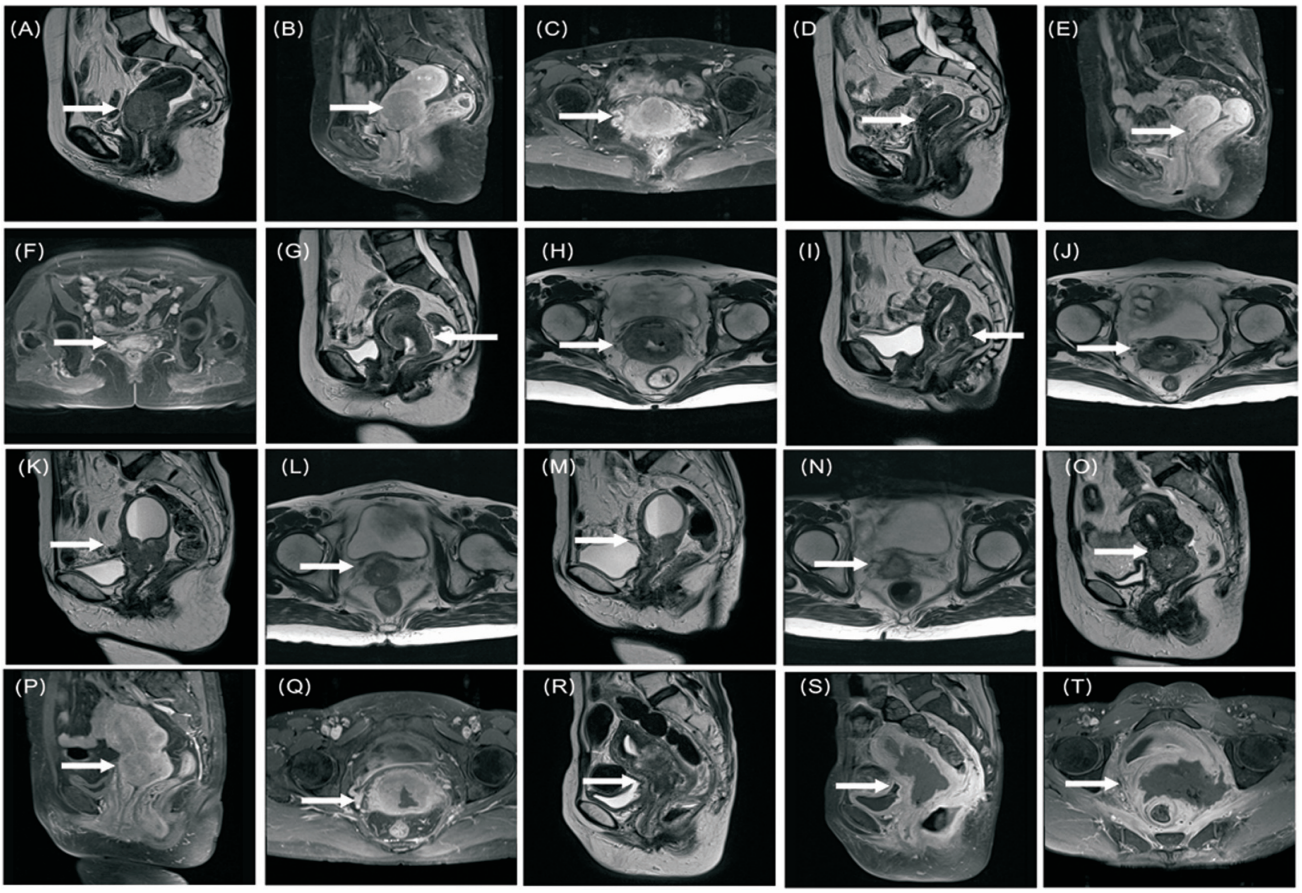

Fig. 1. Four cases of cervical carcinoma with FIGO stage III, showing markedly different responses to radiotherapy. (A–F) A 49-year-old woman with IIIC cervical cancer, experienced CR after treatment. T2-weighted sagittal (A), T1-weighted contrast-enhanced sagittal (B) and T1-weighted contrast-enhanced axial images (C) show cervical cancer with the long diameter about 6.0 cm. After radiotherapy, the mass disappeared and could not be displayed on MRI (D–F). (G–J) A 63-year-old woman with IIIB cervical cancer, experienced partial remission after treatment. T2-weighted sagittal (G) and axial images (H) show cervical cancer with the long diameter about 5.1 cm. After radiotherapy, the long diameter of mass was reduced to 3.2 cm (I,J). (K–N) A 72-year-old woman with IIIC cervical cancer, experienced stable disease after treatment. T2-weighted sagittal (K) and axial images (L) show cervical cancer with the long diameter about 3.9 cm. After radiotherapy, the long diameter of mass was 3.1 cm, which was slightly smaller than that before treatment (M,N). (O–T) A 48-year-old woman with IIIC cervical cancer, experienced progressive disease after treatment. T2-weighted sagittal (O), T1-weighted contrast-enhanced sagittal (P) and T1-weighted contrast-enhanced axial image (Q) show cervical cancer with the long diameter about 4.1 cm. After radiotherapy, the tumor increased significantly with the long diameter about 7.4 cm, and invaded the bladder, rectum and pelvic wall (R–T).

predictive factors of a better response to RT, which is consistent with previous reports. The TRL and PLR are proved prognostic factors influenced by the immune environment to the host, which are associated with the systemic inflammatory response.

Numerous studies have investigated the relationship between TRL and outcomes in cancer patients [16,17], suggesting an association between TRL and resistance to RT. Cho *et al*. [18] retrospectively studied 2456 cervical cancer patients who received RT or CCRT, in order to evaluate the predictive values of TRL for treatment outcome. Their results indicated that compared with TRL-negative patients, TRL-positive patients showed a significantly lower percentage of CR, as well as had larger tumor size, advanced clinical stage and more frequent lymph node metastases. In contrast with TRL-negative patients, OS and locoregional failure-free survival (LFFS) were significantly shorter in TRL-positive patients, revealing a poor response to radiation therapy in TRL-positive patients. A study of cervical cancer patients by Mabuchi *et al*. [19] revealed that TRL-positive was significantly associated with larger tumors, higer tumor stage, and lower overall survival (OS). The study further indicated that granulocyte colony-stimulating factor (G-CSF) may be an underlying cause of the rapidly developing and radioresistant character of TRL-positive patients with cervical cancer.

Table 2. The comparison of treatment response between different peripheral blood inflammation indicators groups in cervical cancer patients referred for radiotherapy.

Variable	CR	PR	SD	PD	Total	χ^2	*p*-value
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)		
SII						8.130	0.043
>475	16 (34.0)^b	22 (46.8)^a	7 (14.9)	2 (4.3)	47 (100)		
≤475	18 (64.3)	5 (17.9)	3 (10.7)	2 (7.1)	28 (100)		
NLR						7.811	0.046
>2.4	12 (32.4)^b	19 (51.4)^a	4 (10.8)	2 (5.4)	37 (100)		
≤2.4	22 (57.9)	8 (21.1)	6 (15.8)	2 (5.3)	38 (100)		
TRL						5.145	0.161
(+)	3 (27.3)	4 (36.4)	2 (18.1)	2 (18.1)	11 (100)		
(–)	31 (48.4)	23 (35.9)	8 (12.5)	2 (3.1)	64 (100)		
PLR						17.243	0.001
>118	16 (30.2)^{b,c}	25 (47.2)^a	9 (17.0)^a	3 (5.7)	53 (100)		
≤118	18 (81.8)	2 (9.1)	1 (4.5)	1 (4.5)	22 (100)		
MLR						9.624	0.022
>0.26	6 (35.3)^b	11 (64.7)^{a,c}	0 (0.0)^b	0 (0.0)	17 (100)		
≤0.26	28 (48.3)	16 (27.6)	10 (17.2)	4 (6.9)	58 (100)		

SII, immune-inflammation index; NLR, neutrophil/lymphocyte ratio; TRL, tumor-related leukocytosis; PLR, platelet/lymphocyte ratio; MLR, monocyte/lymphocyte ratio; CR, complete response; PR, partial remission; SD, stable disease; PD, progressive disease. The superscripts a, b, c indicates significance of multiple testing among CR, PR, SD, PD. a, compared with CR; b, compared with PR; c, compared with SD.

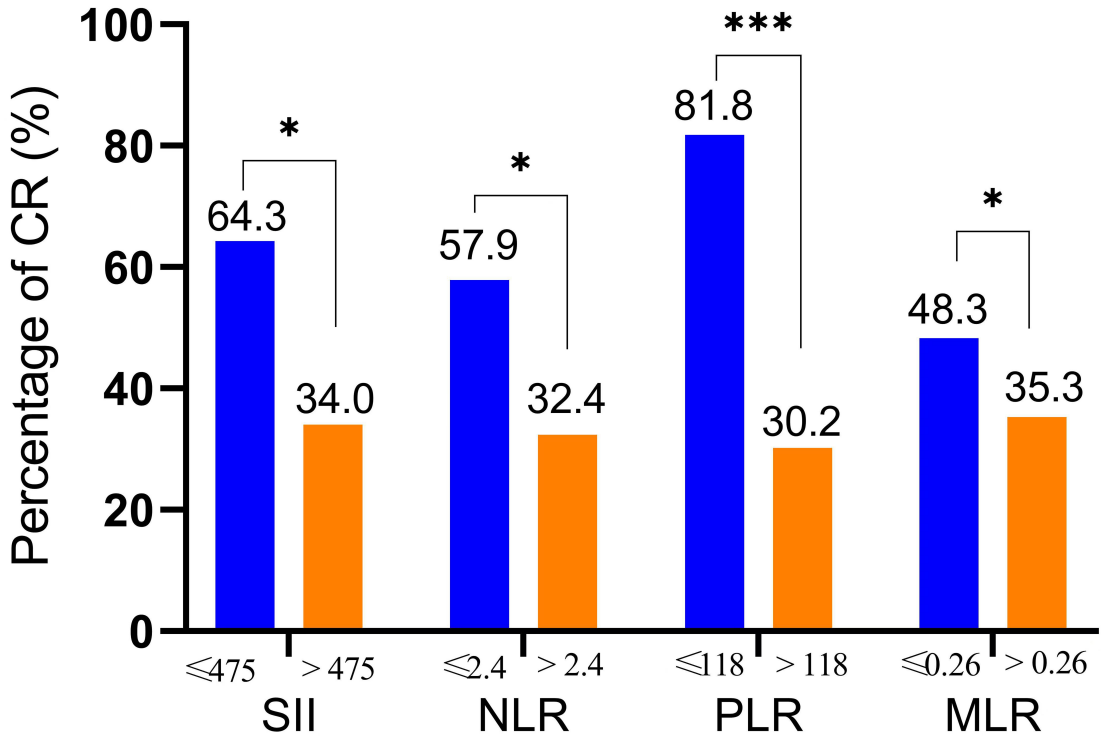

Fig. 2. The percentage of CR in different groups of peripheral blood inflammation indicators. *, $p < 0.05$; ***, $p < 0.001$.

Although the primary role of platelets is considered to be wound healing, hemostasis and thrombosis, studies have focused on the function of platelets in cancer ogenesis, tumor biology and inflammation. Elevation of platelet count has been proved to be related to tumor aggressiveness and decreased survival in colon, pancreatic, and lung cancer [20,21]. In a study conducted by Wang *et al.* [22], 120 patients with unresectable gastric cancer were assessed. The

Table 3. Univariate and multivariate ordinal logistic regression analysis with regard to treatment response evaluated by RECIST in cervical cancer patients referred for radiotherapy.

Variable	*n*	Univariate analysis		*p*-value	Multivariate analysis		*p*-value
		Odds ratio (95% CI)			Odds ratio (95% CI)		
Age							
≤50 years	31	1.201	(0.507–2.843)	0.678	1.508	(0.576–3.955)	0.403
>50 years	44	1 (Ref.)			1 (Ref.)		
FIGO stage							
IB–IIB	15	1.844	(0.595–5.714)	0.289	1.401	(0.403–4.870)	0.596
IIIA–IIIB	10	0.535	(0.153–1.870)	0.327	0.525	(0.131–2.109)	0.363
IIIC–IVA	50	1 (Ref.)			1 (Ref.)		
Tumor diameter							
≤40 mm	32	0.995	(0.423–2.341)	0.990	0.509	(0.181–1.429)	0.220
>40 mm	43	1 (Ref.)			1 (Ref.)		
SII							
≤475	28	2.581	(1.024–6.475)	0.044	1.005	(0.257–3.920)	0.974
>475	47	1 (Ref.)			1 (Ref.)		
NLR							
≤2.4	38	1.925	(0.814–4.549)	0.136	0.775	(0.222–2.716)	0.691
>2.4	37	1 (Ref.)			1 (Ref.)		
TRL							
(+)	11	0.329	(0.100–1.083)	0.068	0.181	(0.043–0.770)	0.021
(–)	64	1 (Ref.)			1 (Ref.)		
PLR							
≤118	22	8.855	(2.689–29.166)	<0.001	16.363	(3.666–73.039)	<0.001
>118	53	1 (Ref.)			1 (Ref.)		
MLR							
≤0.26	58	0.921	(0.335–2.540)	0.875	0.409	(0.122–1.369)	0.147
>0.26	17	1 (Ref.)			1 (Ref.)		

CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; SII, immune-inflammation index; NLR, neutrophil/lymphocyte ratio; TRL, tumor-related leukocytosis; PLR, platelet/lymphocyte ratio; MLR, monocyte/lymphocyte ratio. RECIST was defined as: 1 = PD; 2 = SD; 3 = PR; 4 = CR.

results demonstrated a close association between low baseline PLR and increased response to chemotherapy, suggesting that PLR may be a candidate blood biomarker in order to distinguish responders from non-responders. Other studies have suggested the important role of serum PLR in inflammation within the tumor microenvironment [23]. Platelets may mediate the tumor microenvironment via dense granules, lysosomes, or α-granules [24,25].

Treatment response was assessed by MRI, which is a major strength of this study. In a previous study conducted by Takai *et al*. [8], the therapeutic response to RT was assessed mainly by CT. MRI has been shown to be superior to physical examination or CT at evaluating morphological characteristics of cervical cancer. With better soft tissue contrast, MRI can accurately measure the size, invasion, and possible metastatic disease in cervical cancer patients [26]. MRI is a better follow-up imaging modality for detection of residual lesions or local recurrence of cervical cancer following RT. Small residual lesions or local recurrence, which is difficult to identify by CT due to poor soft tissue contrast, can be visible on an MRI [27]. Therefore, treatment response was assessed by MRI in our study, so as to make the results more accurate and reliable. Accurate evaluation of treatment response makes it possible to better formulate the need for further local or systematic treatments.

We acknowledge several limitations of our study. The major limitation is that this is a retrospective study in a single center, with a relatively small population and short follow-up duration. Consequently, a larger research population with longer follow-up time is needed to support our findings. Currently, we are planning prospective studies in order to evaluate the utility of finding predictive factors in patients with other cancers, such as colorectal, lung or nasopharyngeal carcinoma.

5. Conclusions

The present study demonstrated that treatment response was significantly different between different groups

of peripheral blood inflammation indicators, including SII, NLR, PLR and MLR. Multivariate logistic regression revealed that TRL-negative and lower PLR patients responded better to radiation therapy than patients with TRL-positive or higher PLR, suggesting radiosensitivity with TRL-negative or lower PLR tumors. Furthermore, our study emphasizes the importance of MRI for follow-up of cervical cancer patients. The result of present study may provide important information for the prediction of treatment response in cervical cancer patients referred for RT. We believe the application of this information obtained prior to treatment would be advantageous and meaningful for choosing an optimal therapeutic approach in order to avoid the higher probability of treatment failure and unfavorable prognosis.

Availability of Data and Materials

The data of this study are available from the corresponding author upon request.

Author Contributions

CL—extraction and drafting of the manuscript; KW and XS—designment and revision, statistical analysis; ZX—collecting clinical data of patients; GY and JL—Evaluating the patient's MRI images. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

The ethic code of this research is: [2021]079, approved by the university of Hong Kong-Shenzhen hospital's Ethics Committee. Written informed consents were obtained from all participants.

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Conflict of Interest

The authors declare no conflict of interest.

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