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Nomogram Predicting Grade ≥2 Acute Radiation Enteritis in Patients With Cervical Cancer Receiving Concurrent Chemoradiotherapy

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Objective: To analyze the risk factors for grade ≥2 ARE in patients with cervical cancer receiving concurrent chemoradiotherapy.

Methods: A total of 273 patients with cervical cancer receiving concurrent chemoradiotherapy at our hospital were retrospectively enrolled. The patients were divided into training and validation groups. Clinical parameters were analyzed using univariate analysis and multivariate logistic regression analysis. A nomogram model was established based on the independent risk factors selected using multivariate logistic regression. The areas under the receiver operating characteristic (ROC) curve, calibration curve, and decision curve analysis (DCA) were used to evaluate the nomogram. The patients were divided into low-score and high-score groups based on the scores calculated using the nomogram model and compared.

Results: Malnutrition, monocyte-lymphocyte ratio ≥0.82 after radiotherapy, platelet-lymphocyte ratio <307.50 after radiotherapy, and bowelbag volume receiving at least 5 and 40 Gy were independent risk factors for grade ≥2 ARE and were incorporated into the nomogram ($P < 0.05$). The ROC curve, calibration curve, and DCA suggested that the nomogram had good discrimination, concordance, and net benefit in the clinical. A medium nomogram score of 146.50 points was used as the cutoff point, and the incidence of grade ≥2 ARE in the high-score group was higher than that in the low-score group ($P < 0.05$).

Conclusion: The nomogram model for grade ≥2 ARE has good predictive ability and clinical utility, and is convenient for clinicians to identify high-risk groups and develop early prevention and treatment strategies.

Key Words: cervical cancer, concurrent chemoradiotherapy, risk factors, acute radiation enteritis, nomogram

(*Am J Clin Oncol* 2024;47:317–324)

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This study was supported by the Natural Science Foundation of Jiangsu Province (BK20211124), and Zhenjiang Key Research and Development Program (SH2023002).

F.C., C.H.D., and J.H.: designed the study. F.C., X.Q.G., and J.H.: collected and analyzed the data and drafted the manuscript. K.J.Z. and Y.P.Y.: checked the data and results. T.Y. and Y.H.: supervised the study and revised the manuscript accordingly.

The authors declare no conflicts of interest.

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DOI: 10.1097/COC.0000000000001096

Cervical cancer is one of the most common gynecological tumors in women.[1,2] There were approximately 600,000 (604,127) new cases of cervical cancer worldwide in 2020, of which nearly 110 000 were in China and 340,000 (341,831) deaths, of which nearly 60,000 were in China.[3] Despite being one of the most preventable cancers, cervical cancer remains the second leading cause of cancer-related death in women aged 20 to 39 years according to cancer statistics, 2023.[4] Concurrent chemoradiotherapy is the treatment of choice for cervical cancer with high risk factors after radical hysterectomy and for those who are ineligible for surgery.[5,6] The advantage of concurrent chemoradiotherapy is that it results in improved survival, but its disadvantage is that it also results in more intestinal reactions.[7–9]

It is estimated that two thirds of all patients with cervical cancer require radiotherapy.[10] However, the intestines are radiosensitive organs and their sensitivity to radiation limits the use of radiotherapy for abdominal and pelvic tumors.[11] Acute radiation enteritis (ARE), which occurs during radiotherapy or within 3 months after radiotherapy, is the most common complication in patients with cervical cancer receiving radiotherapy.[12] This causes nausea, emesis, diarrhea, abdominal pain, tenesmus, etc., affecting the quality of life of patients and even the progress of radiotherapy, which may compromise treatment effectiveness.[13,14] Cervical cancer patients with grade 2 or higher (grade ≥2) acute radiation enteritis have obvious clinical symptoms that require clinical intervention; otherwise, the radiotherapy process may be interrupted or even terminated.[15,16] It is of great significance to identify the occurrence of grade ≥2 ARE as early as possible, which can prompt early corresponding positive measures to prevent the development of grade ≥2 ARE and improve the quality of life.

An increasing number of studies have revealed that inflammatory indices, including the neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), and platelet-lymphocyte ratio (PLR), are important markers of the inflammatory status.[17–19] Studies have shown that inflammatory indices can effectively predict radiation pneumonitis.[20,21] However, the correlation between inflammatory indices and ARE has not yet been well studied. Although there is increasing evidence that some clinical, dosimetric, and biological factors are related to ARE occurrence, there is no consensus on the prediction of grade ≥2 ARE in patients with cervical cancer receiving concurrent chemoradiotherapy.[16,22]

In this study, we retrospectively analyzed the correlation between common clinical data, inflammatory indices, dosimetric parameters, and grade ≥2 ARE in patients with cervical cancer treated with concurrent chemoradiotherapy. A nomogram model was established according to the independent risk factors, and the model was verified and

evaluated, which may provide a clinical reference for clinicians to prevent grade 2 or higher acute radiation enteritis.

METHODS

Patients

A total of 273 patients with cervical cancer who received concurrent chemoradiotherapy at the radiotherapy department of our hospital between January 2014 and December 2022 were reviewed from the electronic medical records in this retrospective study. The inclusion criteria were as follows: (1) cervical cancer diagnosed by pathological examination, (2) pelvic radiotherapy for the first time, (3) International Federation of Gynecology and Obstetrics (FIGO 2014) stage IB-IVA, and (4) follow-up for at least 3 months after radiotherapy. The exclusion criteria were as follows: (1) distant metastasis at diagnosis (FIGO stage IVB), (2) history of chronic bowel disease, (3) other serious diseases such as abnormal cardiopulmonary function, (4) periaortic lymph node metastasis, and (5) failure to complete the prescribed radiotherapy. No interventions were applied to the patients in this study and the study was conducted with permission from the ethics review committee of our hospital (approval no. KY2021K0901).

TABLE 1. The Baseline Characteristics of All Patients in the Training and Validation Group (n,%)

	Training group (n = 227), n (%)		Validation group (n = 46), n (%)	
Characteristics	**Grade < 2 ARE**	**Grade ≥ 2 ARE**	**Grade < 2 ARE**	**Grade ≥ 2 ARE**
Age (y)				
< 50	89 (91.8)	8 (8.2)	14 (87.5)	2 (12.5)
≥ 50	93 (71.5)	37 (28.5)	24 (80.0)	6 (20.0)
Comorbidity				
No	145 (83.3)	29 (16.7)	24 (80.0)	6 (20.0)
Yes	37 (69.8)	16 (30.2)	14 (87.5)	2 (12.5)
Nutrition				
Well	116 (89.9)	13 (10.1)	23 (95.8)	1 (4.2)
Poor	66 (67.3)	32 (32.7)	15 (68.2)	7 (31.8)
Hemoglobin (g/L)				
< 100	19 (82.6)	4 (17.4)	37 (82.2)	8 (17.8)
≥ 100	163 (79.9)	41 (20.1)	1 (1.0)	0
BMI (kg/m^2)				
18.5-23.9	121 (84.0)	23 (16.0)	21 (84.0)	4 (16.0)
< 18.5 or ≥ 24	61 (73.5)	22 (26.5)	17 (81.0)	4 (19.0)
Tumor size				
< 4 cm	77 (81.1)	18 (18.9)	22 (88.0)	3 (12.0)
≥ 4 cm	105 (79.5)	27 (20.5)	16 (76.2)	5 (23.8)
Surgery				
No	105 (77.2)	31 (22.8)	24 (82.8)	5 (17.2)
Yes	77 (84.6)	14 (15.4)	14 (82.4)	3 (17.6)
Differentiation				
Unknown	50 (75.8)	16 (24.2)	13 (86.7)	2 (13.3)
Well-moderate	80 (80.0)	20 (20.0)	21 (84.0)	4 (16.0)
Poor	52 (85.2)	9 (14.8)	4 (66.7)	2 (33.3)
Lymphatic metastasis				
No	128 (81.5)	29 (18.5)	31 (86.1)	5 (13.9)
Yes	54 (77.1)	16 (22.9)	7 (70.0)	3 (30.0)
FIGO stage				
I-II	140 (80.9)	33 (19.1)	34 (85.0)	6 (15.0)
III-IV	42 (77.8)	12 (22.2)	4 (66.7)	2 (33.3)
Radiotherapy technology				
3DCRT	83 (73.5)	30 (26.5)	7 (87.5)	1 (12.5)
IMRT	99 (86.8)	15 (13.2)	31 (81.6)	7 (18.4)
Prescription dose				
45 Gy	97 (80.2)	24 (19.8)	21 (84.0)	4 (16.0)
50 Gy	85 (80.2)	21(19.8)	17(81.0)	4(19.0)
Boost to lymph node				
No	139 (80.8)	33 (19.2)	5 (62.5)	3 (37.5)
Yes	43 (78.2)	12 (21.8)	33 (86.8)	5 (13.2)
Brachytherapy				
No	72 (85.7)	12 (14.3)	17 (81.0)	4 (19.0)
Yes	110 (76.9)	33 (23.1)	21 (84.0)	4 (16.0)
Radiotherapy intent				
Definitive	105 (77.2)	31 (22.8)	24 (82.8)	5 (17.2)
Adjuvant	77 (84.6)	14 (15.4)	14 (82.4)	3 (17.6)

TABLE 2. ROC Curve Analysis of Inflammatory Indexes in the Diagnosis of Grade ≥2 Acute Radiation Enteritis in the Training Group

Variable	AUC	Best cutoff (95% CI)	*P*
NLR before RT	0.521	1.60 (0.429-0.613)	0.659
MLR before RT	0.521	0.19 (0.437-0.605)	0.664
PLR before RT	0.562	164.39 (0.466-0.659)	0.195
NLR after RT	0.530	24.63 (0.431-0.630)	0.530
MLR after RT	0.614	0.82 (0.521-0.706)	0.018
PLR after RT	0.570	307.50 (0.479-0.660)	0.148

Concurrent Chemoradiotherapy Regimen

All patients enrolled in this study underwent simulated enhanced computed tomography (CT) using a vacuum pad fixation device during normal breathing. The clinical target volume (CTV) and organs at risk (OARs) were contoured by the radiotherapist according to the delineation standard of the Radiation Therapy Oncology Group (RTOG) for cervical cancer, and a margin of 5 mm was added to the CTV to generate the planning target volume (PTV) at our

TABLE 3. Univariate Analysis of Clinical and Inflammatory Parameters for Predicting Grade ≥2 Acute Radiation Enteritis in the Training Group

Characteristics	Comparison method	χ^2 value	*P*
Age (y)	<50 vs. ≥50	14.281	<0.001
Comorbidity	No vs. yes	4.674	0.031
Nutrition	Well vs. poor	17.858	<0.001
Hemoglobin (g/L)	<100 vs. ≥100	0.095	0.758
BMI (kg/m^2)	Normal vs. high or low	3.676	0.055
Tumor size (cm)	<4 vs. ≥4	0.079	0.779
Surgery	No vs. yes	1.883	0.170
Differentiation	Unknown vs. well-moderate vs. poor	1.799	0.407
Lymphatic metastasis	No vs. Yes	0.586	0.444
FIGO stage	I-II vs. III-IV	0.256	0.613
Radiotherapy technology	CRT vs. IMRT	6.402	0.011
Prescription dose (Gy)	45 vs. 50	0.000	0.996
Boost to lymph node	No vs. Yes	0.182	0.670
Brachytherapy	No vs. Yes	2.573	0.109
Radiotherapy intent	Definitive vs. adjuvant	1.883	0.170
NLR before RT	<1.60 vs. ≥1.60	2.043	0.153
MLR before RT	<0.19 vs. ≥0.19	1.718	0.190
PLR before RT	<164.39 vs. ≥164.39	6.884	0.009
NLR after RT	<24.63 vs. ≥24.63	6.990	0.008
MLR after RT	<0.82 vs. ≥0.82	6.762	0.009
PLR after RT	<307.50 vs. ≥307.50	7.597	0.006

TABLE 4. Dosimetric Comparison of Intestine Between the Grade <2 ARE Group (n = 45) and the Grade ≥2 ARE Group (n = 182)

Parameters	Grade < 2 ARE group	Grade ≥ 2 ARE group	Z value	*P*
Bowelbag (%)				
V5	87.92 (84.00, 96.91)	97.12 (91.69, 98.84)	−4.449	<0.001
V10	82.38 (76.63, 88.70)	87.40 (78.12, 91.42)	−1.929	0.054
V20	71.34 (65.46, 78.59)	77.03 (63.38, 82.57)	−1.432	0.152
V30	49.01 (42.90, 57.81)	57.94 (51.64, 60.11)	−2.271	0.023
V40	27.54 (23.52, 33.32)	38.47 (31.91, 42.53)	−4.698	<0.001
V50	5.27 (0.00, 10.32)	9.64 (0.00, 20.50)	−1.171	0.242
Dmean (Gy)	28.12 (25.17, 31.15)	33.78 (28.26, 34.82)	−3.973	<0.001
Rectum (%)				
V5	100.00 (99.37, 100.00)	100.00 (100.00, 100.00)	−3.606	<0.001
V10	99.22 (97.34, 100.00)	100.00 (99.55, 100.00)	−3.461	0.001
V20	97.86 (95.50, 100.00)	100.00 (98.23, 100.00)	−3.402	0.001
V30	96.81 (92.78, 99.83)	98.73 (96.07, 100.00)	−2.559	0.010
V40	86.43 (79.30, 94.08)	94.90 (86.28, 99.91)	−3.002	0.003
V50	6.03 (0.00, 37.57)	33.56 (0.00, 76.22)	−1.541	0.123
Dmean (Gy)	45.82 (42.35, 48.15)	46.04 (44.57, 50.07)	−0.870	0.385

institution. Among the OARs, the bowelbag was delineated as the junction between the outermost edge of the small intestine and the sigmoid, ascending, transverse, and descending colon, including the entire small and large intestine, except for the rectum and anus. The Eclipse treatment planning system (TPS) was used to design 3-dimensional conformal radiotherapy (3DCRT) or intensity-modulated radiotherapy (IMRT). The prescription dose to the PTV was 45 to 50 Gy in 1.8 to 2.0 Gy/fraction, with positive lymph nodes simultaneously boosted by 10 to 20 Gy, once daily, 5 fractions per week. For the PTV, at least 95% of the volume was required to reach the prescribed dose, and the OARs dose limits were as follows: V50, the percentage of bladder volume receiving 50 Gy, was <50% (bladder V50 < 50%); femoral head V50 < 5%; Dmax, maximum dose of rectum, was <105% of the prescribed dose (rectum Dmax < 105 prescribed dose); and bowelbag V40 < 50%, bowelbag Dmax < 52 Gy. Nonsurgical patients received definitive radiotherapy (external beam radiotherapy and brachytherapy) with a total dose of 80 to 85 Gy. Patients with positive surgical margins also received brachytherapy, with the vaginal submucosa 0.5 cm as the reference point. The chemotherapy regimen was based on cisplatin, 30 to 40 mg/m^2, once a week for a total of 4 to 6 sessions.

Data Collection

Clinicopathological and treatment data, including age, comorbidity (hypertension/diabetes), nutrition, hemoglobin level, body mass index (BMI), tumor size, surgery, differentiation, lymphatic metastasis, FIGO stage, and radiotherapy technology, etc., were collected from electronic medical records. Laboratory data including neutrophil, monocyte, platelet, and lymphocyte counts, were collected from the electronic medical records at 2 time points: within 1 week before RT and within 1 week after RT completion. NLR, MLR, and PLR were calculated as the ratio of neutrophil count to lymphocyte count, monocyte count to lymphocyte count, and platelet count to lymphocyte count, respectively. Dosimetric parameters of the bowelbag and rectum, including the mean dose (Dmean) and volume receiving ≥ × Gy (Vx), were recorded from the dose-volume histogram of the treated 3DCRT or IMRT plans.

Evaluation of ARE

From the beginning of radiotherapy until 3 months after the end of radiotherapy, the clinical symptoms of ARE recorded in the medical records, such as diarrhea and abdominal pain were collected. The grade of acute radiation enteritis was assessed according to the US Department of Health and Human Services (HHS) Common Terminology Criteria for Adverse Events (CTCAE) 5.0 for the most severe clinical symptoms. The patients were divided into 2 groups: grade <2 (grade <2 ARE group) and grade ≥2 (grade ≥2 ARE group).

Statistical Analysis

All data collected in this study were analyzed using SPSS (version 22.0) and Rstudio (R 3.4.1). Count data were expressed as the number of cases and percentages, and Pearson's χ^2 test was used for comparisons between groups. The best cutoff values of inflammatory data and dosimetric parameters for predicting the risk of grade ≥2 ARE were calculated using the Youden index by the receiver operating characteristic (ROC) curve. The dosimetric parameters were expressed as median (upper quartile, lower quartile), and the Mann-Whitney *U* test was used for comparison between

TABLE 5. Multivariate Logistic Analysis of Influencing Factors Associated With Grade ≥2 ARE

					95%CI		
Factors	B	SE	Wald	Exp (B)	Lower	Upper	*P* value
Nutrition	1.166	0.494	5.578	3.208	1.219	8.439	0.018
MLR after RT	1.482	0.522	8.063	4.401	1.582	12.239	0.005
PLR after RT	−1.285	0.513	6.269	0.277	0.101	0.756	0.012
Bowelbag V5	0.206	0.098	4.398	1.229	1.014	1.489	0.036
Bowelbag V40	0.161	0.059	7.455	1.174	1.046	1.319	0.006

TABLE 6. ROC Curve Analysis of Significant Dosimetric Parameters in the Diagnosis of Grade ≥2 Acute Radiation Enteritis in the Training Group

Variable	AUC	Best cutoff (%)	95% CI	*P*
Bowelbag V5	0.714	89.51	0.635-0.794	<0.001
Bowelbag V40	0.726	35.60	0.625-0.828	<0.001

groups. The factors with $P<0.05$ in univariate analysis were analyzed by multivariate logistic regression analysis. A nomogram model was established based on the results of the multivariate logistic regression analysis. The area under the ROC curve (AUC) was used to evaluate the ability of the nomogram to correctly predict the incidence of grade ≥2 ARE. Calibration curve and decision curve analysis (DCA) were used to assess the accuracy and clinical effectiveness of the nomogram model, respectively. The nomogram score for each patient was calculated, and the 2 risk groups were classified for the training and validation groups, respectively. The Pearson's χ^2 test was used to compare the 2 risk groups.

RESULTS

Clinical Characteristics of Patients

A total of 273 patients with cervical cancer treated with concurrent chemoradiotherapy were enrolled in accordance with the inclusion and exclusion criteria from the electronic medical records of our hospital. Taking the visit time on December 31, 2020, as the dividing line, 273 patients were divided into a training group of 227 cases and a validation group of 46 cases. In the training group, 167 (73.6%) patients experienced ARE after RT. According to the CTCAE 5.0, 45 (19.8%) patients had grade 2 or higher ARE, including 39 cases of grade 2 ARE and 6 cases of grade 3 ARE. Correspondingly, 35 (76.1%) patients developed ARE in the validation group, among which 8 (17.4%) patients had grade 2 or higher ARE, including 7 cases of grade 2 ARE and 1 case of grade 3 ARE.

The detailed clinicopathological and treatment characteristics of 227 patients in the training group and 46 patients in the validation group were presented in Table 1. For the inflammatory indices of the training group, including NLR before RT, MLR before RT, PLR before RT, NLR after RT, MLR after RT, and PLR after RT, the best cutoff values were 1.60, 0.19, 164.39, 24.63, 0.82, and 307.50, respectively (Table 2).

Univariate Analysis of the Clinical Characteristics and Grade ≥ 2 ARE for the Training Group

Table 3 showed the relationship between clinical data and the risk of grade ≥2 ARE in patients with cervical cancer receiving concurrent chemoradiotherapy. Univariate analysis showed that the incidence of grade ≥2 ARE in patients with cervical cancer who received concurrent chemoradiotherapy was significantly correlated with age ($P<0.001$), comorbidity ($P=0.031$), nutrition ($P<0.001$), radiotherapy technology ($P=0.011$), PLR before RT ($P=0.009$), NLR after RT ($P=0.008$), MLR after RT ($P=0.009$), and PLR after RT ($P=0.006$). Other clinical data, such as hemoglobin, BMI, tumor size, surgery, lymphatic metastasis, FIGO stage, prescription dose, lymph node boost, and brachytherapy, were not correlated with the occurrence of grade ≥2 ARE ($P>0.05$).

Comparison of Dosimetric Parameters Between Grade <2 ARE and Grade ≥2 ARE Group for the Training Group

The comparison of dosimetric parameters between the grade ≥ 2 ARE group and grade <2 ARE group of patients with cervical cancer receiving concurrent chemoradiotherapy was shown in Table 4. The dose-volume of the intestines, including the bowelbag and rectum, were higher in the grade ≥2 ARE group than those in the grade <2 ARE group. For the bowelbag, the differences in V5, V30, V40, and Dmean were statistically significant ($P<0.05$). The rectum V5, V10, V20, V30, and V40 in the grade ≥2 ARE group were significantly higher than those in the grade <2 ARE group. There were no significant differences in the

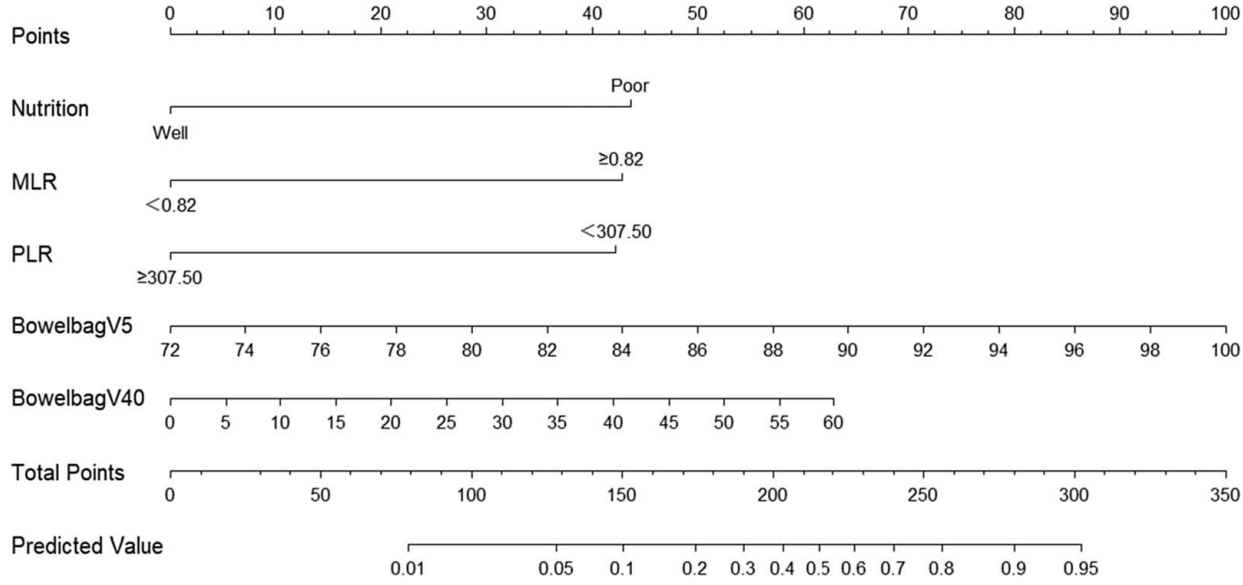

FIGURE 1. Nomogram predicting the risk of grade grade ≥2 ARE for cervical cancer treated with concurrent chemoradiotherapy.

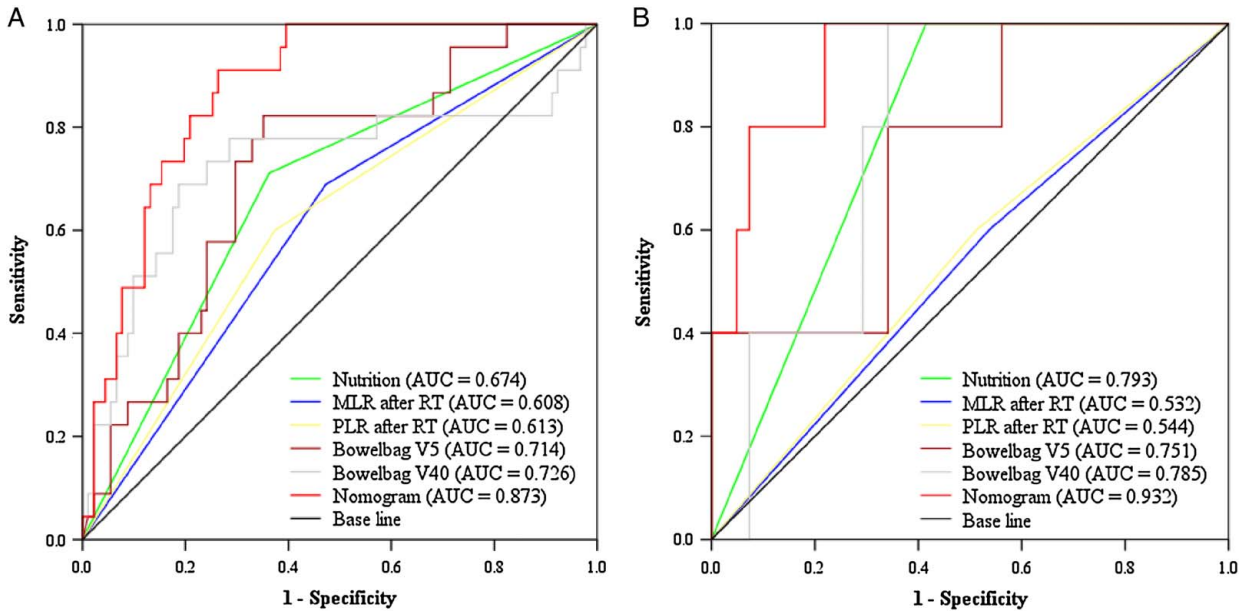

FIGURE 2. Receiver operating characteristic curve of the nutrition, MLR after RT, PLR after RT, bowelbag V5, bowelbag V40, and nomogram model in the training (A) and validation (B) groups. AUC > 0.80 indicates good predictive ability. full color online

other dosimetric parameters of the bowelbag and rectum between the 2 groups ($P > 0.05$).

Clinical and Dosimetric Factors Predicting Grade ≥ 2 ARE for the Training Group

The significant factors in univariate analysis, such as age, comorbidity, nutrition, radiotherapy technology, PLR before RT, NLR after RT, MLR after RT, PLR after RT, V5, V30, V40, Dmean of the bowelbag, and V5, V10, V20, V30, V40 of the rectum were included in the multivariate logistic regression analysis. And the results were listed in Table 5. Multivariate analysis indicated that nutrition ($P = 0.018$), MLR ≥ 0.82 after RT ($P = 0.005$), PLR < 307.50 after RT ($P = 0.012$), and bowelbag V5 and V40 ($P = 0.036$ and 0.006) were independent predictive factors for grade ≥ 2 acute radiation enteritis in patients with cervical cancer undergoing concurrent chemoradiotherapy. Table 6 presented the best cutoff values of significant dosimetric parameters in the multivariate analysis, including V5 and V40 of the bowelbag, which were helpful for clinicians to design radiotherapy plans.

Establishment and Validation of the Nomogram Predicting Model

On the basis of the results of the multivariate logistic regression analysis, a nomogram model was established to predict the risk of grade ≥ 2 ARE in patients with cervical cancer receiving concurrent chemoradiotherapy. Bowelbag

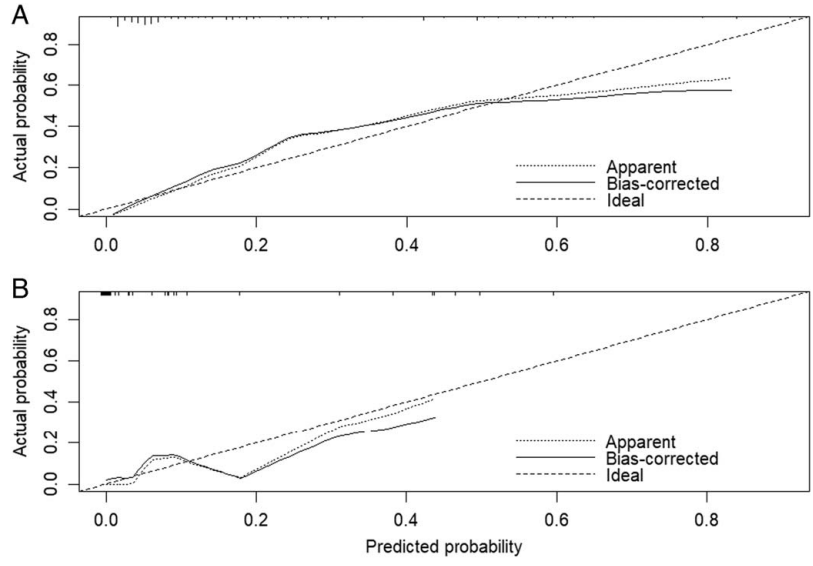

FIGURE 3. Calibration curves of the nomogram model predicting grade ≥ 2 ARE in the training (A) and validation (B) groups.

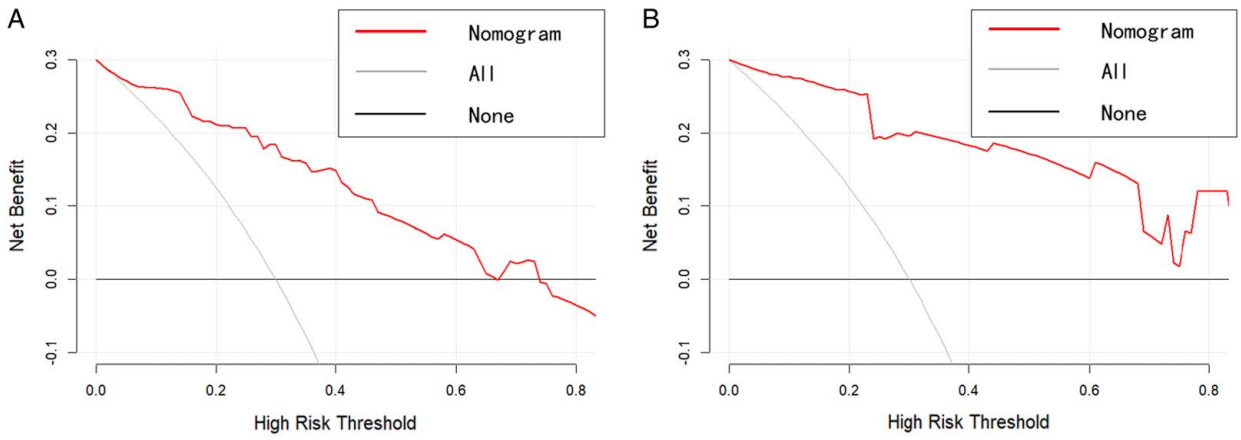

FIGURE 4. Decision curves of the nomogram model predicting grade ≥ 2 ARE in the training (A) and validation (B) groups. full color online

V5 and V40 showed a relatively large proportion of the score, followed by nutrition, MLR after RT, and PLR after RT (Fig. 1). Each independent risk factor was scored separately and each score was added to obtain the total score, which corresponded to the probability of predicting grade ≥2 ARE.

The AUC of ROC curves in the training and validation groups predicting the occurrence of grade ≥2 ARE were 0.873 (95% CI: 0.827-0.920) and 0.932 (95% CI: 0.813-0.947), which were larger than those of other independent factors, proving that the nomogram model had good discrimination (Fig. 2). The AUC of the nomogram was above 0.80, which proved that the nomogram had a good predictive ability. The prediction probability was consistent with the actual probability, indicating that the model had a good calibration, as shown by the calibration curves of the internal and external validation (Fig. 3). The DCA of the training and validation groups graphically showed that if the risk threshold was from 0 to approximately 0.7, the net benefit to patients was greater than the 2 extreme curves (all curve and none curve), proving that this range had a good clinical treatment efficiency (Fig. 4).

According to the score of each patient calculated by the nomogram model in the training group, we used a median score of 146.50 points as the cutoff point to divide the patients of the training group and validation groups into low-score and high-score groups, respectively (Tables 7 and 8). The incidence of grade ≥2 ARE in the high-score group was higher than that in the low-score group in the validation group, which was consistent with the results in the training group ($P < 0.05$).

DISCUSSION

In the present study, the incidence of acute radiation enteritis in 273 patients with cervical cancer receiving concurrent chemoradiotherapy was 73.6%, of which 19.8% were grade ≥ 2 according to CTCAE 5.0. A previous series of studies showed that the incidence of ARE in patients with cervical cancer receiving radiotherapy was 54% to 75%, and the incidence of grade ≥2 ARE was 22% to 45%, which were roughly similar to our results.[23–25] The results of the present study showed that malnutrition, MLR ≥ 0.82 after RT, PLR < 307.50 after RT, and higher V5 and V40 of the bowelbag were the independent risk factors for grade ≥2 ARE in patients with cervical cancer undergoing concurrent chemoradiotherapy.

Bullock et al[26] reported that malnourished patients with cancer had poor treatment outcomes and increased complications after radiotherapy. Therefore, in this study, all patients were regularly screened for nutritional risk (at least once a week), and patient-generated subjective global assessment (PG-SGA) was used for nutritional assessment in patients at nutritional risk to determine the presence of malnutrition.[27] Multivariate Logistic regression analysis showed that the incidence of grade ≥ 2 ARE in malnourished patients was 3.208 times higher than that in well-nourished patients ($P = 0.018$). This may be because malnutrition affects the repair and digestion-absorption functions of intestinal tissue, thereby increasing the risk of radiation enteritis. Therefore, comprehensive nutritional status assessment of patients with cervical cancer and early nutritional intervention are of great significance for the prevention of grade ≥2 ARE complications.

Complete blood count is a routine, inexpensive, and simple examination that provides information about blood components. NLR, MLR, and PLR are simple indices of the systemic inflammatory response and have been confirmed to be associated with intestinal problems, such as Crohn disease (CD), ulcerative colitis (UC), and acute intestinal obstruction.[28–30] This study aimed to investigate

TABLE 7. Incidence Rate of Grade ≥2 ARE in the Training Group

Group	Grade <2 ARE group	Grade ≥ 2 ARE group	Z value	*P*
Low-score group	110 (0.982)	2 (0.018)	45.258	<0.001
High-score group	72 (0.626)	43 (0.374)	—	—

TABLE 8. Incidence Rate of Grade ≥2 ARE in the Validation Group

Group	Grade <2 ARE group	Grade ≥2 ARE group	Z value	*P*
Low-score group	28 (0.933)	2 (0.067)	6.905	0.009
High-score group	10 (0.625)	6 (0.375)	—	—

whether NLR, MLR, and PLR can be used as novel non-invasive biomarkers for the risk of grade ≥2 ARE. This study found that patients with MLR ≥ 0.82 or PLR < 307.50 after RT had a higher proportion of grade ≥2 ARE. These inflammatory indices are routinely used in clinical practice and can be obtained early in the course of radiotherapy by blood routine examination, which are of great significance for the early prediction of the occurrence and severity of acute radiation enteritis in clinical practice.

In this study, the dose-volume of the bowelbag and rectum were related to the occurrence of grade ≥2 ARE, and bowelbag V5 and V40 were independent risk factors for acute radiation enteritis. In our opinion, 3DCRT versus IMRT for ARE is essentially a comparison of the intestinal irradiation dose. Therefore, when we performed the multivariate analysis, the intestinal irradiation dose was found to be an independent factor rather than radiotherapy technology. Moreover, previous studies have shown that dose-volume parameters, such as V5, V10, and V30-45, are closely related to the occurrence and severity of intestinal reaction.[31–33] Holyoake et al[31] found that both low dose and high dose could predict intestinal toxicity risk, which was consistent with the dosimetric results of our study. Therefore, in clinical radiotherapy planning, it is necessary to improve the dose distribution of the bowelbag, not only to pay attention to the high-dose irradiation area of the bowelbag, but also to reduce the low-dose irradiation area of the bowelbag to reduce the severity of radiation enteritis.

The nomogram model can graphically and visually visualize the results of the multivariate logistic regression analysis. Therefore, establishing an intuitive, simple, and effective nomogram model can guide clinicians to prevent and treat acute radiation enteritis. The results of the nomogram model for the risk of grade ≥2 ARE in patients with cervical cancer receiving concurrent chemoradiotherapy showed that the AUC of the ROC curve were 0.873 and 0.932 for the training and validation groups, respectively, indicating that the model had good discrimination ability. The calibration curve drawn between the predicted and actual values indicated good consistency of the nomogram model, and the DCA showed that the model had a good clinical effect. Clinicians can use the nomogram prediction model constructed in this study to predict the high risk of grade ≥2 ARE for cervical cancer patients receiving concurrent chemoradiotherapy, and take corresponding intervention measures, such as improving the nutritional status of patients, reducing the irradiation dose of bowelbag in the radiotherapy plan, reducing MLR, increasing PLR, etc., to prevent grade ≥2 ARE as soon as possible. However, our study had several limitations. This was a retrospective, single-center study with a limited sample size, which may have resulted in a selection bias. In addition, many factors affect the specific values of inflammatory indices. Therefore, it is possible to prospectively collect larger samples and refine subgroup analyses to assess the reliability of the independent risk factors in future.

CONCLUSIONS

In conclusion, malnutrition, MLR ≥ 0.82 after RT, PLR < 307.50 after RT, and higher bowelbag V5 and V40 were the independent risk factors for grade ≥ 2 ARE in patients with cervical cancer receiving concurrent chemoradiotherapy. The nomogram prediction model based on these results has good predictive performance and clinical utility, which can provide a reference for the prevention of grade ≥2 ARE; however, prospective studies with large samples and multiple centers are still needed to further verify our results.

ACKNOWLEDGMENTS

The authors thank the Institute of Radiation Oncology, Affiliated Hospital of Jiangsu University, for supporting this study.

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