



Pretreatment neutrophil-lymphocyte and platelet-lymphocyte ratio predict clinical outcome and prognosis for cervical Cancer

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ABSTRACT

Variations in systemic inflammatory response biomarker levels have been associated with adverse clinical outcome in various malignancies. In this study, we aimed to evaluate the predictive and prognostic role of the pretreatment neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in cervical cancer. We retrospectively investigated 616 patients who underwent initial radical hysterectomy with pelvic lymphadenectomy for cervical cancer between July 2012 and December 2014 in China. Their clinical and histopathological markers and complete blood counts were obtained and analyzed. Then we chose the group of 339 of the total 616 patients who were not combined preoperative radiotherapy or chemotherapy for the survival analysis. Prognostic factors were assessed by univariate and multivariate analyses. The ROC curve revealed NLR and PLR had significant ability to predict parametrial involvement, and the cutoff values for NLR and PLR were 2.5 and 138.8 respectively. Clinicopathologic analysis showed that NLR was linked to age, parametrial involvement, tumor-invasion depth and histologic grade, and PLR was related to age, parametrial involvement, tumor-invasion depth and FIGO stage. Univariate analysis identified high PLR as a significant poor predictor for progression-free survival (PFS) and overall survival (OS), and NLR exhibited no predict power on OS or PFS. Multivariable analysis showed that PLR was an independent predictor of PFS, but not OS. NLR and PLR were associated with the clinical characteristics of cervical cancer. Additionally, PLR had independence prognostic value for PFS in patients with cervical cancer receiving radical hysterectomy with pelvic lymphadenectomy.

1. Introduction

Even though the incidence and mortality of invasive cervical cancer have steadily decreased [1,2], cervical cancer remains the third most common malignancy of women worldwide, and approximately 250,000 patients die from this disease each year [1,2]. The primary treatment of early stage is either surgery or radiation therapy. Bilateral pelvic lymph node dissection, with or without para-aortic lymph node sampling, is a necessary component of primary surgical treatment. Nowadays, the prediction of cervical cancer progression or recurrence is mainly using the postoperative prognostic factors, such as lymph node (LN) status, histologic grade and depth of invasion [3]. Actually, we cannot apply

these pathological prognostic factors for prediction of prognosis in cases of advanced disease, because the treatment is concurrent chemoradiation but not surgery [4,5]. Although clinical staging is a strong preoperative predictor of outcome, the clinical stage had been shown to be frequently inaccurate, especially in cases of more advanced disease [4,6]. Predictive biomarkers may enable a far better risk stratification for progression, in order to select appropriate treatment and provide individual adjuvant therapy following surgery. Therefore, a non-invasive and readily accessible preoperative test to estimate survival probability and prognosis in cervical cancer is required [7].

Inflammation is a key characteristic of the tumor microenvironment and plays a central role in the initiation, promotion, progression,

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invasion and metastasis of a tumor [8,9]. Since hematological markers of inflammation that are readily measured in the clinic, it has been frequently reported that a combined index using neutrophil, platelet and lymphocyte counts in the form of NLR and PLR, which have been used as cost-effective and simple parameters of systemic inflammation or stress in critically ill patients without cancer [4,10], may also be related to prognosis in many types of cancers, including ovarian cancer [11], gastric cancer [12], endometrial cancer [13] and renal cell carcinoma [14]. More and more researchers focus on the application of NLR and PLR in cervical cancer [3,7,9]. Chen et al.'s study has confirmed the prognostic value of NLR and PLR in cervical cancer [3], while some investigators reached the different conclusion [9,13]. Zhang et al. indicated that elevated pretreatment values of NLR and PLR correlate with unfavorable histopathological characteristics [7]. However, their utility for managing cervical cancer remains to be determined. Considering the limitation of the small sample sizes in previous studies, a comprehensive analysis of the association of these markers with cancer clinicopathological features would help establish their potential for managing cervical cancer. While, little is known about the prognostic values of pretreatment NLR and PLR in cervical cancer patients treated with initial radical surgery without neoadjuvant chemotherapy or primary radiation therapy. Thus, the aim of the present study was to assess the prognostic and predictive values of pretreatment NLR and PLR in cervical cancer patients receiving initial radical hysterectomy with pelvic lymphadenectomy. In this study, we assessed correlations between pretreatment levels of these markers with the tumor-invasion depth, lymph nodes metastasis, stage of the disease and other clinicopathological characteristics of squamous cell cervical carcinoma, which accounts for the majority of cervical cancers.

2. Material and methods

2.1. Patients and data collection

This retrospective study examined the records of a sequential series patients with histopathologically diagnosis of primary Cervical squamous cell carcinoma between July 2012 and December 2014 within the West China Second University Hospital, Sichuan University. Primary surgery included radical hysterectomy and bilateral pelvic lymph node dissection with (or without) the para-aortic lymph node sampling. Patients were excluded if they with pregnancy, missing routine blood tests, hematological disease, inflammatory disease or died in the peri-operative period. Finally, a total of 616 patients were enrolled in our study. All data were obtained from patient medical records and patients were clinically staged according to the FIGO clinical staging system. Other variables in the study included age, tumor grade, LNM, tumor-invasion depth, parametrial involvement and lymphovascular space invasion (LVSI). Patients' full blood count data (including absolute leukocyte, neutrophil, eosinophil, basophil, monocyte, lymphocyte and platelet counts) were collected from a time frame for < 2 days after admission and prior to treatment and used to calculate NLR and PLR.

In addition, a group of 339 of the total 616 cervical cancer patients who were not combined preoperative radiotherapy or chemotherapy were enrolled for the survival analysis, considering the effect of chemoradiotherapy to survive; we excluded its interference to our results. Patients had follow-up examinations approximately 3-monthly for the first year, 6-monthly for the next four years, and every year thereafter. A few patients were reviewed in their local regional hospital because of some reasons. Followed up by outpatient and telephone mainly. During the routine follow-up, imaging studies including computed tomography or magnetic resonance imaging and chest X-ray were performed annually. When tumor recurrence was suspected based on clinical findings or imaging studies, biopsy of that lesion was performed on a case by case basis. Deadline for follow-up is August 1, 2017. We defined the PFS as the time from the initial treatment to relapse noted on images, or the last follow-up visit, and the OS at the time from the initial treatment to

death due to cervical carcinoma, or the last follow-up visit.

This study was submitted to and approved by the Ethics Commission of Chengdu Medical College and West China Second University Hospital, Sichuan University. This is a retrospective study, so the content to participate is not applicable.

2.2. Statistical analysis

IBM SPSS software (Statistical Package for the Social Sciences; Version 22.0) was used for statistical analyses. Missing data were processed by pairwise exclusion. The significance of the differences in laboratory parameters between patients and controls was evaluated using the Mann-Whitney U test. NLR and PLR cutoff optimisation was performed using the standard ROC curve analysis. The biggest Youden index (sensitivity + specificity-1) was selected as the optimal cut-off point. Continuous data were analyzed using median, interquartile ranges (IQRs) and 95% confidence interval (CI). The associations of NLR and PLR with clinicopathologic variables were analyzed using the χ^2 test or the Fisher's exact test. ROC curve analysis was used to assess the predictive significance of NLR and PLR for parametrial involvement. Survival analyses on categorical variables were performed using the Kaplan–Meier method and significant differences between groups were identified using the log-rank test. Univariable and multivariable survival analyses were performed using Cox proportional hazards models. All statistical tests used in this study were two-sided and *p*-values of < 0.05 were considered significant.

3. Results

3.1. Comparison of laboratory parameters of cervical cancer patients with cervical intraepithelial neoplasia controls

The laboratory parameters of patients with cancer and cervical intraepithelial neoplasia controls were shown in Table 1. Cancer patients had significantly higher total white blood cell (WBC), neutrophil and platelet counts. And the hemoglobin count was significantly lower in patients with cancer. The mean value of PLR was higher in patients with cervical cancer. But there was no significant difference in lymphocyte count and the mean value of NLR between groups.

3.2. Patient characteristics

Patient's parameters were shown in Table 2. Median age at diagnosis was 45 years (range 21–75). Among the 616 patients, the majority of patients (66%) were diagnosed at an early stage (IA-IIA), and the majority of histologic grade (68.3%) was assessed as poorly differentiated, some missing data of patients were showed in Table 2. By tumor-invasion depth, 63 (10.2%), 238 (38.6%) and 190 (30.8%) cases were divided into full-thickness, $\geq 1/2$ and < 1/2, respectively. The LNM

Table 1
Comparison of laboratory parameters in cervical cancer patients with controls.

Variables	Controls	Cervical cancer patients	<i>P</i> value
	300	365	
RBC ($10^9/L$)	4.39(3.99–5.20)	4.32(2.09–6.36)	0.015
WBC ($10^9/L$)	6.10(4.20–8.70)	6.60(2.70–19.70)	0.001
Neutrophil ($10^9/L$)	4.01(2.46–7.01)	4.40(0.58–16.78)	0.001
Lymphocyte($10^9/L$)	1.57(0.99–3.40)	1.50(0.39–3.44)	0.446
Platelet ($10^9/L$)	177(146–402)	194(70–598)	0.001
Hb (g/L)	131(115–148)	128(24–169)	0.006
NLR	2.63(1.27–5.8)	2.82(0.48–25.63)	0.007
PLR	113(112–217)	127(37–442)	0.001

Mann-Whitney U test. CIN, cervical intraepithelial neoplasia; WBC, white blood cell; Hb, hemoglobin; NLR, Neutrophil-lymphocyte ratio; PLR, Platelet-Lymphocyte Ratio.

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