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ORIGINAL RESEARCH

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Pretreatment anemia status and elevated PLR affect the prognosis of locally advanced cervical squamous cell carcinoma patients treated with concurrent chemoradiotherapy

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Abstract

Objective: To assess the prognostic value of platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and systemic immune-inflammation index (SII) in locally advanced cervical squamous cell carcinoma (LACSC) treated with concurrent chemoradiotherapy (CCRT) regimens. **Methods**: The contribution of systemic immune inflammatory response markers (NLR, PLR, LMR, SII), inflammatory cells (lymphocytes, neutrophils, monocytes, platelets), and hematocrit in predicting the outcomes of concurrent chemoradiotherapy treatment in LACSC patients was examined using the Kaplan-Meier univariate survival analysis method. Variables that were significant for the univariate analysis were included in the multivariate regression analysis to confirm the independent prognostic factors affecting concurrent chemoradiotherapy in LACSC patients. **Results**: Univariate analysis showed that age ($p = 0.024$), PLR ($p = 0.007$), NLR ($p = 0.089$), LMR ($p = 0.021$), SII ($p = 0.087$), and Hb ($p = 0.004$) were all prognostic factors affecting OS (over survival). Multivariate regression analysis revealed that PLR ($p = 0.066$) and Hb ($p = 0.045$) before concurrent chemoradiotherapy were independent risk factors of OS in the studied population. Moreover, these two factors were significantly correlated (correlation coefficient Rs = –0.426, $p = 0.000$). **Conclusions**: The results suggested that elevated PLR and anaemia are likely to have poorer prognoses in LACSC patients who initially received radical CCRT. Moreover, pre-treatment anemia status may exacerbate the prognostic effects of PLR.

Keywords

Locally advanced cervical cancer; Concurrent chemoradiotherapy; Prognosis; Systemic immune inflammatory index; Anemia

1. Introduction

Economic development greatly affects the incidence and mortality rates of cervical cancer [1]. The status of cervical cancer remains critical in China, which is considered as the largest developing country [2]. The mortality rates of lung, breast, prostate and colorectal cancers, which are the four major cancers globally, have significantly declined [3] unlike cervical and uterine corpus cancers [4]. Due to its relative importance, extensive research on cervical cancer is being conducted in China. The famous "five trials" showed that cisplatin-based concurrent chemoradiotherapy significantly improved the survival of patients compared with radiotherapy alone, but its efficacy is still unsatisfactory. Recurrence and metastasis of cervical cancer are the two main causes of mortality after initial treatment [5, 6]. Currently, the staging system set by the International Federation of Gynecology and Obstetrics (FIGO) is considered the main reference used by clinicians for the assessment criteria to predict the prognosis of cervical cancer patients. Tumor risk assessment includes histological subtype, tumor size, invasion depth, lymph node status, and lymphovascular space involvement [7]. However, not all progression patterns can be explained using this risk stratification system; therefore, it is reasonable to stratify high-risk subgroups. Cervical cancer requires the study of novel markers that are unrelated to tumor characteristics.

In recent years, many studies have shown that systemic inflammatory responses are involved in the prognosis of cancer patients [8]. Markers that have a prognostic value in malignancies, such as hepatocellular carcinoma, esophageal cancer, colorectal cancer, and small cell lung cancer include neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte to monocyte ratio (LMR), and systemic immune-inflammation index (SII). High SII has been

reported to be associated with poor postoperative prognosis in patients with cervical cancer [9]. However, in the era of intensity-modulated radiation therapy, the individual prognostic values of PLR, NLR, LMR, and SII have not been systematically evaluated in patients with locally advanced cervical cancer who are undergoing concurrent chemoradiotherapy. In this study, we collected data about patients having locally advanced cervical squamous carcinoma (LACSC) who underwent concurrent chemoradiotherapy at the First Affiliated Hospital of Zhengzhou University between October 2013 and December 2015. The external radiation therapy technique used for the patients was intensity-modulated radiation therapy, and 3D intensity-modulated radiation therapy was used as intracavitary brachytherapy. The chemotherapy regimen was a combination of paclitaxel and carboplatin (TP). We observed the correlation between SII before treatment and the treatment prognosis with the aim of exploring a cheaper and more convenient clinical application index.

2. Materials and methods

Patients with locally advanced cervical cancer and a pathological biopsy showing squamous cell carcinoma of the cervix between October 2013 and December 2015 at our institution were selected. The patients were undergoing inpatient treatment with radical concurrent chemoradiotherapy. The 2009 FIGO staging system was used. Using the hospital's patient and radiotherapy management system, an initial search was conducted using "cervical cancer" as the search keyword, followed by further review, screening of medical records, and phone follow-ups.

The inclusion criteria were as follows: (a) between 20 and 75 years of age; (b) confirmed pathological biopsy of squamous cell carcinoma; (c) no distant metastasis confirmed by preoperative imaging; (d) no preoperative antitumor-related treatment; (e) complete clinicopathological information and available follow-up information.

The exclusion criteria were as follows: (a) pathological biopsy of non-squamous cell carcinoma; (b) missing clinical, laboratory, and follow-up information; (c) received blood transfusion within 2 months prior to treatment; (d) active comorbid infection; (e) presence of other malignancies; (f) death within 30 days of treatment or postoperative death from other non-tumor related causes; (g) those with inflammatory diseases, such as sepsis, HIV infection, systemic lupus erythematosus, inflammatory bowel disease, and rheumatoid arthritis.

2.1 Treatment

Radiotherapy was performed using external pelvic irradiation with 3D intracavitary brachytherapy. Conventional segmentation was used, 5 times/week at 50 Gy/25 times. The dose for pathological lymph nodes was increased by 14 Gy/7 times. External irradiation was performed using intensity modulated radiation therapy with a 6MV-X-linear accelerator. Intracavitary brachytherapy was performed using a Nucletron-pass high-dose-rate Ir-192 brachytherapy machine, and 3D-brachytherapy was also performed. The HRCTV target area dose was 24–32 Gy/4–6 times, 2 times/week, and performed at the end of external irradiation. Total radiotherapy duration was 7–8 weeks. All patients received platinum-based concurrent chemoradiotherapy using the "TP" regimen (paclitaxel 135–150 mg/m^{2}combined with carboplatin 300–400 mg/m^2, q3W), and all enrolled patients completed the treatment.

2.2 Data collection and follow-up

All enrolled patients have undergone routine inpatient examinations, such as routine blood tests, liver, and kidney functions, electrolytes, and imaging, such as pelvic enhanced MRI, and chest and whole abdomen enhanced CT combined with cervical ultrasound 1 week before radical concurrent chemoradiotherapy. Pathological biopsy confirmed the diagnosis of squamous cell carcinoma. Radical concurrent chemoradiotherapy was subsequently performed. The medical records of eligible patients were reviewed, and phone follow-up was conducted to collect and record information on examinations, laboratory tests, survival status, and time of death. Follow-up visits included clinical examinations every 3 months for the first 2 years, twice a year for the next 3 years, and annually thereafter. Pelvic MRI and retroperitoneal and enhanced chest CT were performed when recurrent symptoms were detected. The final follow-up date was 22 March 2020. Phone, outpatient, or inpatient follow-up was done. Overall survival was defined as the time between the date of first admission and the occurrence of LACSC-related death. All patients were followed up for 4–68 months, with a median follow-up duration of 52 months. The baseline characteristics of enrolled patients are shown in Table 1. Mean age (±SD): 52.11 (±10.52) years; median: 52 years, range: 26–75 years.

2.3 Calculation of systemic immune inflammatory response markers

A literature search using Pubmed and Wanfang databases resulted in the identification of four systemic immunoinflammatory markers, including NLR, PLR, LMR, and SII. They were calculated as shown in Table 2.

2.4 Statistical analysis

SPSS Statistics 20.0 software (IBM, Armonk, New York, USA) was used to process and analyze the data. Categorical variables were described using frequencies and percentages. Ratios were compared using the Chi-square test (Fisher's exact test). Ordinal variables were compared using the Kruskal-Wallis univariate ANOVA non-parametric test. Survival curves were plotted using the Kaplan-Meier curve method, and univariate survival curves were compared using the log-rank test. The values closest to the maximum sensitivity and specificity were calculated by ROC curves and selected as the cut-off points for PLR, NLR, LMR, and SII before treatment. The cut-off points were used to divide patients into high- and low-level groups. Spearman's rank correlation coefficient was used to test correlation between different factors. All the above statistical tests were two-tailed, and a difference of $p < 0.1$ was considered to be statistically significant.

TABLE 1. Baseline characteristics of enrolled patients.

Clinicopathological characteristics	N (%)	5-year survival	Tumor-related deaths
FIGO stages			
IB2–II	80	55	25
III–IVA	33	24	9
Large mass			
No	34	23	11
Yes	79	56	23
Lymph node			
(+)	55	35	20
(–)	58	44	14

FIGO, International Federation of Gynecology and Obstetrics.

TABLE 2. Calculation of systemic immune inflammatory response markers.

Systemic immune inflammatory response index	Calculation method
PLR	Absolute peripheral blood platelet count (10^9/L)/absolute peripheral blood lymphocyte count (10^9/L)
NLR	Absolute peripheral blood neutrophil count (10^9/L)/absolute peripheral blood lymphocyte count (10^9/L)
LMR	Absolute peripheral blood lymphocyte count (10^9/L)/absolute peripheral blood monocyte count (10^9/L)
SII	Absolute peripheral blood platelet count (10^9/L) × Absolute peripheral blood neutrophil count (10^9/L)/Absolute peripheral blood lymphocyte count (10^9/L)

PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; SII, systemic immune-inflammation index.

3. Results

(1) Survival outcome characteristics of the enrolled patients

The median follow-up duration was 52 months (4–68) as of the last follow-up date (22 March 2020). Of these patients, 33 (29.2%) died and 79 (69.9%) survived, with overall survival rates of 86.2%, 67.8%, and 65.6% at 1, 3, and 5 years, respectively. The median survival was 55.5 months, as shown in Fig. 1.

(2) Calculation and determination of the optimal cut-off values are shown in Table 3.

(3) Analysis of prognostic factors

Univariate analysis showed that age (p = 0.019), PLR (p = 0.007, Fig. 2A), LMR (p = 0.023), Hb (p = 0.002, Fig. 3A), and FIGO stage (p = 0.047) were all prognostic factors affecting OS (over survival). Univariate analysis showed that age (p = 0.031), PLR (p = 0.007, Fig. 2B), LMR (p = 0.028), and Hb (p = 0.003, Fig. 3B) were all prognostic factors influencing PFS (progression-free survival). The variables that were significant for univariate analysis were included in the Cox proportional risk model for multivariate regression analysis. In this study population, it was found that before concurrent chemoradiotherapy, PLR and Hb were independent risk factors affecting both OS (p = 0.066, and p = 0.045, respectively) and PFS (p = 0.063, p = 0.065, respectively).

(5) Relationship between different PLR groups and each clinicopathological parameter

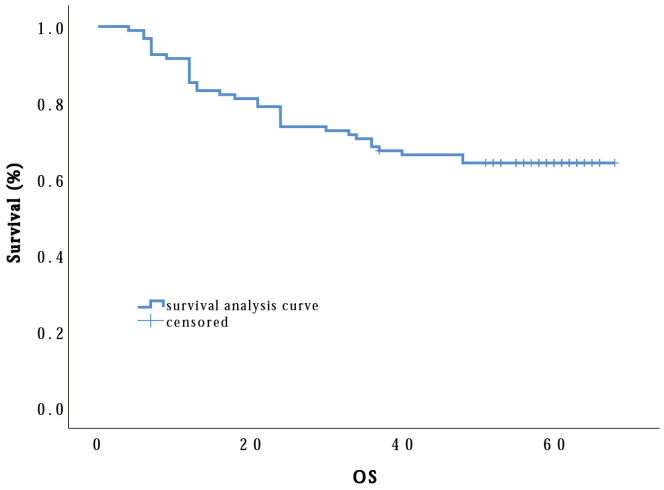

FIGURE 1. Survival analysis function after censoring (OS survival curve of 113 LACSC patients).

In this study, 113 patients with locally advanced cervical cancer were divided into low- and high-level groups based on the PLR threshold calculated from the ROC curve. The differences in clinicopathological parameters between the groups were compared. As shown in Table 4, high PLR levels were significantly correlated with age (p = 0.000) and anemia (p = 0.000).

TABLE 3. Optimal cut-off values for NLR, PLR, LMR, and SII from ROC curve analysis.

Factor	Cut-off value	AUC	95% CI	Sensitivity (%)	Specificity (%)
PLR	123.36	0.595	0.483–0.708	75.8	53.2
NLR	2.26	0.554	0.444–0.664	57.6	60.7
LMR	2.98	0.584	0.469–0.699	55.7	63.6
SII	587.82	0.559	0.443–0.675	57.6	62.0

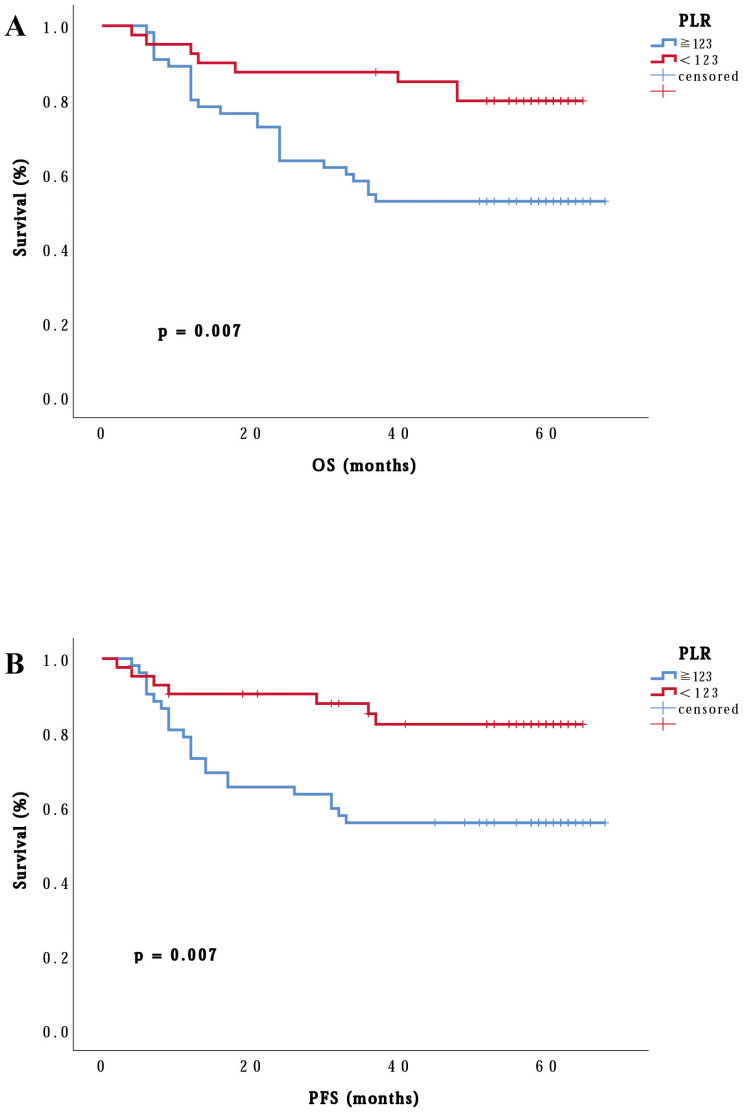

FIGURE 2. Kaplan-Meier survival curves showing a significant correlation between (A) PLR and OS and (B) PLR and PFS for locally advanced cervical squamous cell carcinoma treated with concurrent chemoradiotherapy.

4. Discussion

The survival of LACSC patients has reached a plateau in the last 20 years (since 1999) when the NCCN (National Comprehensive Cancer Network) recommended CCRT (concurrent chemoradiotherapy) as the preferred treatment method for LACSC. This study found that the median time to progression was 17.5 months, with a mean of 19.91 months and a range between 2 and 49 months, where treatment failure occurred mainly within 2 years of diagnosis. One of the various aspects

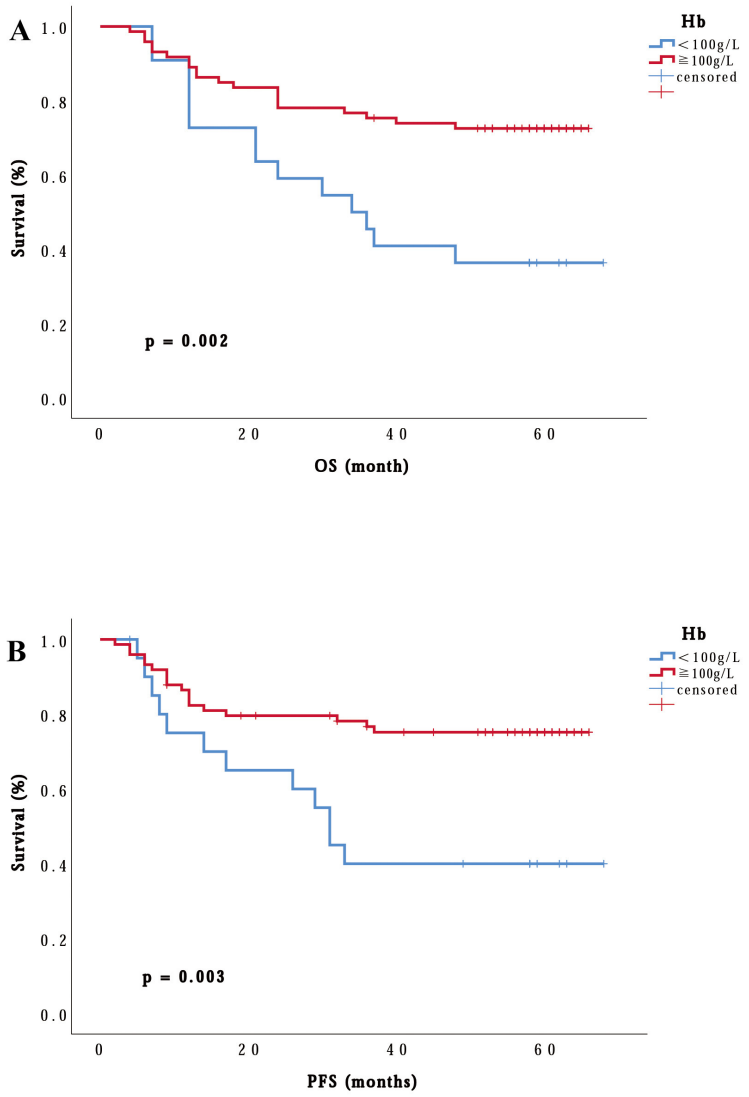

FIGURE 3. Kaplan Meier survival curves showing a significant correlation between (A) Hb and OS and (B) Hb and PFS for locally advanced cervical squamous cell carcinoma treated with concurrent chemoradiotherapy.

that have been studied to improve the treatment outcome is the use of systemic therapy. In addition to CCRT regimens such as induction chemotherapy or consolidation chemotherapy, other regimens have shown uncertain advantages over CCRT alone, and thus need to be further explored in well-designed trials. Therefore, adding new agents, modifying existing regimens, intensifying treatment regimens, combining local therapy with CCRT regimens, or adding targeted therapies or immunotherapy may be approaches to improve and optimize the prognosis of LACSC patients [10]. In addition, exploring the underlying cause for the insensitivity towards radiotherapy in some patients is a feasible and important objective. In this study, we investigated the prognostic factors affecting LACSC in terms of patient's age, mass size, anemia status, chemotherapy course completion, presence/absence of lymph node metastasis, FIGO stage, pathological type, PLR, NLR, LMR, SII, and response after concurrent chemoradiotherapy. In this study, we found that anemia and PLR, which is one of the systemic inflammatory response indices before concurrent chemoradiotherapy, were independent prognostic factors, and there was a negative correlation between them.

The study of inflammation and tumors dates to the 19th century, when the German scholar Rudolf Virchow observed large numbers of infiltrating leukocytes in a surgically resected tumor tissue. This observation gave rise to the hypothesis that tumors may originate from an inflammatory response. In recent years, more studies and epidemiological investigations have led to an increasing emphasis on this link. In addition, a review published in Cell in 2011 proposed 10 classical hallmarks of malignant tumors, of which the pro-tumor inflam-

TABLE 4. Relationship between PLR levels and clinicopathological features in 113 LACSC patients.

Factor	n	PLR >123.36	PLR <123.36	Correlation coefficient *Rs*	*p* value
Age				0.363	0.000
≤50 years old	52	38	14		
>50 years old	61	25	36		
Anemia				–0.426	0.000
<110 g/L	34	28	6		
≥110 g/L	79	35	44		
FIGO stage					0.377
I–IIB	81	42	39		
IIIA–IVA	32	21	11		
Lump size					0.137
≥4 cm	80	48	32		
<4 cm	33	15	18		
Lymph node involvement					0.317
Positive	59	30	29		
Negative	54	33	21		

matory response is one of the newly added features [11, 12]. Chronic inflammation and malignancy are complementary and mutually reinforcing. Not only can chronic inflammation promote tumor growth, but it can also exacerbate the degree of inflammatory response, thus forming a vicious cycle. Multiple inflammation-related signaling pathways, such as the transcription factor NF-κB and STAT3 signaling pathway, are involved in these processes. In addition, chronic inflammation can recruit many bone marrow progenitor cells into the tumor tissue through the release of related cytokines, which evolve into different types of immunosuppressive cells under the influence of tumor microenvironment. This generates a type of immunosuppressive microenvironment, thus helping tumor cells evade immune surveillance. As a result of angiogenesis, these cells gradually develop and mature, penetrate the basement membrane, and eventually spread to distant sites under the action of chemokines. Recent studies have shown that the systemic inflammatory response is closely related to tumor proliferation and progression [13]. For example, vascular endothelial growth factor (VEGF) plays an important role in the angiogenesis and metastasis of tumor cells. In addition, platelets adhering to tumor cells can promote the formation of tumor neovascularization by secreting VEGF, while increasing the permeability of microvessels, thereby promoting the spread of tumor cells. Platelets protect tumor cells from cytolysis and can interact directly with tumor cells to synergistically activate the TGFβ/Smad and NF-κB pathways in cancer cells, induce epithelial-mesenchymal transition, and can promote metastasis. In addition, platelets can secrete inflammatory proteins, such as IL-6 and TNF-α, which are associated with tumor cell metastasis and may stimulate tumorigenesis and promote metastasis by synthesizing angiogenic factors, such as platelet-derived growth factors and VEGF [14]. In addition, platelets can secrete growth-promoting factors, chemokines, pro-angiogenic regulatory proteins, secreted protein hydrolases and particles in the tumor microenvironment. Activated platelets promote the growth and invasion of tumor cells.

Many studies have been conducted on systemic inflammatory indices as prognostic factors, and there is growing evidence of the value of PLR in predicting survival in solid tumors. PLR has been shown to be an independent risk factor for poor OS in lung cancer [15], breast cancer [16, 17], colorectal cancer [18], endometrial cancer [19] and ovarian cancer [20]. There is also a growing number of studies in cervical cancer that have yielded inconsistent results. Many studies have investigated the prognostic correlation factors of preoperative systemic immune-inflammatory index and postoperative cervical cancer survival [21, 22]. Relatively few studies have investigated the prognostic correlation factos of LACSC patients treated with concurrent chemoradiotherapy. Thus, the aim of the present study was to investigate the prognostic correlation factors of PLR, NLR, LMR, and SII in LACSC patients, and uncover the relationship between inflammatory indices and clinical characteristics. We found that PLR and anemia status were factors affecting disease control after concurrent chemoradiotherapy or independent risk factors affecting PFS and OS. Our findings are the same as reported by Theodora A.Koulis [23], that pre-treatment anemia and thrombocytosis was prognostic factors in patients with cervical cancer treated with radical chemoradiotherapy. Some scholars have found the same phenomenon in patients undergoing concurrent chemo-radiation for anal cancer [24, 25]. More significantly, we found that there was a negative correlation between anemia and PLR.

In this study, we found that anemia and elevated PLR, which is one of the systemic inflammatory response indices before concurrent chemoradiotherapy, were independent prognostic factors, and there was a negative correlation between them. Several researches have proven that preoperative hemoglobin level was related to the prognosis of lung adenocarcinoma [26], colorectal cancer [27], cervical cancer [28]. Studies also demonstrated that thrombocytosis and anemia occur in

tumor patients. As Georgios Gakis, *et al.* [29] reviewed that growing tumors induce secretion of growth factors and cytokines which may cause bone marrow suppression and disorders of iron metabolism, resulting in tumor-induced anemia, and is able to stimulate platelet production. It has also been shown that hypoxia and ischemia alter platelet phenotypes and change platelet response to agonists because of changes in the expression levels of the signal transduction pathway proteins [30]. Therefore, based on our findings and a review of relevant literature, we hypothesize that anemia status and elevated PLR affect the outcome of radiotherapy in patients with locally advanced cervical cancer to some extent. To further validate this hypothesis, our group will increase the number of included patients and utilize basic studies.

5. Conclusions

This study investigated the prognostic value of systemic immune inflammatory response markers (NLR, PLR, LMR, SII), inflammatory cells (lymphocytes, neutrophils, monocytes, platelets), and hematocrit in predicting the outcomes of CCRT treatment in LACSC patients. The results suggested that elevated PLR and anaemia before concurrent chemoradiotherapy are likely to have poorer prognoses. Moreover, pre-treatment anemia status may exacerbate the prognostic effects of PLR.

ABBREVIATIONS

PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; SII, systemic immune-inflammation index; LACSC, locally advanced cervical squamous cell carcinoma; FIGO, International Federation of Gynecology and Obstetrics; TP, paclitaxel and carboplatin; VEGF, vascular endothelial growth factor; NCCN, National Comprehensive Cancer Network; CCRT, concurrent chemoradiotherapy.

AUTHOR CONTRIBUTIONS

MD take the responsibility for the whole work and plan the entire study. MD contributed to drafting the manuscript and prepared the tables and figures. YS contributed to the review of related literature. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University (approval no.: 2019-KY-381). We waived the informed consent because this is a retrospective study. Reassuringly, we de-identified all details of patients.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2018; 68: 394–424.

[2] Zhu J, Wu XH. Review of advances in cervical cancer research in 2019. Journal of Multidisciplinary Cancer Management (Electronic Version). 2020; 6 (In Chinese).

[3] Henley SJ, Thomas CC, Lewis DR, Ward EM, Islami F, Wu M, *et al*. Annual report to the nation on the status of cancer, part II: Progress toward Healthy People 2020 objectives for 4 common cancers. Cancer. 2020; 126: 2250–2266.

[4] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA: A Cancer Journal for Clinicians. 2020; 70: 7–30.

[5] Cohen PA, Jhingran A, Oaknin A, Denny L. Cervical cancer. The Lancet. 2019; 393: 169–182.

[6] Liontos M, Kyriazoglou A, Dimitriadis I, Dimopoulos M, Bamias A. Systemic therapy in cervical cancer: 30 years in review. Critical Reviews in Oncology/Hematology. 2019; 137: 9–17.

[7] Marth C, Landoni F, Mahner S, McCormack M, Gonzalez-Martin A, Colombo N. Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2017; 28: iv72–iv83.

[8] Sasano T, Mabuchi S, Kozasa K, Kuroda H, Kawano M, Takahashi R, *et al*. The Highly Metastatic Nature of Uterine Cervical/Endometrial Cancer Displaying Tumor-Related Leukocytosis: Clinical and Preclinical Investigations. Clinical Cancer Research. 2018; 24: 4018–4029.

[9] Huang H, Liu Q, Zhu L, Zhang Y, Lu X, Wu Y, *et al*. Prognostic Value of Preoperative Systemic Immune-Inflammation Index in Patients with Cervical Cancer. Scientific Reports. 2019; 9: 3284.

[10] Verma J, Monk BJ, Wolfson AH. New Strategies for Multimodality Therapy in Treating Locally Advanced Cervix Cancer. Seminars in Radiation Oncology. 2016; 26: 344–348.

[11] Porta C, Riboldi E, Sica A. Mechanisms linking pathogens-associated inflammation and cancer. Cancer Letters. 2011; 305: 250–262.

[12] Hanahan D, Weinberg R. Hallmarks of Cancer: the next Generation. Cell. 2011; 144: 646–674.

[13] Peng D, Zhang C, Gong Y, Hao H, Guan B, Li X, *et al*. Prognostic significance of HALP (hemoglobin, albumin, lymphocyte and platelet) in patients with bladder cancer after radical cystectomy. Scientific Reports. 2018; 8: 794.

[14] Tesfamariam B. Involvement of platelets in tumor cell metastasis. Pharmacology & Therapeutics. 2016; 157: 112–119.

[15] Zhu X, Song H, Chen Y, Han F, Wang Q, Cui Y. Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio in Blood to Distinguish Lung Cancer Patients from Healthy Subjects. Disease Markers. 2020; 2020: 8844698.

[16] Kim J, Jung EJ, Kim J, Lee HS, Kwag S, Park J, *et al*. Dynamic changes of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio predicts breast cancer prognosis. BMC Cancer. 2020; 20: 1206.

[17] Graziano V, Grassadonia A, Iezzi L, Vici P, Pizzuti L, Barba M, *et al*.

Combination of peripheral neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio is predictive of pathological complete response after neoadjuvant chemotherapy in breast cancer patients. The Breast. 2019; 44: 33–38.

[18] Hu Z, Tan S, Chen S, Qin S, Chen H, Qin S, *et al*. Diagnostic value of hematological parameters platelet to lymphocyte ratio and hemoglobin to platelet ratio in patients with colon cancer. Clinica Chimica Acta. 2020; 501: 48–52.

[19] Ni L, Tao J, Xu J, Yuan X, Long Y, Yu N, *et al*. Prognostic values of pretreatment neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in endometrial cancer: a systematic review and meta-analysis. Archives of Gynecology and Obstetrics. 2020; 301: 251–261.

[20] Wang N, Li C, Yang Y, Guan Y, Wang F, Wang Y, *et al*. The Use of Platelet/Lymphocyte Ratio and Cancer Antigen 125 Combined with Magnetic Resonance Diffusion-Weighted Imaging in Diagnosis of Recurrent Ovarian Cancer and Neuropathic Pain. World Neurosurgery. 2021; 149: 502–510.

[21] Huang H, Liu Q, Zhu L, Zhang Y, Lu X, Wu Y, *et al*. Prognostic Value of Preoperative Systemic Immune-Inflammation Index in Patients with Cervical Cancer. Scientific Reports. 2019; 9: 3284.

[22] Chao B, Ju X, Zhang L, Xu X, Zhao Y. A Novel Prognostic Marker Systemic Inflammation Response Index (SIRI) for Operable Cervical Cancer Patients. Frontiers in Oncology. 2020; 10: 766.

[23] Koulis TA, Kornaga EN, Banerjee R, Phan T, Ghatage P, Magliocco AM, *et al*. Anemia, leukocytosis and thrombocytosis as prognostic factors in patients with cervical cancer treated with radical chemoradiotherapy: a retrospective cohort study. Clinical and Translational Radiation Oncology. 2017; 4: 51–56.

[24] Franco P, Montagnani F, Arcadipane F, Casadei C, Andrikou K, Martini S, *et al*. The prognostic role of hemoglobin levels in patients undergoing concurrent chemo-radiation for anal cancer. Radiation Oncology. 2018; 13: 83.

[25] Casadei-Gardini A, Montagnani F, Casadei C, Arcadipane F, Andrikou K, Aloi D, *et al*. Immune inflammation indicators in anal cancer patients treated with concurrent chemoradiation: training and validation cohort with online calculator (ARC: Anal Cancer Response Classifier). Cancer Management and Research. 2019; 11: 3631–3642.

[26] Ogawa H, Fujibayashi Y, Nishikubo M, Nishioka Y, Tane S, Kitamura Y, *et al*. Prognostic significance of preoperative haemoglobin a1c level in patients with lung adenocarcinoma. Interactive CardioVascular and Thoracic Surgery. 2021; 33: 534–540.

[27] Yalav O, Topal U, Unal AG, Eray IC. Prognostic significance of preoperative hemoglobin and albumin levels and lymphocyte and platelet counts (HALP) in patients undergoing curative resection for colorectal cancer. Annali Italiani di Chirurgia. 2021; 92: 283–292.

[28] Li B, Shou Y, Zhu H. Predictive value of hemoglobin, platelets, and D-dimer for the survival of patients with stage IA1 to IIA2 cervical cancer: a retrospective study. Journal of International Medical Research. 2021; 49: 3000605211061008.

[29] Gakis G, Todenhöfer T, Stenzl A. The prognostic value of hematological and systemic inflammatory disorders in invasive bladder cancer. Current Opinion in Urology. 2011; 21: 428–433.

[30] Cameron SJ, Mix DS, Ture SK, Schmidt RA, Mohan A, Pariser D, *et al*. Hypoxia and Ischemia Promote a Maladaptive Platelet Phenotype. Arteriosclerosis, Thrombosis, and Vascular Biology. 2018; 38: 1594–1606.

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