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Original Article

Prognostic significance of systemic inflammatory response markers NLR, PLR, and MLR in advanced high-risk endometrial cancer following radiotherapy

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Abstract: Objective: This study aims to evaluate the relationship between systemic inflammatory response markers and the short-term prognosis of patients with endometrial cancer after comprehensive treatment. Methods: This retrospective study analyzed the baseline data from 156 endometrial cancer patients who received postoperative radiotherapy at the gynecology department of ChangZhi People Hospital Affiliated to ChangZhi Medical College. Optimal cutoff values for preoperative hematological indicators were determined using receiver operating characteristic (ROC) curves. The Kaplan-Meier method was used for univariate analysis to describe survival time and the 5-year overall survival rate of patients, as well as to plot the survival curve for endometrial cancer. Multivariate regression analysis was employed to identify independent risk factors for patient survival prognosis and to establish a multivariate prediction model. Results: By the end of the follow-up period, 42 patients (26.9%) were alive, and 114 patients (73.1%) had died. The shortest survival period was 21 months, the longest was 73 months, and the median survival time was 51 months. The 5-year survival rate was 39.3%. The prognostic nomogram model for endometrial cancer included 7 risk factors: age, pathological stage, interval time to postoperative chemotherapy, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR). The Hosmer-Lemeshow test result for this model showed that the area under the ROC curve was 0.995 (95% CI: 0.989-1.000), with an optimal cutoff value of 0.485, a sensitivity of 0.951, and a specificity of 0.71616. The internal validation results of the model showed a C-index of 0.995, indicating a good fit and high predictive value of the model. Conclusion: Pre-treatment peripheral blood levels of PLR, NLR, and MLR were higher in deceased patients who received postoperative radiotherapy for advanced endometrial cancer compared to survivors. A multivariate prediction model based on preoperative and intraoperative baseline data can effectively predict patient prognosis.

Keywords: Inflammatory response markers, endometrial cancer, prognosis, radiotherapy, multivariate prediction model

Introduction

Endometrial cancer, a type of malignant tumor originating in the endometrium, is increasingly recognized as a significant health concern among women [1, 2]. The rising incidence of this cancer has drawn widespread attention, with various factors contributing to its rise, including the rapid development of modern society and the increasingly fast pace of people's lives [3, 4]. Prolonged work pressure, irregular eating habits, lack of exercise, high-stress environments, and an imbalanced diet structure characterized by excessive intake of high-fat and high-sugar foods can not only lead to weight gain but may also increase the risk of developing endometrial cancer [5]. Additionally, environmental pollution and genetic factors may also increase the incidence of endometrial cancer to some extent [6, 7].

For the treatment of endometrial cancer, a comprehensive approach involving various treatment methods is essential to achieve optimal

therapeutic effect. Among various treatments, surgical intervention stands out to be prevalent and fundamental [8, 9]. Surgery mainly involves the excision of tumor tissue to achieve a curative effect. However, in cases where surgery is not feasible, radiotherapy can also serve as a primary treatment method. Radiotherapy utilizes high-energy radiation to eliminate or damage cancer cells, impeding their growth and spread. Consequently, it emerges as a primary treatment method for rescuing high-risk advanced patients and preventing disease recurrence [10, 11]. Changes in the levels of biomarkers associated with systemic inflammatory responses and adverse clinical outcomes are linked to a variety of malignant neoplasms. Inflammatory biomarkers, as potential prognostic indicators, can elucidate the inflammatory status in different cancer types. Furthermore, the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) have been found to be correlated with the prognosis of numerous tumors; however, there is a paucity of research focused on their predictive value in endometrial cancer [12]. Based on this background, our study aims to further validate the treatment prognosis and influencing factors in endometrial cancer patients, while also exploring the role of serum inflammation markers NLR, PLR, and MLR in predicting prognosis, in order to improve the overall diagnosis and treatment level of endometrial cancer.

Materials and methods

Patient selection

The baseline data of 188 endometrial cancer patients who underwent radiotherapy after surgery at the gynecology department of ChangZhi People hospital Affiliated to ChangZhi Medical College from January 2017 to December 2022 were collected. After screening, 156 patients were included and followed up for 6 years, with their survival status recorded. Patients were divided into the survival group and the death group according to their survival status (**Figure 1**). This study was approved by the ethics committee of ChangZhi People hospital Affiliated to ChangZhi Medical College.

Inclusion criteria

1. Patients diagnosed with endometrial cancer through pathological biopsy. 2. Patients classified as pathological stage III or higher. 3. Patients with complete and standard medical records, including present and past medical history, as well as complete preoperative laboratory and imaging results. 4. Patients aged 18-80 years. 5. Patients with a KPS score > 70.

Exclusion criteria

1. Patients with confirmed tumors in other anatomical locations. 2. Patients with incomplete radiotherapy plans or those unable to complete radiotherapy. 3. Patients with distant metastases. 4. Patients with severe dysfunction of major organs such as the heart or kidneys. 5. Patients with severe dysfunction of the hematological or immune systems. 6. Patients with incomplete clinical data.

Data acquisition

Patient blood test results, surgical methods, and radiotherapy methods were obtained from the electronic medical record system. Surgical methods: All patients underwent total hysterectomy + bilateral salpingo-oophorectomy + pelvic lymphadenectomy ± para-aortic lymphadenectomy. Pathological and cytological examinations of the lesion tissues and peritoneal washings were conducted by pathology departments to comprehensively assess the pathological staging of the patients. Radiotherapy: The radiotherapy plan was formulated using the Varian radiotherapy system. Intensity-modulated radiotherapy (IMRT) was performed using 6MV-X rays for external beam radiation therapy. Before the radiotherapy, patients took 50 ml of iodixanol for bowel preparation. Target areas for radiotherapy included the iliac, external iliac, internal iliac, parametrial, obturator, presacral lymph node regions, and the upper part of the vagina. The decision to perform extended-field radiotherapy was based on cervical involvement. The radiotherapy dose and schedule were as follows: 1.8 Gy-2.0 Gy per session, with a total dose of 45-50 Gy over 25-28 sessions [13].

Primary observational indicators

The primary indicators were preoperative blood routine lymphocyte count, neutrophil count, and platelet count. Peripheral venous blood was collected from all patients on an empty stomach within 7 days before surgery, and the

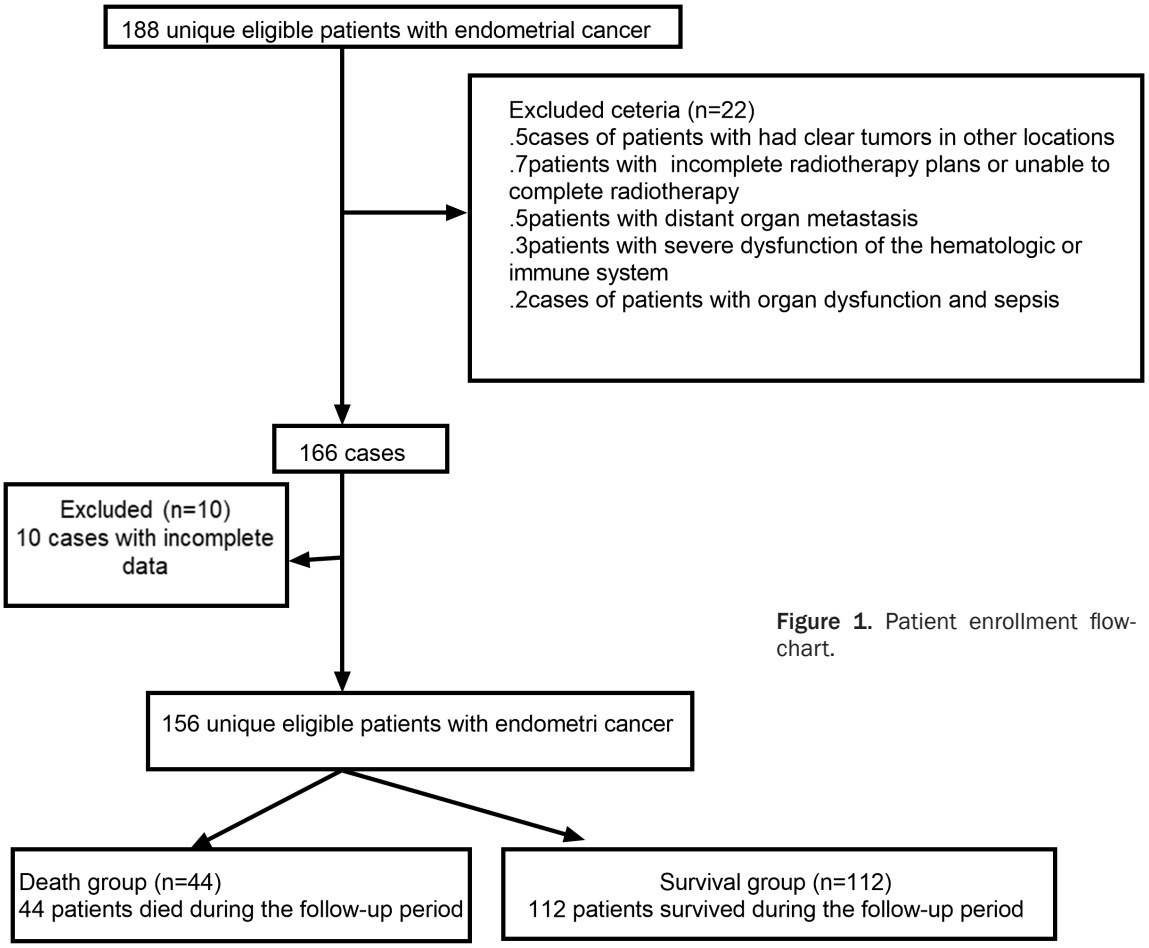

Figure 1. Patient enrollment flowchart.

count levels of neutrophils, lymphocytes and platelets were measured. The methods were as follows: 2 mL of fasting venous blood was placed in an EDTA-K2 anticoagulant tube and shaken evenly. Each specimen was analyzed using the XE-2100 automated hematology analyzer and its corresponding reagents (Sysmex, Japan) to complete the routine blood test. The factors influencing patient survival and the predictive role of serum inflammatory markers PLR, NLR, and MLR on patient prognosis were analyzed. The liver and kidney function were detected by the Hitachi 7080 automatic biochemical analyzer (Item No. HC00301298) and Hepatic lipase Activity Assay Kit, Visible spectrophotometry (Item No. BA1144-50) according to the specification parameters.

Data analysis

Data analysis was performed using SPSS 26.0 software. Measurement data were expressed as mean ± SEM. The t-test was employed to analyze measurement data following a normal distribution. The paired sample t-test was applied for intra-group comparisons, while the independent sample t-test or Mann-Whitney U test (in cases of non-normal distribution) was used for inter-group comparisons. Count data were expressed as rates (percentages) and analyzed using the Chi-square (X^2) test. Variables with statistical significance in univariate analysis were subsequently included in a logistic regression model to calculate odds ratios (OR) and their corresponding 95% confidence interval (CI). The "rms" package in R software version 4.3 was used to construct a nomogram prediction model for the prognosis of endometrial cancer. The model's fit was evaluated using the Hosmer-Lemeshow test. Internal validation of the nomogram model was performed by plotting a calibration curve, and the predictive performance of the nomogram was assessed through decision curve analysis. The receiver operating characteristic (ROC)

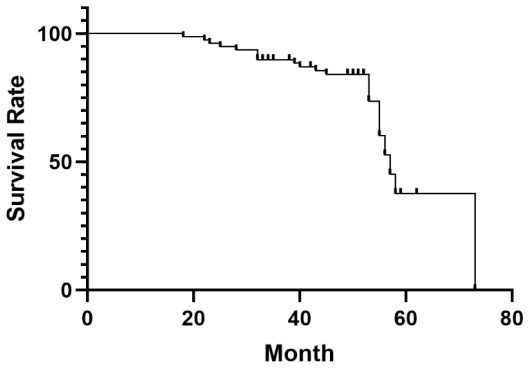

Figure 2. Overall survival curve of the patients.

curve for each inflammatory factor was generated using SPSS software, with the area under curve (AUC) and its corresponding 95% confidence interval (95% CI) calculated. Statistical significance was defined as a *P*-value of less than 0.05.

Results

Patient survival

A total of 156 patients were included in this study. As of the follow-up date, January 31, 2023, 42 patients were alive and 114 had died. The shortest survival period was 21 months, the longest was 73 months, and the median survival time was 51 months. The 5-year survival rate was 39.3%. The overall survival curve for the patients is shown in **Figure 2**.

Comparison of baseline data between survivors and deceased patients

There were statistically significant differences between survivors and deceased patients in terms of age, pathological stage, interval time to postoperative radiotherapy, lymph node metastasis, and KPS score. However, there were no statistically significant differences in menopausal status, BMI, underlying diseases, or smoking/alcohol history. Detailed information is provided in **Table 1**.

Comparison of peripheral blood-related indicators between survivors and deceased patients

There were no statistically significant differences between survivors and deceased patients in terms of hemoglobin levels, white blood cell count, and liver and kidney function (all P > 0.05) (**Table 2**).

Comparison of peripheral blood tumor markers between survivors and deceased patients

No statistically significant differences were found between survivors and deceased patients regarding the pre-treatment tumor markers YKL-40, HE4, CA125, and CA-199 (all P > 0.05) (**Figure 3**).

Comparison of peripheral blood PLR, NLR, and MLR between survivors and deceased patients

The peripheral blood PLR, NLR, and MLR levels of survivors were lower than those of deceased patients, and the differences were statistically significant (**Figure 4**).

Predictive efficacy of serum PLR, NLR, and MLR for patient death

The results of this study showed that the sensitivity of PLR, NLR, and MLR in predicting patient death was 86.3%, 96.1%, and 90.2%, respectively. The specificity was 55.6%, 63.0%, and 70.4%, respectively. The AUC was 0.674, 0.874, and 0.718, respectively. Details are presented in **Table 3** and **Figure 5**.

Multivariate analysis of patient prognosis

Univariate analysis indicated that factors, such as age, pathological stage, interval time to postoperative radiotherapy, lymph node metastasis, KPS score, and PLR, NLR, and MLR, affected the prognosis of endometrial cancer patients undergoing comprehensive treatment. Subsequent multivariate analysis revealed that age, interval time to postoperative radiotherapy, lymph node metastasis, and the groupings of PLR, NLR, and MLR were independent prognostic factors for patient mortality. Details are displayed in **Tables 4** and **5**.

Evaluation and validation of the nomogram prediction model for endometrial cancer prognosis

A prognosis prediction model for endometrial cancer was established incorporating various factors (**Figure 6**). An ROC curve was constructed based on the relationship between the predicted *P* values and the prognosis of endome-

Table 1. Comparison of general data between the two groups

Index	Death group (n = 114)	Survival group (n = 42)	Statistical value	P
Age	73.2±3.9	65.4±4.2	18.773	< 0.001
BMI	25.3±3.3	25.6±3.6	0.551	0.430
Menopause			0.004	0.945
Yes	86	32		
No	28	10		
Pathological stage			0.724	0.394
III	32	16		
IV	82	26		
KPS score	55.3±5.0	62.4±4.2	8.442	0.021
Interval of postoperative radiotherapy	3.5±0.3	2.2±0.4	9.240	0.003
Lymph node metastasis			11.760	0.000
Yes	90	16		
No	24	26		
Underlying disease (Yes/No)	22/68	10/32	0.003	0.955
Smoking/drinking history	18/16	8/6	0.867	0.766

Table 2. Comparison of blood routine and liver and kidney function between the two groups

Group	WBC ($\times 10^9$)	Hemoglobin (g/L)	AST (U/L)	ALT (U/L)	Scr (mmol/L)
Survival group (n = 42)	9.76±1.1	12.5±2.0	21.6±2.5	23.4±2.8	72.7±4.7
Death group (n = 114)	9.53±1.2	12.8±2.2	22.4±2.7	22.6±2.5	72.4±5.3
Statistical value	0.773	0.882	0.674	0.591	0.653
P	0.684	0.721	0.504	0.486	0.676

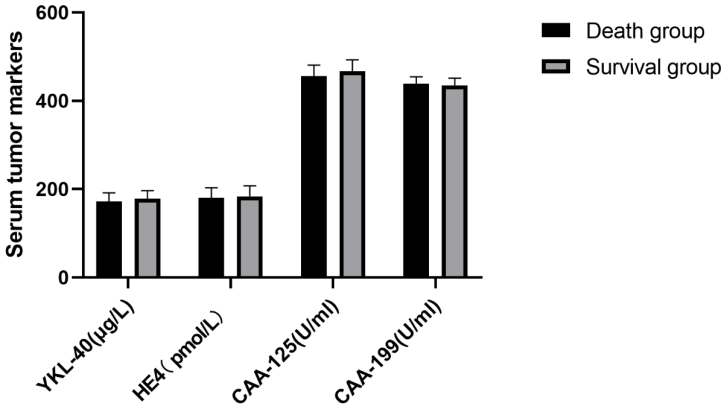

Figure 3. Comparison of preoperative tumor markers between the two groups.

trial cancer (**Figure 7**). The AUC was 0.995 (95% CI: 0.989-1.000), with an optimal cutoff value of 0.485. The model demonstrated a sensitivity of 0.951 and a specificity of 0.716. The Hosmer-Lemeshow test showed no statistically significant difference between the predicted and observed values ($\chi^2 = 2.465$, P = 0.883), indicating a good fit of the model to the observed data.

Using the Bootstrap method with 1000 resampling iterations, a calibration curve was plotted to determine the internal validation of the nomogram model. The calibration curve yielded a consistency index of 0.955, and the curve was closely aligned with the standard curve, indicating strong agreement between the nomogram model's predictions and actual risk (**Figure 8A**, **8B**).

Discussion

Endometrial cancer is one of the most common gynecological malignancies, ranking second in incidence rate after cervical and ovarian cancers [14, 15]. The early symptoms of this cancer are often subtle, which can lead to delayed diagnosis and missed treatment opportunities. Most patients with endometrial cancer may experience symptoms such as abnormal vaginal bleeding, lower abdominal pain, and abnormal discharge in the initial stages. Consequently, prompt differenti-

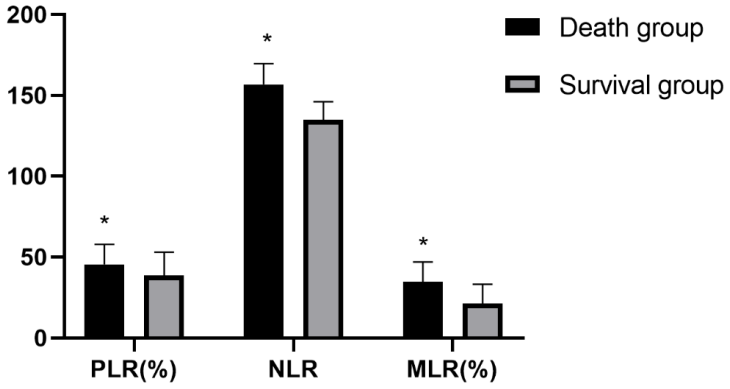

Figure 4. Comparison of peripheral blood PLR, NLR and MLR between the two groups.

Table 3. Diagnostic efficacy of serum PLR, NLR and MLR

Index	Cut-off value	Sensitivity	Specificity	AUC	95% CI
PLR	2.85	86.3	55.6	0.674	0.540-0.807
NLR	134.45	96.1	63.0	0.874	0.739-0.935
MLR	0.32	90.2	70.4	0.718	0.599-0.836

Note: PLR: platelet-to-lymphocyte ratio, NLR: neutrophil-to-lymphocyte ratio, MLR: monocyte-to-lymphocyte ratio.

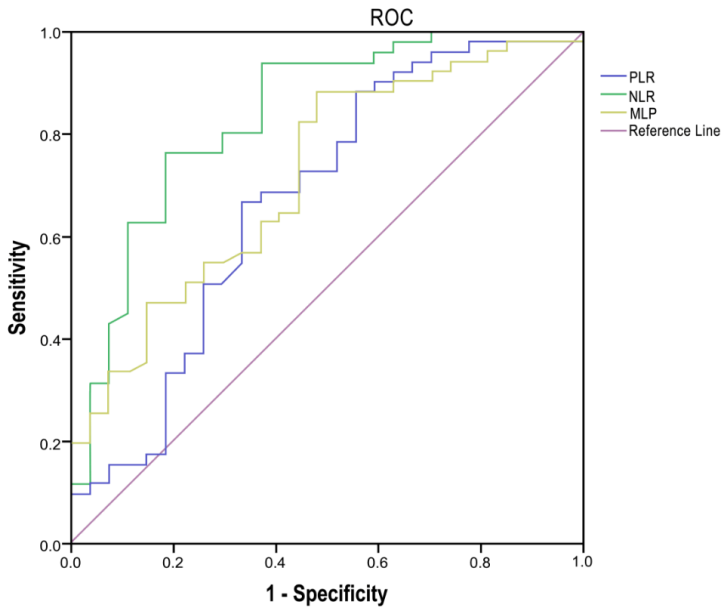

Figure 5. Diagnostic efficacy of serum PLR, NLR, and MLR.

ation of endometrial cancer can be challenging, leading to some patients being diagnosed at advanced stages. In such cases, a combination of surgery and radiotherapy has become the primary treatment. Effective evaluation of these treatment methods is crucial for improving the diagnosis and treatment of advanced high-risk endometrial cancer. The results of this study showed that the 5-year survival rate of patients undergoing comprehensive treatment was close to 40%. This result aligns with previous research conclusions, indicating the potential effectiveness of comprehensive treatment [16, 17].

Inflammation, while serving as the body's natural defense mechanism against external invasion, can also become a potential threat for various diseases. The dual nature of inflammation adds complexity to this study, especially in the context of endometrial cancer, where its role has become increasingly crucial [18, 19]. Studies have shown that a long-term chronic inflammatory environment can induce genetic mutations in endometrial cells, which may lead to the development of precancerous lesions [20]. Additionally, inflammation can stimulate the release of growth factors, cytokines, and molecules that can promote cell proliferation and inhibit apoptosis, thus creating a conducive environment for the development of endometrial cancer. Furthermore, inflammation is closely related to the tumor microenvironment, the local environment where tumor cells reside, including adjacent cells, blood vessels, and extracellular matrix. Chronic inflammation often leads to the recruitment of immune cells, such as macrophages and T cells, to the tumor microenvironment. These cells can directly promote tumor cell proliferation and metastasis, as well as secrete various cytokines that alter the microenvironment in ways that support tumor growth and invasion [21]. Therefore, the relationship between inflammation and endometrial cancer is complex, encompassing cellular, molecular, and microenvironmental

Table 4. Logistic multi-factor regression analysis assignment

Factor	Variable	Assignment
Pathological stage	X1	III = 1, IV = 0
Lymph node metastasis or not	X2	Yes = 1, No = 0
PLR	X3	> 2.85 = 1, ≤ 23 = 0
NLR	X4	> 134.45 = 1, ≤ 134.45 = 0
MLR	X5	> 0.32 = 1, ≤ 0.32 = 0

Note: PLR: platelet-to-lymphocyte ratio, NLR: neutrophil-to-lymphocyte ratio, MLR: monocyte-to-lymphocyte ratio.

Table 5. Multivariate logistic regression analysis of poor prognosis in endometrial cancer patients

Variable	Standardized β	OR	95% CI	P
Age	0.567	1.68	1.04-3.53	0.025
Pathological stage	0.434	1.38	1.22-2.75	0.035
Lymph node metastasis	0.673	2.15	1.31-3.58	0.024
Interval of postoperative radiotherapy	0.539	1.72	1.09-2.59	0.047
PLR	0.309	1.87	1.65-3.49	0.039
NLR	0.564	1.59	1.32-2.59	0.014
MLR	0.419	1.43	1.17-2.92	0.007

Note: PLR: platelet-to-lymphocyte ratio, NLR: neutrophil-to-lymphocyte ratio, MLR: monocyte-to-lymphocyte ratio.

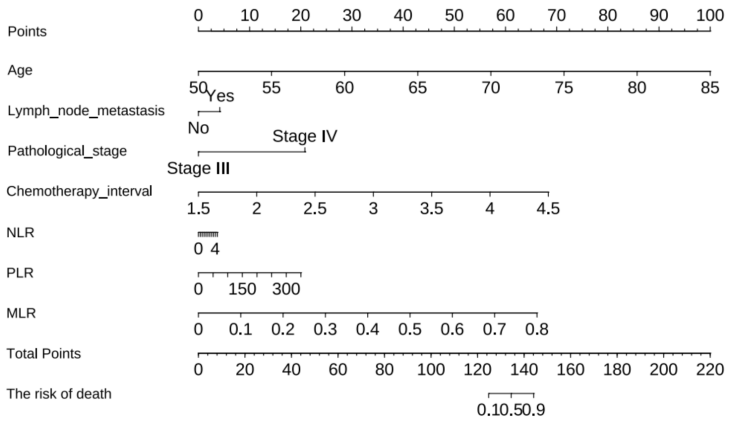

Figure 6. Treatment prognosis of patients with endometrial cancer.

dimensions. Consequently, inflammatory markers hold promise as important indicators for assessing the risk and prognosis of endometrial cancer.

The results of this study indicated that the sensitivity, specificity, and the AUC for PLR, NLR, and MLR in predicting patient mortality were all favorable. Additionally, multivariate analysis confirmed these factors as independent predictors of patient prognosis. The underlying mechanisms may involve the roles of neutrophils and lymphocytes. Neutrophils, as a predominant type of white blood cell, act as the first line of defense against infections. They respond rapidly to inflammatory signals by phagocytizing pathogens or releasing bactericidal chemicals to combat external threats. Lymphocytes, on the other hand, are a crucial component of the immune system primarily responsible for recognizing and memorizing foreign antigens and regulating the immune response. Lymphocytes include various types, such as T cells, B cells, and natural killer (NK) cells, each performing different immune functions. In a healthy condition, neutrophils and lymphocytes maintain a relatively balanced state, jointly protecting the body from diseases. However, this balance can be disrupted in the presence of inflammation, tumors, or other diseases. Studies have found that inflammatory responses can lead to an increase in neutrophil count, while certain tumor conditions may impair the function of lymphocytes, resulting in an elevated NLR. These observations corroborate previous studies indicating that the inflammatory cell scores composed of leukocyte component derivatives in blood routine hold significant diagnostic and prognostic value in tumor treatment [22-24].

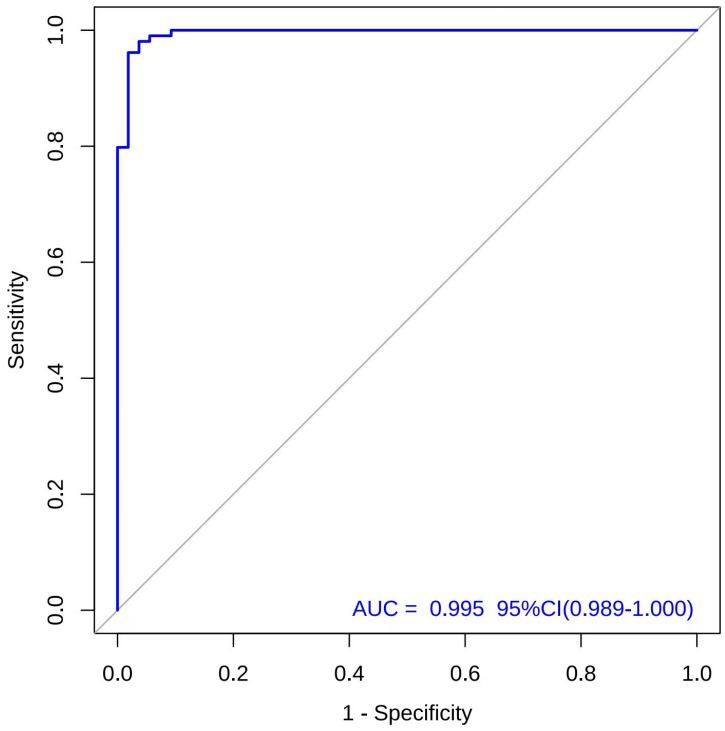

Figure 7. Evaluation of a nomogram prediction model.

Previous research has indicated that PLR, serving as a marker of the body's inflammatory and immune status, primarily relies on platelets, a crucial blood component involved in coagulation and hemostasis. An elevation in PLR levels typically signifies the presence of an inflammatory response or tissue injury within the body. Lymphocytes, however, being a critical component of the immune system, indicate compromised immunity or immune suppression when their number decreases. Therefore, PLR indirectly indicates the body's current inflammatory status and immune competence by reflecting the relative changes in platelet and lymphocyte counts [25]. Our study revealed that the peripheral PLR of deceased patients was higher than that of survivors. This can be attributed to several factors: tumor cells can suppress the host's immune response through various mechanisms, including altering lymphocyte function and numbers. Meanwhile, tumor growth and metastasis are often accompanied by inflammatory reactions, creating a microenvironment that supports tumor survival and dissemination. The progression of the tumor may also be influenced by the stimulation of platelet proliferation and activation. These results are consistent with previous research findings [26].

The MLR of survivors was lower than that of deceased patients [27]. Our study confirms the correlation between MLR and patient prognosis. The possible reasons are as follows: Monocytes and lymphocytes, as two key players in the immune system, perform different tasks. They are responsible for recognizing specific pathogens, producing antibodies, and directly killing infected cells. Under normal circumstances, these two types of cells maintain a certain balance that preserves health. However, this balance can be disrupted by diseases such as tumors. Monocytes may be recruited into the tumor microenvironment and transform into tumor-associated macrophages, promoting tumor growth and metastasis. Meanwhile, the tumor can suppress lymphocyte activity or reduce their numbers by interfering with their production or promoting apoptosis. It can also change MLR, making MLR an important indicator for evaluating the prognosis of endometrial cancer treatment. These findings support previous research conclusions [27, 28].

Furthermore, when investigating the baseline data impacting patient prognosis, the results showed that factors such as age, pathological stage, longer interval time to postoperative radiotherapy, and lymph node metastasis influenced post-treatment outcomes. These factors likely affect the patient's basic functional reserve and the extent of tumor infiltration before surgery. Additionally, these factors can impact treatment-related prognosis, which is consistent with the conclusions of previous studies [29].

In summary, peripheral blood PLR, NLR, and MLR in patients with endometrial cancer demonstrate favorable predictive value regarding treatment and are worth clinical recommendation. However, this study is limited by its single-center design and relatively small sample size,

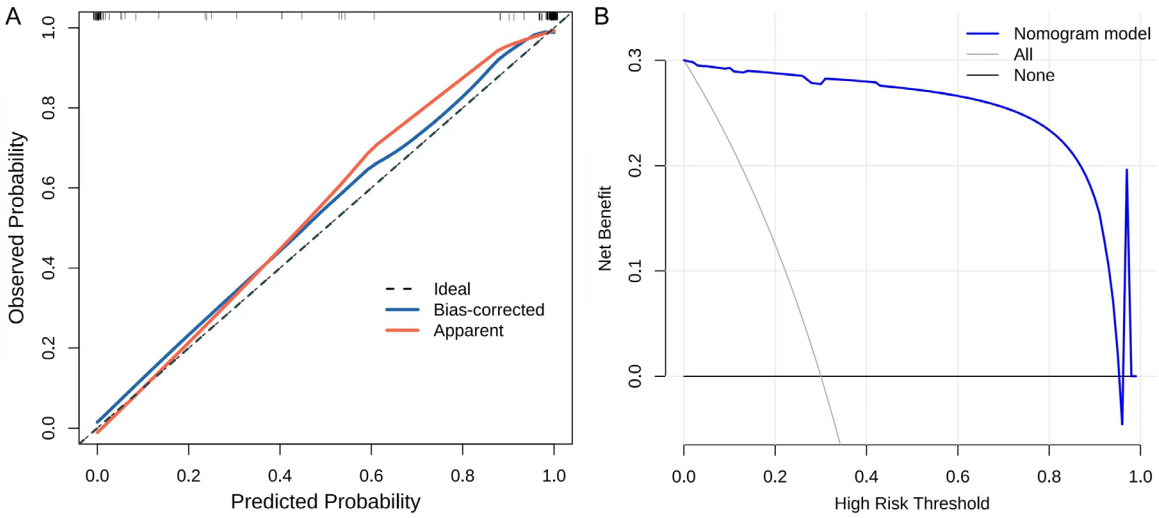

Figure 8. Nomogram prediction model for treatment prognosis in endometrial cancer patients. A. Calibration curve of Nomogram prediction model for treatment prognosis in endometrial cancer patients; B. Decision curve of Nomogram prediction model for treatment prognosis in endometrial cancer patients.

necessitating further validation through multicenter, large-sample studies. Additionally, the diagnostic cutoff values for PLR, NLR, and MLR are essential to solidify the conclusions of this study. Finally, due to the limited number of patients, this study did not include an external validation set and only used the original dataset for both training and validation. Future studies should include a sufficient number of cases for external validation to further improve the accuracy of the findings of this study.

Disclosure of conflict of interest

None.

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