Clinical Surgical Oncology 3 (2024) 100058

Contents lists available at ScienceDirect

Clinical Surgical Oncology

journal homepage: www.journals.elsevier.com/clinical-surgical-oncology

Original Article

Diagnostic sensitivity of immune-inflammatory cell proportion in early diagnosis of endometrial cancer

Li Sun [a,1], Shujie Zhai [b,1], Guojia Wu [b,1], Jie Gu [b], Yiran Huang [b], Dandan Hong [b], Jianmei Wang [a,**], Yongmei Li [b,*]

[a] Department of Gynaecology and Obstetrics, The Second Hospital of Tianjin Medical University, Tianjin, 300211, China
[b] Department of Pathogen Biology, School of Basic Medical Sciences, Tianjin Medical University, Tianjin, 300070, China

ARTICLE INFO

Handling editor: Nicole Liu

Keywords:
Immune-inflammatory cell proportion
Receiver operating characteristic curve
Endometrial cancer

ABSTRACT

Background: Previous studies have shown that inflammation is closely linked to the occurrence and progression of cancer. While the role of immune-inflammatory cell proportions in cancer prognosis has been demonstrated, further research is required to fully understand their predictive value. This study aims to investigate the potential of immune-inflammatory cell proportions, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), red blood cell distribution width-to-platelet ratio (RPR), and monocyte-to-lymphocyte ratio (MLR), in predicting endometrial cancer (EC).

Methods: In this study, 18 patients with EC were included to create receiver operating characteristic (ROC) curves for NLR, MLR, PLR, and RPR, and the area under the curve (AUC) was calculated. Binary LOGISTIC regression analysis was then used to develop composite indicators. Subsequently, ROC curves were generated for the combined indicators, and the corresponding AUCs were calculated to evaluate the diagnostic efficacy of NLR, MLR, PLR, and RPR individually and in combination. The model was validated in an additional cohort.

Result: In the single-indicator ROC analysis, the baseline AUC for NLR was 0.724, with a significance level of $p < 0.05$, indicating good predictive power. For the two-indicator combined ROC analysis, the combined AUC of NLR with each of the three other indicators was greater than 0.724 with a significance level of $p < 0.05$. In the three-indicator combined ROC analysis, the baseline AUC of the combined indicators (including NLR) was greater than 0.766, and a p value of 0.001. Moreover, the baseline AUC of the validation set was 0.726.

Conclusion: Our findings suggest that the immune-inflammatory cell ratios, especially NLR, have a good predictive value for EC. Furthermore, the combined predictive value of the immune-inflammatory cell ratio is more effective than using individual applications.

1. Introduction

Inflammation is considered one of the six biological abilities involved in the onset and progression of tumors and is considered one of the hallmarks of cancer (Cupp et al., 2020). Cancer itself is a systemic disease that leads to changes in the function and composition of the entire immune system (Hiam-Galvez et al., 2021). Given this, tumor lymphocyte infiltration has been found to be a good indicator of prognostic in various types of tumors. Tumor-infiltrating lymphocytes (TILs) are a pivotal part of the adaptive immune system and play a key role in tumor immunology, impacting the progression of cancer (Yin et al., 2022; Tille et al., 2020). TILs have become a research hotspot in recent years and have been associated with the prognosis of melanoma, renal cell carcinoma, breast cancer, and colon cancer (Burke and Young, 2019). For example, in colorectal cancer (CRC), TILs mainly consist of dendritic cells, demonstrating the value of TILs in predicting prognosis (Qin et al., 2022). In esophageal neuroendocrine tumors (E-NENs), a lower presence of TILs results in weaker anti-tumor immunity, potentially leading to a poor prognosis (Zhang et al., 2023a). As mentioned before, inflammation is not only linked to tumor progression but also closely associated with tumorigenesis, similar to tumor lymphocyte infiltration. Therefore, exploring the potential for markers related to inflammation or tumor

* Corresponding author.
** Corresponding author.
E-mail addresses: wangjianmei@tmu.edu.cn (J. Wang), liym@tmu.edu.cn (Y. Li).
[1] Li Sun, Shujie Zhai, and Guojia Wu contributed equally to this article and should be considered as co-first authors.

https://doi.org/10.1016/j.cson.2024.100058
Received 8 April 2024; Received in revised form 30 July 2024; Accepted 3 September 2024
Available online 7 September 2024

lymphocyte infiltration in the early diagnosis of tumors is still worthwhile.

There are various markers associated with inflammation, including neutrophil count and its percentage of total white blood cells, lymphocyte count and its percentage of total white blood cells, and monocyte count and its percentage of total white blood cells. Additionally, there are simple blood routine tests derived from these indicators, such as peripheral blood neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), red blood cell distribution width to platelet ratio (RPR), and monocyte-to-lymphocyte ratio (MLR). These ratios are widely used to predict cancer prognosis, including endometrial cancer (EC), as the ratio index can serve as a biomarker for at least two aspects of the body. In the case of NLR, it can combine two markers of the innate immune response (neutrophils) and adaptive immunity (lymphocytes) of the immune system (Buonacera et al., 2022). Thus, the above-derived blood routine indexes have become the focus of clinical research due to their convenient collection methods and low economic burden on patients. However, most of the current studies focus on evaluating the role of the above single blood routine index in the prognosis of cancer (Lisanti et al., 2022; Cucurull et al., 2019; Plaja et al., 2023; Arora et al., 2023; Androsova et al., 2022; Zhang et al., 2023b; Leng et al., 2022a). For example, the correlation between NLR or PLR and the overall survival and disease-free survival of EC has been confirmed (Leng et al., 2022a).

EC, the sixth most common type of gynecologic cancer worldwide (Sung et al., 2021), has been an increase in incidence every year. Early diagnosis of EC is crucial, as it can be insidious, leading to a poor prognosis for many patients (Crosbie et al., 2022; Brooks et al., 2019). Laboratory diagnostic markers for EC include cancer antigen 125 (CA125), human epididymis protein 4 (HE4), and cancer antigen 199 (CA199) (Li et al., 2009, 2019; Behrouzi et al., 2021; Mohamed et al., 2020; Dey et al., 2023). Among them, CA125 is vulnerable to inflammation and endometriosis (Quan et al., 2021) and is affected by various pathological and physiological conditions (Li et al., 2019), making its usefulness in diagnosing EC very limited. Similarly, CA199 also faces similar problems. HE4, being a new indicator, requires further research to clarify its diagnostic value in EC in a large number of research samples (Li et al., 2009; Mohamed et al., 2020). Therefore, further research on laboratory diagnostic indicators of EC is still necessary.

This study aims to investigate the diagnostic value of new blood routine indexes (alone or in combination) such as NLR, MLR, PLR, and RPR for EC. Clinical data from a tertiary hospital in North China will be collected and analyzed to establish a real-time, dynamic, convenient, and reliable prediction model. Our model will provide clinicians with a more comprehensive diagnosis basis for EC.

2. Methods

2.1. Sample data

We collected the medical records of patients diagnosed with endometrial cancer (EC) in the Second Hospital of Tianjin Medical University, as well as the medical records of patients with various non-endometrial cancers such (NEC) as ovarian serous cystadenoma and ovarian mature cystic teratoma. It is important to note that the EC patient data including the hospital during the period from September 1, 2022 to June 30, 2023 in 19 patients with EC, and the discharge of 35 patients with EC since January 1, 2024. The dataset was partitioned chronologically, with cases preceding 2024 allocated to the training set and those from 2024 onward to the validation set.

All patients included in this study must meet the following criteria: They must have an EC diagnosis made by an experienced pathologist. Patients with insufficient medical record details were excluded. Patients would be ruled out if they have hematologic disease, other types of cancers, short-term and long-term inflammatory diseases, autoimmune diseases, or thrombotic diseases.

Demographic and clinicopathological variables including age, time to admission, primary diagnosis comorbidities, and hematologic inflammatory markers such as platelet count (PLT), red blood cell distribution width (RDW), the absolute value of the neutrophil count (Neu), the absolute value of lymphocyte count (Lym), and the absolute value of monocytes count (Mon) were retrieved from the patient's medical records. Additionally, the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), red blood cell distribution width-to-platelet ratio (RPR), and monocyte-to-lymphocyte ratio (MLR) were calculated.

2.2. Analysis methods

SPSS 27.0 software was utilized for statistical analysis. The normality assumptions for MLR, NLR, PLR, and RPR were tested using the Shapiro-Wilk test. Wilcoxon rank-sum test was used to analyze the differences in variables between the training set and validation set, including age, EC%, NLR, MLR, RPR, and PLR. Bivariate Pearson's correlation coefficients were calculated to evaluate the linear correlation between variables. Multicollinearity among variables was diagnosed through the variance inflation factor. Univariate and multivariate LOGISTIC regression analysis were used to identify the independent risk factors for EC. Receiver operating characteristic (ROC) curves were generated to evaluate the diagnostic efficacy of the models, with the area under the curve (AUC) calculated for assessment. The optimal model was chosen by comparing the AUC and the fitting parameters, including the Akaike information criterion (AIC), Bayesian information criterion (BIC), and Nagelkerke's R Square. $p < 0.05$ was considered statistically significant.

3. Results

3.1. Patient characteristics

The study included a total of 151 patients. The training set initially had 62 patients, and after excluding 3 extreme values, 59 patients remained. Among these, 18 cases (30.5%) were endometrial carcinoma (EC), 41 cases (69.5%) were ovarian serous cystadenoma and mature ovarian cystic teratoma (referred to as non-endometrial cancer, NEC). In the validation set, there were 89 patients, including 24 cases (27.0%) of EC and 65 cases (73.0%) of NEC. The general patient data is summarized in Table 1. The median age of patients in the training set was 42 years old (ranging from 17 to 85 years old), of which the median age of EC patients was 66.5 years old (ranging from 35 to 85 years old) and the median age of NEC patients was 37 years old (ranging from 17 to 71 years old). The median age of validation set patients was 56 years old (ranging from 25 to 78 years old), with the median age of EC patients at 56 years old (ranging from 42 to 78 years old and the median age of NEC patients at 52 years age (ranging from 25 to 77 years old).

Table 1
The general information of the patients.

Item	Training set	Validation set	*p* value
Age [median, range]	42 (17–85)	56 (25–78)	0.386
EC%	18 (30.50%)	24 (27.00%)	0.142
NLR	2.208 (1.031–5.564)	2.179 (0.733–5.831)	0.707
MLR	0.191 (0.103–0.488)	0.179 (0.081–0.342)	0.840
RPR	0.163 (0.103–0.315)	0.161 (0.108–0.299)	0.665
PLR	150.000 (73.482–408.333)	169.802 (90.574–390.123)	0.507

Abbreviations: EC, endometrial cancer; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; RPR, red blood cell distribution width-to-platelet ratio; PLR, platelet-to-lymphocyte ratio.

3.2. Determination of one-way index and construction of ROC curve for a single indicator

The mean values of NLR, MLR, RPR, and PLR were 2.4900, 0.2024, 0.1700, and 164.4090, respectively. Because not all the indicators in the data presented normal distribution, data transformation was performed for non-normally distributed data. NLR was transformed using the natural logarithm. While MLR, RPR, and PLR were transformed using the log10 function. We constructed ROC curves for each indicator to determine the diagnostic value of each indicator in EC patients (Fig. 1). However, other individual indicators did not have significant diagnostic value except for NLR. As shown in Table 2, the AUC of baseline ln (NLR), baseline log10 (MLR), baseline log10 (RPR) and baseline log10(PLR) were 0.724 (95% Confidence interval (CI): 0.584–0.863, $p < 0.05$), 0.668 (95% CI: 0.517–0.820, $p < 0.05$), 0.616 (95% CI: 0.452–0.780, not significant), and 0.529 (95% CI: 0.361–0.697, not significant), respectively.

3.3. Construction of ROC curve for the combined indicators

To solve the multicollinearity among independent variables, principal component analysis (PCA) was utilized to extract common factors, followed by LOGISTIC binary regression analysis to build seven sets of joint indicators. These combined indicators consisted of pairs of indicators such as ln (NLR) and log10 (MLR), ln (NLR) and log10 (RPR), log10(NLR) and log10(PLR), log10 (MLR) and log10 (RPR), log10 (MLR) and log10(PLR), log10 (RPR) and log10(PLR), and triples of indicators such as ln (NLR), log10 (MLR) and log10 (RPR), ln (NLR), log10 (MLR) and log10(PLR), ln (NLR), log10 (RPR) and log10(PLR), and log10 (MLR), log10 (RPR) and log10(PLR). The unified ROC curve for these indicators was constructed: with Fig. 2 for pairs and Fig. 3 for triples.

In Table 3, the baseline AUC for the combined measure of ln (NLR) and log10 (MLR) was 0.725 (95% CI: 0.586–0.864, $p = 0.006$). The baseline AUC for the combined measure of ln (NLR) and log10 (RPR) was 0.766 (95% CI: 0.642–0.889, $p = 0.001$). Additionally, the baseline AUC for the combined measure of ln (NLR) and log10(PLR) was 0.756 (95% CI: 0.633–0.880, $p = 0.002$). For the combined measure of log10 (MLR) and log10 (RPR), the baseline AUC was 0.679 (95% CI: 0.525–0.833, $p < 0.05$). Similarly, for the combined measure of log10 (MLR) and log10(PLR), the baseline AUC was 0.686 (95% CI: 0.536–0.836, $p < 0.05$). Lastly, and the baseline AUC for the combined measure of log10 (RPR) and log10(PLR) was 0.604 (95% CI: 0.442–0.766) indicating that it was not statistically significant. Furthermore, the baseline AUC for the combined measure of ln (NLR), log10 (MLR) and log10 (RPR) was 0.774 (95% CI: 0.654–0.894, $p = 0.001$). The baseline AUC for the combined measure of ln (NLR), log10 (MLR) and log10(PLR) was 0.770 (95% CI: 0.643–0.897, $p = 0.001$). Additionally, the baseline AUC for the combined measure of ln (NLR), log10 (RPR) and log10(PLR) was 0.766 (95% CI: 0.644–0.887, $p = 0.001$). The baseline AUC for the combined measure of log10 (MLR) and log10 (RPR) was 0.679 (95% CI: 0.525–0.833, $p < 0.05$). Moreover, the baseline AUC for the combined measure of log10 (MLR) and log10(PLR) was 0.686 (95% CI: 0.536–0.836, $p < 0.05$). Lastly, the baseline AUC for the combined measure of log10 (RPR) and

Table 2
Baseline AUC for individual measures.

Test Result Variable(s)	Area	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
lnNLR	0.724	0.007	0.584	0.863
lgMLR	0.668	0.041	0.517	0.820
lgRPR	0.616	0.159	0.452	0.780
lgPLR	0.529	0.723	0.361	0.697

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; RPR, red blood cell distribution width-to-platelet ratio; PLR, platelet-to-lymphocyte ratio.

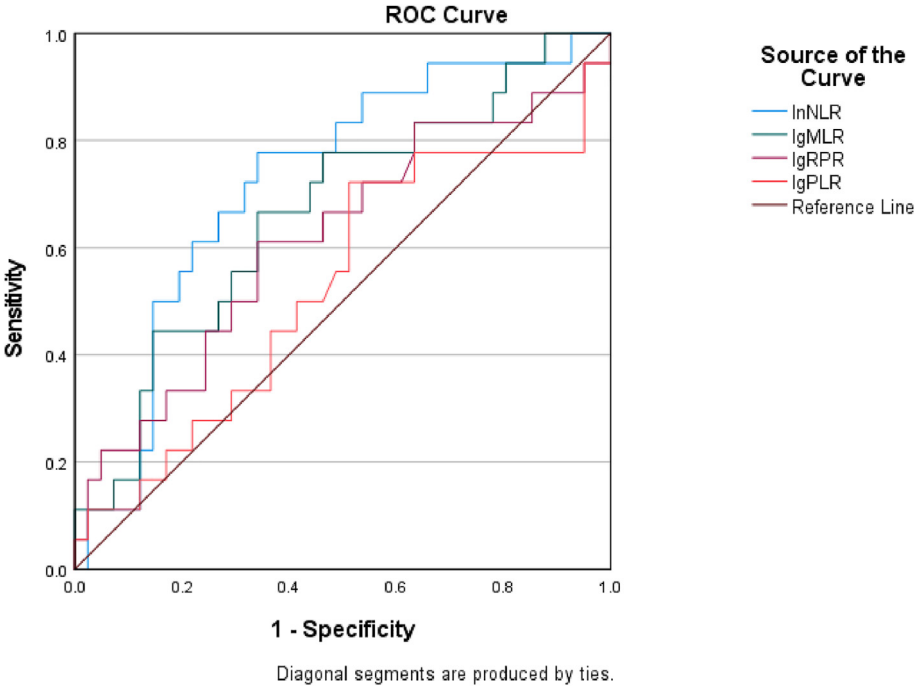

Fig. 1. ROC curves for individual indicator.

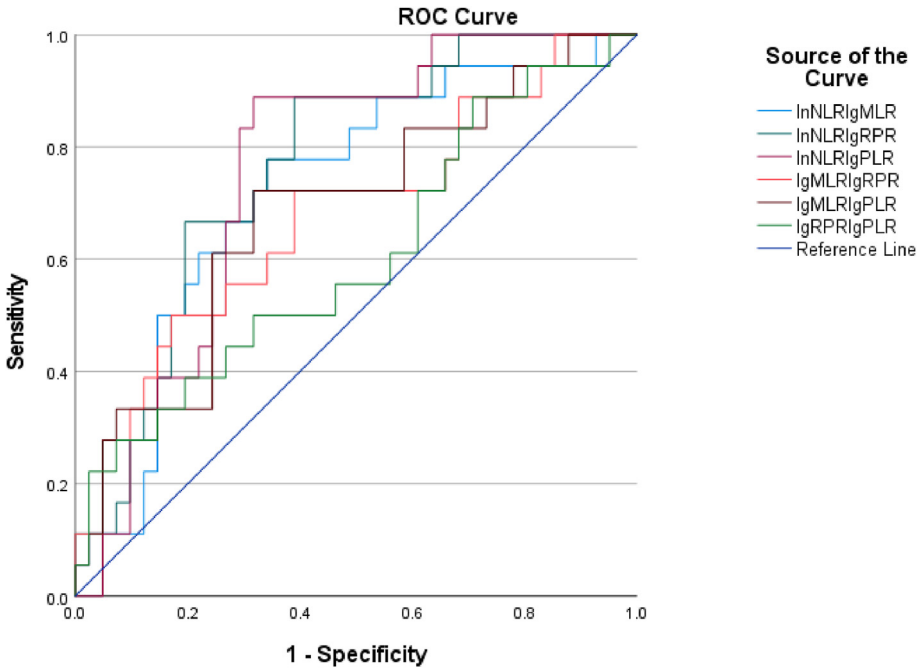

Fig. 2. ROC curve of dual indicators.

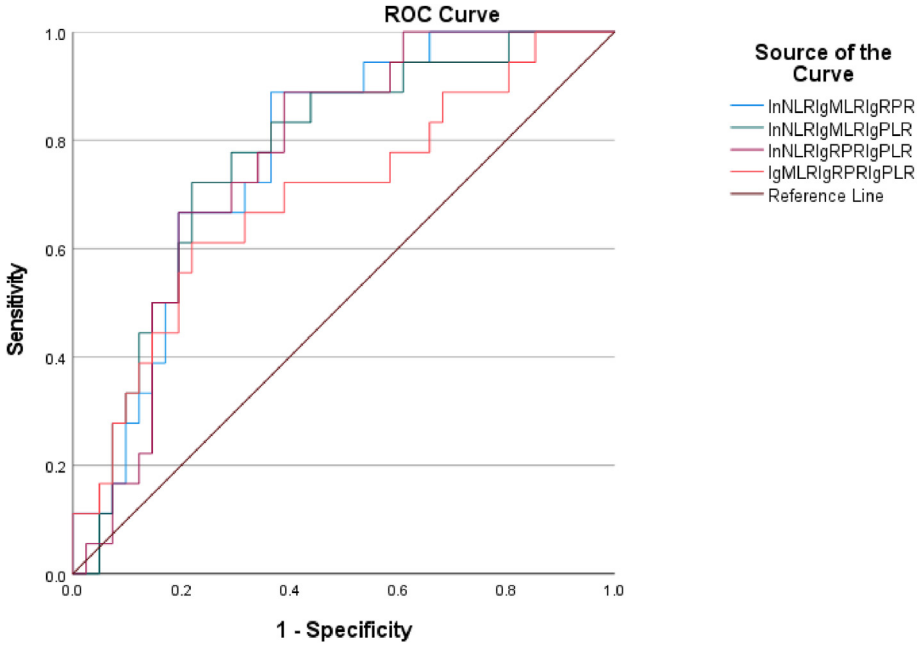

Fig. 3. ROC curve of the triple indicators.

log10(PLR) was 0.604 (95% CI: 0.442–0.766, not significant).

Based on the AUC results of each model, we chose the model that combines ln (NLR), log10 (MLR), and log10 (RPR) as the best predicted model. This model has an AIC of 43.147, BIC of 49.380, and Nagelkerke's R Square of 0.486, making it the best-fitting model among all the index models for triple combinations. The Hosmer and Lemeshow Test showed that the model has good calibration ($p > 0.05$). Additionally, the model coefficients of the combined indexes of ln (NLR), log10 (MLR) and log10 (RPR) also showed good significance. The common factor coefficients of ln (NLR) and log10 (MLR) extracted by PCA were 1.696 ($p = 0.002$), the coefficient of lgRPR was 16.628 ($p = 0.01$), and the constant was 11.244 ($p = 0.018$), as shown in Table 4. Furthermore, the model was validated in an additional cohort of 24 consecutive EC patients (Fig. 4). The baseline AUC of the validation set was 0.726 (95% CI: 0.609–0.844, $p = 0.001$)

4. Discussion

This study examined the diagnostic significance of NLR, PLR, MLR, and RPR for EC. We performed LOGISTIC regression analysis and

Table 3
Baseline AUC for the combined measures.

Test Result Variable(s)	Area	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
lnNLRlgMLR	0.725	0.006	0.586	0.864
lnNLRlgRPR	0.766	0.001	0.642	0.889
lnNLRlgPLR	0.756	0.002	0.633	0.880
lgMLRlgRPR	0.679	0.030	0.525	0.833
lgMLRlgPLR	0.686	0.024	0.536	0.836
lgRPRlgPLR	0.604	0.205	0.442	0.766
lnNLRlgMLRlgRPR	0.774	0.001	0.654	0.894
lnNLRlgMLRlgPLR	0.770	0.001	0.643	0.897
lnNLRlgRPRlgPLR	0.766	0.001	0.644	0.887
lgMLRlgRPRlgPLR	0.696	0.017	0.546	0.847

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; RPR, red blood cell distribution width-to-platelet ratio; PLR, platelet-to-lymphocyte ratio.

constructed ROC curves using data from 148 patients. Our findings showed that using these indicators in combination is more useful than using them individually. We observed that NLR and MLR have excellent diagnostic value when used alone or in combination. Moreover, we found that the combination of NLR, MLR, and RPR was especially effective for the clinical diagnosis of EC. Our findings could be benefit for clinical work related to tumors by increasing the early detection of tumors and giving more patients to receive timely treatment.

The tumor microenvironment of EC is characterized by significant immune cell infiltration, with notable changes in lymphocytes, neutrophils, and monocytes (Dey et al., 2023). Therefore, NLR, MLR, and PLR, as white blood cell-related indicators, may have better diagnostic efficacy for EC tumor microenvironment changes when used together. The good performance of RPR in the combined index may be due to the clinical relevance of red cell distribution width (RDW) for EC (Bussies et al., 2020), and the role of thrombocytosis as a biomarker in type II non-endometrioid endometrial cancer (Eoh et al., 2023). In the current study of individual blood routine-related indicators in the EC diagnosis, we found that single indicators such as PLR or RPR were not significant or satisfactory for EC diagnosis. However, MLR and NLR showed good diagnostic effects and significance, which is consistent with recent reports on the tumor microenvironment of EC (Dey et al., 2023). This indicates that our research concept is reliable and that these indicators can provide a diagnostic reference for EC. More importantly, when dual and triple measures were analyzed together, most of them showed better diagnostic power and significance, except for the paired combination of RPR and PLR. However, it is worth noting that the diagnostic efficacy of combining these indicators is not always better than using them individually. One example is that the combination of NLR, PLR, and MLR did not significantly improve the diagnosis of atherosclerosis among diabetic patients in comparison to NLR alone (Ning et al., 2022). Therefore, further exploration is needed to explore the usefulness of the above blood routine indicator, whether used individually or in combination.

In contrast to previous studies focusing on the prognostic value of blood routine indicators in cancer patients, such as EC (Leng et al., 2022b; Li et al., 2022), colorectal cancer (Mortazavizadeh et al., 2017), lung cancer (Aydın et al., 2018), bladder cancer (Qin et al., 2020), gastric cancer (Zurlo et al., 2022), and breast cancer (Truffi et al., 2022; Gasparri et al., 2023), recent reports have been exploring the application of these blood routine indexes in tumor prediction. For example, they have been used in predicting early gastric cancer (Karra et al., 2023) and intermediate-risk ovarian cancer (Liu et al., 2022). Our current study is centered on the application of combined indicators in diagnosing EC. ROC curves were plotted to represent the risk distribution of affected and non-affected individuals (Janssens and Martens, 2020). The AUC is commonly used to assess the ability of a predictive or prognostic model to distinguish who will or will not develop the disease (Janssens and Martens, 2020). Although the current AUC value is not very ideal, it may be associated with our sample size and its distribution imbalance. Smaller sample sizes can inflate accuracy metrics due to a lack of representativeness and can result in overfitting and inflated accuracy estimates (Zhai et al., 2019). Therefore, despite our promising results, further validation in larger and more balanced cohorts using robust statistical methods is necessary.

In summary, the combined analysis of NLR, MLR, RPR, and PLR has a good diagnostic value for EC. This may provide new opportunities for early EC diagnosis and also offer ideas for the early diagnosis of other tumors.

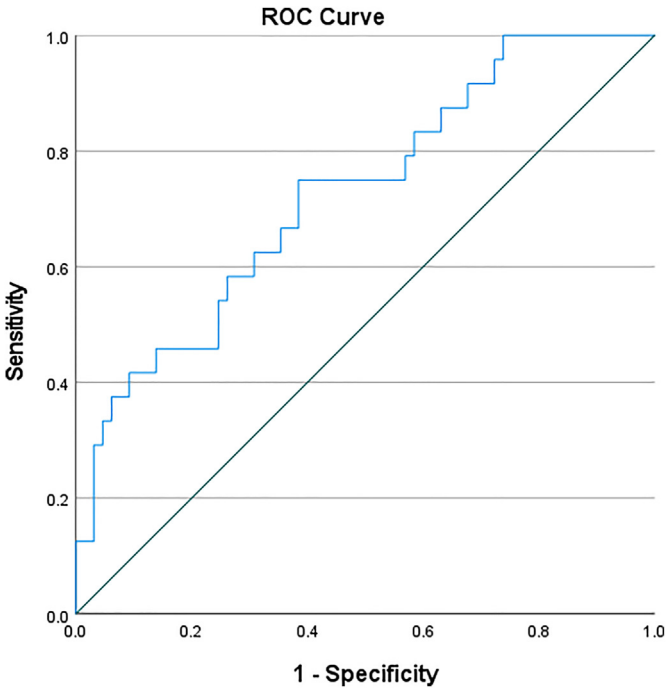

Fig. 4. The optimal model of validation set ROC curve
In the validation set, the binary logistics regression model coefficients were used to calculate the prediction probability and the ROC curves of NLR, MLR and RPR were drawn using the prediction probability value.

Table 4
Optimal model coefficients.

Variables of interest	B	S.E.	Wald	df	Sig.	Exp(B)	95% CI for Exp(B)	
							Lower	Upper
FAC(lnNLRlgMLR)	1.696	0.555	9.346	1.000	0.002	5.452	1.838	16.173
lgRPR	16.628	6.447	6.653	1.000	0.010	16645900.363	54.183	5113918259396.600
Constant	11.244	4.767	5.563	1.000	0.018	76418.953		

FAC(lnNLRlgMLR) = 0.952×lnNLR + 0.952×lgMLR.
Abbreviations: NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; RPR, red blood cell distribution width-to-platelet ratio.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgments

This work was supported by grant from the Common Project of Tianjin Municipal Education Commission (No 2023KJ030 for L.S.).

References

Androsova, A., Orlova, R., Ivanova, A., et al., 2022. Neutrophil-to-lymphocyte ratio (NLR), derived neutrophil-to-lymphocyte ratio (dNLR) and lymphocytes counts as a possible prognostic factor in neuroendocrine tumors of the gastrointestinal tract. Am Soc Clin Oncol Educ Book 40 (16_Suppl. l).

Arora, R., Alam, F., Zaka-Ur-Rab, A., et al., 2023. Peripheral neutrophil to lymphocyte ratio (NLR), a cogent clinical adjunct for Ki-67 in breast cancer. J. Egypt. Natl. Cancer Inst. 35 (1), 43. https://doi.org/10.1186/s43046-023-00200-4.

Aydın, F., Ince, N., Karaman, E., et al., 2018. P1. 09-24 the effects of NLR and PLR of effect on prognosis in patients with the lung cancer. J. Thorac. Oncol. 13 (10), S559.

Behrouzi, R., Barr, C.E., Crosbie, E.J., 2021. HE4 as a biomarker for endometrial cancer. Cancers 13 (19), 4764.

Brooks, R.A., Fleming, G.F., Lastra, R.R., et al., 2019. Current recommendations and recent progress in endometrial cancer. CA A Cancer J. Clin. 69 (4), 258–279.

Buonacera, A., Stancanelli, B., Colaci, M., et al., 2022. Neutrophil to lymphocyte ratio: An emerging marker of the relationships between the immune system and diseases. Int. J. Mol. Sci. 23 (7), 3636.

Burke, J.D., Young, H.A., 2019. IFN-Γ: A cytokine at the right time, is in the right place. Semin. Immunol. 43, 101280.

Bussies, P., Eta, A., Pinto, A., et al., 2020. Thrombocytosis as a biomarker in Type II, non-endometrioid endometrial cancer. Cancers 12 (9), 2379.

Crosbie, E.J., Kitson, S.J., McAlpine, J.N., et al., 2022. Endometrial cancer. Lancet. 399 (10333), 1412–1428.

Cucurull, M., Felip, E., Garcia, J.J., et al., 2019. Prognostic value of monocyte to lymphocyte ratio (MLR) in epithelial ovarian cancer (EOC). Am Soc Clin Oncol Educ Book 37 (15_Suppl. l).

Cupp, M.A., Cariolou, M., Tzoulaki, I., et al., 2020. Neutrophil to lymphocyte ratio and cancer prognosis: An umbrella review of systematic reviews and meta-analyses of observational studies. BMC Med. 18 (1), 360.

Dey, D.K., Krause, D., Rai, R., et al., 2023. The role and participation of immune cells in the endometrial tumor microenvironment. Pharmacol. Ther. 251, 108526.

Eoh, K.J., Lee, T.K., Nam, E.J., et al., 2023. Clinical relevance of red blood cell distribution width (RDW) in endometrial cancer: A retrospective single-center experience from Korea. Cancers 15 (15), 3984.

Gasparri, M.L., Albasini, S., Truffi, M., et al., 2023. Low neutrophil-to-lymphocyte ratio and pan-immune-inflammation-value predict nodal pathologic complete response in 1274 breast cancer patients treated with neoadjuvant chemotherapy: A multicenter analysis. Ther. Adv. Med. Oncol 15, 17588359231193732.

Hiam-Galvez, K.J., Allen, B.M., Spitzer, M.H., 2021. Systemic immunity in cancer. Nat. Rev. Cancer 21 (6), 345–359.

Janssens, A.C.J.W., Martens, F.K., 2020. Reflection on modern methods: Revisiting the area under the ROC curve. Int. J. Epidemiol. 49 (4), 1397–1403.

Karra, S., Gurushankari, B., Rajalekshmy, M.R., et al., 2023. Diagnostic utility of NLR, PLR and MLR in early diagnosis of gastric cancer: An analytical cross-sectional study. J. Gastrointest. Cancer 54 (4), 1322–1330.

Leng, J., Wu, F., Zhang, L., 2022a. Prognostic significance of pretreatment neutrophil-to-lymphocyte Ratio, platelet-to-lymphocyte ratio, or monocyte-to-lymphocyte ratio in endometrial neoplasms: A systematic review and meta-analysis. Front. Oncol. 12, 734948.

Leng, J., Wu, F., Zhang, L., 2022b. Prognostic significance of pretreatment neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, or monocyte-to-lymphocyte ratio in endometrial neoplasms: A systematic review and meta-analysis. Front. Oncol. 12, 734948.

Li, J., Dowdy, S., Tipton, T., et al., 2009. HE4 as a biomarker for ovarian and endometrial cancer management. Expert Rev. Mol. Diagn 9 (6), 555–566.

Li, J., Wang, X., Qu, W., et al., 2019. Comparison of serum human epididymis protein 4 and CA125 on endometrial cancer detection: A meta-analysis. Clin. Chim. Acta 488, 215–220.

Li, Q., Kong, F., Ma, J., et al., 2022. Nomograms based on fibrinogen, albumin, neutrophil-lymphocyte ratio, and carbohydrate antigen 125 for predicting endometrial cancer prognosis. Cancers 14 (22), 5632.

Lisanti, C., Basile, D., Garattini, S.K., et al., 2022. The SAFFO study: Sex-related prognostic role and cut-off definition of monocyte-to-lymphocyte ratio (MLR) in metastatic colorectal cancer. Cancers 15 (1), 175.

Liu, Z., Wu, J., Wang, X., et al., 2022. Multivariate logistic regression analysis of the correlation between five biomarkers and ovarian cancer in patients with intermediate-risk: A prospective cross-sectional study. Front. Cell Dev. Biol. 10, 876071.

Mohamed, S.S., Abdelhafeez, M.A., Mohamed, H.F., et al., 2020. Evaluation of serum human epididymis secretory protein 4 (HE4) in benign endometrial disease and endometrial cancer. QJM-Int. J. Med. 113 (Suppl. ment_1), hcaa056, 028.

Mortazavizadeh, S.M.R., Ayoughi, Y., Moghimi, M., 2017. The combination analysis of tumor infiltration lymphocyte with neutrophil to lymphocyte ratio may predict prognosis of colorectal cancer in stage I-III. Ann. Oncol. 28, v599.

Ning, P., Yang, F., Kang, J., et al., 2022. Predictive value of novel inflammatory markers platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio, and monocyte-to-lymphocyte ratio in arterial stiffness in patients with diabetes: A propensity score-matched analysis. Front. Endocrinol. 13, 1039700.

Plaja, A., Teruel, I., Ochoa-de-Olza, M., et al., 2023. Prognostic role of neutrophil, monocyte and platelet to lymphocyte ratios in advanced ovarian cancer according to the time of debulking surgery. Int. J. Mol. Sci. 24 (14), 11420.

Qin, T., Yu, H., Wang, B., et al., 2020. PD-L1 and neutrophil to lymphocyte ratio (NLR) as predictive panel of prognosis in bladder cancer. Am. Soc. Clin. Oncol. Educ. Book 38 (15_Suppl. l).

Qin, M., Chen, G., Hou, J., et al., 2022. Tumor-infiltrating lymphocyte: Features and prognosis of lymphocytes infiltration on colorectal cancer. Bioengineered 13 (6), 14872–14888.

Quan, Q., Liao, Q., Yin, W., et al., 2021. Serum HE4 and CA125 combined to predict and monitor recurrence of type II endometrial carcinoma. Sci. Rep. 11 (1), 21694.

Sung, H., Ferlay, J., Siegel, R.L., et al., 2021. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA A Cancer J. Clin. 71 (3), 209–249.

Tille, J.C., Vieira, A.F., Saint-Martin, C., et al., 2020. Tumor-infiltrating lymphocytes are associated with poor prognosis in invasive lobular breast carcinoma. Mod. Pathol. 33 (11), 2198–2207.

Truffi, M., Sottotetti, F., Gafni, N., et al., 2022. Prognostic potential of immune inflammatory biomarkers in breast cancer patients treated with neoadjuvant chemotherapy. Cancers 14 (21), 5287.

Yin, W., Jin, J., Bao, H., et al., 2022. Tumor-infiltrating lymphocytes-based subtypes and genomic characteristics of EBV-associated lymphoepithelioma-like carcinoma. J. Pathol. 257 (5), 650–662.

Zhai, C., Cong, H., Hou, K., et al., 2019. Clinical outcome comparison of percutaneous coronary intervention and bypass surgery in diabetic patients with coronary artery disease: A meta-analysis of randomized controlled trials and observational studies. Diabetol. Metab. Syndrome 11, 110.

Zhang, L., Yu, B., Liu, Z., et al., 2023a. Analysis of the clinicopathological characteristics, prognosis, and lymphocyte infiltration of esophageal neuroendocrine neoplasms: A surgery-based cohort and propensity-score matching study. Cancers 15 (6), 1732.

Zhang, Z., Chu, R., Kong, B., et al., 2023b. A novel prognostic model for high-grade endometrial cancer using combined neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR). Am. Soc. Clin. Oncol. Educ. Book 41 (16_Suppl. l).

Zurlo, I.V., Schino, M., Strippoli, A., et al., 2022. Predictive value of NLR, TILs (CD4+/CD8+) and PD-L1 expression for prognosis and response to preoperative chemotherapy in gastric cancer. Cancer Immunol. Immunother. 71 (1), 45–55.