RESEARCH ARTICLE

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Study on Preoperative Neutrophil/Lymphocyte (NLR) and Platelet/Lymphocyte Ratio (PLR) as a Predictive Factor in Endometrial Cancer

Teerapat Muangto[1], Karicha Mairaing[1]*, Yenrudee Poomtavorn[1], Yuthadej Thaweekul[1], Awassada Punyashthira[1], Nopwaree Chantawong[1], Pattra Wisarnsirirak[1], Junya Pattaraarchachai[2], Komsun Suwannarurk[1]

Abstract

Objective: To evaluate predictive factors between serum inflammatory markers and malignancy potential of endometrium. **Methods:** This retrospective study was conducted at the gynecological oncology unit, department of obstetrics and gynecology, at the faculty of medicine of Thammasat University. The study period was from 2017 to 2020. Endometrial cancer and benign gynecologic disease cases who underwent hysterectomy (with or without adnexectomy) during the study period were recruited. Demographic characteristics, histopathology reports and serum markers were also collected. **Results:** The study included a study group of 49 participants with endometrial cancer and a control group consisting of 119 cases of benign uterine disease. The study group had statistically significantly higher mean ages, proportional menopausal status and instances of underlying diseases when compared with the control group. Neutrophil/Lymphocyte ratios (NLR) and Platelet/Lymphocyte ratios (PLR) could not meaningfully predict the malignant potential of endometrium in hysterectomy specimens. NLR and PLR were statistically associated with depth of myometrial invasion (MI) in endometrial cancer cases. NLR equal to or greater than 1.93 predicted MI more than half thickness with sensitivity, specificity, accuracy, positive (PPV) and negative predictive value (NPV) at a percentage of 83.3, 52.8, 37.0, 90.5 and 60.4, respectively. PLR equal to or greater than 134.95 predicted MI of greater than fifty percent thickness with sensitivity, specificity, accuracy, PPV and NPV at 75.0, 55.6, 36.0, 87.0 and 60.4 percent, respectively. **Conclusion:** NLR and PLR have positive associations with myometrial invasion of endometrial cancer.

Keywords: Endometrial cancer- NLR- PLR- Myometrial invasion

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Introduction

Currently, endometrial cancer (EC) is the second most common gynecologic malignancy in developed countries. 417,367 new cases of EC were reported worldwide in 2020. In Thailand, EC is the second most common gynecological malignancy in women, following cervical cancer, with 4,524 new cases in 2020 (Sung et al., 2021).

Most EC cases present with abnormal vaginal bleeding, especially post-menopausal bleeding, which can often lead to early stage diagnosis. The most common form of EC treatment is surgical staging surgery. Surgical staging procedures include hysterectomy (either exploratory laparotomy or laparoscopic approach) with bilateral salpingo-oophorectomy (BSO), peritoneal washing for cytology, pelvic and/or para-aortic lymphadenectomy. Myometrial invasion (MI) is a metric of stage I determination. EC cases who had MI less or more than half were diagnosed with stage IA or IB, respectively. Intraoperative MI evaluation factors in the surgeon's decision whether to prescribe pelvic and/or para-aortic lymphadenectomy. However, the role of systematic lymphadenectomy is still controversial (Hacker et al., 2015). Pre-operative management included assessment of the patient's general health, medication and co-morbidities prior to surgery. Preoperative imaging (either computerized topography (CT) or magnetic resonance imaging (MRI)) was performed to assess cancer invasion and extent.

Present cancerous cells induce production of circulatory cytokines and chemokines. Both substances stimulate the host's systemic inflammatory response by increasing neutrophils and platelets and decreasing lymphocyte count (Hacker et al., 2015). Hematologic parameters such as neutrophil/lymphocyte ratio (NLR)

*[1]Department of Obstetrics and Gynaecology, Faculty of Medicine, Thammasat University, Pathumthani, Thailand. [2]Chulabhorn International College of Medicine, Thammasat University, Pathumthani, Thailand. *For Correspondence: Khunpa_kiki@hotmail.com*

and platelet/lymphocyte ratio (PLR) were reported for association with cancer extension. These parameters were analyzed to assess the probability of malignancy potential or predictive markers in multiple cancers (Hacker et al., 2015). Previous literature reported that hematologic parameters could predict EC diagnosis and prognosis (Acmaz et al., 2014; Kurtoglu et al., 2015; Cumming et al, 2015; Haruma et al., 2015; Li et al., 2015; Temur et al., 2018; Ural et al., 2015).

The aim of this study was to evaluate the association of hematologic parameters as a predictor of potential malignancy or myometrial invasion of EC.

Materials and Methods

This retrospective case control study was conducted in the gynecologic oncology division, department of obstetrics and gynecology, faculty of medicine, Thammasat University, Thailand. The study period was between January 2017 and June 2020. The study protocol was approved by Thammasat University Hospital ethics committee (MTU-EC-OB-6-239/62).

Participants were cases who underwent Pivot type I hysterectomy due to indication of EC (study) and benign gynecologic diseases (control) during the period of study. Exclusion criteria included mesenchymal uterine cancer, other malignancies, synchronous malignancies, acute inflammatory disease, autoimmune disease and myeloproliferative disorders. All EC cases underwent hysterectomy via exploratory laparotomy. Myometrial Invasion (MI) was evaluated by intraoperative gross examination of uterine specimens. Pelvic and para-aortic lymph node sampling was performed in suspicion of more than half MI, moderated and poorly differentiated cancer according to GOG 33, ASTEC and CONSORT study (Hacker et al., 2015).

Sample size was calculated by G*power 3.1.7 computerized program (Faul et al., 2007). Effective size, confidential interval, absolute precision error and power test were set at 0.5, 95%, 0.08 and 0.8, respectively. Number of participants in the study and control groups were a 1:2 ratio. The study and control groups that gave statistical significance were at least 48 and 96 cases, respectively. An additional twenty percent for incomplete data was supplemented. The sample size in this study was 180 cases.

Clinicopathologic characteristics included age, body mass index (BMI), parity, menopause status, clinical presentation and underlying disease. Cancer characteristics were histological cell type, cancer staging, myometrial invasion (MI), adjacent organ involvement, presence of lymph-vascular space invasion (LVSI) and peritoneal washing for cytology. Pre-operative hematological values were reviewed from the electronic medical records system at Thammasat University Hospital (TUH). Complete blood count (CBC) obtained within one month prior to surgery were recorded. Absolute neutrophil, lymphocyte and platelet counts were calculated. Ratio of neutrophils/lymphocytes and platelets/lymphocytes were defined as neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR), respectively.

Data was analyzed by using Statistical Package for Social Sciences version 26.0 software (SPSS Inc, Chicago, IL, USA). Continuous and category data were expressed by mean ±standard deviation (SD) and chi-square or Fisher-exact test with appropriate application.

Results

During the period of study, a total of 168 cases were enrolled as presented in Figure 1. There were 49 EC and 119 benign uterine neoplasm cases in the study and control group, respectively. Participant clinical characteristics were described in Table 1. Mean age of the study group was significantly higher than the control group (59.9 and 47.1 years). Nulliparity and BMI of both groups were comparable. Study group had more menopausal participants, abnormal vaginal bleeding manifestation, hypertension and diabetes mellitus than the control group with statistical significance. Eighty percent of the study group were stage I EC (40/49) and endometrioid cell type (41/49). Positive LVSI and peritoneal washing for cytology were present at 12.5 (6/49) and 14.6 (7/49) percent, respectively.

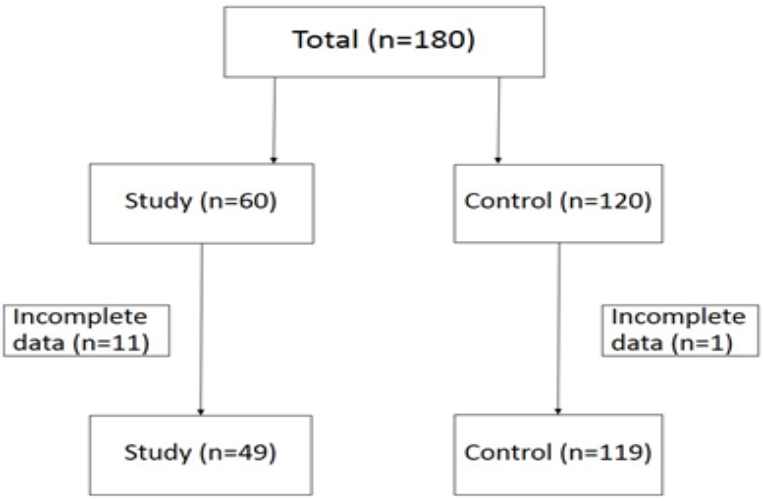


Figure 1. Flow of the Study. Study: endometrial cancer, Control: benign gynecologic cases

Table 1. Demographic Characters Endometrial Cancer (Study) and benign Gynecologic Cases (Control)

	Study (n = 49)*	Control (n = 119)*	p-value
Age(year)*	59.90±8.84	47.10±12.08	0.001
BMI(kg/m^2)**	27.13±5.46	24.92±5.13	0.51
<18.5	2 (4.08)	7 (5.88)	
18.5-24.99	13 (26.53)	63 (52.94)	
25-29.99	23 (46.94)	31 (26.05)	
≥30	11 (22.45)	18 (15.13)	
Nulliparity	13 (26.53)	38 (31.93)	0.489
Menopause	35 (71.43)	31 (26.05)	<0.001*
Symptoms			
Bleeding	47 (95.92)	44 (36.97)	<0.001*
Mass	1 (2.04)	32 (26.89)	0.005
Underlying disease			
Non	16 (32.65)	84 (70.59)	<0.001*
DM	12 (24.49)	9 (7.56)	0.006
HT	23 (46.94)	16 (13.45)	<0.001
Histology			
Endometriod	41 (83.7)		
Serous	5 (10.2)		
Others	3 (6.1)		
FIGO Stage I	40 (81.6)		
LVSI +ve	6 (12.5)		
Cytology +ve	7 (14.6)		

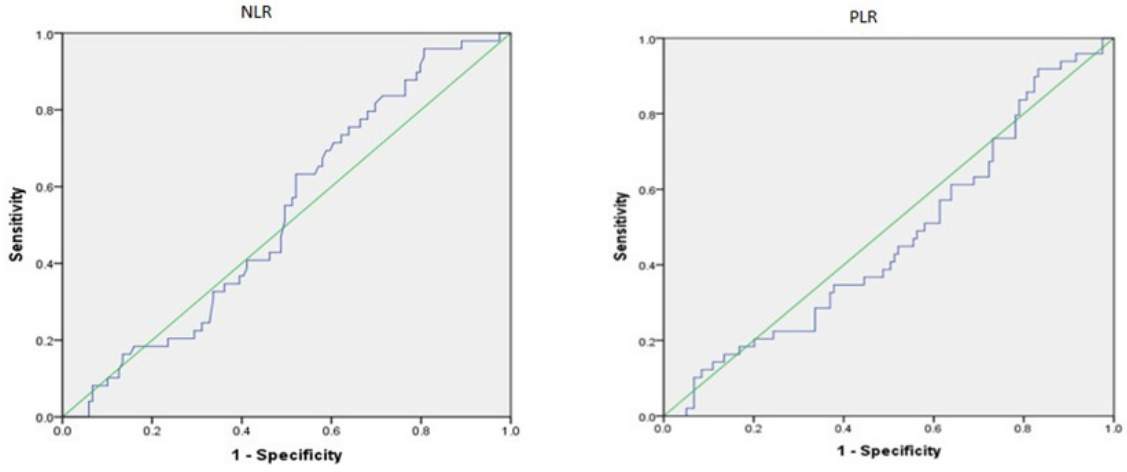
*n(%), **mean ± standard deviation (S.D), BMI, body mass index; UD, underlying disease; DM, diabetic mellitus; HT, hypertension; Others, poorly differentiated cell type; LVSI, lympho-vascular space invasion; Cytology +ve, intraperitoneal cytology

Hematologic parameter ratios (NLR and PLR) were calculated to pathological reports of EC cases as presented in Table 2. Subgroup analysis in EC cases, pre-operative NLR and PLR were higher in case with myometrial invasion (MI) more than half thickness with statistical difference. However, lower uterine and cervical involvement, tumor size ≥ 2cm, lympho-vascular space invasion and positive intraperitoneal cytology were not associated with NLR and PLR as shown in Table 2.

NLR and PLR of study and control groups were comparable and could not predict potential malignancy as shown in Figure 2a and 2b. A receiver operating characteristic curve (ROC) between NLR/PLR and MI more than half thickness was generated as shown in Figure 3a and 3b. NLR and PLR could robustly predict MI of more than half thickness. Appropriate cut-off values of NLR and PLR for MI greater than half thickness prediction were selected at more than 1.93 and 134.95, respectively. NLR equal to or greater than 1.93 gave sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy for MI prediction at 83.3, 52.8, 37.0, 90.5 and 60.4 percent, respectively as shown in Table 3. Sensitivity, specificity, PPV, NPV and accuracy of PLR equal and more than 134.95 for MI prediction were 75.0, 55.6, 36.0, 87.0 and 60.4 percent, respectively as presented in Table 3. Combination of NLR and PLR was further analyzed for improved acumen prediction as shown in Table 3. PLR equal and more than 134and/or NLR equal and more than 1.93 in combination for MI prediction greater than half thickness gave sensitivity, specificity, PPV, NPV and accuracy at a percentage of 91.7, 38.9, 33.3, 93.3 and 52.1, respectively.

Discussion

Cytokine and chemokine from tumor cells production induced an inflammatory response reflected by abnormal change of leukocyte and platelet ratio (Hacker et al., 2015). The current study was conducted in early stage endometrial cancer (EC) and benign gynecologic cases who had some different demographic characteristics. The study group had significantly more age, menopausal status, uterine bleeding and underlying disease especially



a b

Figure 2. Receiver Operating Characteristic Curve for Prediction of NLR (a) and PLR (b) to Predict Malignancy Potential. ROC, Receiver operating characteristic curve; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio

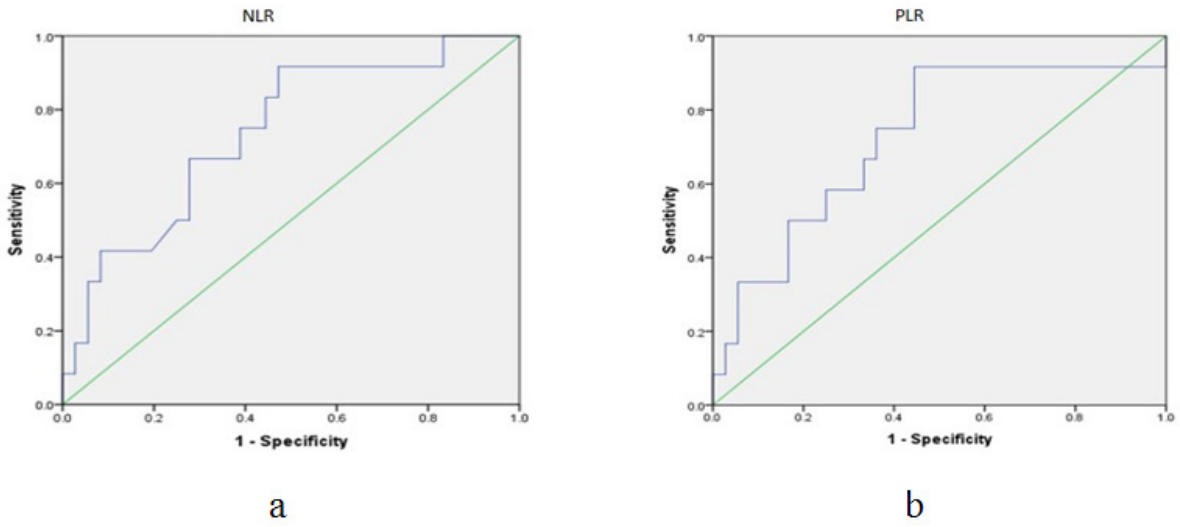


Figure 3. Receiver Operating Characteristic Curve for Prediction of NLR (a) and PLR (b) to MI. ROC, Receiver operating characteristic curve; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; MI, myometrial invasion more than half of thickness

diabetes mellitus and hypertension than control group. Most of the control group presented with pelvic mass and less underlying disease than the study group. Preoperative neutrophil, lymphocyte and platelet ratio were the scope of this study to predict either malignancy potential or and myometrial invasion (MI).

Preoperative NLR between benign gynecologic and EC cases did not differ to statistical significance. It indicated that preoperative NLR could not predict the potential of cancer in preoperative gynecologic surgery. Kurtoglu and Pergialiotis reported the NLR in EC cases from Turkey and Greece in 2015 and 2018, respectively. Their studies concluded that NLR was not associated with cancer prediction (Kurtoglu et al., 2015; Pergialiotis et al., 2018). The current study supported Kurtoglu and Pergialiotis's finding.

Literature from Turkey in 2014, Acmaz and Ural reported NLR of EC cases was significantly higher than endometrial hyperplasia and normal cases (Acmaz et al., 2014; Ural et al., 2014). From Acmaz and Ural's studies, NLR could predict malignancy potential among preoperative gynecologic surgery. In 2018 Bacanakgil from Turkey reported that NLR could predict malignancy potential in lieu with Acmaz and Ural literatures (Bacanakgil et al., 2018). The findings in this study contradicted findings from Acmaz, Ural and Bacanakgil. This difference might be attributed to a difference in demographic characteristics of EC cases. EC cases in current study were mainly in stage I while EC cases in Acmaz, Ural and Bacanakgil's study included all stages

Table 2. Area under Curve (AUC) and Cut- off Values in the Receiver Operating Characteristic Curve

		Cut-off value	AUC	SD	Sensitivity	1-specificity	*p-value*
Total	NLR	1.94	0.53	0.05	0.55	0.5	0.552
	PLR	162.84	0.47	0.48	0.35	0.4	0.545
MI	NLR	1.93	0.74	0.02	0.83	0.44	0.014
	PLR	135.00	0.73	0.09	0.75	0.44	0.021
LI	NLR	1.93	0.57	0.11	0.54	0.57	0.451
	PLR	113.37	0.68	0.83	0.85	0.6	0.056
CI	NLR	2.01	0.7	0.23	0.67	0.47	0.241
	PLR	131.19	0.7	0.13	0.68	0.53	0.241
AI	NLR	2.28	0.35	0.21	0.5	0.39	0.470
	PLR	147.82	0.32	0.17	0.5	0.46	0.380
size	NLR	1.77	0.37	0.1	0.68	0.64	0.204
	PLR	151.81	0.46	0.98	0.4	0.46	0.684
LVSI	NLR	1.89	0.38	0.09	0.5	0.6	0.334
	PLR	128.46	0.32	0.08	0.33	0.61	0.161
Cytology	NLR	2.03	0.31	0.09	0.29	0.49	0.118
	PLR	147.82	0.29	0.09	0.29	0.49	0.072

MI, myometrial involvement; LI, lower uterine involvement; CI, cervical involvement; AI, adnexa involvement; Size, tumor size ≥ 2 cm; LVSI, lympho-vascular space invasion; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; Cytology, intraperitoneal cytology

Table 3. Diagnostic Sensitivity, Specificity, PPV, NPV and Accuracy between MI and Pre-operative Serum Markers

	Value	Sensitivity	Specificity	PPV	NPV	Accuracy
NLR*	≥1.93	83.33	52.78	37.04	90.48	60.42
		51.6-97.91	34.49-69.59	27.71-37.44	72.09-97.22	45.27-74.23
PLR*	≥134.95	75	55.56	36	86.96	60.42
		42.81-94.51	38.10-72.06	25.63-47.87	70.57-94.88	45.27-74.23
Combine*		91.67	38.89	33.33	93.33	52.08
		61.52-99.79	23.14-56.54	26.80-40.57	67.22-98.96	37.19-66.71

*% (95% confidential interval; CI): NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; value, cut-off value; PPV, positive predictive value; NPV, negative predictive value; combine, NLR≥ 1.93 or/and PLR≥ 134.95

of EC (stage I, II, III and IV). More advanced stages of EC reflected more invasion of cancer in MI and adjacent tissues. Another finding from Acmaz, Ural and Bacanakgil's studies, preoperative NLR of endometrial hyperplasia and normal cases were comparable.

Preoperative PLR between benign gynecologic and EC cases in the current study were not statistically differenct. It had similar characteristics to NLR in that it could not predict the potential of cancer or not in preoperative gynecologic surgery. Pergialiotis, Kurtoglu, Ural and Bacanakgil reported the PLR in EC cases from Greece and Turkey in year 2018, 2015, 2014 and 2018, respectively. PLR was not associated with cancer prediction among preoperative gynecologic surgery from their studies. (Ural et al., 2014; Kurtoglu et al., 2015; Pergialiotis et al., 2018; Bacanakgil et al., 2018). The present study supported Pergialiotis, Kurtoglu, Ural and Bacanakgil's finding. In Acmaz' study, both NLR and PLR were higher in EC than control cases (Acmaz et al., 2014). NLR reflected the systemic inflammatory response. Increased NLR had been associated with tumor progression. NLR and PLR were usually changed together. From Acmaz's study, leukocytosis reported while others study did not reported leukocytosis. This might be an interference factor for inflammatory cell ratio.

Although NLR and PLR were not able to predict the diagnosis of endometrial cancer in our study. Further analysis among EC cases, high NLR and PLR were associated with deep myometrial invasion (MI). High degree of MI was associated with high stages of cancer, MI less or more than half of myometrial thickness were categorized as stage IA and IB, respectively (Hacker et al., 2015). Haruma reported from Japan in 2015 that preoperative NLR in EC cases were associated with poor prognosis prediction of disease (Haruma et al., 2015). Reported from Turkey in year 2015, Temur's study showed that preoperative NLR and PLR were related to deep MI (Temur et al., 2015). Preoperative NLR and PLR were important prognostic factors for advanced stages of EC by Cummimgs's literature from the UK in 2015 (Cummings et al., 2015). The findings of the current study supported the previous study of Haruma, Temur and Cummings (Haruma et al., 2015; Temur et al., 2018; Cummings et al., 2015). From previous studies, NLR could predict survival among EC cases. Literature from China, Dong and Cong's study stated that high NLR related value related to more advanced cancer stages (Dong et al., 2020; Cong et al., 2019). However, the findings of the current study were in line with Dong and Cong's study but it was far from the scope of study. The strength of the current study was as a comparative study between endometrial cancer cases who underwent surgical staging and the cases who underwent hysterectomy from benign conditions with nearly comparable demographic characteristics. A limitation of this study was its nature as a retrospective study.

In conclusion, preoperative NLR and PLR were unable to predict the probability of endometrial cancer in our study. However, NLR and PLR could predict the depth of myometrial invasion among EC cases. Even though myometrial invasion could be preoperative evaluated in either magnetic resonance imaging (MRI), computerized tomography (CT) or ultrasonographic study. Intraoperative MI evaluation helped the surgeon to decide whether pelvic and para-aortic lymphadenectomy. Gross examination or frozen section for histopathology might be used in some institutes. In some situation that MI was questionable, high preoperative NLR and PLR were prognostic tools for helping the surgeon to determine whether to perform more aggressive surgery or not.

In conclusion, preoperative NLR and PLR could predict myometrial invasion among endometrial cancer but not cancer probability in general gynecology surgery.

Author Contribution Statement

All authors contributed equally in this study.

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Conflict of interest

Authors report no conflict of interest.

References

Acmaz G, Aksoy H, Unal D, et al (2015). Are neutrophil/lymphocyte and platelet/lymphocyte ratios associated with endometrial precancerous and cancerous lesions in patients with abnormal uterine bleeding. *Asian Pac J Cancer Prev*, **4**, 1689-92.

Bacanakgil BH, Kaban I, Unal F, et al (2019). Predictive value of hematological inflammatory markers in endometrial

neoplasia. *Asian Pac J Cancer Prev*, **6**, 1529-32.
Cho H, Hur HW, Kim SW, et al (2009). Pre-treatment neutrophil to lymphocyte ratio is elevated in epithelial ovarian cancer and predicts survival after treatment. *Cancer Immunol Immunother*, **58**, 15–23.
Cong R, Kong F, Ma J, et al (2020). Combination of preoperative neutrophil-lymphocyte ratio, platelet-lymphocyte ratio and monocyte-lymphocyte ratio: a superior prognostic factor of endometrial cancer. *BMC Cancer*, **20**, 464.
Cummings M, Merone L, Keeble C, et al (2015). Preoperative neutrophil: lymphocyte and platelet: lymphocyte ratios predict endometrial cancer survival. *Br J Cancer*, **113**, 311–20.
Dong Y, Cheng Y, Wang J (2019). The ratio of neutrophil to lymphocyte is a predictor in endometrial cancer. *Open Life Sci*, **14**, 110-8.
Faul F, Erdfelder E, Lang AG (2007). G* Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods*, **39**, 175-91.
Hacker NF, Friedlander ML (2015). Uterine cancer. In Berek and Hacker's gynecologic oncology 6th ed, Eds Berek JS. Wolters Kluwer. Philadelphia, pp 390-442.
Haruma T, Nakamura K, Nishida T, et al (2015). Pre-treatment neutrophil to lymphocyte ratio is a predictor of prognosis in endometrial cancer. *Anticancer Res*, **35**, 337-44.
Kurtoglu E, Kokcu A, Celik H, et al (2016). Platelet indices may be useful in discrimination of benign and malign endometrial lesions, and early and advanced stage endometrial cancer. *Asian Pac J Cancer Prev*, **13**, 5397-400.
Li J, Lin J, Luo Y, et al (2015). Multivariate analysis of prognostic biomarkers in surgically treated endometrial cancer. *PLoS One*, **10**, e0130640.
Pergialiotis V, Oikonomou M, Damaskou V, et al (2018). Platelet to lymphocyte and neutrophil to lymphocyte ratio as predictive indices of endometrial carcinoma: Findings from a retrospective series of patients and meta-analysis. *J Gynecol Obstet Hum Reprod*, **47**, 511–6.
Sung H, Ferlay J, Siegel RL, et al (2021). Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*, **3**, 209-49.
Temur I, Kucukgoz Gulec U, Paydas S, et al (2018). Prognostic value of pre-operative neutrophil/lymphocyte ratio, monocyte count, mean platelet volume, and platelet/lymphocyte ratio in endometrial cancer. E*ur J Obstet Gynecol Reprod Biol*, **226**, 25–9.
Ural ÜM, Şehitoğlu İ, Tekin YB, et al (2015). Neutrophil to lymphocyte and platelet to lymphocyte ratios in patients with endometrial hyperplasia and endometrial cancer. *J Obstet Gynaecol Res*, **41**, 445–8.