# Pre-treatment Neutrophil to Lymphocyte Ratio Is a Predictor of Prognosis in Endometrial Cancer

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**Abstract**. *Background/Aim: Inflammation and tumor immunology are important in the prognosis of various cancers. We herein investigated whether pre-treatment neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) and serum cancer antigen 125 (CA125) predict recurrence and survival in patients with endometrial cancer (EC). Patients and Methods: We collected complete blood counts and clinicopathological data from medical records of 320 patients with EC; their pre-treatment NLR, PLR and CA125 were analyzed for correlations with recurrence and survival, retrospectively. Results: Disease-free survival (DFS) and overall survival (OS) rates of patients with high NLR and CA125 were significantly shorter than those for patients with low NLR and CA125 (DFS: p=0.002 and p<0.001; OS: p<0.001 and p<0.001, respectively). Furthermore, NLR was also an independent predictive factor for mortality in multivariate analysis (hazard ratio (HR)=3.318; 95% confidence interval (CI)=1.154-9.538; p=0.026). Conclusion: Pre-treatment NLR is a predictor of poor prognosis in EC.*

Endometrial cancer (EC) is the most common gynecological malignancy in the Western world with an estimated 49,560 new patients in the United States in 2012 (1). In Japan, EC is the second most common gynecologic malignancy and has increased in recent years. Poor prognostic factors for EC include advanced stage, type II cancer, deep myometrial invasion, adnexal metastasis and lymph node metastasis (2, 3). Several studies of EC have associated elevated serum cancer antigen 125 (CA125) levels with advanced-stage and disease recurrence (4-6). However, its 5-year overall survival (OS) rate is 80% (7) and these parameters are not sufficient to predict prognosis accurately for EC. Therefore, new approaches for pre-treatment assessment of EC are pivotal in improving prognoses.

Inflammation and immunology are important in cancer progression and metastasis (8). Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) are indices of systemic inflammation and immunology. Pre-treatment NLR or PLR in peripheral blood have been shown to be predictive for outcomes, such as ovarian (9, 10), breast (11), gastric (12), colon (13) and lung cancer (14). Suh *et al*. reported that NLR and PLR were significantly higher in EC patients with lymph node metastasis than in those without (15). Wang *et al*. reported that pre-treatment NLR and PLR were significantly associated with cervical invasion in EC (16).

However, whether NLR and PLR are associated with outcomes for patients with EC is unclear. Herein, we investigated correlations between pre-treatment NLR, PLR, CA125 and recurrence and mortality in EC.

## Patients and Methods

*Study population*. This retrospective study reviewed the medical records of 320 patients with EC who were treated at the Department of Obstetrics and Gynecology of Okayama University Hospital between January 2002 and December 2012 and extracted clinical and pathological data, including age, pre-treatment complete blood count (CBC), serum CA125, surgical International Federation of Gynecology and Obstetrics (FIGO) stage, tumor histology, myometrial invasion, lymph node metastasis, cervical invasion, ovarian metastasis, washing cytology, date of progression, date of last follow-up visit and patients' status at last visit. For patients who underwent neo-adjuvant chemotherapy, we collected data from magnetic resonance imaging (MRI) and positron emission tomography (PET) or/and computed tomography (CT). All patients were treated according to the Japan Society of Gynecologic Oncology (JSGO) clinical guidelines.

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*Key Words:* Endometrial cancer, neutrophil to lymphocyte ratio, prognosis.

Table I. *Patients' characteristics*.

| Age at diagnosis | Median, 57.5 Numbers | Range, 23-86 (%) |
|---|---|---|
| Stage | | |
| IA | 186 | 58.1 |
| IB | 41 | 12.8 |
| II | 26 | 8.1 |
| IIIA | 8 | 2.5 |
| IIIB | 3 | 0.9 |
| IIIC1 | 17 | 5.3 |
| IIIC2 | 12 | 3.8 |
| IVA | 1 | 0.3 |
| IVB | 26 | 8.1 |
| Histology | | |
| Endometrioid adenocarcinoma G1 | 166 | 51.8 |
| Endometrioid adenocarcinoma G2 | 68 | 21.3 |
| Endometrioid adenocarcinoma G3 | 40 | 12.5 |
| Serous adenocarcinoma | 17 | 5.3 |
| Clear cell adenocarcinoma | 3 | 0.9 |
| Mixed carcinoma | 2 | 0.6 |
| Undifferentiated carcinoma | 5 | 1.6 |
| Squamous cell carcinoma | 1 | 0.3 |
| Carcinosarcoma | 18 | 5.6 |

Adjuvant chemotherapy was administered depending on risk factors (FIGO stage and histological grade), patient preference and physician discretion. Chemotherapy consisted of paclitaxel at a dose of 180 mg/m$^2$ infused over 3 hours and carboplatin dosed for an area under the concentration-time curve of 5 for 3-6 cycles. The study protocol was approved by the Institutional Review Board of Okayama University Hospital. Informed consent was obtained from all patients.

*Laboratory data collection*. Each subject had a CBC, differential WBC count and serum CA125 recorded within a month prior to treatment. The NLR was defined as absolute neutrophil count divided by absolute lymphocyte count; PLR was defined as absolute platelet count divided by lymphocyte count (Bayer HealthCare, Diagnostics Division, Tarrytown, NY, USA). Serum CA125 level was measured with an electrochemiluminescence immunoassay on a Roche/Hitachi Modular Analysis E170 (Roche Diagnostics, Tokyo, Japan).

*Statistical analysis*. Statistical analyses were performed using the Mann-Whitney *U*-test for comparisons with controls. Receiver operating characteristic (ROC) curves of DFS and OS were generated for pre-treatment NLR, PLR and CA125 to determine optimally sensitive and specific cut-off values that predict recurrence and death. For DFS and OS rates, the patients were divided into groups based on pre-treatment NLR, PLR and CA125 cut-off values derived from the ROC curves. DFS and OS of the groups were analyzed using the Kaplan-Meier method. Differences between the recurrence and survival curves were examined using the log-rank test. We performed univariate and multivariate analyses using Cox's proportional hazards model to determine which factors predict DFS and OS after adjusting for effects of known prognostic factors. Analyses were performed using the SPSS software version 20.0 (SPSS Inc., Chicago, IL, USA). $p<0.05$ was considered statistically significant.

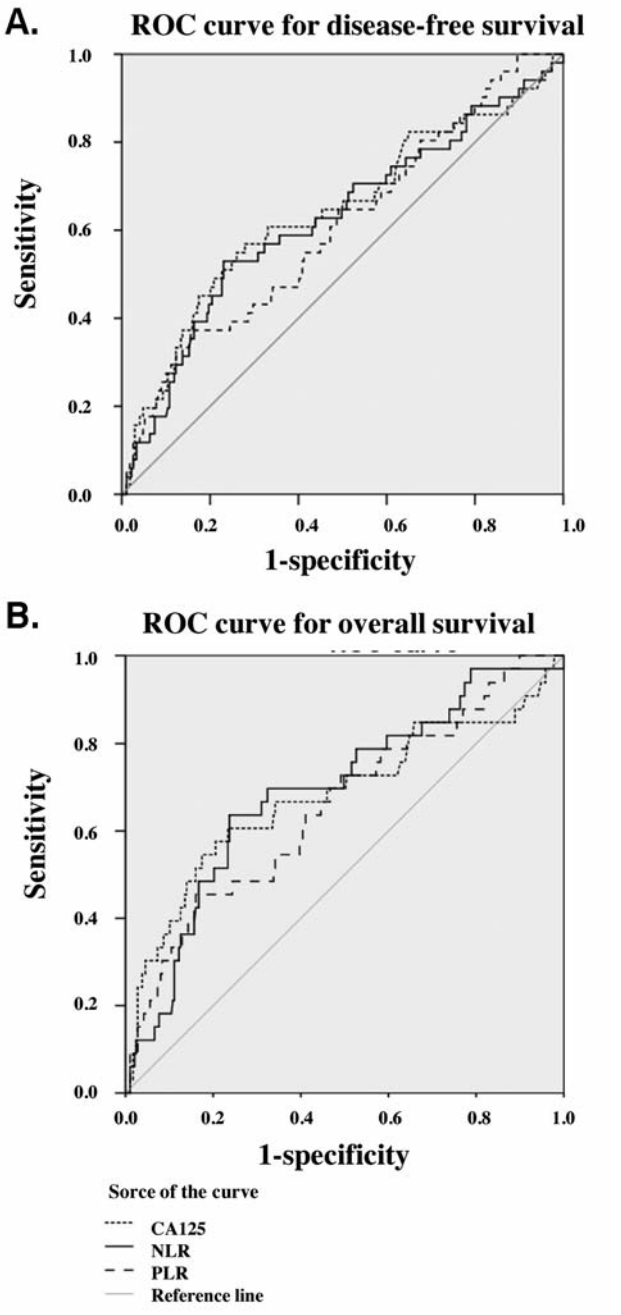


Figure 1. *Receiver operating characteristic (ROC) curves for A, Disease-free survival (DFS) of NLR, PLR and CA125 to predict recurrence. Optimal NLR, PLR and CA125 cut-off value to predict recurrence was 2.41, 175.72 and 27.95 U/ml respectively. B, Overall survival (OS) of NLR, PLR, and CA125 to predict survival. Optimal NLR, PLR and CA125 cut-off value to predict survival was 2.70, 174.02 and 27.95 U/ml respectively.*

Table II. *NLR, PLR and serum CA125 level in relation to FIGO stage and histology on pre-treatment assessment of endometrial cancer.*

| | | N | NLR Mean±SE | *p*-Value | PLR Mean±SE | *p*-Value | CA125 Mean±SE | *p*-Value |
|---|---|---|---|---|---|---|---|---|
| Stage | | | | <0.001* | | <0.001* | | <0.001* |
| I | | 227 | 2.444±1.186 | | 163.617±71.770 | | 48.206±161.093 | |
| II | | 26 | 2.920±1.704 | | 174.517±66.592 | | 41.742±51.792 | |
| III | | 40 | 3.334±1.996 | | 230.690±136.387 | | 111.623±221.259 | |
| IV | | 27 | 3.957±2.365 | | 276.043±125.614 | | 240.315±343.505 | |
| Histology | | | | 0.008* | | 0.005* | | 0.076 |
| Endometrioid adenocarcinoma | G1 | 166 | 2.570±1.385 | | 169.215±75.202 | | 65.840±213.435 | |
| Endometrioid adenocarcinoma | G2 | 68 | 2.521±1.340 | | 168.662±78.470 | | 45.158±61.950 | |
| Endometrioid adenocarcinoma | G3 | 40 | 3.204±1.663 | | 228.727±123.953 | | 73.928±121.605 | |
| Others | | 46 | 3.338±2.265 | | 220.806±133.646 | | 129.428±266.081 | |

*Mann-Whitney *U*-test. Abbrevations: NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

Table III. *Pre-treatment NLR, PLR and serum CA125 levels in relation to clinical factors in patients with endometrial cancer.*

| | N | NLR Mean±SE | *p*-Value | PLR Mean±SE | *p*-Value | CA125 Mean±SE | *p*-Value |
|---|---|---|---|---|---|---|---|
| FIGO stage | | | <0.001* | | <0.001* | | 0.002* |
| I /II | 253 | 2.492±1.253 | | 164.737±70.978 | | 47.542±153.439 | |
| III/IV | 67 | 3.719±2.246 | | 222.480±127.513 | | 162.456±278.277 | |
| Histology | | | 0.003* | | <0.001* | | 0.087 |
| G1+G2 | 232 | 2.558±1.374 | | 168.872±76.261 | | 59.556±183.519 | |
| G3+others | 88 | 3.253±1.982 | | 223.712±127.214 | | 103.359±210.122 | |
| Myometrial invasion | | | <0.001* | | <0.001* | | 0.005* |
| <1/2 | 219 | 2.481±1.240 | | 166.184±71.733 | | 46.881±150.548 | |
| ≥1/2 | 101 | 3.331±2.057 | | 220.770±123.248 | | 125.205±252.256 | |
| Cervical invasion | | | 0.108 | | 0.024* | | 0.243 |
| Negative | 295 | 2.678±1.491 | | 179.067±91.059 | | 65.632±193.628 | |
| Positive | 25 | 3.526±2.400 | | 261.071±148.768 | | 113.539±115.570 | |
| Lymph node metastasis | | | 0.001* | | <0.001* | | 0.019* |
| Negative | 276 | 2.571±1.351 | | 171.523±78.142 | | 55.787±161.527 | |
| Positive | 44 | 3.929±2.409 | | 250.337±143.563 | | 176.017±313.906 | |
| Ovarian metastasis | | | 0.008* | | 0.001* | | 0.022* |
| Negative | 294 | 2.623±1.407 | | 173.977±84.137 | | 59.029±174.152 | |
| Positive | 26 | 4.186±2.684 | | 280.865±142.655 | | 213.080±311.113 | |
| Peritoneal cytology | | | 0.115 | | 0.492 | | 0.102 |
| Negative | 266 | 2.670±1.514 | | 179.944±93.395 | | 59.389±174.874 | |
| Positive | 51 | 3.051±1.854 | | 189.740±92.445 | | 102.529±155.534 | |

*Mann-Whitney *U*-test. FIGO, International Federation of Gynecology and Obstetrics; LVS, lymphovascular space; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; CA125, cancer antigen 125.

## Results

We enrolled a total of 320 patients (median age=57.5 years; range=23-86 years) who also underwent routine clinical staging and physical examination; 297 of these patients underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy and partial omentectomy with or without pelvic and/or para-aortic lymphadenectomy; 23 patients who were not operable received neo-adjuvant chemotherapy.

Their cancers were staged according to the FIGO staging system; the local extent of disease was diagrammed on a tumor staging form for each patient (Table I). Median pre-treatment values were NLR: 2.376 (range=0.396-10.709); PLR: 162.148 (range, 48.371-697.695); and CA125: 20.7U/ml (range=0.4-1,690 U/ml). FIGO stage was significant associated with median NLR, PLR and CA125 ($p<0.001$ for each; Table II). Histology was significantly associated with pre-treatment NLR ($p=0.008$) and PLR ($p=0.005$) but not CA125.

Table IV. *Univariate and multivariate analysis for disease-free survival and overall survival of patients with endometrial cancer, by prognostic factors.*

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| Disease-free survival | Hazard ratio | 95%CI | *p*-Value | Hazard ratio | 95%CI | *p*-Value |
| FIGO stage | 8.686 | 4.925-15.317 | <0.001* | 2.588 | 0.970-6.905 | 0.058 |
| Histology | 5.462 | 3.092-9.650 | <0.001* | 2.24 | 1.174-4.275 | 0.014* |
| Deep myometrial invasion | 4.579 | 2.591-8.095 | <0.001* | 1.653 | 0.837-3.262 | 0.148 |
| Cervical invasion | 2.75 | 1.518-4.980 | 0.001* | 1.092 | 0.504-2.363 | 0.824 |
| Lymph node metastasis | 8.602 | 4.815-15.369 | <0.001* | 1.926 | 0.754-4.920 | 0.171 |
| Ovarian metastasis | 4.745 | 2.470-9.115 | <0.001* | 1.025 | 0.456-2.304 | 0.952 |
| Peritoneal cytology | 3.109 | 1.726-5.602 | <0.001* | 1.753 | 0.932-3.297 | 0.082 |
| NLR | 2.365 | 1.341-4.173 | 0.003* | 1.693 | 0.888-3.229 | 0.110 |
| PLR | 1.599 | 0.922-2.772 | 0.095 | | | |
| CA125 | 2.962 | 1.687-5.200 | <0.001* | 1.299 | 0.693-2.434 | 0.415 |
| Overall survival | Hazard ratio | 95%CI | *p*-Value | Hazard ratio | 95%CI | *p*-Value |
| FIGO stage | 12.193 | 5.779-25.722 | <0.001* | 2.463 | 0.686-8.848 | 0.167 |
| Histology | 8.709 | 4.040-18.773 | <0.001* | 4.076 | 1.704-9.747 | 0.002* |
| Deep myometrial invasion | 5.175 | 2.507-10.680 | <0.001* | 1.336 | 0.555-3.216 | 0.519 |
| Cervical invasion | 3.413 | 1.859-6.266 | <0.001* | 1.408 | 0.584-3.396 | 0.446 |
| Lymph node metastasis | 12.726 | 6.122-26.454 | <0.001* | 3.045 | 0.974-9.517 | 0.055 |
| Ovarian metastasis | 5.266 | 2.422-11.449 | <0.001* | 1.045 | 0.393-2.780 | 0.929 |
| Peritoneal cytology | 3.157 | 1.508-6.605 | 0.002* | 2.082 | 0.945-4.587 | 0.069 |
| NLR | 4.088 | 1.945-8.590 | <0.001* | 3.318 | 1.154-9.538 | 0.026* |
| PLR | 2.054 | 1.021-4.132 | 0.043* | 0.546 | 0.192-1.552 | 0.256 |
| CA125 | 3.612 | 1.751-7.452 | 0.001* | 1.196 | 0.511-2.796 | 0.68 |

*0.05, Mann-Whitney U test. FIGO, International Federation of Gynecology and Obstetrics; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; CA125, cancer antigen 125; CI, confidence interval.

When patients were sorted into binary sets (high/low, positive/negative, *etc.*) for various clinicopathological factors, NLR was significantly associated with histology ($p=0.003$), FIGO stage ($p<0.001$), myometrial invasion ($p<0.001$), lymph node metastasis ($p=0.001$) and ovarian metastasis ($p=0.008$); PLR was significantly associated with histology ($p<0.001$), FIGO stage ($p<0.001$), myometrial invasion ($p<0.001$), cervical invasion ($p=0.024$), lymph node metastasis ($p=0.001$) and ovarian metastasis ($p=0.001$); and CA125 level was significantly associated with higher FIGO stage ($p=0.002$), myometrial invasion ($p=0.005$), lymph node metastasis ($p=0.019$) and ovarian metastasis ($p=0.022$) (Table III).

Median DFS and OS times of all patients were 42.0 and 49.4 months, respectively; follow-up periods were 1-130 months for both. For DFS, the NLR cut-off value was 2.41 (area under the curve (AUC)=0.624, sensitivity: 62.7%, specificity: 56.1%), the PLR cut-off value was 175.72 (AUC=0.606, sensitivity; 52.9%, specificity; 59.1%) and the CA125 cut-off value was 27.95 U/ml (AUC=0.639, sensitivity; 60.8%, specificity; 66.9%) (Figure 1). For OS, the NLR cut-off value was 2.70 (AUC: 0.691, sensitivity: 69.7%, specificity: 67.6%), the PLR cut-off value was 174.02 (AUC: 0.655, sensitivity: 63.6%, specificity: 58.9%) and the CA125 cut-off value was 27.95 U/ml (AUC: 0.679, sensitivity: 66.7%, specificity: 63.8%).

When patients were classified into those above and below each cut-off value for DFS and OS (Figures 2 and 3), Kaplan-Meyer curves of DFS and OS rates show that patients with high NLR and CA125 had significantly shorter rates than those of patients with low NLR and CA125 (DFS: $p=0.002$ and $p<0.001$, OS: $p<0.001$ and $p<0.001$, respectively). Although high PLR was associated with shorter OS than low PLR ($p=0.039$), DFS did not significantly differ between the high- and low-PLR groups ($p=0.096$).

We used Cox's proportional hazards model to identify predictors of recurrence and death with EC (Table IV). On DFS, all factors other than PLR were significantly associated with recurrence for EC in univariate analysis but only histology was an independent predictor of recurrence in multivariate analysis (hazard ratio (HR)=2.240, 95% confidence interval (CI)=1.174-4.275, $p=0.014$). For OS, univariate analysis associated all factors with mortality but only histology (HR=4.076, 95% CI: 1.705-9.747, $p=0.002$) and NLR (HR=3.318, 95%=CI=1.154-9.538, $p=0.026$) were independently associated with survival in EC in multivariate analyses.

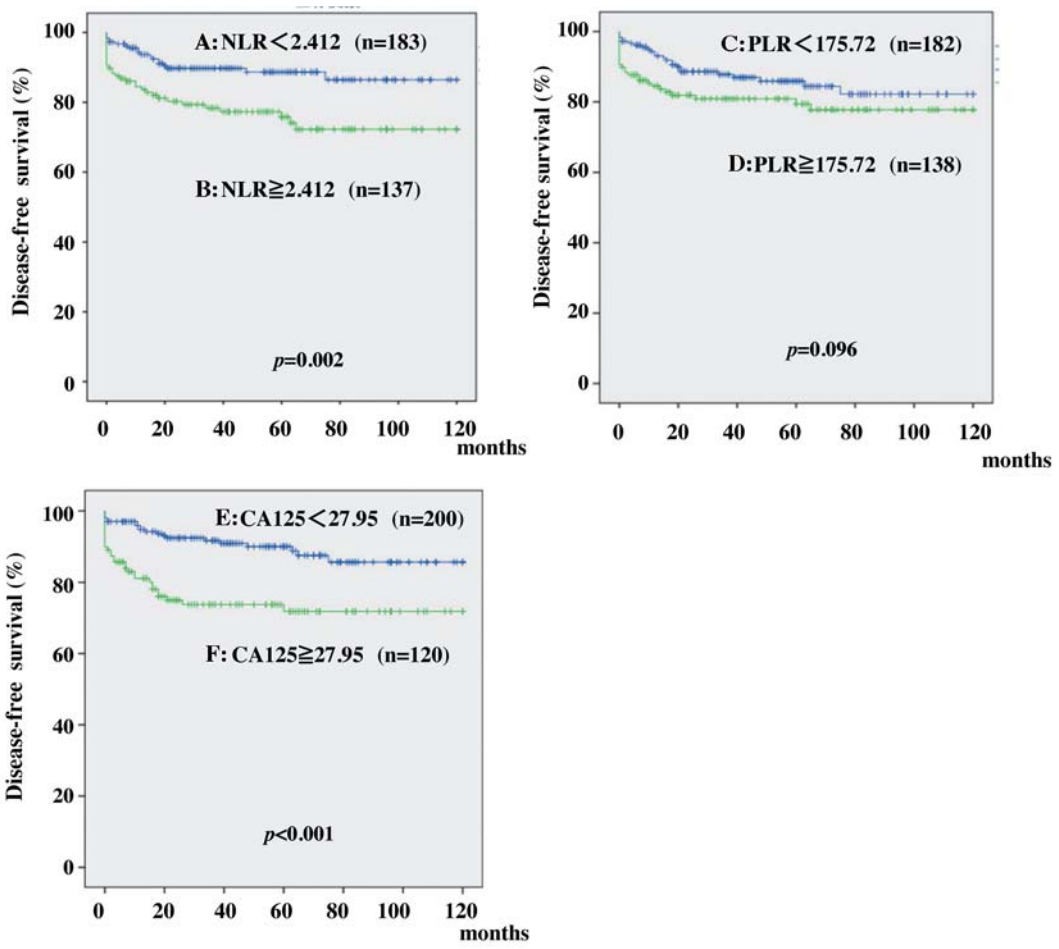


Figure 2. *Kaplan-Meier plots for disease-free survival (DFS) rates of 320 patients with endometrial cancer by their pre-treatment NLR, PLR and the serum CA125 values. A: NLR <2.41 (n=183); B: NLR ≥2.41 (n=137); C: PLR <175.72 (n=182); D: PLR ≥175.72 (n=138). E: Serum CA125 <27.95 U/ml (n=200); F: serum CA125 ≥27.95 U/ml (n=120).*

## Discussion

To our knowledge, this is the first study to describe an association between pre-treatment NLR and prognosis in EC. We have correlated pre-treatment NLR, PLR and CA125 with almost all factors associated with poor prognosis, except for peritoneal cytology and histology for CA125. Patients with high NLR and CA125 had significantly shorter DFS and OS than patients with low NLR and CA125. High PLR was correlated with shorter OS than was low PLR. Multivariate analyses also showed high NLR, but not high PLR or CA125, to be an independent prognostic factor for mortality in EC.

Clinical studies have associated pre-treatment peripheral-blood NLR with patient outcomes in various cancers (9, 10-14). Although inflammation and cancer have been strongly linked (17, 18), the mechanism between pre-treatment neutrophilia and leukocytosis and tumor progression is unclear. Reportedly, neutrophils release inflammatory cytokines, leukocytic factors and other phagocytic mediators that can damage cellular DNA, inhibit apoptosis and promote angiogenesis (18-20), whereas lymphocytes, such as $CD3^+$ T cells and NK cells, exhibit potent anti-cancer activities that can inhibit growth and metastasis (21). Together, these properties would explain poor survival in EC patients with high NLR.

PLR is also a representative index of systemic inflammation and immune function and its prognostic value has been studied in several cancers (10, 14). Platelets can release potent mitogens or adhesive glycoproteins, such as platelet-derived growth factor, transforming growth factor-ß and vascular endothelial growth factor (22-24). In our study, although PLR was associated with almost all

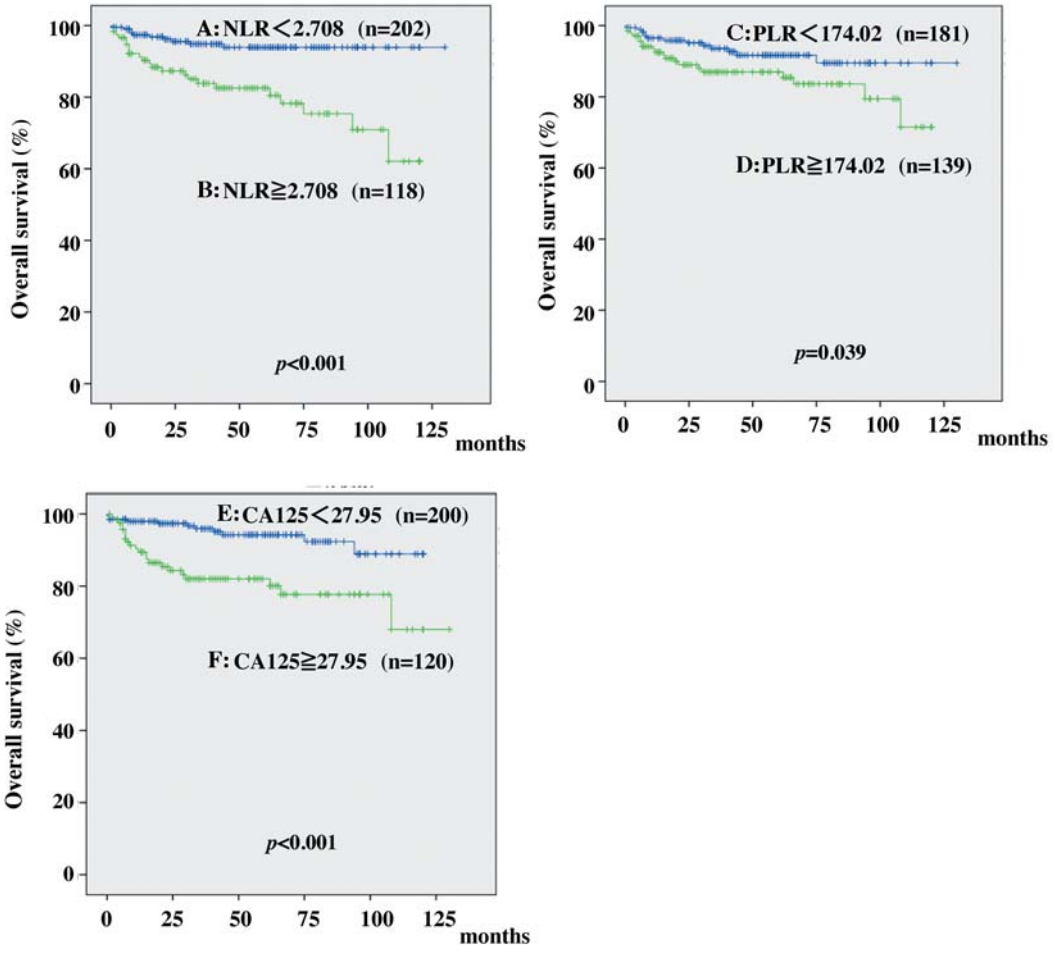


Figure 3. *Kaplan-Meier plots for the overall survival (OS) rates of 320 patients with endometrial cancer by their pre-treatment NLR, PLR and the serum CA125 values. A: NLR <2.70 (n=202); B: NLR ≥2.70 (n=118); C: PLR <174.02 (n=181); D: PLR ≥174.02 (n=139). E: Serum CA125 <27.95 U/ml (n=200); F: serum CA125 ≥27.95 U/ml (n=120).*

predictors of poor prognosis and patients with high PLR had shorter OS, PLR was not an independent predictor of poor prognosis. High CA125 levels have been associated with increased incidence of extra-uterine disease, advanced surgical stage, lymph node metastasis and poor prognosis (25-27). Our study also found that patients with high CA125 levels had poor prognosis; however, high CA125 was not an independent predictor of poor outcome, which suggests that NLR is a better predictive factor than CA125 in EC.

Our results indicate that survival of patients with EC depends on histology but is also affected by pre-treatment NLR, which suggest that the immune system is important in this disease and also that restoring immunocompetence and nutritional states could improve prognosis of these patients. Moreover, NLR is calculated from a convenient and inexpensive test that can provide useful prognostic information for the management and treatment of EC.

We acknowledge that our study has certain limitations. We had relatively few subjects and the median follow-up duration was rather short. Data from future prospective studies with more patients and longer follow-up periods would clarify the significance of our findings.

In conclusion, high pre-treatment NLR can predict poor prognosis in patients with endometrial cancer.

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