Research Article

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The ratio of neutrophil to lymphocyte is a predictor in endometrial cancer

1 Introduction

Endometrial cancer (EC) is the most common gynecological malignancy in the world, accounting for 7% of all female cancers in 2016 [1]. In China, EC is the second largest gynecological tumor after cervical cancer, with 63,400 estimated new cases and 21,800 estimated deaths in 2015. The cancer incidence has increased at a rate of 3.7% per year [2]. ECs are mainly adenocarcinomas and diagnosed at an early stage. Although surgical removal and adjuvant therapy based on patient characteristic have improved the prognosis, about 20% of EC patients still show relapse and die within 5 years after surgery [3]. Also, women with advanced-stage or recurrent EC have poor clinical outcomes.

Traditionally, recognized independent prognostic factors include age, Federation of Gynecology and Obstetrics (FIGO) stage, histology grade, histopathological subtype, tumor size and lymphovascular invasion (LVSI). These factors have been widely used in risk stratification and tailoring treatment strategies and have significantly improved prognosis in EC. However, these tumor-related risk factors are not accurate enough to predict risk of EC recurrence and the outcomes. Currently, with the development of genomics, more molecular biomarkers have been found and can be used as drug targets or prognostic factors for disease recurrence or survival. Use of these biomarkers can provide novel options for patients but is time-consuming and expensive for most patients. Therefore, more effective, economical and convenient indicators are urgently needed to assist clinicians in preoperative risk stratification and administering treatment strategies.

An increasing amount of evidence supports the role of inflammation and immunology in carcinogenesis, progression and prognosis [4 - 9]. Peripheral blood cells are potential biomarkers of tumor immunity and have pivotal roles in the systemic inflammatory response during all stages of malignancies.

Neutrophils represent approximately 50% to 70% of all white blood cells. They are indicators of the inflammation
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The NLR was defined as absolute neutrophil count divided by absolute lymphocyte count. Overall survival (OS) was defined as the time between the date of hysterectomy-based surgical staging and the date of death or the last follow-up if the patient was alive. Cancer-specific survival (CSS) was defined as the time between the date of hysterectomy-based surgical staging and the date of death due to EC or the last follow-up if the patient was alive. Disease-free survival (DFS) was defined as the time between hysterectomy-based surgical staging and the date of first recurrence or last follow-up if there was no recurrence [23]. The primary endpoint was OS. Secondary endpoints included CSS and DFS.

Informed consent: Informed consent has been obtained from all individuals included in this study.

Ethical approval: The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the ethics committee of Peking University People’s Hospital (approval no. 2016PHB054-01).

2 Materials and methods

2.1 Patients

Retrospective data were collected for patients who underwent surgical staging procedures at Peking University People’s Hospital between January 2010 and December 2016. Patients with inflammatory disease, hematological disease, autoimmune disease, or concurrent second malignancies or who were missing preoperative complete blood cell counts or complete blood cell counts performed more than 1 week before surgery were excluded.

The surgical procedures consisted of at least total hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO). TAH, BSO and systematic lymphadenectomy were performed for patients with FIGO stage IB or higher, grade 3 endometrioid adenocarcinoma, non-endometrioid histology, LVS1 or tumor > 2 cm. Postoperative adjuvant treatments were tailored to the pathology findings in accordance with the institutional treatment guidelines and FIGO guidelines. Adjuvant chemotherapy or radiotherapy was recommended for patients with any recurrence risk factors. The cancer was staged according to the 2009 FIGO guidelines and was graded according to the FIGO classification. Data on age, complete blood cell count within 1 week before surgery, FIGO stage, histologic grade, histopathological subtype, presence of LVS1, lymph node status, peritoneal cytology, history of adjuvant chemotherapy and radiotherapy were obtained from medical records.

The NLR was defined as absolute neutrophil count divided by absolute lymphocyte count. Overall survival (OS) was defined as the time between the date of hysterectomy-based surgical staging and the date of death or the last follow-up if the patient was alive. Cancer-specific survival (CSS) was defined as the time between the date of hysterectomy-based surgical staging and the date of death due to EC or the last follow-up if the patient was alive. Disease-free survival (DFS) was defined as the time between hysterectomy-based surgical staging and the date of first recurrence or last follow-up if there was no recurrence [23]. The primary endpoint was OS. Secondary endpoints included CSS and DFS.

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2.2 Statistical analysis

Categorical data were compared by chi-square test or two-tailed Fisher exact test, as appropriate. The optimal cut-off value was estimated by using the package Cut-off Finder in R software. We plotted receiver operating characteristic (ROC) curves of NLR for OS, CSS and DFS. An optimal cut-off value that maximized the sum of sensitivity and specificity in the ROC curve was used. Survival was analyzed by the Kaplan–Meier method, and significant differences in survival were identified by log-rank test. Univariable and multivariable analyses involved Cox proportional-hazards models, estimating hazard ratios (HRs) and 95% confidence intervals (CIs). All statistical tests involved use of R v2.12.2. All statistical analyses were two-tailed, and p<0.05 was considered statistically significant.
3 Results

3.1 Patient populations and clinicopathologic characteristics

The clinicopathologic characteristics of the 510 patients are summarized in Table 1. The median age at diagnosis was 56 years (range 23–83). All patients underwent hysterectomy-based surgical staging for EC. In total, 406 (79.6%), 25 (4.9%), 64 (12.6%), and 15 (2.9%) patients had stage I, II, III, and IV disease, respectively. Most ECs had endometrioid histology (86.3%) and were low grade (grade 1–2, 76.7%). Overall, 81% of the patients underwent lymphadenectomy (pelvic/para-aortic) and 26.5% received adjuvant chemotherapy, 24% adjuvant radiotherapy and 14.9% simultaneous adjuvant chemotherapy and radiotherapy. In total, 48 (11.6%) patients had lymph node involvement and 96 (18.8%) had LVSI. The median NLR was 2.30 (range 0.70–13.04) and median follow-up was 41 months (range 1–91 months). In all, 22 patients died from cancer-related causes, and 3 from suicide; 39 had tumor recurrence.

Table 1. Clinicopathologic characteristics of patients with endometrial cancer (n=510).

| Characteristic               | n  | (%)  |
|-----------------------------|----|------|
| Age (year) median (range)   | 56 | 23-83|
| FIGO stage                  |    |      |
| I                           | 406| 79.6%|
| II                          | 25 | 4.9% |
| III                         | 64 | 12.6%|
| IV                          | 15 | 2.9% |
| Histology grade             |    |      |
| G1                          | 171| 33.5%|
| G2                          | 220| 43.1%|
| G3                          | 119| 23.3%|
| Histology type              |    |      |
| Endometrioid                | 440| 86.3%|
| Nonendometrioid             | 70 | 13.7%|
| LN metastasis               |    |      |
| Absent                      | 365| 88.4%|
| Present                     | 48 | 11.6%|
| Peritoneal cytology         |    |      |
| Absent                      | 352| 91.0%|
| Present                     | 35 | 9.0% |
| LVSI                        |    |      |
| Absent                      | 414| 81.2%|
| Present                     | 96 | 18.8%|
| NLR median (range)          | 2.3| 0.70-13.04|

FIGO=International Federation of Gynaecology and Obstetrics; LN=lymph node; LVSI=lymphovascular space invasion; NLR=neutrophil:lymphocyte ratio
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Table 2 Clinical and pathological characteristics of patients with endometrial cancer by high and low NLR (n=510).

| Characteristic          | NLR-low(<2.47) | NLR-high(≥2.47) | P-value |
|-------------------------|----------------|-----------------|---------|
| Age (year)              |                |                 |         |
| <60                     | 184 (65.7%)    | 154 (67.0%)     | 0.768   |
| ≥60                     | 96 (34.3%)     | 76 (33.0%)      |         |
| FIGO stage              |                |                 |         |
| I–II                    | 245 (87.5%)    | 186 (80.9%)     | 0.039   |
| III–IV                  | 35 (12.5%)     | 44 (19.1%)      |         |
| Histology grade         |                |                 | 0.005   |
| G1/G2                   | 228 (81.4%)    | 163 (70.9%)     |         |
| G3                      | 52 (18.6%)     | 67 (29.1%)      |         |
| Histology type          |                |                 | 0.055   |
| Endometrioid            | 249 (88.9%)    | 191 (83.0%)     |         |
| Nonendometrioid         | 31 (11.1%)     | 39 (17.0%)      |         |
| LN metastasis           |                |                 | 0.041   |
| Absent                  | 209 (91.3%)    | 156 (84.8%)     |         |
| Present                 | 20 (8.7%)      | 28 (15.2%)      |         |
| Peritoneal cytology     |                |                 | 0.070   |
| Absent                  | 197 (93.4%)    | 155 (88.1%)     |         |
| Present                 | 14 (6.6%)      | 21 (11.9%)      |         |
| LVSI                    |                |                 | 0.194   |
| Absent                  | 233 (83.2%)    | 181 (78.7%)     |         |
| Present                 | 47 (16.8%)     | 49 (21.3%)      |         |

NLR=neutrophil:lymphocyte ratio; FIGO=International Federation of Gynaecology and Obstetrics; LN=lymph node; LVSI= lymphovascular space invasion. Significant p values are in bold, by chi-square test

(P<0.039), histology grade (P=0.005), and lymph node metastasis (P=0.041).

3.3 Univariable and multivariable analyses for OS, CSS and DFS (Tables 3 to 5, Figure 1)

Prognostic variables for univariable analysis included age, FIGO stage, histology grade, histopathological subtype, peritoneal cytology and presence of lymphovascular space invasion, a known independent prognostic indicator for EC. Depth of myometrial invasion, cervical involvement and lymph-node status form part of the FIGO staging system and, as such, were not included as independent variables in the analysis.

Kaplan–Meier analysis for OS, CSS and DFS (Figure 1) revealed significantly worse OS, CSS and DFS for patients with high preoperative NLR. On univariable analysis, factors associated with OS were age (HR 4.7; 95% CI, 1.7-13.1; P=0.003), FIGO stage (HR 5.4; 95% CI, 1.8-15.7; P=0.002), and NLR (HR 4.7; 95% CI, 1.5-14.1; P=0.006) (Table 3). Independent predictors of CSS were also age, FIGO stage and NLR [HR 4.5 (95% CI, 1.5-13.6; P =0.008), HR 5.6 (95% CI, 1.7-18.3; P =0.004) and HR 3.6 (95% CI, 1.1-11.5; P =0.028), respectively] (Table 4). Independent predictors of DFS were age (HR 2.2; 95% CI, 1.0-4.8; P = 0.045), FIGO stage (HR 4.4; 95% CI, 1.8-10.5; P =0.001), histology grade (HR 4.2; 95% CI, 1.3-13.5; P =0.016), peritoneal cytology (HR 3.2; 95% CI, 1.2-8.2; P =0.016) and NLR (HR 2.3; 95% CI, 1.0-5.2; P =0.044) (Table 5).

4 Discussion

Neutrophils are indicators of the whole inflammation microenvironment state of the body, and lymphocytes are the main components of antitumor immunity. Lymphocytes are generally reduced in various types
Table 3. Univariable and multivariable analysis of factors, including NLR cut-off, associated with overall survival with endometrial cancer.

| Characteristic       | Univariable | Multivariable |
|----------------------|-------------|---------------|
|                      | HR (95% CI) | P-value       | HR (95% CI) | P-value |
| Age (year)           |             |               |             |         |
| <60                  | 1 (Reference) |               | 1 (Reference) |         |
| ≥60                  | 3.1 (1.4–6.9) | 0.006         | 4.7 (1.7–13.1) | 0.003   |
| FIGO stage           |             |               |             |         |
| I–II                 | 1 (Reference) |               | 1 (Reference) |         |
| III–IV               | 21.8 (8.7–54.7) | <0.001     | 5.4 (1.8–15.7) | 0.002   |
| Histology grade      |             |               |             |         |
| G1/G2                | 1 (Reference) |               | 1 (Reference) |         |
| G3                   | 15.4 (5.8–41.0) | <0.001   | 2.6 (0.6–11.1) | 0.207   |
| Type                 |             |               |             |         |
| Type I               | 1 (Reference) |               | 1 (Reference) |         |
| Type II              | 11.6 (5.2–25.8) | <0.001  | 1.2 (0.3–5.0) | 0.763   |
| Peritoneal cytology  |             |               |             |         |
| Absent               | 1 (Reference) |               | 1 (Reference) |         |
| Present              | 10.5 (4.4–25.2) | <0.001  | 2.7 (0.9–8.3) | 0.084   |
| LVSİ                 |             |               |             |         |
| Absent               | 1 (Reference) |               | 1 (Reference) |         |
| Present              | 8.2 (3.7–18.4) | <0.001  | 2.6 (0.9–7.3) | 0.071   |
| NLR                  |             |               |             |         |
| Low                  | 1 (Reference) |               | 1 (Reference) |         |
| High                 | 3.9 (1.5–9.7) | 0.004       | 4.7 (1.5–14.1) | 0.006   |

NLR=neutrophil:lymphocyte ratio; HR=hazard ratio; 95% CI=95% confidence interval; FIGO=International Federation of Gynaecology and Obstetrics; LN=lymph node; LVSİ= lymphovascular space invasion. Significant p values are in bold, by chi-square test; Bold values indicate statistical significance.

Table 4. Univariable and multivariable analysis of factors, including NLR cut-off, associated with cancer-specific survival with endometrial cancer.

| Characteristic       | Univariable | Multivariable |
|----------------------|-------------|---------------|
|                      | HR (95% CI) | P-value       | HR (95% CI) | P-value |
| Age (year)           |             |               |             |         |
| <60                  | 1 (Reference) |               | 1 (Reference) |         |
| ≥60                  | 3.0 (1.3–7.0) | 0.011       | 4.5 (1.5–13.6) | 0.008   |
| FIGO stage           |             |               |             |         |
| I–II                 | 1 (Reference) |               | 1 (Reference) |         |
| III–IV               | 23.8 (8.8–64.5) | <0.001   | 5.6 (1.7–18.3) | 0.004   |
| Histology grade      |             |               |             |         |
| G1/G2                | 1 (Reference) |               | 1 (Reference) |         |
| G3                   | 17.4 (5.9–51.5) | <0.001  | 2.8 (0.5–15.6) | 0.236   |
| Histology type       |             |               |             |         |
| Endometrioid         | 1 (Reference) |               | 1 (Reference) |         |
| Nonendometrioid      | 13.5 (5.7–32.3) | <0.001  | 1.5 (0.3–7.9) | 0.618   |
| Peritoneal cytology  |             |               |             |         |
| Absent               | 1 (Reference) |               | 1 (Reference) |         |
| Present              | 11.5 (4.5–29.5) | <0.001  | 2.9 (0.9–9.5) | 0.088   |
| LVSİ                 |             |               |             |         |
| Absent               | 1 (Reference) |               | 1 (Reference) |         |
| Present              | 6.7 (2.9–15.6) | <0.001  | 1.7 (0.6–5.4) | 0.350   |
| NLR                  |             |               |             |         |
| Low                  | 1 (Reference) |               | 1 (Reference) |         |
| High                 | 3.2 (1.3–8.3) | 0.014       | 3.6 (1.1–11.5) | 0.028   |

NLR=neutrophil:lymphocyte ratio; HR=hazard ratio; 95% CI=95% confidence interval; FIGO=International Federation of Gynaecology and Obstetrics; LN=lymph node; LVSİ= lymphovascular space invasion. Significant p values are in bold, by chi-square test; Bold values indicate statistical significance.
of tumors [26, 27]. Patients with relative lymphopenia might have abnormal immune function and reduced antitumor ability, which increases the potential of cancer progression and worse outcome [12]. As in our study, the neutrophil count in the death group was higher than that in the survival group (4.5*10^9/L VS 4.3*10^9/L), and the lymphocyte count in the death group was lower than in that in the survival group (1.8*10^9/L VS 1.4*10^9/L). The ratio of neutrophil to lymphocyte (NLR), the more intuitive indicator, might be a good reflection of tumor burden and immune status.

The NLR is an important feature of the systemic inflammatory response [28]. Elevated NLR has been associated with poor prognosis in many solid tumors [29]. Increased NLR during treatment was found to be associated with low response rate and poor outcomes in metastatic renal cell carcinoma [30]. Here we found elevated NLR as an independent prognostic factor for OS as well as CSS and DFS. Recently, Haruma et al. and Cummings et al. found elevated NLR as a prognostic factor for poor OS and CSS [24, 31], which is in agreement with our study; however, Takahashi et al. found leukocytosis (neutrophil count ≥7200/µl) but not NLR as an independent predictor of survival outcome [32]. In the Li et al. study, NLR was associated with poor OS in the log-rank test but was not significant on multivariable analysis [25]. The selection of the cut-off value for NLR might explain the different findings.

Even though elevated NLR was found to be associated with poor prognosis in many cancers, the best cut-off value is still unknown. The cut-off values were mostly determined by the ROC curve and had a wide range (1.9-5.0) in different cancers [33]. The cut-off ranged from 2.1 to 3.0 in bladder cancer [15, 34, 35], 2.0 to 5.0 in colorectal cancer [18, 36, 37], 2.5 to 5.0 in lung cancer [19, 38, 39], 1.9 to 5.0 in cervical cancer [40-42], and 2.4 to 4.68 in EC [24, 25]. We used an optimal cut-off that maximized the sum of sensitivity and specificity in the ROC curve in our study. For OS, CSS and DFS, the best cut-off for NLR was 2.47, 2.62, and 2.47, respectively, and the corresponding AUC was 0.68, 0.66, and 0.60, respectively. In predicting CSS, the cut-offs 2.47 and 2.62 had almost the same AUC value. We chose a concordant and optimization process for the NLR cut-off of 2.47 to predict OS, CSS and DFS in EC. Cummings et al. chose 2.4 for the NLR cut-off according to ROC curves for OS and CSS, and Haruma et al. chose 2.41 and 2.70 as cut-off values for DFS and OS according to ROC curves, respectively. Both studies demonstrated the association between elevated NLR and survival outcomes in EC. Takahashi et al. chose a mean value (3.0) as a cut-off, and Li et al. chose 4.68 (cited from other cancer studies); neither found an association between NLR and survival outcomes. Our study found NLR (cut-off 2.47) as an independent prognostic factor for OS and also for CSS and DFS in this cohort of EC patients.

Previous studies have shown a strong association between elevated NLR and poor prognosis in various cancers. We found that elevated NLR is significantly
Elevated NLR is due to relative increase in neutrophil count or relative decrease in lymphocyte count. The imbalance of neutrophils and lymphocytes in the tumor microenvironment plays a role in cancer progression. NLR might be a circulatory marker reflecting increased cancer aggressiveness. Our results suggest that survival of patients with EC depends on traditional risk factors but is also affected by pre-treatment NLR, so inhibiting the inflammatory reaction and improving the immune ability could improve prognosis with EC. Moreover, NLR is calculated by use of an inexpensive, routine and convenient test, and it can provide useful information for management and treatment outcomes with EC. Our data revealed that NLR (cut-off 2.47) may be an independent prognostic factor for OS and also for CSS and DFS.

However, our study has some limitations. First, although 510 patients were enrolled and the data were associated with advanced FIGO stage, increased histology grade, and lymph node metastasis, which can worsen the prognosis. The mechanism underlying neutrophilia and lymphopenia and carcinogenesis as well as tumor progression is still unclear. Neutrophils can promote tumorogenesis and cancer development by multiple mechanisms. They can increase DNA mutations via the release of reactive oxygen species; facilitate cancer cell proliferation via the secretion of cytokines and chemokines; promote vascularization via the secretion of vascular endothelial growth factor; enhance tumor cell invasiveness and metastasis by secreting proteases, elastase and matrix metallopeptidase 9 (MMP-9); and suppress effective antitumor immunity of CD8+ T cells via the release of nitric oxide synthase and arginase [29]. Lymphocytes have potent anti-cancer activity, and they play an important role in the immune defense against tumor cells [43]. Previous studies have found an association of decreased tumor-infiltrating lymphocyte count with worse survival outcomes in colorectal cancer [44], esophageal cancer [45] and ovarian cancer [46].

Elevated NLR is due to relative increase in neutrophil count or relative decrease in lymphocyte count. The imbalance of neutrophils and lymphocytes in the tumor microenvironment plays a role in cancer progression. NLR might be a circulatory marker reflecting increased cancer aggressiveness.

Our results suggest that survival of patients with EC depends on traditional risk factors but is also affected by pre-treatment NLR, so inhibiting the inflammatory reaction and improving the immune ability could improve prognosis with EC. Moreover, NLR is calculated by use of an inexpensive, routine and convenient test, and it can provide useful information for management and treatment outcomes with EC. Our data revealed that NLR (cut-off 2.47) may be an independent prognostic factor for OS and also for CSS and DFS.

However, our study has some limitations. First, although 510 patients were enrolled and the data were

Table 5. Univariable and multivariable analysis of factors, including NLR cut-off, associated with disease-free survival with endometrial cancer.

| Characteristic       | Univariate       | P-value | Multivariate     | P-value |
|----------------------|------------------|---------|------------------|---------|
| Age(year)            |                  |         |                  |         |
| <60                  | 1 (Reference)    |         | 1 (Reference)    |         |
| ≥60                  | 2.0 (1.1- 3.7)   | **0.033** | 2.2 (1.0- 4.8)  | **0.045** |
| FIGO stage           |                  |         |                  |         |
| I–II                 | 1 (Reference)    |         | 1 (Reference)    |         |
| III–IV               | 11.6 (6.1- 22.2) | **<0.001** | 4.4 (1.8- 10.5) | **0.001** |
| Histology grade      |                  |         |                  |         |
| G1/G2                | 1 (Reference)    |         | 1 (Reference)    |         |
| G3                   | 11.6 (5.6- 23.7) | **<0.001** | 4.2 (1.3- 13.5) | **0.016** |
| Histology type       |                  |         |                  |         |
| Endometrioid         | 1 (Reference)    |         | 1 (Reference)    |         |
| Nonendometrioid      | 9.3 (4.9- 17.4)  | **<0.001** | 1.0 (0.3- 3.2)  | 0.961   |
| Peritoneal cytology  |                  |         |                  |         |
| Absent               | 1 (Reference)    |         | 1 (Reference)    |         |
| Present              | 9.9 (4.7- 20.7)  | **<0.001** | 3.2 (1.2- 8.2)  | **0.016** |
| LVSI                 |                  |         |                  |         |
| Absent               | 1 (Reference)    |         | 1 (Reference)    |         |
| Present              | 5.3 (2.8- 10.0)  | **<0.001** | 1.1 (0.4- 2.6)  | 0.908   |
| NLR                  |                  |         |                  |         |
| Low                  | 1 (Reference)    |         | 1 (Reference)    |         |
| High                 | 2.2 (1.1- 4.2)   | **0.018** | 2.3 (1.0- 5.2)  | **0.044** |

NLR=neutrophil:lymphocyte ratio; HR=hazard ratio; 95% CI=95% confidence interval; FIGO=International Federation of Gynaecology and Obstetrics; LN=lymph node; LVSI= lymphovascular space invasion. Significant p values are in bold, by chi-square test; Bold values indicate statistical significance.
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