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## Significance of monocyte counts on tumor characteristics and survival outcome of women with endometrial cancer

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### Abstract

**Objective.**—Tumor-associated macrophages are known to be associated with decreased survival of patients with endometrial cancer. Given the physiological link of circulating monocytes as a progenitor of tumor-associated macrophages, monocyte counts were examined for tumor characteristics and survival in endometrial cancer.

**Methods.**—A retrospective study was conducted to examine consecutive patients with endometrial cancer with all histologic types who underwent hysterectomy-based surgical staging between 2003 and 2013 ( $n = 541$ ). Preoperative monocyte counts were correlated to patient demographics, pathological findings, complete blood count results, and survival outcomes.

**Results.**—Median monocyte counts were  $0.5 \times 10^9/L$ . Monocyte counts significantly correlated with all other complete blood count components, with neutrophil counts having the most significant association ( $r = 0.52$ ,  $p < 0.001$ ). Elevated monocyte counts (defined as  $>0.7 \times 10^9/L$ ) when compared to lower counts were significantly associated with an increased risk of  $>50\%$  myometrial tumor invasion (29.2% versus 22.0%, odds ratio [OR] 1.59, 95% confidence interval [CI] 1.01–2.45,  $p = 0.045$ ), pelvic lymph node metastasis (39.0% versus 18.8%, OR 2.76, 95% CI 1.35–5.62,  $p = 0.007$ ), and advanced-stage (stage I through IV, 18.5%, 24.6%, 32.5%, and 41.5%,

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#### Disclosure

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.ygyno.2015.05.019>.

$p = 0.001$ ). In survival analysis, elevated monocyte counts were associated with decreased disease-free survival (5-year rates, 71.0% versus 84.5%,  $p = 0.001$ ) and overall survival (77.2% versus 89.3%,  $p < 0.001$ ). In multivariate analysis, elevated monocyte counts remained an independent prognostic factor for decreased disease-free (hazard ratio [HR] 1.74, 95% CI 1.02–2.96,  $p = 0.041$ ) and overall (HR 2.63, 95% CI 1.37–5.05,  $p = 0.004$ ) survival.

**Conclusions.**—Elevated monocyte counts were associated with aggressive tumor features and poor survival outcomes of patients with endometrial cancer.

## Keywords

Endometrial cancer; Monocyte; Survival outcome

## 1. Introduction

In 2015, endometrial cancer continues to be the most common gynecologic malignancy in the United States, with more than 54,000 new cases estimated to be diagnosed this year [1]. The majority of endometrial cancers are low-grade tumors with early-stage disease, and the mainstay of treatment approach for endometrial cancer is surgery, which includes hysterectomy, adnexectomy, and possible lymphadenectomy. In a fraction of endometrial cancer patients, additional systemic chemotherapy and/or radiotherapy are indicated [2]. Due to the favorable tumor characteristics in endometrial cancer, long remission and cure of disease is possible in the majority of patients. However, despite a multidisciplinary approach with surgery, chemotherapy, and radiotherapy, certain endometrial cancer patients develop disease recurrence where cure can be difficult and challenging. Therefore, novel approaches for identifying these tumors that are likely to recur may allow for optimization of treatment in these patients and improved survival.

The interaction between host immune cells and cancer cells has been identified as a key to tumor suppression or progression in various types of malignancies including endometrial cancer [3,4]. Tumor-associated macrophages (TAMs) appear to be a key mediator of this interaction, and multiple studies have shown that increased accumulation of TAMs in the tumor site of the uterus is associated with aggressive tumor behaviors (higher stage and grade, lymphovascular space invasion [LVSI], and deep myometrial tumor invasion) and decreased survival outcome of endometrial cancer patients [5-10]. TAMs are the differentiated form of monocytes outside of the vasculature (monocyte–macrophage lineage) [11,12], and are one of the inflammatory cell types found in the tumor microenvironment known to have a pivotal role in the immune response to cancer [13,14]. That is, TAMs in the tumor microenvironment are recruited from tumors and differentiated into polarized M2 macrophages that are a source and target of cytokines, chemokines, and growth factors, which results in cancer progression and suppression of anti-tumor immune system [12,15]. While TAMs adversely impact the prognosis of endometrial cancer patients, the association of monocyte counts and endometrial cancer progression has not been well studied. Given that circulating monocytes in blood vessels function as a precursor and potential origin of TAMs, monocyte counts were examined and correlated to tumor characteristics and survival outcomes of endometrial cancer patients in this study.

## 2. Patients and Methods

### 2.1. Eligibility

After Institutional Review Board (IRB) approval was obtained at the University of Southern California, the institutional database for endometrial cancer was utilized to identify the patients. This study included consecutive endometrial cancer patients with all histologic subtypes who were treated with hysterectomy-based surgical staging at Los Angeles County Medical Center between April 2003 and March 2013. Excluded cases were those without laboratory results at the time of cancer diagnosis, or if the final diagnosis was uterine sarcoma or endometrial hyperplasia. Among eligible cases, the following information were abstracted from medical records: (i) patient demographics, (ii) pathology results for hysterectomy-based surgical staging, (iii) laboratory results for complete blood counts obtained at the time of endometrial cancer diagnosis prior to surgical staging, and (iv) survival outcome. The STrengthening the Reporting of OBServational studies in Epidemiology (STROBE) guidelines were consulted for reporting in a retrospective cohort study [16]. Some of the patients in this study were within the context of our previous studies [17-20].

### 2.2. Clinical information

Archived medical records were reviewed to abstract the clinical information for eligible cases. (i) Patient demographics included age at surgery, ethnicity, and body mass index (BMI, expressed in  $\text{kg}/\text{m}^2$ ). (ii) Pathology results for hysterectomy-based surgical staging included histology subtype, grade, stage, depth of myometrial tumor invasion (%), presence of LVSI, and pelvic/aortic lymph node metastasis. For lymph node results, total number of sampled nodes and number of positive lymph nodes were also recorded. (iii) Laboratory results for complete blood counts included absolute neutrophil, lymphocyte, monocyte, eosinophil, and basophil counts (expressed in  $\times 10^9/\text{L}$ ), hemoglobin (expressed in  $\text{g}/\text{dL}$ ), and platelet counts (expressed in  $\times 10^9/\text{L}$ ) were abstracted. (iv) For survival outcomes, disease-free survival (DFS) and disease-specific overall survival (OS) were abstracted.

### 2.3. Definition

The cutoff values for complete blood counts were based on the previous studies for endometrial cancer: Neutrophil-to-lymphocyte ratio (N/L ratio, defined as the proportional ratio of absolute neutrophil counts over lymphocyte counts) of 3.0 [21], hemoglobin of 12.0  $\text{g}/\text{dL}$  [22], and platelet of  $400 \times 10^9/\text{L}$  [20]. Because no prior study examined the significance of monocyte counts on endometrial cancer survival, monocyte counts were categorized into three groups (1%–33%ile 0.4, 34%–66%ile 0.5–0.6, and 67%–100%ile,  $0.7 \times 10^9/\text{L}$ ). Various cutoff values for monocyte counts were examined and a count of  $0.7 \times 10^9/\text{L}$  was confirmed as the cutoff value to maximize the survival outcomes for DFS and OS (Table S1A). Neutrophil counts of  $5.5 \times 10^9/\text{L}$  were used for the cutoff value to maximize the survival outcome for DFS and OS in our study (Table S1B). Lymphocyte, eosinophil, and basophil counts were not associated with survival outcome and therefore median values were used for the cutoff.

Lymph node ratio (LNR) was defined as the percent ratio of positive metastatic lymph node number per total sampled lymph nodes per case [23]. Endometrial cancer grade was based on the International Federation of Gynecology and Obstetrics (FIGO), and cancer stage was reclassified based on the 2009 FIGO staging system [24]. DFS was defined as the time interval between hysterectomy-based surgical staging and the date of first recurrence or the date of last follow-up date if there was no recurrence. OS was defined as the time interval between the date of hysterectomy-based surgical staging and the date of death due to endometrial cancer of the last follow-up date if the patient was alive.

#### 2.4. Statistical analysis

The primary objective of the analysis was to correlate monocyte counts to tumor factors from the hysterectomy specimen. The secondary objective of the analysis was to determine the survival significance of monocyte counts in endometrial cancer patients. Continuous variables were examined for normality by Kolmogorov-Smirnov test expressed with mean ( $\pm$ standard deviation) or median (range) as appropriate, and Spearman's correlation coefficient was performed for statistical evaluation among the continuous variables. Median values of monocyte counts among multiple groups were examined by Mann-Whitney *U* test or Kruskal-Wallis test as appropriate. Using a cutoff value of elevated monocyte counts ( $0.7 \times 10^9/L$ ), the statistical accuracy for pelvic and aortic lymph node metastasis was determined (sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV], and accuracy). Categorical or ordinal variables were expressed as a percentage (%), and Fisher's exact test or chi-square test was used to determine the statistical significance expressed with odds ratio (OR) and 95% confidence interval (CI).

For survival analysis, log-rank test was used for univariate analysis. A Cox proportional hazard regression model was used for multivariate analysis with conditional backward method given the degree of freedom in this sample size. That is, all covariates with  $p < 0.10$  in univariate analysis were initially entered into the model. Then, the least significant covariate was removed from the model until all the covariates in the final model remained  $p < 0.10$ . These covariates entered in the initial model included age ( $<60$  versus  $\geq 60$ ), ethnicity (non-Hispanic versus Hispanic), BMI ( $<30$  versus  $\geq 30$  kg/m<sup>2</sup>), histologic subtype (endometrioid versus non-endometrioid), grade (1–2 versus 3), stage (I versus II–IV), depth of myometrial tumor invasion ( $\leq 50\%$  versus  $>50\%$ ), LVSI (absence versus presence), neutrophil counts ( $<5.5$  versus  $\geq 5.5 \times 10^9/L$ ), N/L ratio ( $<3.0$  versus  $\geq 3.0$ ), monocyte counts ( $<0.7$  versus  $\geq 0.7 \times 10^9/L$ ), hemoglobin ( $\geq 12.0$  versus  $<12.0$  g/dL), and platelet counts ( $<400$  versus  $\geq 400 \times 10^9/L$ ). Statistical significance of survival analysis was expressed with hazard ratio (HR) and 95% CI. Kaplan-Meier method was used to construct survival curves. All statistical analyses were two-tailed, and  $p < 0.05$  was considered statistically significant. Statistical Package of Social Science (SPSS, Inc., version 12.0, Chicago, IL) was used for statistical analysis.

### 3. Results

The schema of patient selection is shown in Figure S1. There were 694 cases of endometrial cancer identified during the study period. Of those, 69 patients did not undergo surgical

staging (chemotherapy alone  $n = 34$ , hormonal therapy for fertility preservation  $n = 18$ , or lost to follow-up after endometrial biopsy for cancer diagnosis  $n = 17$ ). The remaining 625 patients underwent hysterectomy-based surgical staging for endometrial cancer. Of those, 29 had no preoperative complete blood counts and another 55 cases did not have cell differential counts. The study population was comprised of the remaining 541 patients with endometrial cancer who underwent hysterectomy-based surgical staging and had preoperative complete blood counts with cell differential counts.

Patient demographics are shown in Table 1. The mean age of the study population was 52.1. The majority of patients were Hispanic (68.9%) and obese (BMI  $\geq 30$  kg/m<sup>2</sup>, 70.8%). The majority of endometrial cancers were of endometrioid histology (81.9%), low grade (grade 1–2, 77.6%), and stage I disease (67.1%). Deep myometrial tumor invasion (>50%) was seen in approximately one-quarter of tumors (24.1%). Pelvic and para-aortic lymphadenectomy was performed in 48.8% and 21.3% of cases, respectively. Among lymph node metastasis cases, LNR was 17.6% in pelvic metastasis and 63.5% in aortic metastasis, respectively. Median follow-up time of the study was 35.0 months. There were 84 (15.5%) cases of recurrence and 56 (10.4%) deaths observed in the study cohort.

The median monocyte count was  $0.5 \times 10^9/L$  (range, 0.0–1.8). The median total white blood cell count was  $8.1 \times 10^9/L$  (range, 3.3–37.2), and the median monocyte proportion was 6.2% (range, 0%–15.6%). Monocyte counts were then correlated to various clinicopathological factors (Tables 2 and 3). Monocyte counts were positively correlated to all of the white blood cell components, with neutrophil count holding the strongest correlation ( $r=0.52$ ,  $p < 0.001$ ), followed by platelet ( $r=0.26$ ,  $p < 0.001$ ), lymphocyte ( $r = 0.23$ ,  $p < 0.001$ ), basophil ( $r = 0.21$ ,  $p < 0.001$ ), N/L ratio ( $r = 0.20$ ,  $p < 0.001$ ), and eosinophil ( $r = 0.12$ ,  $p = 0.004$ ) counts. Monocyte counts were negatively correlated to hemoglobin levels ( $r=-0.17$ ,  $p < 0.001$ ). Monocyte counts were also significantly correlated to total white blood cell counts ( $r = 0.62$ ,  $p < 0.001$ ). Results of other correlations are shown in Table S2.

Of the tumor factors, monocyte counts were positively correlated to the depth of myometrial tumor invasion ( $r = 0.11$ ,  $p = 0.014$ ) and to pelvic LNR ( $r = 0.15$ ,  $p = 0.021$ ). Elevated monocyte counts  $\geq 0.7 \times 10^9/L$  were significantly associated with tumor invasion into the outer half of the myometrial layer (monocyte counts  $\geq 0.7$  versus  $<0.7 \times 10^9/L$ , 29.1% versus 20.6%, OR 1.59, 95% CI 1.01–2.49,  $p = 0.045$ ). Elevated monocyte counts  $\geq 0.7 \times 10^9/L$  predicted pelvic lymph node metastasis (monocyte counts  $\geq 0.7$  versus  $<0.7 \times 10^9/L$ , 39.0% versus 18.8%, OR 2.76, 95% CI 1.35–5.62,  $p=0.007$ ). Sensitivity, specificity, PPV, and NPV, accuracy of elevated monocyte counts  $\geq 0.7 \times 10^9/L$  for pelvic lymph node metastasis were 39.0%, 81.2%, 27.6%, 87.9%, and 74.6%, respectively. When the depths of myometrial tumor invasion and monocyte counts were combined, it significantly stratified the risk of pelvic lymph node metastasis ( 50% invasion + monocyte counts  $<0.7 \times 10^9/L$  0.3%, 50% invasion + monocyte counts  $\geq 0.7 \times 10^9/L$  18.8%, >50% invasion + monocyte counts  $<0.7 \times 10^9/L$  31.3%, and >50% invasion + monocyte counts  $\geq 0.7 \times 10^9/L$  40.0%,  $p < 0.001$ ). Elevated monocyte counts  $\geq 0.7 \times 10^9/L$  were also correlated with advanced-stage disease (proportion of monocyte counts  $\geq 0.7 \times 10^9/L$ , stage I 18.5%, stage II 24.6%, stage III 32.5%, and stage IV 41.5%, respectively,  $p=0.001$ , chi-square test). Monocyte counts were not associated with age, BMI, grade, or histology (all  $p > 0.05$ ).

Next, survival analyses were performed (Tables 4 and 5). In univariate analysis, elevated monocyte counts were significantly associated with decreased DFS (5-year rates, 0.7 versus  $<0.7 \times 10^9/L$ , 71.0% versus 84.5%, HR 2.22, 95% CI 1.36–3.64,  $p = 0.001$ ). When monocyte counts were grouped into 1%–33%ile ( $<0.4 \times 10^9/L$ ), 34%–66%ile ( $0.5\text{--}0.6 \times 10^9/L$ ), and 67%–100%ile ( $0.7 \times 10^9/L$ ), 5-year DFS rates showed a threshold pattern with monocyte counts  $0.7 \times 10^9/L$ , demonstrating the poorest DFS rate compared to other groups (83.6%, 83.3%, and 59.3%, respectively,  $p = 0.005$ ; Fig. 1A). Other clinicopathological factors significantly associated with decreased PFS included age  $\geq 60$ , non-endometrioid histology, grade 3 tumor, stage II–IV disease, myometrial tumor invasion  $>50\%$ , LVSI, neutrophil counts  $\geq 5.5 \times 10^9/L$ , N/L ratio  $\geq 3.0$ , hemoglobin  $<12.0$  g/dL, and platelet counts  $\geq 400 \times 10^9/L$  (all  $p < 0.05$ ). Being Hispanic and obesity (BMI  $\geq 30$  kg/m<sup>2</sup>) were associated with improved DFS (both  $p < 0.05$ ). After controlling for these significant covariates found in univariate analysis, multivariate analysis showed that monocyte counts  $0.7 \times 10^9/L$  remained an independent prognostic factor associated with decreased DFS (adjusted-HR 1.74,  $p = 0.041$ ). Other independent prognostic factors for decreased DFS included non-endometrioid histology (adjusted-HR 1.98,  $p = 0.007$ ), myometrial tumor invasion  $>50\%$  (adjusted-HR 2.35,  $p < 0.001$ ), grade 3 tumors (adjusted-HR 2.59,  $p = 0.001$ ), and stage II–IV disease (adjusted-HR 4.91,  $p < 0.001$ ).

For OS analysis (Table 5), an elevated monocyte count  $0.7 \times 10^9/L$  was significantly associated with decreased OS (5-year rates, 0.7 versus  $<0.7 \times 10^9/L$ , 77.2% versus 89.3%, HR 3.13, 95% CI 1.74–5.62,  $p < 0.001$ ) in univariate analysis. Monocyte counts  $0.7 \times 10^9/L$  had the poorest 5-year OS rate compared to other groups ( $<0.4$ ,  $0.5\text{--}0.6$ , and  $0.7 \times 10^9/L$ ; 88.9%, 89.8%, and 77.2%,  $p < 0.001$ , Fig. 1B). In multivariate analysis, an elevated monocyte count  $0.7 \times 10^9/L$  remained an independent predictor for decreased OS (adjusted-HR, 2.63,  $p = 0.004$ ). In addition, non-endometrioid histology (adjusted HR 2.63,  $p = 0.003$ ), grade 3 tumors (adjusted HR 2.85,  $p = 0.002$ ), stage II–IV disease (adjusted HR 3.47,  $p = 0.003$ ), and myometrial tumor invasion  $>50\%$  (adjusted HR 2.91,  $p < 0.001$ ) remained independent prognostic factors for decreased OS.

#### 4. Discussion

The key findings of our study were that elevated monocyte counts were significantly associated with an increased risk of deep myometrial tumor invasion, pelvic lymph node metastasis, and advanced stage disease, which resulted in decreased survival in endometrial cancer patients. These results support previous findings demonstrating the association between increased accumulation of TAMs and decreased survival in endometrial cancer. While our study did not address the direct correlation between circulating monocyte counts and TAMs in the uterine specimen, our results indirectly point toward a potential biological plausibility of monocyte–macrophage lineage in endometrial cancer biology.

There have been few previous studies that examined the significance of monocytes in endometrial cancer [25,26]. Patients with endometrial cancer have significantly higher monocyte counts in pretreatment blood samples compared to healthy non-cancer controls [26]. In other types of gynecologic malignancy, an elevated circulating monocyte count was associated with decreased survival in both ovarian and cervical cancers [27,28]. However, to

date, no study has reported the impact of monocyte counts on endometrial cancer survival. Our study therefore validates the prognostic significance of monocyte counts in endometrial cancer. Altered functionality of circulating monocytes has been demonstrated in patients with endometrial cancer including increased vascular endothelial growth factor (VEGF) receptor 1 expression on the cell surface [25]. VEGF produced by the tumor is one of the major driving forces for recruitment of circulating monocytes into the tumor microenvironment. It is speculated then, that tumors not only have paracrine effects on macrophages to shape them into TAMs in the local tumor microenvironment, but they also may have distant effects that modulate global monocyte functions in endometrial cancer. TAMs also produce various signals including tumor growth factors, angiogenic factors, and matrix metalloproteases; and these ultimately promote cancer progression and invasion [12]. Whether the elevated monocyte counts in endometrial cancer is secondary to a paraneoplastic syndrome via the tumor and bone marrow circuit remains unknown and warrants further study.

Leukocytosis is known to be a prognostic factor for decreased survival in endometrial cancer patients [21,22,29]. The hypothesis behind this association includes tumor-related leukocytosis (TRL) driven by granulocyte colony-stimulating factor (GCSF) produced from the tumor [21]. However, these studies examined the survival impacts of total white blood cell counts and neutrophil counts on endometrial cancer, but not monocyte counts. Therefore, it is not known if TRL is related to GCSF produced from the tumor (direct effect) or to the TAM-related pro-inflammatory cytokine response (indirect effect). Our results showed that both elevated neutrophil counts and monocyte counts were associated with decreased DFS and OS in univariate analysis. In addition, monocyte counts and neutrophil counts were positively and strongly correlated with each other ( $r=0.52$ ). However, when neutrophil and monocyte counts were entered into the multivariate model for DFS and OS, only monocyte count remained an independent prognostic factor for decreased DFS and OS (Tables 4 and 5). As the generally accepted model of the immune-mediated response places macrophages as the upstream cell player to neutrophils, it is speculated that TAMs can also be an alternative or complementary cause of TRL to the tumor-related GCSF pathway.

A prior study showed that neutrophil counts  $7.2 \times 10^9/L$  were seen in 8.3% of patients with endometrial cancer and were associated with decreased survival outcomes [21]. In our study, neutrophil counts  $7.2 \times 10^9/L$  were seen in 26.1% of patients and this was a significantly higher proportion compared to the prior study (OR 2.90, 95% CI 1.98–4.23,  $p < 0.001$ ). In addition, neutrophil counts  $7.2 \times 10^9/L$  were not associated with survival outcomes in our study (Table S1B). Our study and the prior study were similar with regard to study sample size (541 versus 501 patients) and treatment failure rate (15.5% versus 12.2%,  $p = 0.13$ ). The main difference between the two studies may be that our study is characterized by a markedly obese population compared to the prior study (mean BMI, 36.1 versus 23.0 kg/m<sup>2</sup>). As shown in our study (Table S2), BMI is significantly positively correlated to neutrophil counts ( $r = 0.14$ ,  $p = 0.001$ ). Increased neutrophil counts in obese patients may occur due to the chronic inflammation related to excess adipose tissue [31]. Therefore, increased neutrophil counts in endometrial cancer may be partly related to non-tumor factors such as obesity. Importantly, our study showed that monocyte counts are not related to BMI

( $r = 0.03$ ,  $p = 0.44$ ; Table S2). This implies that monocyte counts are more reliable markers for prognosis of endometrial cancer than neutrophil counts.

Possible clinical utility of our results may include an application to immunotherapy in endometrial cancer patients with elevated monocyte counts. That is, TAMs are known to inhibit T cell activation via the interaction between programmed cell death 1 (PD-1) and its ligand (PD-L1), leading to suppression in anti-tumor activity [30]. Because increased monocyte counts may reflect increased TAM accumulation with PD-1 mediated anti-tumor immunosuppression, blocking this PD-1/PD-L1 interaction may be an attractive pathway for anti-tumor immunotherapy [32]. Evaluation of monocyte counts is relatively simple compared to TAMs in the uterine specimen obtained by hysterectomy, and therefore, assessing monocyte counts can be a possible screening strategy to triage a group of endometrial cancer patients as candidates for PD-1/PD-L1 immunotherapy. Another clinical opportunity for targeting TAMs may include bisphosphonates. For example, zoledronic acid inhibits the production of matrix metalloproteases from TAMs and reverses TAM phenotype from immunosuppressive M2 macrophages to tumoricidal M1 macrophages [33]. Indeed, bisphosphonates are recognized for potential roles in cancer prevention [34]. Further study is warranted for therapeutic implications of bisphosphonates in patients with endometrial cancer.

In summary, our study highlighted the importance of monocyte counts in the management of endometrial cancer patients. Adopting monocyte count evaluation into practice may potentially have a wide variety of implications for surgical management, treatment strategy, and survival assessment. Lastly, our results propose the definition of tumor-related monocytosis as monocyte counts of  $0.7 \times 10^9/L$  based on survival impact with this cutoff value. Further validation in other populations is needed.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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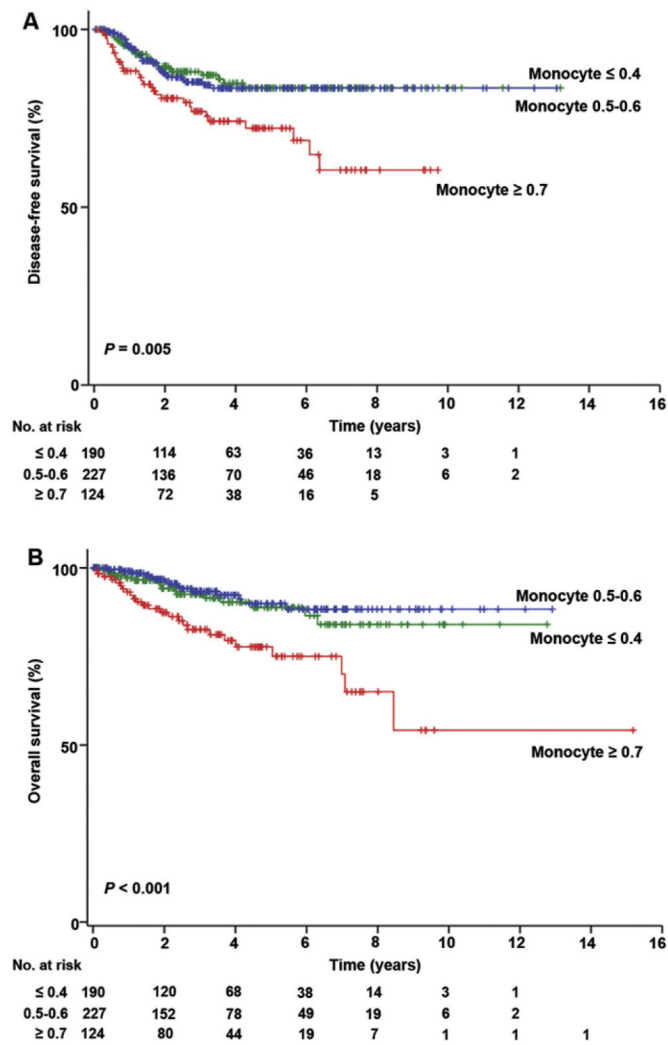


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**HIGHLIGHTS**

- Monocyte counts obtained prior to hysterectomy-based surgical staging were correlated to tumor characteristics and survival of patients with endometrial cancer.
- Elevated monocyte counts were associated with aggressive tumor behavior including deep myometrial tumor invasion, lymph node metastasis, and advanced stage.
- Elevated monocyte counts were an independent prognostic factor for decreased survival outcome of endometrial cancer patients.



**Fig. 1.** Monocyte counts and survival outcome of endometrial cancer. Kaplan-Meier methods for survival curves per monocyte counts ( $\times 10^9/L$ ). (A) Disease-free survival and (B) overall survival are shown based on monocyte count at the time of endometrial cancer diagnosis.

**Table 1**

Patient demographics of endometrial cancer.

	<i>N</i> = 541 (100%)
Age (years)	52.1 ( $\pm$ 10.5)
<60	409 (75.6%)
60	132 (24.4%)
Ethnicity	
Caucasian	56 (10.4%)
African	26 (4.8%)
Hispanic	373 (68.9%)
Asian	86 (15.9%)
BMI (kg/m <sup>2</sup> )	36.1 ( $\pm$ 9.9)
<30	157 (29.2%)
30	381 (70.8%)
Histology	
Endometrioid	443 (81.9%)
Serous	37 (6.8%)
Clear cell	27 (5.0%)
Others <sup>a</sup>	34 (6.3%)
Grade	
1	291 (53.8%)
2	129 (23.8%)
3	121 (22.4%)
Stage	
I	363 (67.1%)
II	57 (10.5%)
III	80 (14.8%)
IV	41 (7.6%)
Myometrial invasion	20 (0–100)
0%	88 (16.7%)
50%	312 (59.2%)
>50%	127 (24.1%)
LVSI	
Absence	438 (81.9%)
Presence	97 (18.1%)
Pelvic lymph node	<i>n</i> = 264
No metastasis	223 (84.4%)
Metastasis	41 (15.5%)
Lymph node ratio (%) <sup>b</sup>	17.9 (3–100)
Aortic lymph node	<i>n</i> = 115
No metastasis	88 (76.5%)

	<i>N</i> = 541 (100%)
Metastasis	27 (23.5%)
Lymph node ratio (%) <sup>b</sup>	63.5 (4–100)

Number (%), mean ( $\pm$ SD), or median (range) are shown. Abbreviations: BMI, body mass index; and LVSI, lymphovascular space invasion.

<sup>a</sup>3 missing for BMI, 14 missing for myometrial invasion, and 6 missing for LVSI.

<sup>b</sup>Among positive lymph node cases.

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**Table 2**

Correlations between monocyte counts and clinicopathological factors (continuous variables).

	Mean ( $\pm$ SD)	Median (range)	<i>r</i> value	<i>p</i> value
Age (year)	52.1 ( $\pm$ 10.5)	53 (24–87)	0.03	0.46
BMI (kg/m <sup>2</sup> )	36.1 ( $\pm$ 9.9)	34.6 (15.6–84.3)	0.03	0.44
Neutrophil ( $\times 10^9$ /L)	5.8 ( $\pm$ 3.0)	5.3 (1.3–29.6)	<b>0.52</b>	<b>&lt;0.001</b>
Lymphocyte ( $\times 10^9$ /L)	2.2 ( $\pm$ 1.5)	2.1 (0.5–30.0)	<b>0.23</b>	<b>&lt;0.001</b>
N/L ratio	3.2 ( $\pm$ 3.0)	2.5 (0.2–37.0)	<b>0.20</b>	<b>&lt;0.001</b>
Eosinophil ( $\times 10^9$ /L)	0.2 ( $\pm$ 0.2)	0.1 (0–1.6)	0.12	0.004
Basophil ( $\times 10^9$ /L)	0.1 ( $\pm$ 0.1)	0 (0–0.5)	<b>0.21</b>	<b>&lt;0.001</b>
Hemoglobin (g/dL)	12.1 ( $\pm$ 2.1)	12.6 (4.8–15.8)	–0.17	<0.001
Platelet ( $\times 10^9$ /L)	306 ( $\pm$ 97)	292 (101–985)	<b>0.26</b>	<b>&lt;0.001</b>

Spearman's correlation coefficient to monocyte counts for *p* values. Significant *p* values with *r* value 0.20 or –0.20 are in bold. Mean ( $\pm$ SD) and median (range) of monocyte counts were 0.5 ( $\pm$ 0.2) and 0.5 (0–1.8), respectively. Abbreviations: SD, standard deviation; BMI, body mass index; and N/L ratio, neutrophil-to-lymphocyte ratio. Metadata are shown in Table S2.

Correlations between monocyte counts and clinicopathological factors (categorical and ordinal variables).

Table 3

	No.	Monocyte counts median (range)	$0.4 \times 10^9/L$ <i>n</i> = 190	$0.5-0.6 \times 10^9/L$ <i>n</i> = 227	$0.7 \times 10^9/L$ <i>n</i> = 124	<i>p</i> value
Ethnicity						<0.001
Caucasian	56	0.55 (0.3–0.9)	10 (17.9%)	30 (53.6%)	16 (28.6%)	
African	26	0.4 (0.1–1.8)	17 (65.4%)	3 (11.5%)	6 (23.1%)	
Hispanic	373	0.5 (0–1.6)	122 (47.7%)	160 (39.5%)	91 (12.8%)	
Asian	86	0.5 (0.1–1.0)	41 (35.1%)	34 (42.0%)	11 (12.8%)	
Histology						0.25
Endometrioid	443	0.5 (0.1–1.6)	157 (35.4%)	187 (42.2%)	99 (22.3%)	
Serous	37	0.5 (0–1.8)	15 (40.5%)	15 (40.5%)	7 (18.9%)	
Clear cell	27	0.6 (0.3–1.2)	8 (29.6%)	8 (29.6%)	11 (40.7%)	
Others	34	0.5 (0.2–1.2)	10 (29.4%)	17 (50.0%)	7 (20.6%)	
Grade						0.51
1	291	0.5 (0–1.3)	103 (35.4%)	125 (43.0%)	63 (21.6%)	
2	129	0.5 (0.1–1.6)	48 (37.2%)	53 (41.1%)	28 (21.7%)	
3	121	0.5 (0.1–1.8)	39 (32.2%)	49 (40.5%)	33 (27.3%)	
Stage						0.0003
I	363	0.5 (0–1.8)	143 (39.4%)	153 (42.1%)	67 (18.5%)	
II	57	0.5 (0.3–1.4)	18 (31.6%)	25 (43.9%)	14 (24.6%)	
III	80	0.5 (0.2–1.5)	17 (21.3%)	37 (29.3%)	26 (32.5%)	
IV	41	0.6 (0.1–1.3)	12 (29.3%)	12 (29.3%)	17 (41.5%)	
LVSI						0.19
Absence	438	0.5 (0–1.8)	158 (36.1%)	186 (42.5%)	94 (21.5%)	
Presence	97	0.5 (0.1–1.1)	30 (30.9%)	40 (41.2%)	27 (27.8%)	
Myometrial invasion						0.005
50%	403	0.5 (0–1.8)	154 (38.2%)	166 (41.2%)	83 (20.6%)	
>50%	127	0.5 (0.1–1.4)	31 (24.4%)	59 (46.5%)	37 (29.1%)	
Pelvic lymph nodes						0.039
No metastasis	223	0.5 (0.1–1.3)	86 (38.6%)	95 (42.6%)	42 (18.8%)	



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	Monocyte counts	$0.4 \times 10^9/L$	$0.5-0.6 \times 10^9/L$	$0.7 \times 10^9/L$	<i>p</i> value
No.	median (range)	<i>n</i>	<i>n</i>	<i>n</i>	
Metastasis	41	0.6 (0.3-1.2)	11 (26.8%)	14 (34.1%)	16 (39.0%)

Mann-Whitney *U* test or Kruskal-Wallis test for *p* values. Significant *p* values are in bold. Abbreviation: LYSI, lymphovascular space invasion.

**Table 4**

Disease-free survival of endometrial cancer.

	Univariate			Multivariate		
	No.	5 years (%)	HR (95% CI)	p value	HR (95% CI)	p value
Age (years)				<0.001		0.086
<60	409	83.8%	1		1	
60	132	67.2%	2.17 (1.39–3.40)		1.57 (0.94–2.63)	
Ethnicity				<b>0.013</b>		
Non-Hispanic	168	70.9%	1			
Hispanic	373	83.9%	0.58 (0.37–0.89)			
BMI (kg/m <sup>2</sup> )				<b>0.003</b>		
<30	157	71.6%	1			
30	381	84.3%	0.53 (0.34–0.82)			
Histology				<0.001		<b>0.007</b>
Endometrioid	443	87.1%	1		1	
Non-endometrioid	98	50.8%	5.21 (3.39–8.00)		1.98 (1.20–3.25)	
Grade				<0.001		<b>0.001</b>
1–2	420	89.7%	1		1	
3	121	49.1%	8.27 (5.29–12.9)		2.59 (1.48–4.52)	
Stage				<0.001		<0.001
I	363	94.2%	1		1	
II-IV	178	55.9%	11.2 (6.31–19.9)		4.91 (2.60–9.27)	
Myometrial invasion				<0.001		<0.001
50%	403	89.8%	1		1	
>50%	127	56.9%	5.36 (3.40–8.43)		2.35 (1.45–3.79)	
LVSI				<0.001		
Absence	438	87.7%	1			
Presence	97	52.6%	4.57 (2.96–7.05)			
Neutrophil (×10 <sup>9</sup> /L)				<b>0.014</b>		
<5.5	284	90.6%	1			
5.5	257	82.8%	1.83 (1.12–2.99)			

	No.	5 years (%)	Univariate		Multivariate	
			HR (95% CI)	p value	HR (95% CI)	p value
N/L ratio				<b>0.038</b>		
<3.0	339	83.3%	1			
3.0	202	75.7%	1.65 (1.02–2.65)			
Monocyte ( $\times 10^9/L$ )				<b>0.001</b>		<b>0.041</b>
<0.7	417	83.4%	1		1	
0.7	124	71.0%	2.22 (1.36–3.64)		1.74 (1.02–2.96)	
Hemoglobin (g/dL)				<b>0.047</b>		
12.0	326	83.6%	1			
<12.0	215	76.0%	1.54 (1.00–2.36)			
Platelet ( $\times 10^9/L$ )				<b>&lt;0.001</b>		
<400	465	83.3%	1			
400	73	64.5%	2.71 (1.69–4.36)			

Log-rank test for univariate analysis (listed only significant variables among all the covariates tested). Cox proportional hazard regression test for multivariate analysis (conditional backward). Significant *p* values are in bold. Abbreviations: HR, hazard ratio; CI, confidence interval; BMI, body mass index; LVS1, lymphovascular space invasion; and N/L ratio, neutrophil-to-lymphocyte ratio.

**Table 5**

Overall survival of endometrial cancer.

	No.	5 years (%)	Univariate		Multivariate	
			HR (95% CI)	p value	HR (95% CI)	p value
Age (years)				<b>0.001</b>		
<60	409	89.2%	1			
60	132	75.6%	2.39 (1.38–4.15)			
Ethnicity				<b>0.007</b>		0.086
Non-Hispanic	168	78.5%	1		1	
Hispanic	373	89.5%	0.49 (0.29–0.83)		0.59 (0.32–1.08)	
BMI (kg/m <sup>2</sup> )				<b>0.004</b>		
<30	157	79.1%	1			
30	381	89.9%	0.47 (0.28–0.80)			
Histology				< <b>0.001</b>		<b>0.003</b>
Endometrioid	443	92.1%	1		1	
Non-endometrioid	98	61.8%	6.24 (3.68–10.6)		2.63 (1.39–4.95)	
Grade				< <b>0.001</b>		<b>0.002</b>
1–2	420	94.0%	1		1	
3	121	61.4%	8.51 (4.86–14.9)		2.85 (1.45–5.61)	
Stage				< <b>0.001</b>		<b>0.003</b>
I	363	96.4%	1		1	
II-IV	178	70.2%	11.2 (5.28–23.6)		3.47 (1.55–7.79)	
Myometrial invasion				< <b>0.001</b>		< <b>0.001</b>
50%	403	93.3%	1		1	
>50%	127	72.2%	5.34 (3.01–9.45)		2.91 (1.60–5.32)	
LYSI				< <b>0.001</b>		
Absence	438	92.1%	1			
Presence	97	66.9%	4.75 (2.78–8.11)			
Neutrophil (×10 <sup>9</sup> /L)						<b>0.034</b>
<5.5	284	90.6%	1			
5.5	257	82.8%	1.92 (1.04–3.52)			

	No.	5 years (%)	Univariate		Multivariate	
			HR (95% CI)	p value	HR (95% CI)	p value
N/L ratio				<b>0.008</b>		
<3.0	339	91.0%	1			
3.0	202	80.2%	2.18 (1.21–3.93)			
Monocyte ( $\times 10^9/L$ )				<b>&lt;0.001</b>		<b>0.004</b>
<0.7	417	89.3%	1		1	
0.7	124	77.2%	3.13 (1.74–5.62)		2.63 (1.37–5.05)	
Hemoglobin (g/dL)				<b>0.047</b>		
12.0	326	89.8%	1			
<12.0	215	81.8%	1.70 (1.00–2.87)			
Platelet ( $\times 10^9/L$ )				<b>&lt;0.001</b>		
<400	465	88.6%	1			
400	73	73.7%	2.59 (1.47–4.58)			

Log-rank test for univariate analysis (listed only significant variables among all the covariates tested). Cox proportional hazard regression test for multivariate analysis (conditional backward). Significant *p* values are in bold. Abbreviations: HR, hazard ratio; CI, confidence interval; BMI, body mass index; LVS1, lymphovascular space invasion; and N/L ratio, neutrophil-to-lymphocyte ratio.