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Original Research

Leukocytosis and thrombocytosis as prognostic factors for women with uterine cervical cancer

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Summary

Purpose of Investigation: The aim of this study was to evaluate whether leukocytosis and thrombocytosis prior to treatment was associated with the prognosis of women with uterine cervical cancer. *Materials and Methods:* The authors assessed 2,267 women who were diagnosed as having FIGO Stages I-IV uterine cervical cancer and were followed up for at least five years. The age, clinical stage, histology, leukocytosis, and thrombocytosis at the initial diagnosis were evaluated for overall survival (OS). *Results:* Leukocytosis and thrombocytosis were identified in 315 and in 134 women, respectively. Fifty-eight had both conditions. Multivariable analysis revealed that age [hazard ratio (HR) 1.7, $p < 0.001$], advanced FIGO Stage (4.8, $p < 0.001$), histology (2.0, $p < 0.001$), leukocytosis (1.5, $p < 0.01$), and thrombocytosis (2.0, $p < 0.01$) were independent factors for decreased OS. OS of women with both thrombocytosis and leukocytosis was the worst ($p < 0.01$). *Conclusion:* Leukocytosis and thrombocytosis were independently associated with decreased OS in women with uterine cervical cancer.

Key words: Cervical cancer; Leukocytosis; Thrombocytosis; Prognosis.

Introduction

Uterine cervical cancer is one of the many female malignancies. The clinical stage for uterine cervical cancer according to the International Federation of Gynecology and Obstetrics (FIGO), age, and histological type are known to be associated with the clinical outcomes of patients. Several investigators have attempted to identify useful prognostic factors including vascular invasion, tumor size, histological type, parametrium invasion, depth of tumor invasion, lymphovascular space involvement, and lymph node metastasis [1-6].

Leukocytosis has been reported as a poor prognostic factor for lung cancer [7, 8]. Leukocytosis prior to treatment [9-11] and at recurrence [12] has been reported to be a poor prognostic factor for women with uterine cervical cancer. On the other hand, associations between thrombocytosis and prognosis in malignancies were first reported by Levin and Conley in 1964 [13]. Thereafter, some inconsistent findings regarding the association has been reported in a meta-analysis of 14 studies including 3,394 patients [14]. Others have also investigated whether leukocytosis or thrombocytosis is a prognostic factor for different malignancies, including anal carcinoma, esophageal carcinoma, colorectal cancer, and ovarian cancer [15-18].

In the present study, the authors evaluated whether leukocytosis and thrombocytosis prior to treatment were associated with prognosis in women with uterine cervical cancer.

Materials and Methods

The authors retrospectively assessed the characteristics and outcomes of 2,334 women with FIGO Stages I-IV cervical cancer who were initially treated at the Kobe University Hospital and Hyogo Cancer Center between January 1990 and January 2012. The institutional ethical boards of both the institutions approved this study. They were followed up for at least five years since the initial treatment. Sixty women with incorrect medical records, three with leukemia, two with idiopathic thrombocytopenic purpura, two with systemic lupus erythematosus, and one with myelodysplastic syndrome were excluded. Ultimately, 2,267 women were enrolled in the study analysis.

Patients were treated as follows: patients aged < 70 years with FIGO Stage Ia1 uterine cervical cancer received abdominal total hysterectomy, while those aged < 70 years with FIGO Stages Ia2-IIb cervical cancer received abdominal radical hysterectomy and pelvic lymphadenectomy. Furthermore, the latter received postoperative radiotherapy when pathological examinations revealed clinical findings, including pelvic lymph node metastasis, positive parametrial involvement, positive surgical margin, deep stromal invasion, and lymphovascular space invasion. Patients with FIGO Stages III-IVa, those aged > 71 years with FIGO Stages Ia2-IIb, and those with FIGO Stages Ia2-IIb and severe complications received radiotherapy with or without platinum-based concurrent chemotherapy. Patients with FIGO Stage IVb received platinum-based chemotherapy. All the patients were periodically followed-up by gynecological oncologists at an out-patient clinic. In case of disease recurrence, patients received either radiotherapy or chemotherapy.

Leukocytosis prior to treatment was defined as a white blood cell (WBC) count of > 9,000/μL and thrombocytosis prior to treatment was defined as a platelet count > 400,000/μL according to

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Table 1. — *The clinicopathological characteristics of the 2,267 patients.*

	Number of patients (%)
All	2,267
Age (years)	
< 50	1,203 (53)
≥ 50	1,064 (47)
FIGO Stage	
I	1,305 (58)
II	578 (25)
III	256 (11)
IV	128 (5.6)
Histology	
SCC	1,764 (78)
Non SCC	503 (22)

SCC: squamous cell carcinoma.

previous reports [9-14]. OS was calculated from the initial treatment date until death or the last examination. Clinical factors assessed included age, stage, histology, leukocytosis, and thrombocytosis were assessed for OS. Patients were divided into four groups including only thrombocytosis, only leukocytosis, both, and none.

All statistical analyses were performed using the SPSS statistics software (version 20). Differences between two groups were compared using the Chi-square test. Survival curves were determined using the Kaplan–Meier method, and compared using the log-rank test and generated Wilcoxon test. Multivariate Cox proportional hazard regression analysis was used to assess clinical factors for OS. The Chi-square for independent test was used for analyzing associations among FIGO Stage, leukocytosis, and thrombocytosis. All tests were two-sided and $p < 0.05$ was considered statistically significant.

Results

The clinicopathological characteristics of the 2,267 women are summarized in Table 1. A total of 315 (13.9%) of the 2,267 women had leukocytosis and 134 (5.9%) had thrombocytosis. Furthermore, 257 (11.3%) women had only leukocytosis, 76 (3.4%) had only thrombocytosis, 58 (2.6%) had both, and 1, 876 (82.8%) had neither.

Table 2 shows associations between FIGO Stage and leukocytosis/thrombocytosis. Both leukocytosis and thrombocytosis were significantly associated with the advanced FIGO stage [df=3, χ^2 value = 122.7, χ^2 (0.95) = 7.8, $p < 0.001$]. Figure 1 shows OS for clinicopathological factors. Patients aged ≥ 50 years, with non-squamous cell carcinoma (SCC), and FIGO Stages III-IV had a significantly shorter OS than those aged < 50 years ($p < 0.001$), SCC ($p < 0.001$), and FIGO Stages I-II ($p < 0.001$), respectively. Patients with leukocytosis showed significantly shorter OS than that those without leukocytosis ($p < 0.01$) and patients with thrombocytosis showed significantly shorter OS than those without thrombocytosis ($p < 0.01$) (Figure 2).

Multivariate analyses of clinical factors for OS using Cox proportional hazard model showed that the age [hazard ratio (HR) = 1.66, $p < 0.001$], FIGO Stages III-IV (HR = 4.82, $p < 0.001$), histology (HR = 2.04, $p < 0.001$), leukocytosis (HR = 1.51, $p < 0.01$), and thrombocytosis (HR = 1.99, $p < 0.01$) were independent prognostic factors (Table 3).

Figure 3 shows the ten-year-survival data for the presence/absence of leukocytosis and thrombocytosis. Patients with both leukocytosis and thrombocytosis had the shortest OS compared to those with only thrombocytosis ($p < 0.01$), only leukocytosis ($p < 0.01$), or neither ($p < 0.01$). The OS of patients with only thrombocytosis was significantly shorter than that of patients with only leukocytosis ($p < 0.01$).

Discussion

In the present study, multivariate analyses revealed age, FIGO Stages III-IV, histology, and leukocytosis as independent prognostic factors for the OS in women with uterine cervical cancer and these results were consistent with those of previous reports [9-11]. Additionally, leukocytosis and thrombocytosis were found to be associated with the advanced clinical stage and decreased OS. To the best of the present authors' knowledge, this is the first report identifying that the OS of patients with only thrombocytosis was shorter than that of patients with only leukocytosis.

Whether increased leukocytes directly cause tumor growth, progression or metastasis remains to be clarified. It is reported that the serum albumin and C-reactive protein levels may predict OS in women with uterine cervical cancer [14]. Patients at the advanced disease stage often manifest complications such as urinary tract infection and

Table 2. — *Relationship between FIGO stage and leukocytosis/thrombocytosis.*

Number of patients (%) n=2,267					
FIGO Stage	I	II	III	IV	*p value
Leukocytosis	113 (8.7)	92 (15.9)	66 (25.8)	44 (34.4)	< 0.001
No leukocytosis	1192 (91.3)	486 (84.1)	190(74.2)	84(65.6)	
Thrombocytosis	39 (3.0)	32 (5.5)	35 (13.7)	28 (22)	< 0.001
No thrombocytosis	1266(97)	546 (94.5)	221(86.3)	100(78)	
					Leukocytosis: > 9,000/μL
					Thrombocytosis: > 400,000/μL

χ^2 test

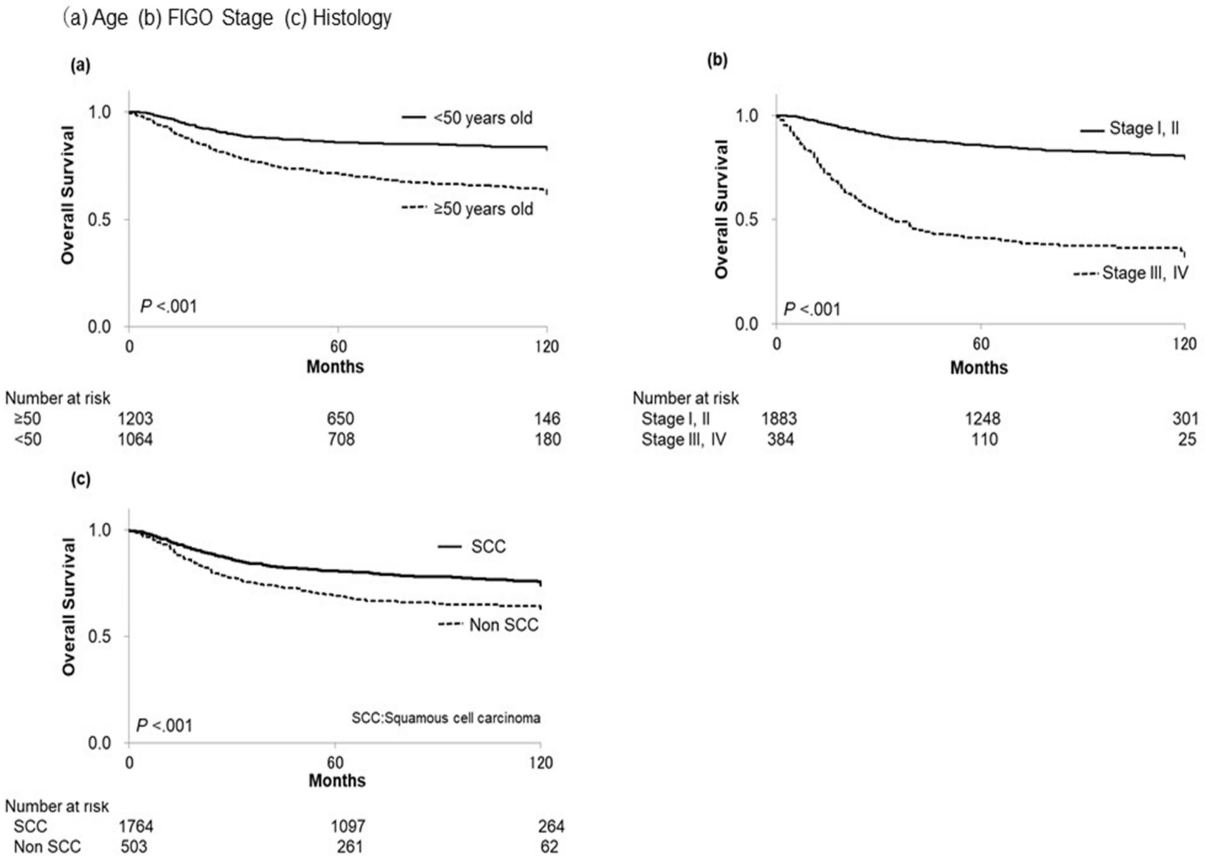

Figure 1. —The OS for clinicopathological factors. (a) Age (b) FIGO Stage (c) Histology.

Patients aged ≥ 50 years, with non-squamous cell carcinoma (SCC), and FIGO Stages III-IV had a significantly shorter OS than those aged < 50 years ($p < 0.001$), SCC ($p < 0.001$), and FIGO Stages I-II ($p < 0.001$), respectively. *P* values were determined by log-rank test.

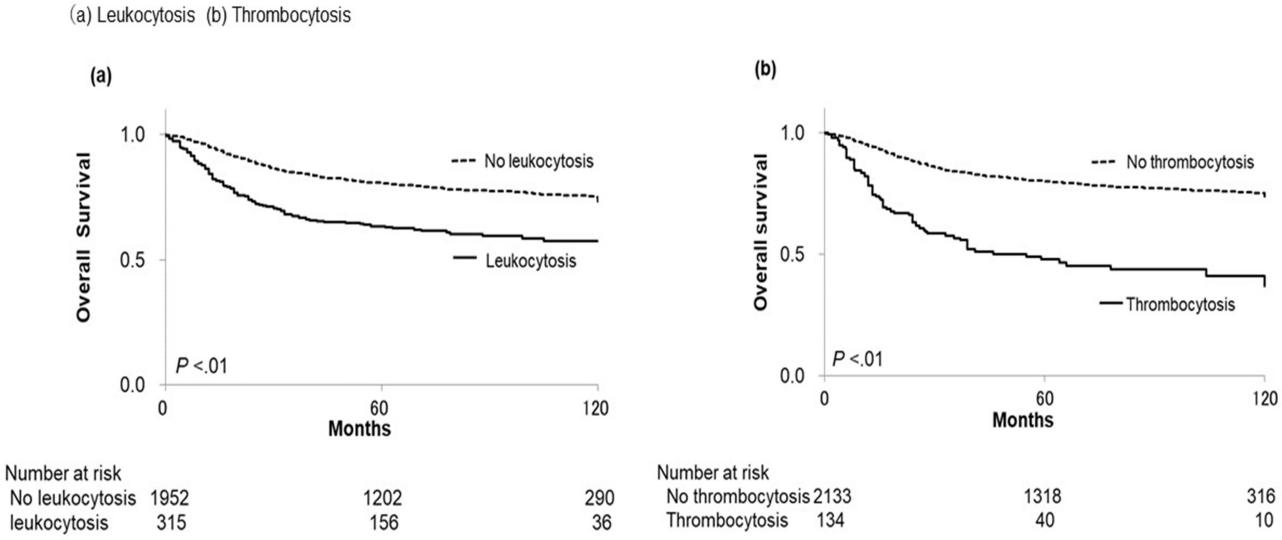

Figure 2. — The prognostic impact of leukocyto-sis and thrombocytosis. (a) Leukocytosis (b) Thrombocytosis.

Patients with leukocytosis showed significantly shorter OS than that those without leukocytosis ($p < 0.01$); and patients with thrombocytosis showed significantly shorter OS than those without thrombocytosis ($p < 0.01$). P values were determined by log-rank test.

Table 3. — *Multivariate analysis, according to the leukocytosis and thrombocytosis.*

Covariates	Number of patients	Hazard ratio (95% CI)	*p*
Age (years)			
< 50	1,203	1 (reference)	< 0.001
≥ 50	1,064	1.66 (1.36–2.03)	
FIGO Stage			
I–II	1,883	1 (reference)	< 0.001
III–IV	384	4.82 (3.98–5.81)	
Histology			
SCC	1,764	1 (reference)	< 0.001
Non SCC	503	2.04 (1.69–2.46)	
Hematological findings			
No leukocytosis	1,952	1 (reference)	< 0.01
Leukocytosis	315	1.51 (1.21–1.85)	
No thrombocytosis	2,133	1 (reference)	< 0.01
Thrombocytosis	134	1.99 (1.33–1.84)	

SCC: squamous cell carcinoma.

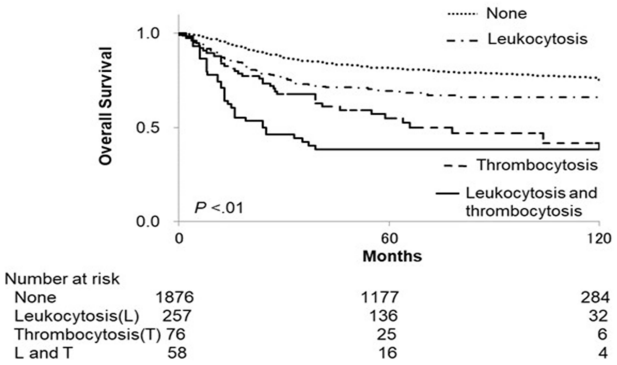

Figure 3. — The ten-year-survival data for the presence/absence of leukocytosis and thrombocytosis.
Patients with both leukocytosis and thrombocytosis had the shortest OS compared with those with only thrombocytosis ($p < 0.01$), only leukocytosis ($p < 0.01$), or neither ($p < 0.01$). The OS of patients with only thrombocytosis was significantly shorter than that of patients with only leukocytosis ($p < 0.01$). *P* values were determined by log-rank test and generated Wilcoxon test.

gastrointestinal infiltration, which suggests an association between prognosis and inflammatory response for advanced tumors. In the present study, however, leukocytosis was determined as a prognostic factor independent of clinical stages or histology. Patients with leukocytosis had high serum levels of granulocyte-colony stimulating factor (G-CSF) [9, 10], while those with malignant tumors producing G-CSF showed a poor prognosis [19]. G-CSF stimulated the proliferation and migration of tumor cell lines, causing persistent angiogenesis and tumor progression in the head and neck SCC [20]. G-CSF may be associated with poor prognosis in women with uterine cervical cancer and leukocytosis.

Thrombocytosis was found to be an independent prognostic factor for women with uterine cervical cancer. Several studies reported similar results [14]. Another report found that thrombocytosis was a poor prognostic factor for ovarian cancer [18]. Among the cytokines and growth factors involved in platelet production, platelet-derived TGF-β enhanced the invasiveness and metastasis in lung cancer [21]. High levels of serum interleukin-6 were associated with poor prognosis in women with uterine cervical cancer [22]. These cytokines may be associated with poor prognosis in women with uterine cervical cancer and thrombocytosis. Further investigation is therefore necessary to clarify this association.

The findings of the present study will provide new perspectives on the clinical management of uterine cervical cancer. Clinical information such as age, disease stage, histology, pretreatment leukocytosis, and thrombocytosis can be collected to estimate the prognosis. Therefore, we can plan the treatment approach for an individual in an inexpensive manner, which is suitable for developing countries. Nevertheless, the present study had several limitations. This was a retrospective study, and the treatment modalities may have affected the results. A prospective cohort study is necessary to determine whether information on leukocytosis and thrombocytosis prior to treatment would facilitate improved prognosis in women with uterine cervical cancer.

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