Role of Reactive Thrombocytosis After Primary Cytoreductive Surgery in Advanced Ovarian Cancer

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Research Article

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Abstract

We investigated the incidence of reactive thrombocytosis after maximal cytoreductive surgery in advanced epithelial ovarian cancer and its role on survival.

We retrospectively reviewed electronic medical records of patients who underwent primary cytoreductive surgery for advanced epithelial ovarian cancer from January 1, 2012, and December 31, 2017. We analyzed the correlation serum platelet counts and prognosis at various time points including before surgery, during peri-operative period, and on each cycle of adjuvant chemotherapy.

474 patients were eligible for the analysis. 401 patients (84.6%) were FIGO stage III and 405 patients (85.4%) were serous adenocarcinoma. 79 patients (22.6%) had splenectomy and optimal cytoreduction was achieved at 326 patients (68.8%). A week after surgery, thrombocytosis was observed in 229 patients (48.3%) patients in the entire cohort. Especially, higher platelet counts were observed in patients with splenectomy compared with patients without splenectomy. In particular, thrombocytosis on 5th cycle of adjuvant chemotherapy showed most significant impact on overall survival in multivariate analysis. In a logistic regression model, splenectomy significantly attributed to thrombocytosis on 5th cycle.

Reactive thrombocytosis after primary cytoreductive surgery is associated with poor survival in advanced epithelial ovarian cancer, particularly when thrombocytosis was observed during adjuvant chemotherapy.

Introduction

Ovarian cancer is the most lethal disease in female genital tract. With relatively stable incidence overtime in most countries, it was estimated that there were 295,414 new cases and 184,799 deaths world-wide in 2018[1,2]. Ovarian cancer accounts for 2.5% of all cancer patients among females, but results in 5% of all cancer deaths because of its high fatality[3]. 4 out of 5 patients are diagnosed with advanced disease, contributing to its poor prognosis[4].

Maximal cytoreductive surgery plus platinum-based combination chemotherapy is a main stay of treatment for advanced epithelial ovarian cancer. Optimal cytoreduction is highly recommended to leave small volume disease, ideally no gross residual, to increase survivals and extra-uterine procedures including resections of bowels, diaphragm, or splenectomy are frequently performed to achieve this goal[5].

Thrombocytosis after surgery for various diseases was observed in patients who had surgery on bowel[6] or bladder[7,8], splenectomy[9,10]. Concerns have been expressed for many years that thrombocytosis may decrease oncological outcomes. However, reports so far have evaluated the role of preoperative platelet counts on survival in bladder[8], breast[11], lung[12], gastric[13], and colorectal[14] cancers. In gynecologic malignancies, thrombocytosis as a paraneoplastic syndrome in ovarian cancer, in which the incidence was reported to range from 22.4 to 62.5%[15], was associated with advanced-stage disease, vascular

thromboembolic complications, higher preoperative levels of CA-125, significantly shorter median time to disease progression[16]. However, it has remained still unclear whether reactive thrombocytosis after surgery is associated with poor survivals particularly in ovarian cancer, although it was demonstrated in several solid malignancies[17–20]. In this study, we investigated the incidence of reactive thrombocytosis after primary cytoreductive surgery and its impact on survivals in advanced epithelial ovarian cancer.

Results

474 patients were eligible for this study. Patients' characteristics were presented in Table 1. Median age was 54 (18–88) year-old and pre-operative CA-125 was 617 (6–16,719) IU/mL. 84.6% (401/474) patients were FIGO stage III and 85.4% (405/474) were serous histology. The rates of R0, R1, and R2 were 46.0% (218/474), 22.8% (108/474), and 31.2% (148/474), respectively meaning that optimal cytoreduction was achieved in 68.8% (326/474) patients after primary cytoreductive surgery. The median interval between surgery and the first cycle of chemotherapy was 11 (6–61) days. Since splenectomy is one of well-known surgical procedures related with reactive thrombocytosis after surgery[9,10], we divided the entire cohort into two groups based on splenectomy. Compared with patients without splenectomy, patients with splenectomy (22.6%, 79/474) showed higher level of preoperative CA-125 (634 IU/mL vs. 859 IU/mL, p = 0.035), more proportion of FIGO stage IV (25.3%, 20/79 vs. 13.4%, 53/395, p = 0.007) and 1 day delay from surgery to the first cycle of chemotherapy (12 days vs. 11 days, p = 0.003). However, there was no significant difference in age, pre-operative platelet count, cell type, and residual disease between two groups. In terms of intervals from surgery to the day of blood test for each cycle of adjuvant chemotherapy, there were delays of 2–4 days in patients with splenectomy compare to patients without splenectomy during adjuvant chemotherapy.

Table 1
Baseline patients' characteristics.

median (range or %)	Total (*n* = 474, 100 %)	No splenectomy (*n* = 395, 77.4 %)	Splenectomy (*n* = 79, 22.6%)	*p-value*
Age, years-old	54 (18–88)	54 (18–88)	55 (33–76)	0.322
Preoperative platelet counts, $x10^3/mm^3$	308 (116–818)	305 (116–818)	325 (121–671)	0.128
Preoperative CA-125, IU/mL	617 (6-16719)	634 (6-15241)	859 (16-16719)	0.035
Number of cycles of adjuvant chemotherapy	6 (0–6)	6 (0–6)	6 (0–6)	0.182
FIGO Stage, *n*				0.007
III	401 (84.6)	342 (86.6)	59 (74.7)	
IV	73 (15.4)	53 (13.4)	20 (25.3)	
Cell type, *n*				0.055
Serous	405 (85.4)	332 (84.1)	73 (92.4)	
Non-serous	69 (14.6)	63 (15.9)	6 (7.6)	
Level of residual disease, *n*				0.962
No gross residual	218 (46.0)	184 (46.6)	34 (43.0)	
1-9mm	108 (22.8)	85 (21.5)	23 (29.1)	
Equal to or more than 10 mm	148 (31.2)	126 (31.9)	22 (27.8)	
Interval between surgery and initiation of the first cycle of chemotherapy, days	11 (6–61)	11 (6–55)	12 (7–61)	0.003
Interval from surgery to, days				
Day of blood test† for 1st cycle Chemotherapy	9 (5–59)	8 (5–52)	10 (6–59)	0.001

†Blood test contains complete blood cell count (CBC), chemistry, electrolyte, tumor marker

CA-125 Cancer antigen 125

median (range or %)	Total (n = 474, 100 %)	No splenectomy (n = 395, 77.4 %)	Splenectomy (n = 79, 22.6%)	*p-value*
Day of blood test† for 2nd cycle Chemotherapy	33 (26–86)	33 (26–81)	36 (28–86)	0.001
Day of blood test† for 3rd cycle Chemotherapy	57 (35–132)	56 (35–132)	60 (48–118)	0.002
Day of blood test† for 4th cycle Chemotherapy	80 (69–155)	80 (70–155)	82 (69–145)	0.006
Day of blood test† for 5th cycle Chemotherapy	104 (91–179)	104 (91–179)	106 (94–166)	0.021
Day of blood test† for 6th cycle Chemotherapy	127 (110–202)	127 (110–202)	128 (114–190)	0.188
Day of blood test† after 6th cycle chemotherapy	153 (133–224)	153 (133–224)	157 (133–211)	0.014
†Blood test contains complete blood cell count (CBC), chemistry, electrolyte, tumor marker				
CA-125 Cancer antigen 125				

Platelet counts were significantly increased after surgery. In entire population, platelet counts significantly elevated on POD7 compared with pre-operative value (344 x 10^3/mm^3 at POD7 vs. 308 x 10^3/mm^3 before surgery, $p < 0.001$). In addition, the prevalence of patients with thrombocytosis increased from 33.1 % before surgery to 48.3 % on POD7. As shown in Fig. 1, these findings were more significant in patients with splenectomy. For example, the median platelet count on POD7 was 526 x 10^3/mm^3 in patients with splenectomy as opposed to 332 x 10^3/mm^3 in patients without splenectomy ($p < 0.001$) and so does the prevalence of thrombocytosis on POD7 (83.5% vs. 41.3%, $p < 0.001$). Throughout the period of adjuvant chemotherapy, patients who had splenectomy showed significantly higher level of platelet counts ($p < 0.001$) and higher prevalence of thrombocytosis ($p < 0.001$) at each time point.

Among time points when platelet counts were available, we tried to find any time points when thrombocytosis is significantly associated with OS and found thrombocytosis on the day of blood test for 5th, 6th cycle or after 6th cycle of adjuvant chemotherapy was significantly associated with OS as shown in Table 2. We selected thrombocytosis on the day of blood test for 5th cycle of adjuvant chemotherapy as a representative marker for reactive thrombocytosis since it showed most significance among above time points. In patients with thrombocytosis at this time point, 46.2% (18/39) showed persistent thrombocytosis at every time point during adjuvant chemotherapy. Survival curves also demonstrated significant difference based on thrombocytosis at the time of 5th cycle of adjuvant chemotherapy as shown in Fig. 2. Median progression free survival was 12.1 months in patients with thrombocytosis and

19.0 months in patients without thrombocytosis (p = 0.001). In terms of OS, survival rate at 3 years was 62.6% in patients with thrombocytosis and 78.8% in patients without thrombocytosis.

Table 2
Univariate analysis: effect of platelet count at each time point on PFS and OS

		PFS		OS	
		HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Before surgery	Without thrombocytosis, *N* = 317	1 (reference)		1 (reference)	
	With thrombocytosis, *N* = 157	1.399 (1.103–1.773)	0.006	1.485 (1.026–2.149)	0.036
POD 1	Without thrombocytosis, *N* = 408	1 (reference)		1 (reference)	
	With thrombocytosis, *N* = 66	1.341 (0.985–1.827)	0.062	0.979 (0.578–1.659)	0.938
POD 7	Without thrombocytosis, *N* = 245	1 (reference)		1 (reference)	
	With thrombocytosis, *N* = 229	1.530 (1.217–1.923)	< 0.001	1.370 (0.955–1.965)	0.087
1st Cycle of chemotherapy	Without thrombocytosis, *N* = 273	1 (reference)		1 (reference)	
	With thrombocytosis, *N* = 191	1.417 (1.119–1.795)	0.004	1.219 (0.836–1.776)	0.302
2nd Cycle	Without thrombocytosis, *N* = 364	1 (reference)		1 (reference)	

Thrombocytosis was defined as platelet count ≥ 3.5 x 10^5/mm^3

PFS progression free survival, *OS* overall survival, *HR* hazard ratio, *CI* confidential interval, *POD* postoperative day. Every cycle represents the day for blood test for each cycle of adjuvant chemotherapy

	With thrombocytosis, *N* = 88	1.383 (1.047–1.827)	0.022	1.332 (0.859–2.064)	0.198
3rd Cycle	Without thrombocytosis, *N* = 370	1 (reference)		1 (reference)	
	With thrombocytosis, *N* = 73	1.692 (1.257–2.278)	0.001	1.412 (0.877–2.275)	0.154
4th Cycle	Without thrombocytosis, *N* = 395	1 (reference)		1 (reference)	
	With thrombocytosis, *N* = 45	1.214 (0.836–1.762)	0.308	1.388 (0.792–2.433)	0.250
5th Cycle	Without thrombocytosis, *N* = 398	1 (reference)		1 (reference)	
	With thrombocytosis, *N* = 39	1.897 (1.296–2.777)	0.001	2.049 (1.145–3.667)	0.016
6th Cycle	Without thrombocytosis, *N* = 402	1 (reference)		1 (reference)	
	With thrombocytosis, *N* = 29	2.352 (1.568–3.529)	< 0.001	2.022 (1.109–3.688)	0.022
After 6th cycle	Without thrombocytosis, *N* = 394	1 (reference)		1 (reference)	

Thrombocytosis was defined as platelet count ≥ 3.5 x 10^5/mm^3

PFS progression free survival, *OS* overall survival, *HR* hazard ratio, *CI* confidential interval, *POD* postoperative day. Every cycle represents the day for blood test for each cycle of adjuvant chemotherapy

	With thrombocytosis, *N* = 27	1.633 (1.056–2.524)	0.027	1.940 (1.009–3.730)	0.047

Thrombocytosis was defined as platelet count ≥ 3.5 x $10^5/mm^3$

PFS progression free survival, *OS* overall survival, *HR* hazard ratio, *CI* confidential interval, *POD* postoperative day. Every cycle represents the day for blood test for each cycle of adjuvant chemotherapy

Multivariate analysis adjusting pre-operative platelet counts, age, FIGO stage, intervals between surgery to the first cycle of adjuvant chemotherapy, and residual diseases, etc. was performed and we found thrombocytosis on the day of blood test for 5th cycle of adjuvant chemotherapy was independent poor prognostic factor for PFS (HR; 1.796, 95%CI; 1.221–2.642, p = 0.003) and OS (HR; 1.871, 95%CI; 1.034–3.386, p = 0.038) as shown in Tables 3 and 4. In addition, levels of residual disease and intervals between surgery and initiation of the first cycle of chemotherapy were also significant prognostic factors for OS. Of note, splenectomy did not have effect on PFS (p = 0.303) nor OS (p = 0.989).

Table 3
Univariate and multivariate analysis for progression free survival

	Univariate		Multivariate	
	HR (95% CI)	***p*-value**	**HR (95% CI)**	***p*-value**
Age	1.002 (0.991–1.013)	0.739	0.993 (0.981–1.005)	0.305
Platelet count, before surgery				
Without thrombocytosis	1 (reference)		1 (reference)	
With thrombocytosis	1.399 (1.103–1.773)	0.006	1.080 (0.834–1.399)	0.441
Platelet count, 5th cycle				
Without thrombocytosis	1 (reference)		1 (reference)	
With thrombocytosis	1.897 (1.296–2.777)	0.001	1.796 (1.221–2.642)	0.003
TTC, days	1.001 (0.995–1.007)	0.701	1.002 (0.996–1.008)	0.738
Stage				
III	1 (reference)		1 (reference)	
IV	1.444 (1.068–1.952)	0.017	1.143 (0.831–1.571)	0.392
CA-125	1.000 (1.000–1.000)	0.006	1.000 (1.000–1.000)	0.100
Splenectomy				
Without splenectomy	1 (reference)		1 (reference)	
With splenectomy	1.419 (1.072–1.877)	0.014	1.130 (0.818–1.561)	0.303
Level of residual disease (N, %)				
No gross residual	1 (reference)		1 (reference)	
1-9mm	1.750 (1.310–2.337)	< 0.001	1.622 (1.203–2.187)	0.002
Equal to or more than 10mm	2.162 (1.658–2.819)	< 0.001	2.076 (1.584–2.719)	< 0.001
Thrombocytosis was defined as platelet count ≥ 3.5 x 10^5/mm^3				
HR hazard ratio, *CI* confidential interval, *CA-125* Cancer antigen 125, *TTC* time from surgery to the first cycle of chemotherapy				

Table 4
Univariate and multivariate analysis for overall survival

	Univariate		Multivariate	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age	1.026 (1.008–1.044)	0.004	1.012 (0.992–1.032)	0.239
Platelet count, before surgery				
Without thrombocytosis	1 (reference)		1 (reference)	
With thrombocytosis	1.485 (1.026–2.149)	0.036	1.244 (0.833–1.859)	0.304
Platelet count, 5th cycle				
Without thrombocytosis	1 (reference)		1 (reference)	
With thrombocytosis	2.049 (1.145–3.667)	0.016	1.871 (1.034–3.386)	0.038
TTC, days	1.011 (1.005–1.016)	< 0.001	1.010 (1.004–1.016)	0.001
Stage				
III	1 (reference)		1 (reference)	
IV	1.267 (0.775–2.072)	0.344	0.927 (0.538–1.596)	0.699
CA-125	1.000 (1.000–1.000)	0.417	1.000 (1.000–1.000)	0.767
Splenectomy				
Without splenectomy	1 (reference)		1 (reference)	
With splenectomy	1.279 (0.837–1.954)	0.254	0.986 (0.597–1.627)	0.989
Level of residual disease (N, %)				
No gross residual	1 (reference)		1 (reference)	
1–9 mm	2.259 (1.408–3.624)	0.001	2.295 (1.390–3.790)	0.001
Equal to or more than 10 mm	2.790 (1.805–4.311)	< 0.001	2.861 (1.805–4.533)	< 0.001
Thrombocytosis was defined as platelet count ≥ 3.5 x 10^5/mm^3				
HR hazard ratio, *CI* confidential interval, *CA-125* Cancer antigen 125, *TTC* time from surgery to the first cycle of chemotherapy				

A logistic regression model was used to find clinical factors attributing thrombocytosis and splenectomy ($p < 0.001$) was the independent factor associated with thrombocytosis on the day of blood test for 5th cycle of adjuvant chemotherapy shown in Supplementary Table 1. Thromboembolic events and overwhelming post-splenectomy infection (OPIS) were not observed during study period in our study population.

Discussion

In this study, reactive thrombocytosis after surgery was frequently found during peri-operative period in patients who had primary cytoreductive surgery and patients who showed persistent thrombocytosis during adjuvant chemotherapy showed poor survivals. Splenectomy during primary cytoreductive surgery independently attributed to persistent thrombocytosis after surgery.

Physiologically, it is well known that platelets are responsible for hemostasis, immunity, and inflammation[21]. However, in malignancy, evidence suggested that platelets have a role of tumor growth and metastasis[22,23]. For example, pre-clinical studies found that activated platelets stimulate angiogenesis by releasing the content of their granules containing numerous growth factors such as platelet-derived growth factor(PDGF) and vascular endothelial growth factors(VEGF)[24]. Platelets protect cancer cells from immune surveillance, and facilitate hematogenic tumor spread forming tumor cell-platelet aggregates in capillary beds[15]. The association of pre-treatment thrombocytosis with poor prognosis has also been described in patients with solid malignancies[8,11–14]. In epithelial ovarian cancer (EOC), most studies showed that thrombocytosis at initial diagnosis was associated with a short PFS or OS[16,25–30]. And one of possible mechanisms explaining pre-operative thrombocytosis in patients with EOC is activated paracrine signaling pathway. For example, interleukin-6 (IL-6) released from ovarian cancer cells can stimulate secretion of thrombopoietin in liver and it eventually leads to thrombocytosis. Then tumor progression and metastasis can be enhanced by thrombocytosis and, in the end, more IL-6 will be released from these tumors as a vicious circle[16]. It is supported by the evidence that silencing IL-6 and thrombopoietin abrogated thrombocytosis in animal model[16], and pre-treatment thrombocytosis in patients with EOC tends to be related with advanced stage, higher grade, higher level of CA-125, larger ascites volume, and more residual disease primary debulking surgery[26–30]. However, the role of reactive thrombocytosis after surgery on survival has not been studied yet not only in EOC but also in other gynecological malignancies.

Besides from thrombocytosis as a response to neoplasms as mentioned above, various conditions such as major trauma[31] and surgeries has also been known to be a cause of thrombocytosis. The overall incidence of thrombocytosis was 18.7% in patients who were admitted to intentional care unit (ICU) for trauma[32] and it was associated with significantly higher rates of complications, particularly venous thromboembolism. In addition, thrombocytosis was associated with the severity of an injury[33]. In another study, persistent thrombocytosis in critically injured patients receiving routine chemoprophylaxis is associated with thrombotic complications[34], suggesting persistent thrombocytosis may be more critical in relation with poor outcomes. There are several reports investigating the effect of thrombocytosis after surgery in solid tumors. Some suggested elevation of platelets count after surgery was associated with post-operative complications[6,35]. For example, 37% patients who had colorectal surgery developed post-operative thrombocytosis (defined as platelets $\geq 5.0 \times 10^5/mm^3$) with a peak at 8 days after surgery (range 1–49 days) and positive correlation between post-operative thrombocytosis and complications was found.[6] In another study looking at patients who had urologic surgery, 90% of patients with post-

operative thrombocytosis (defined as platelets ≥ 5.0 × 10^5/mm^3) were diagnosed with post-operative complications such as urosepsis, hemorrhage, and thromboembolism, etc[35].

There is very limited evidence investigating the impact of post-operative thrombocytosis on survival outcomes and one study showed that post-operative thrombocytosis (11.9% patients under the definition of platelets > 4.0 × 10^5/mm^3) was one of significant independent prognostic markers for poor survival in patients with colorectal cancers (in a multivariate analysis, HR; 1.98, 95%CI; 1.12–3.49, p = 0.018)[18]. In our study, 8.92% in all study population (32.4% in patients with splenectomy and 4.40% in patients without splenectomy) showed post-operative thrombocytosis (defined as platelets ≥ 3.5 × 10^5/mm^3) on the 5th cycle of chemotherapy approximately 3 months after surgery when it has the most significant impact on survival and the HR for OS was 1.871 (95%CI; 1.034–3.386, p = 0.038) which is corresponding well with that of the above study. Considering that reactive thrombocytosis after splenectomy for non-malignant disease persisted for 1 year[10], platelets count in our study, specifically of patients with splenectomy, might have been undermeasured due to bone marrow suppression from chemotherapy.

Since the definition of thrombocytosis, the timing of blood test showing thrombocytosis, and number of cycles of adjuvant chemotherapy that patients received should be specific to our cohort, it must be difficult to extrapolate our results to general population. However, our finding that not only thrombocytosis on 5th cycle but also on 6th cycle or thereafter was still associated with significant poor overall survival suggests that there is a strong tendency that subgroup of patients who showed persistent thrombocytosis throughout primary treatment have poor survivals. Also, as opposed to patients who had suboptimal cytoreduction, patients with optimal cytoreduction are highly likely to show persistent thrombocytosis in our analysis. There is a report showing that a greater rise in the platelet count in the caesarean section group compared with the vaginal delivery group[36] in pregnant women suggesting positive correlation between level of surgical trauma and severity of thrombocytosis. However, it is still unclear whether the surgical complexity (e.g. surgical extents, multiple procedures, etc.) in surgical patients is associated with severity of surgery induced thrombocytosis. On the other hand, reactive thrombocytosis is one of well-known complications from splenectomy[37]. Because old platelets are destroyed by phagocytosis in the spleen after circulating 7–11 days in the blood, about 75% of individuals without myeloproliferative disorders develop thrombocytosis after splenectomy in general population[9]. In our study, 92.0% patients who had splenectomy showed thrombocytosis on approximately 7–9 days after surgery, respectively, which led us to consider splenectomy as one of confounders in our study. In multivariate analyses, we found splenectomy itself was not associated with poor survival but as one of main contributors to persistent thrombocytosis after surgery. We should be careful to interpret these findings since suboptimal debulking is still independent poor prognostic factor for survivals in our study suggesting that advantages from removing tumors on spleen to achieve optimal cytoreduction may outweigh disadvantages from splenectomy induced thrombocytosis. Also, we cannot say that transfusion of platelets should be avoided even when bone marrow suppression is critical during chemotherapy from our results. Nevertheless, we need new strategies to increase

oncological outcomes in subgroup of patients with advanced EOC, especially who had persistent thrombocytosis after splenectomy during primary cytoreductive surgery.

Apart from retrospective study design, there are more limitations in our study. We did not provide any role of platelet count in predicting complications after surgery[38,39] as suggested by previous studies, which may be useful in communication about post-operative course and when to start adjuvant chemotherapy with patients and their caregivers. And definition of thrombocytosis is arbitrary, and adjuvant chemotherapy may have affected platelet count. However, as of our knowledge, this is the first article demonstrating the relationship between persistent thrombocytosis after primary cytoreductive surgery and oncologic outcomes as previous studies have described that thrombocytosis at initial diagnosis is associated with negative oncologic outcome in EOC[16,25–30].

In conclusion, this study demonstrated that persistent post-operative thrombocytosis is frequently observed during adjuvant chemotherapy, especially in patients who had splenectomy or optimal cytoreduction. Although it was not clearly defined, persistent thrombocytosis may be a negative prognostic factor for survival outcomes in patients with advanced EOC who underwent primary cytoreductive surgery.

Methods

Ethical issues

This retrospective study was conducted according to the guidelines in the Declaration of Helsinki. It has been approved by the Institutional Review Board (IRB) (No, 2020-03-141-001) of Samsung Medical Center. This retrospective study does not require additional sample collection from the patient, only the records of surgery and tests that have already been performed. Even without the subject's consent, there is no risk to the subject due to this study. For the above reaseons, an informed consent from the patient is not necessary for this study. This has been approved by the IRB Committee.

Intervention

We selected patients for study with following inclusion criteria: Patients (1) who undergone primary debulking surgery at Samsung Medical Center from January 1, 2012 to December 31, 2017 (2) diagnosed with epithelial ovarian, fallopian, or peritoneal cancer (described as EOC) (3) diagnosed with advanced stage (FIGO stage III and IV). Patients who were treated with neoadjuvant chemotherapy (NAC), diagnosed with non-epithelial histology, early stage (FIFO stage I-II), or hematologic disease (e.g. idiopathic thrombocytosis, idiopathic thrombocytopenic purpura, etc.) were excluded. Among 674 patients diagnosed with advanced ovarian cancer during the study period, 125 patients who had NAC, 55 patients who did not have maximal cytoreductive surgery, and 22 patients who were non-epithelial ovarian cancer on final pathology were excluded remaining 474 patients for the analysis.

For patients newly diagnosed with advanced EOC, platinum-based combination chemotherapy, mainly tri-weekly intravenous paclitaxel plus carboplatin, was followed for 6 cycles after primary cytoreductive surgery. Routine prophylactic anticoagulation management was performed in all patients and vaccination to decrease the risk of overwhelming postsplenectomy sepsis was given to patients who had splenectomy at time of primary cytoreductive surgery.

Platelet counts were collected from the results of complete blood cell count (CBC) which was routinely done for all patients within 1 month prior to primary cytoreductive surgery, every other day after surgery during peri-operative period (post-operative day (POD) 1, POD3, POD5, POD7, etc.) and a couple of days before each cycle of adjuvant chemotherapy. In case that multiple CBC results were found due to transfusion at each time point, the platelets count from the CBC before transfusion were used for the analysis. Overall, we could obtain at least 10 serial platelets counts over 6 months during primary treatment for these patients. Besides serum platelet counts, clinical variables such as age, pre-operative CA-125, FIGO stage, histology, and level of residual disease (complete gross resection = R0, gross residual disease less than 1 cm = R1, gross residual disease equal to or more than 1 cm = R2) after primary cytoreductive surgery, etc. were collected retrospectively. Optimal cytoreduction was defined as residuals less than 1cm (R0 + R1).

We defined thrombocytosis as platelet count $\geq 3.5 \times 10^5/mm^3$ based on previous studies[11,12,20,40]. Among time points after surgery, we sought to find the best timing where thrombocytosis is most significantly associated with overall survival (OS). Then thrombocytosis at this time point as a representing value of reactive thrombocytosis after surgery was analyzed with other variables including pre-operative thrombocytosis, age, level of residual disease, etc. in a Cox model. Progression-free survival (PFS) was defined as the time from surgery to the recurrence or last follow-up. OS was defined as the time from surgery to the date of death or last follow-up.

All statistical analyses were performed using IBM SPSS statistics software Version 25.0 (IBM Corp. Armonk, New York, USA). For analysis of data characteristic's distribution, median (range) or mean (standard deviation) were used to describe continuous variables. Categorical variables were shown as frequency (percentage). After confirmation of normal distributions with the Shapiro–Wilk test, the Mann–Whitney test was performed to compare median values, and Student-t test was used to compare mean values. Fisher's exact test or chi-square test was used to compare categorical variables. For analysis of survival outcome, Kaplan Meier method with the log-rank test was used. For a multivariate analysis, cox proportion hazard model with backward selection was used. Binary logistic regression analysis was used to identify attributable factors for reactive thrombocytosis after surgery. p-value < 0.05 were considered as statistically significant.

Declarations

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Author contributions

Yoo-Young Lee: Conceptualization, Funding acquisition, Methodology, Supervision, Writing – review and editing; **Myeong-Seon Kim:** Supervision, Statistical analysis, Writing – review and editing; **Seung Hun Baek:** Data collection, Statistical analysis, Writing – original draft; **Joseph J. Noh:** Data collection; **Jung In Shim:** Data collection; **Jun Hyeok Kang:** Data collection; **Soo Young Jeong:** Data collection; **Chel Hun Choi:** Methodology; **Tae-Joong Kim:** Methodology; **Jeong-Won Lee:** Methodology

Competing interests

The authors declare no competing interests.

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Figures

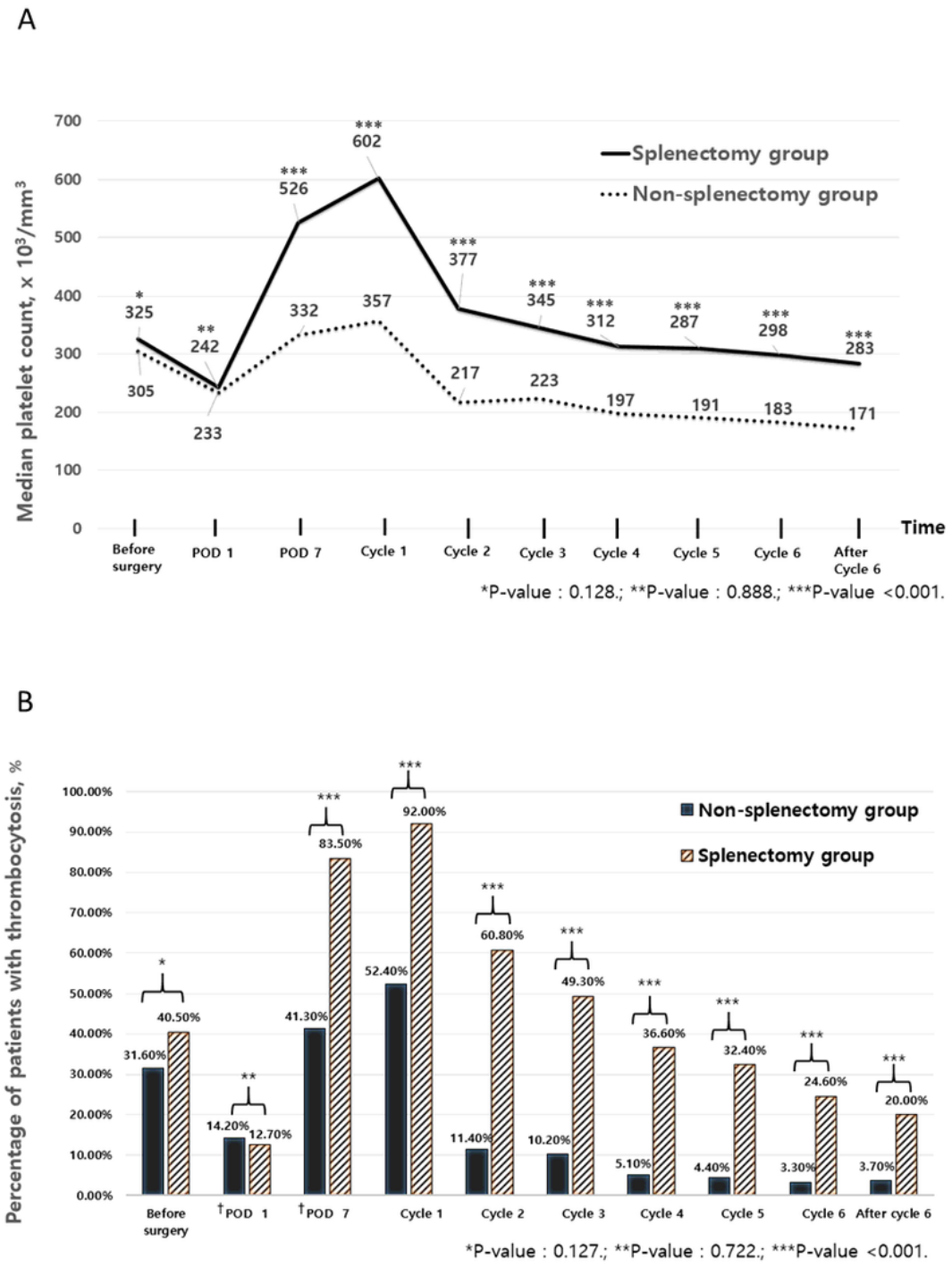

Figure 1

Trends of platelet counts and thrombocytosis during treatment. (a) Median platelet count during perioperative period and during adjuvant chemotherapy. (b) Percentage of patients with thrombocytosis during perioperative period and during adjuvant chemotherapy. Cycle 1 represents a day of blood test for the 1st cycle of adjuvant chemotherapy. POD, postoperative day.

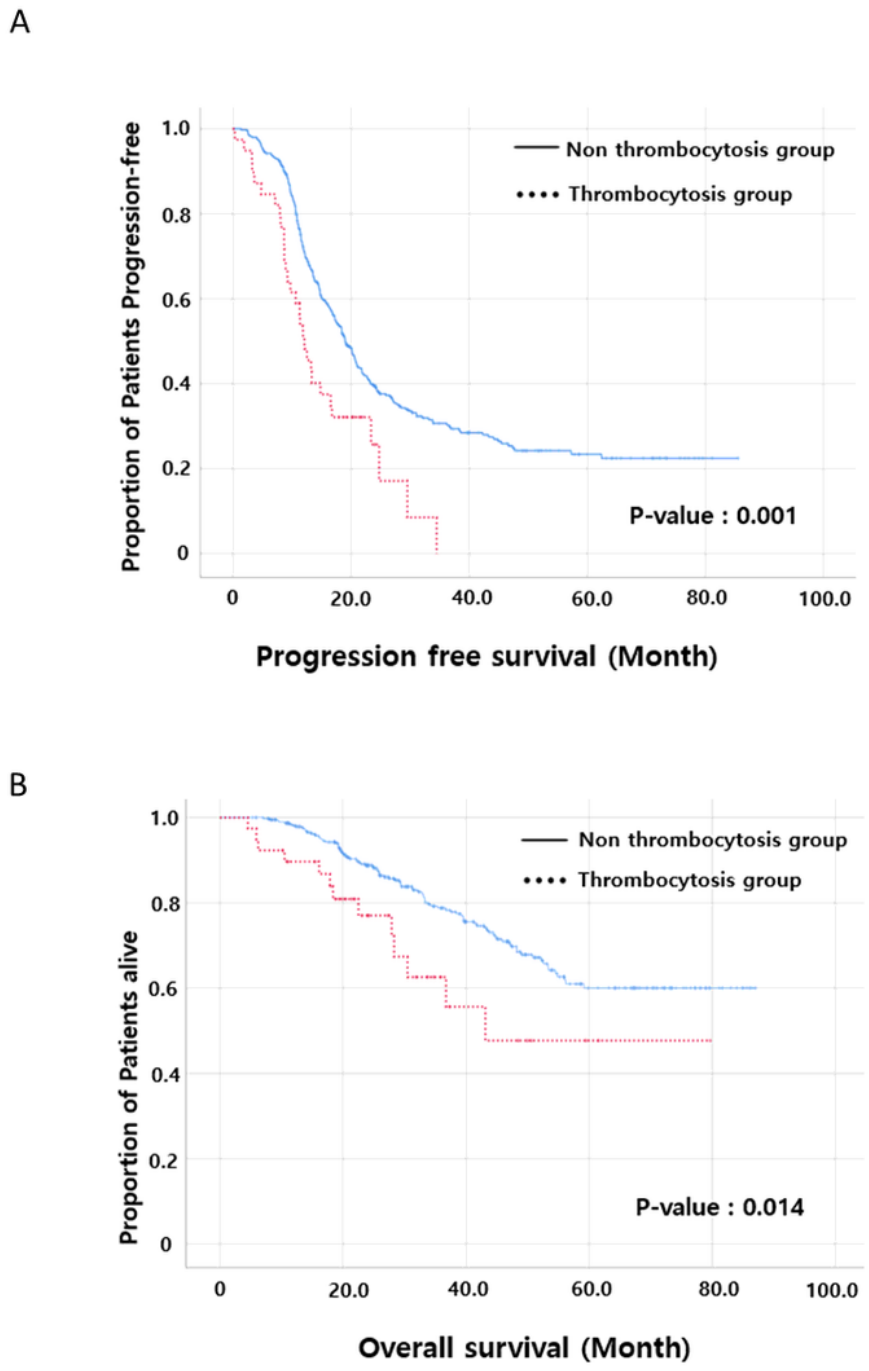

Figure 2

Kaplan-Meier analysis based on thrombocytosis at 5th cycle (a) Progression free survival. (b) Overall survival.

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