

HJOG 2024, 23 (3), 218-224 | DOI: 10.33574/HJOG.0568

# Post-splenectomy thrombocytosis and survival outcomes of patients submitted to maximal effort cytoreductive surgery for advanced epithelial ovarian cancer

Vasilios Pergialiotis<sup>1</sup>, Dimitrios Efthymios Vlachos<sup>1</sup>, Loukas Feroussis<sup>1</sup>, Vasilios Lygizos<sup>1</sup>, Ioannis Rodolakis<sup>1</sup>, Konstantinos Bramis<sup>2</sup>, Eleftherios Zachariou<sup>1</sup>, Georgios Daskalakis<sup>1</sup>, Nikolaos Thomakos<sup>1</sup>, Dimitrios Haidopoulos<sup>1</sup>

<sup>1</sup>First Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, "Alexandra" General Hospital, Athens, Greece.

<sup>2</sup>2nd Department of Surgery, Medical School, National and Kapodistrian University of Athens, Athens, Greece

---

## Correspondence

Vasilios Pergialiotis, MD, MSc, PhD, 6 Danaïdon str. Halandri 15232 - Greece, e-mail: pergialiotis@yahoo.com

## Abstract

**Background:** Splenectomy is a very common procedure that is frequently necessary in cases requiring upper abdominal surgery for ovarian cancer. To date, the impact of postoperative thrombocytosis on ovarian cancer survival has not been studied. In the present retrospective cohort study we chose to evaluate the impact of post-splenectomy thrombocytosis on survival outcomes of patients with advanced epithelial ovarian cancer that were submitted to maximal effort cytoreductive procedures.

**Methods:** We conducted a retrospective cohort study based on cases that had major debulking procedures, involving upper abdominal surgery for epithelial ovarian cancer.

**Results:** Overall, 82 women had splenectomy of whom, 52 (63%) developed thrombocytosis. The results of the univariate analysis revealed that postoperative thrombocytosis did not increase the risk of disease recurrence (62.94 months (31.71, 93.27) vs 31.40 months (21.39, 41.41) log-rank=.683). Similar results were obtained for overall survival of included patients which was comparable among the two groups (87.50 months (53.47, 121.52) vs 47.78 months (34.30, 61.25), log-rank=.511). Logistic regression analysis revealed that only age was a predictive factor of postoperative thrombocytosis with an effect of minimal clinical importance (OR 0.94, 95% CI 0.89, 1.00).

**Conclusion:** Post-splenectomy thrombocytosis does not affect the survival outcomes of patients with advanced epithelial ovarian cancer that undergo major debulking procedures. This might be explained by the underlying mechanisms which in the case of postoperative thrombocytosis seem to be completely disconnected from the pathophysiology of cancer.

**Key words:** Vaginal birth, cesarean section, VBAC, trial of labor, TOLAC, obstetricians, attitude

## Introduction

With an estimated lifetime risk of 1 in 78 women and a lifetime risk of disease-specific death of 1 in 108 women, ovarian cancer is the third most frequent gynecologic malignancy encountered globally<sup>1</sup>. The risk of ovarian cancer is influenced by several major risk factors, such as advanced age, past radiation exposure, nulliparity, genetic mutations, obesity, and family history<sup>2</sup>. Since there are currently no established screening methods, it is uncommon for the disease to be discovered early. As a result, most cases are referred for diagnosis when the tumor load causes symptoms like dyspepsia, bloating, and abdominal pain.

The prevalence and histological patterns of ovarian cancer vary around the world, but because the disease typically manifests at an advanced stage, it is regarded as systemic in most cases. As a result, chemotherapy, which primarily consists of a combi-

nation of platinum (carboplatin) and taxane (paclitaxel) chemotherapy, is the main treatment for ovarian cancer<sup>3</sup>. When combined with anti-VEGF (vascular endothelial growth factor) therapy, the use of PARP (poly-ADP ribose polymerase) inhibitors has significantly extended overall and recurrence-free survival in certain populations with known mutations in the BRCA 1 and BRCA 2 genes and those with homologous recombination deficiency<sup>3</sup>. Platinum resistant disease is considered an ominous sign according to the findings of several studies<sup>4,5</sup>.

Despite advances in the medical treatment of the disease surgical intervention remains essential because complete tumor debulking increases the patients' survival rates considerably. Since most of the evidence is still inconclusive and stems from studies with methodological flaws in terms of the population included and procedure completion adequacy, it is still unclear whether primary debulking surgery improves survival over interval debulking<sup>6-8</sup>.

In light of this data, medical professionals endeavored to broaden the scope of surgical operations, which progressively became more intricate as gynecologic oncologists acquired greater expertise and were able to execute multiorgan excisions and upper abdominal surgeries. Despite its impact on patients' perioperative morbidity, maximal effort cytoreductive treatments significantly improve survival for patients with ovarian cancer and appear to be linked with acceptable morbidity that does not necessarily exclude the use of adjuvant chemotherapy<sup>9,10</sup>. These days, splenectomy is a very common operation for upper abdominal surgery for ovarian cancer since patients with advanced stage disease who undergo primary debulking surgery typically develop hepatic

Table 1. Patient characteristics

Variable	
Age	67 (27-89)
Stage	
IIIb-IIIc	55
IV	27
Smoking	22
ECOG status	
ECOG 0-1	65
ECOG 2-3	14
Operation setting	
PDS51	
IDS31	
Tumor resection	
Complete	69
Optimal (<1cm)	8
Surgical complexity	
Intermediate	17
High	65

Table 2. Cox-regression multivariate analysis for recurrence free and overall survival

Factor	Recurrence free survival		Overall survival	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
ECOG status				
ECOG 0-1	Ref	.864	Ref	.690
ECOG 2-3	0.92 (0.33, 2.52)		1.31 (0.35, 4.87)	
Operation setting				
PDS	Ref	.031	Ref	.074
IDS	1.68 (1.05, 2.70)		1.87 (0.94, 3.72)	
Tumor resection				
Complete	Ref	.577	Ref	.308
Optimal (<1 cm)	1.43 (0.41, 4.97)		1.99 (0.53, 7.50)	
Surgical complexity				
High	Ref	.347	Ref	.448
Intermediate	1.22 (0.67, 4.31)		0.89 (0.72, 2.43)	
Thrombocytosis				
No	Ref	.129	Ref	.064
Yes	1.84 (0.84, 4.07)		2.55 (0.91, 7.11)	

and surface metastases<sup>10-12</sup>.

Splenectomy significantly affects the number of postoperative platelets, resulting in postoperative thrombocytosis. The impact of pretreatment thrombocytosis has been reviewed by several researchers and in a recent meta-analysis we designated that it significantly affects ovarian cancer survival. The actual underlying pathophysiology has not been elucidated fully; however, it seems that the release of

pro-inflammatory and inflammatory factors from the disease itself results in a cascade that promotes cancer progression. Paraneoplastic thrombocytosis seems to be a component of this vicious circle as it is associated with the secretion of these markers.

To date, the impact of postoperative thrombocytosis on ovarian cancer survival has not been studied. We speculated that its occurrence might affect patients' survival rates, despite the fact that it cannot

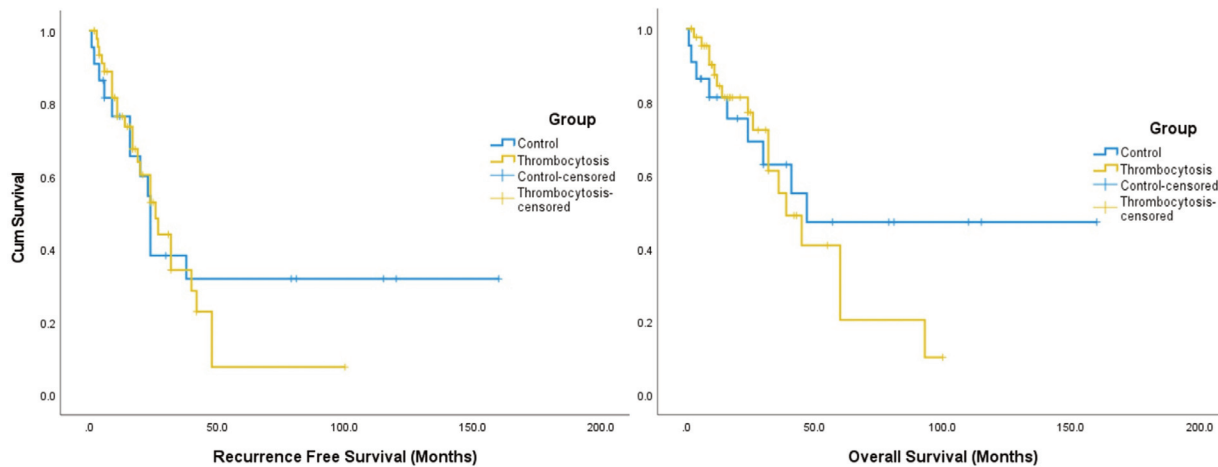


Figure 1. Kaplan-Meier curves for recurrence free survival and overall survival outcomes.

be considered a paraneoplastic phenomenon, given that a known predisposing factor is present. In the present retrospective cohort study we chose to evaluate the impact of post-splenectomy thrombocytosis on survival outcomes of patients with advanced epithelial ovarian cancer that were submitted to maximal effort cytoreductive procedures.

## Methods

The methodological design of this study has been previously presented. Briefly the present cohort is based on a consecutive series of patients that were surgically treated for advanced epithelial ovarian cancer between January 2016 and December 2021. Based on the patient's performance status and tumor load, either interval debulking surgery (IDS) or primary debulking surgery (PDS) was chosen. Factors that prohibited patients per se from undergoing surgery included the existence of extra-abdominal metastases or substantial liver parenchymal disease that required hepatic excision beyond the scope of splenoid resection. The study was designed in accordance with the declaration of Helsinki for medical research involving human subjects and the institutional review board of our hospital approved this study prior to its onset (IRB approval number: 781/21).

### Definitions

The surgical complexity of the procedures was evaluated with the Mayo Clinic (Aletti) score that assigns points of surgical complexity according to the number of excised organs and extent of tumor debulking. The summarized score is categorized as low complexity when  $\leq 3$  points are assigned, intermediate complexity when 4-7 points are assigned and high complexity in the presence of  $> 7$  points.

Survival outcomes were recorded from the onset of diagnosis until clinical or radiology findings of disease relapse (for recurrence free survival) and until

Table 3. Logistic regression analysis for the possibility of thrombocytosis

Factor	Recurrence free survival	
	Odds ratio (95% CI)	p-value
Age	0.94 (0.89, 1.00)	.050
Stage		
IIIb-IIIc	Ref	
IV	3.08 (0.73, 13.04)	.127
Operation setting		
PDS	Ref	
IDS	0.56 (0.26, 1.21)	.141
Smoking	0.64 (0.17, 2.40)	.511
Surgical complexity		
High	Ref	
Intermediate	2.83 (0.67, 11.94)	.155
Residual disease		
No residual disease	Ref	
$< 1$ cm	0.66 (0.11, 4.09)	.655

patient death (for overall survival) respectively. Patient records were used to record disease relapse and/or death for cases that had been clinically reviewed during the last 30 days; for the remaining patients, information on survival was obtained through direct phone calls.

The presence of postoperative thrombocytosis was documented within a timeframe of 30 days from the surgical procedure and the highest platelet value was obtained from the complete blood count (CBC) test. In the literature several cut-off points have been described for pre-treatment thrombocytosis. In the present study we determined that an optimal cut-off of 350.000/ml would best describe the occurrence of postoperative thrombocytosis, given the actual distribution of platelets following a splenectomy.

### Statistical analysis

Statistical analysis was performed using the SPSS 20.0 program (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). Evaluation of the normality of distributions was performed with graphical methods and the

Kolmogorov-Smirnoff analysis. The differences of continuous variables were assessed using the Mann-Whitney and Kruskal-Wallis test (due to the abnormal distribution that was observed during the evaluation of normality) whereas dichotomous variables were analyzed with the chi-square test. Fisher's exact test was applied wherever the number of observations was lower than five in the case of dichotomous variables. The Kaplan-Meier method was carried out to perform survival-analyses. The level of significance for all analyses was set to  $p < .05$ .

## Results

We were able to identify 245 that had maximal effort debulking procedure for epithelial ovarian cancer. Of those, 22 were excluded due to absence of relevant data. Overall, 82 women had splenectomy of whom, 52 (63%) developed thrombocytosis. The characteristics of included patients are depicted in Table 1. Of those, 44 women developed disease recurrence, and 31 women ultimately died from the disease.

The results of the univariate analysis revealed that postoperative thrombocytosis did not increase the risk of disease recurrence (62.94 months (31.71, 93.27) vs 31.40 months (21.39, 41.41) log-rank=.683) (Figure 1). Similar results were obtained for overall survival of included patients which was comparable among the two groups (87.50 months (53.47, 121.52) vs 47.78 months (34.30, 61.25), log-rank=.511) (Figure 1).

Multivariate analysis indicated that thrombocytosis had an effect on the overall survival of patients which, however, did not reach the level of statistical significance ( $p=.064$ ) (Table 2). Of all the remaining factors that were selected in the predictive model for recurrence free and overall survival, only the setting of the operation had a significant effect which was mainly seen in recurrence free survival, whereas the overall survival was close to the level of statistical

significance.

Logistic regression analysis revealed that only age was a predictive factor of postoperative thrombocytosis with an effect of minimal clinical importance (OR 0.94, 95% CI 0.89, 1.00).

## Discussion

The findings of our study suggest that post-splenectomy thrombocytosis does not affect the progression free survival nor the overall survival of patients. This result is in partial contrast to that of our previous meta-analysis which indicated that pre-treatment thrombocytosis is an essential factor that directly affects patients' survival rates<sup>13</sup>.

Researchers have found previously that the release of cytokines in patients with ovarian cancer causes thrombopoiesis, which is why paraneoplastic thrombocytosis manifests as a component of the inflammatory process that accompanies<sup>14</sup>. This observation explains why pre-treatment thrombocytosis might affect patients' survival as it indicates that it is a part of a vicious circle that repeatedly results in excretion of inflammatory factors that consequently increase the number of thrombocytes. This explains why some studies revealed that patients with significant reduction in platelet number post-chemotherapy had increased survival rates<sup>15-16</sup>.

Post-splenectomy thrombocytosis is considered reactive and is considered the result of the operation, including the inflammatory process that accompanies it. In most cases it becomes evident within the first month from the operation and persists for an unpredictable and greatly variable period of time<sup>17,18</sup>. Considering this it does not seem to be directly related to the actual tumor load and the process that accompanies it, therefore, partially explaining why it does not predispose to worse survival outcomes. The actual reasons of postoperative thrombocytosis have not been completely elucidated. It is believe that patients

undergoing splenectomy for non-traumatic diseases are more prone to develop thrombocytosis when pre-operative platelet counts are increased within the normal limits and that men are more prone to develop the condition compared to women<sup>19</sup>. In our series, none of the factors that were considered as potential contributors, considering the burden of the disease, patients' age and smoking status were either predictive or clinically meaningful, indicating the difficulty to detect patients at risk.

### ***Strengths and limitations of our study***

Our study is based on one of the largest cohorts of patients that is derived from a single institution that is accredited by ESGO as a center of excellence for the management of patients with ovarian cancer. In the present series we indicated for the first time in the international literature the lack of an association between postoperative (post-splenectomy) thrombocytosis and ovarian cancer survival.

On the other hand, despite the use of a continuous series of patients, the retrospective design of our study cannot completely preclude the possibility of bias, including selection and confounding bias. Moreover, the retrospective nature of the study, precluded the investigation of the specific cause of death of included patients; therefore, the actual cancer specific survival remains unknown, as well as the actual proportion of patients that actual return to normal platelet counts and the interval until this phenomenon occurs.

### **Conclusion**

Post-splenectomy thrombocytosis does not affect the survival outcomes of patients with advanced epithelial ovarian cancer that undergo major debulking procedures. This might be explained by the underlying mechanisms which in the case of postoperative thrombocytosis seem to be completely disconnected from the pathophysiology of cancer.

### **References**

1. R.L. Siegel, K.D. Miller, N.S. Wagle, A. Jemal, Cancer statistics, 2023, *CA Cancer J Clin* 73(1) (2023) 17-48.
2. M. Andreou, M. Kyprianidou, C. Cortas, I. Polycarpou, D. Papamichael, P. Kountourakis, K. Giannakou, Prognostic Factors Influencing Survival in Ovarian Cancer Patients: A 10-Year Retrospective Study, *Cancers (Basel)* 15(24) (2023).
3. N. Colombo, C. Sessa, A. du Bois, J. Ledermann, W.G. McCluggage, I. McNeish, P. Morice, S. Pignata, I. Ray-Coquard, I. Vergote, T. Baert, I. Belaroussi, A. Dashora, S. Olbrecht, F. Planchamp, D. Querleu, ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease†, *Ann Oncol* 30(5) (2019) 672-705.
4. K.S. Okunade, A. Soibi-Harry, T. Onyeka, J.B. Ogunyemi, T. Thomas-Ogodo, A.A. Adejimi, A.C. Okoro, B. Osunwusi, S.R. Garba, R.I. Anorlu, Timing of recurrence and overall survival in epithelial ovarian cancer: A 10-year retrospective review, *HJOG* 2022(21) (2022) 3.
5. A. Havasi, S.S. Cainap, A.T. Havasi, C. Cainap, Ovarian Cancer-Insights into Platinum Resistance and Overcoming It, *Medicina (Kaunas)* 59(3) (2023).
6. S.M. Sørensen, C. Høgdall, B.J. Mosgaard, M.I.R. Dalgaard, M.P. Jensen, K. Fuglsang, T.H. Schnack, Residual tumor and primary debulking surgery vs interval debulking surgery in stage IV epithelial ovarian cancer, *Acta Obstet Gynecol Scand* 101(3) (2022) 334-343.
7. V. Ghirardi, M.C. Moruzzi, N. Bizzarri, V. Vargiu, M. D'Indinosante, G. Garganese, T. Pasciuto, M. Loverro, G. Scambia, A. Fagotti, Minimal residual disease at primary debulking surgery ver-

- sus complete tumor resection at interval debulking surgery in advanced epithelial ovarian cancer: A survival analysis, *Gynecol Oncol* 157(1) (2020) 209-213.
8. C. Bian, K. Yao, L. Li, T. Yi, X. Zhao, Primary debulking surgery vs. neoadjuvant chemotherapy followed by interval debulking surgery for patients with advanced ovarian cancer, *Arch Gynecol Obstet* 293(1) (2016) 163-168.
  9. D. Haidopoulos, V. Pergialiotis, E. Zachariou, I. Sapantzoglou, N. Thomakos, E. Stamatakis, N. Alexakis, Maximal Effort Cytoreduction in Epithelial Ovarian Cancer: Perioperative Complications and Survival Outcomes from a Retrospective Cohort, *J Clin Med* 12(2) (2023).
  10. V. Pergialiotis, E. Zachariou, V. Lygizos, D.E. Vlachos, E. Stamatakis, K. Angelou, G. Daskalakis, N. Thomakos, D. Haidopoulos, Splenectomy as Part of Maximal-Effort Cytoreductive Surgery in Advanced Epithelial Ovarian Cancer, *Cancers (Basel)* 16(4) (2024).
  11. H. El Hajj, D. Ferraioli, P. Meus, F. Beurrier, O. Tredan, I. Ray-Coquard, N. Chopin, Splenectomy in epithelial ovarian cancer surgery, *Int J Gynecol Cancer* 33(6) (2023) 944-950.
  12. S.A. Said, M.A. van der Aa, G. Veldmate, J.A. de Hullu, A.M. van Altena, Oncologic outcomes after splenectomy during initial cytoreductive surgery in advanced epithelial ovarian cancer: a nationwide population-based cohort study, *Acta Obstet Gynecol Scand* 101(1) (2022) 56-67.
  13. V. Pergialiotis, L. Vogiatzi Vokotopoulou, D.E. Vlachos, M. Liontos, E. Kontomanolis, N. Thomakos, Pre-treatment thrombocytosis and ovarian cancer survival: A meta-analysis, *Eur J Obstet Gynecol Reprod Biol* X 22 (2024) 100312.
  14. R.L. Stone, A.M. Nick, I.A. McNeish, F. Balkwill, H.D. Han, J. Bottsford-Miller, R. Rupairmoole, G.N. Armaiz-Pena, C.V. Pecot, J. Coward, M.T. Deavers, H.G. Vasquez, D. Urbauer, C.N. Landen, W. Hu, H. Gershenson, K. Matsuo, M.M. Shahzad, E.R. King, I. Tekedereli, B. Ozpolat, E.H. Ahn, V.K. Bond, R. Wang, A.F. Drew, F. Gushiken, D. Lamkin, K. Collins, K. DeGeest, S.K. Lutgendorf, W. Chiu, G. Lopez-Berestein, V. Afshar-Kharghan, A.K. Sood, Paraneoplastic thrombocytosis in ovarian cancer, *N Engl J Med* 366(7) (2012) 610-8.
  15. D.H. Hufnagel, G.D. Cozzi, M.A. Crispens, A. Beeghly-Fadiel, Platelets, Thrombocytosis, and Ovarian Cancer Prognosis: Surveying the Landscape of the Literature, *Int J Mol Sci* 21(21) (2020).
  16. H. Eggemann, J. Ehrlicke, T. Ignatov, F. Fettke, A. Semczuk, S.D. Costa, A. Ignatov, Platelet Count After Chemotherapy is a Predictor for Outcome for Ovarian Cancer Patients, *Cancer Invest* 33(5) (2015) 193-6.
  17. C.M. Sande, S.M. Maliske, M.B. Zimmerman, D.A. Reinke, U. Perepu, C.J. Holman, Impact of Splenectomy on Post-Surgical Platelet Count, *Blood* 132 (2018) 4981.
  18. C. Sande, S. Maliske, M.B. Zimmerman, D.A. Reinke, U. Perepu, C. Holman, Impact of Splenectomy on Postsurgical Platelet Count, *American Journal of Clinical Pathology* 152(Supplement\_1) (2019) S24-S25.
  19. R.M. Dragomir, M.D. Hoge, M.A. Moga, D.G. Festila, C.P. Cobelschi, Predictive Factors for Platelet Count Variation After Splenectomy in Non-Traumatic Diseases, *Journal of Clinical Medicine* 8(1) (2019) 82.

*Received 28-4-2024*

*Revised 12-5-2024*

*Accepted 25-5-2024*