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Could Preoperative Thrombocytosis be a Marker in Different Gynecological Malignancies?

Hadeer Ahmed Mosaad Ahmed[2*], Mohammad Ahmad ELsayed Mohammad Emam[1], Maher ELesawyElgaly[1]
[1]Department of Obstetrics and Gynecology, Ministry of Health and Population, Sinbellawin General Hospital, Egypt
[2]Department of Obstetrics and Gynecology, Faculty of Medicine, Mansoura University, Egypt
***Corresponding author:** Hadeer Ahmed Mosaad Ahmed, **Mobile:** (+20) 01062791338, **Email:** hadeerahmed8@gmail.com

ABSTRACT

Background: Thrombocytosis is a condition in which the platelet (PLT) count exceeds 400,000/µl. It could be considered a bad indicator for several forms of malignant tumours.

Objective: The aim of this work was to study if thrombocytosis could be a marker in gynecological malignancies.

Patients and methods: This cross-sectional observational study was conducted on 196 patients who had gynecological malignancies at Gynecology and Obstetrics Department, Mansoura University Hospital through the period from March 2022 to November 2023

Results: The correlation analysis revealed that there was a significant relation between type of cancer and thrombocytosis. In endometrial carcinoma there was 27 patients (40.9%) had stage 1 a and 8 of them (12.1%) had thrombocytosis. 29 patients (43.9%) had stage 1 b and 2 patients (6.1%) had stage 3 and all of them had thrombocytosis. 8 patients (12.1%) had stage 4. In sarcoma there was 5 patients (45.1%) had stage 1 a and 6 patients (54.9%) had stage 4. In ovarian cancer (OC) there was 3 patients (5.7%) had stage 1 a, 20 patients (37.7%) had stage 1 b and 4 of them (7.5%). 16 patients (30.2%) had stage 2 b and 5 of them had thrombocytosis. 14 patients (26.4%) had stage 3 and 5 of them had thrombocytosis.

Conclusion: Thrombocytosis could be a marker in gynecological malignancies. there was significant relation between type of cancer and thrombocytosis. In which thrombocytosis was found in endometrial carcinoma, ovarian cancer and cancer cervix respectively.

Keywords: Thrombocytosis, Gynecological malignancies, Platelet counts.

INTRODUCTION

Thrombocytosis is a condition that occurs when the PLT count exceeds 400,000/µl. It is classified into two groups: primary thrombocytosis and secondary thrombocytosis [1, 2].

It is of great significance to differentiate between primary and secondary thrombocytosis as it interferes with the diagnosis and treatment as well as overall outcomes. Primary thrombocytosis could develop as a result of abnormal upregulation of PLT formation [3]. Secondary thrombocytosis is described as an abnormal elevation of PLT count owing to underlying occasions, diseases, or the usage of some drugs [4]. Secondary thrombocytosis is the most frequent type and is often detected during conventional laboratory analysis. Secondary thrombocytosis represents about 95% of all cases of thrombocytosis [2].

It could be considered a bad indicator for several forms of malignant tumours. In such contexts, the actual etiology of the secondary thrombocytosis isn't clear. On the other hand, it seems that circulating cytokines and growth factors have essential roles [5].

With regard to thrombocytosis in endometrial cancer (EC), a lot of researches recorded that 7–41% of cases with EC suffer from thrombocytosis with different cut-offs [6]. Additionally, it has been demonstrated that there is a significant relationship between thrombocytosis and stages of the disease, recommending that cases with advanced stages are more susceptible to suffer from thrombocytosis [7, 8]. Also, thrombocytosis in ovarian cancer. Thrombocytosis was significantly correlated with advanced stage and higher grade epithelial ovarian tumours (EOT) [9], lymph node (LN) metastases, increased ascites volume, and less optimal tumour cytoreduction with significantly shorter disease-free survival (DFS) and overall survival (OS) [10].

About thrombocytosis in cervical cancer, a limited number of studies on cervical cancer have evaluated thrombocytosis as a prognostic indicator in cases receiving chemoradiotherapy. Moreover, **Sharma and Singh** [10] and **Cheng *et al.*** [11] revealed a positive relationship between thrombocytosis and poor outcomes. Thrombocytosis was demonstrated to be accompanied by advanced stages, bulky disease, and positive pelvic LN.

As well, thrombocytosis in vulvar cancer was reported in 14.9% of cases with vulvar cancers and in 15.46% of cases with squamous cell vulvar cancers. There was no significant association between thrombocytosis and the following; tumour size, LN metastases, or disease stage. The five year survival rate was comparable between cases with thrombocytosis and cases with normal PLT counts, with an insignificant difference (89.29% versus 76.47 % respectively) [12, 13].

We aimed to study if thrombocytosis could be a marker in gynecological malignancies.

PATIENTS AND METHODS

This cross-sectional observational study was conducted on 196 patients who had gynecological malignancies at Gynecology and Obstetrics

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Department, Mansoura University Hospital from March 2022 to November 2023.

Inclusion criteria: Patients diagnosed with gynecological malignancies.

Exclusion criteria: Inflammation (Rheumatoid arthritis, inflammatory bowel disease, and sarcoidosis), infection (Acute bacterial, viral, or chronic infectious conditions e.g., tuberculosis)**,** Post splenectomy, iron deficiency**,** compromised liver and kidney function tests and patients who received chemotherapy or radiotherapy.

$$\text{Sample size} = \frac{z^2 xp(\vdash p)}{e^2}$$

Sample size calculation: It was based on prevalence of thrombocytosis at gynecological malignancies (15% endometrial malignancy). Using Epi Info version 7.2.4.0 to calculate sample size using α error = 0.05%, 95% CI, then the total calculated sample size was 196 cases:

• z = z-score, e = margin of error, p = standard of deviation

Methods:

Patients were subjected to detailed history, physical examination and investigational studies.

Analytical methods

Sample collection: Under a complete aseptic condition, three ml of venous blood were withdrawn from the cases using a syringe and put on a test tube containing EDTA to perform CBC using an automated cell counter.

Platelet counts: Automated platelet counts through automated cell count and manual platelet counts. PLT counts were performed by using a commercial diluting system, hemocytometer, and a microscope. In addition, PLT clumping diminished the hemocytometer PLT count. PLT count measured from a blood smear examination. In a well-prepared smear, PLT were measured by counting the average number of PLT detected per 100x oil immersion field in the monolayer. Generally, 10 oil immersion fields were counted and the results averaged. Then, platelets were measured based on the this formula: Estimated PLT count/µL = average count in 10 fields x15,000.

Imaging techniques: Transvaginal US, magnetic resonance imaging and computed tomography.

Ethical consideration: Study protocol was submitted for approval by IRB, Faculty of Medicine, Mansoura University. Informed written consent was obtained from each studied subject. All cases could withdraw themselves from the study. Confidentiality was respected and collected data weren't used for any other purposes. Every phase of the study was conducted in accordance with the Helsinki Declaration.

Statistical Analysis:

All data were collected and statistically analyzed using SPSS version 22.0. Descriptive statistics: Mean ± SD and range for parametric numerical data, while median and IQR for non-parametric numerical data, frequency and percentage for non-numerical data. Student t test was utilized to assess the statistical significance of the difference between two study group means. Paired T-test 2)twice for identical group. For comparing categorical data, χ^2-test, likelihood ratio, Fisher's exact test, continuity correction, linear by linear relationship ere used. Level of significance: $P \leq 0.05$.

RESULTS

Table (1) showed that, the mean age was 49.96 ± 14.9 years, the mean of Parity was 2.9 ± 2.1, and the mean BMI was 29.3 ± 14.1 kg/m^2. 42 patients (21.4%) had DM, 52 patients (26.5%) had HTN, 105 patients (53.6%) were rural, and 91 patients (46.4%) were urban**.**

Table (1): Distribution of patients' characteristics in the studied patients

Parameters	Studied group N=196
Age (Years) 49.96 ± 14.9	
Parity 2.9 ± 2.1	
BMI (kg/m^2) 29.3 ± 14.1	
DM	**42 (21.4%)**
HTN	**52 (26.5%)**
Residence	
Rural	**105 (53.6%)**
Urban	**91 (46.4%)**

SD; Standard Deviation DM; Diabetes Mellitus BMI; Body Mass Index HTN; Hypertension.

Regarding type of cancer, table (2) and figure (1) showed that 66 patients (33.7%) had endometrial carcinoma with 10 patients (15.2%) had thrombocytosis, 11 patients (5.6%) had sarcoma, 53 patients (27.1%) had ovarian cancer with 14 patients had thrombocytosis (26.4%), 56 patients (28.6%) had cancer cervix with 7 patients had thrombocytosis (12.5%), 5 patients (2.5%) had GTN, and 5 patients (2.5%) had vulvar carcinoma.

Table (2): Distribution of type of cancer and thrombocytosis among studied group

Parameters	Studied group N=196	
type of cancer	Study group N=196	Thrombocytosis 31(15.8%)
Endometrial carcinoma	66 (33.7%)	10 (15.2%)
Sarcoma	11 (5.6%)	0 (0%)
Ovarian cancer	53(27.1%)	14 (26.4%)
Cancer cervix	56 (28.6%)	7 (12.5%)
GTN	5(2.5%)	0 (0%)
Vulvar carcinoma	5(2.5%)	0 (0%)

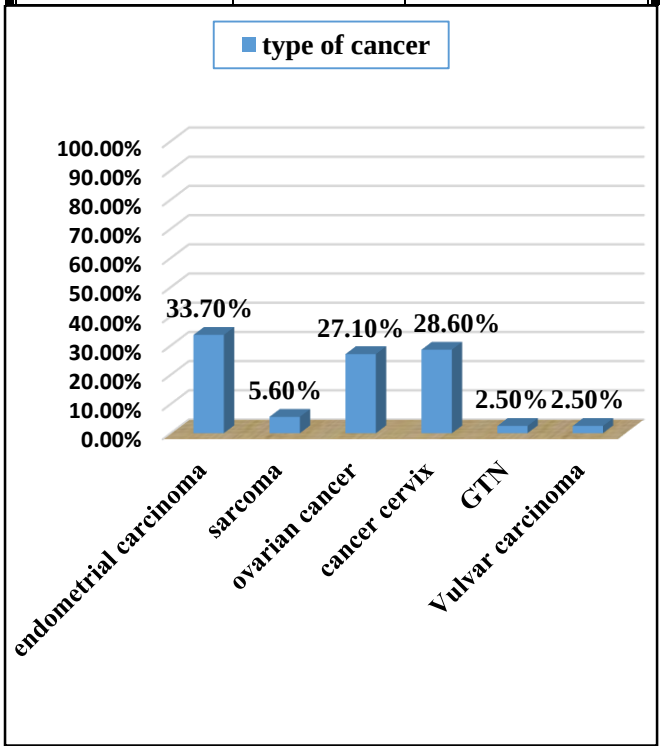

Figure (1): Distribution of type of cancer in the studied group.

In endometrial carcinoma, there was 27 patients (40.9%) had stage 1 a with 8 of them (12.1%) had thrombocytosis, 29 patients (43.9%) had stage 1 b, 2 patients (6.1%) had stage 3 with all of them had thrombocytosis, and 8 patients (12.1%) had stage 4. In sarcoma, there was 5 patients (45.1%) had stage 1 a and 6 of patients (54.9%) had stage 4.

In ovarian cancer, there was 3 patients (5.7%) had stage 1 a, 20 patients (37.7%) had stage 1 b with 4 of them (7.5%) had thrombocytosis, 16 patients (30.2%) had stage 2 b with 5 of them had thrombocytosis, and 14 of patients (26.4%) had stage 3 with 5 of them had thrombocytosis. In cancer cervix, there was 6 patients (10.7%) had stage 1 a, 21 patients (37.5%) had stage 1 b with 3 of them (5.4%) had thrombocytosis, 16 patients (28.6%) had stage 2 b, 13 patients (23.2%) had stage 3 with 2 of them had thrombocytosis.

In GTN, there was 3 patients (60%) had stage 1 a, and 2 patients (40%) had stage 1 b. In vulvar carcinoma, there was 1 patient (20%) had stage 2 b, 3 patients (60%) had stage 3, and 1 patient (20%) had stage 4 (Table 3).

Table (3): Relation between type of cancer, stage and thrombocytosis in the studied group.

Parameters	Studied group N=196		
	Stage		Thrombo-cytosis
Endometrial carcinoma (N=66)	Stage 1 a	27 (40.9%)	8 (12.1%)
	Stage 1 b	29 (43.9%)	0 (0%)
	Stage 3	2 (3.1%)	2 (3.1%)
	Stage 4	8 (12.1%)	0 (0%)
sarcoma (N=11)	Stage 1 a	5 (45.1%)	0 (0%)
	Stage 4	6 (54.9%)	0 (0%)
Ovarian cancer (N=53)	Stage 1 a	3 (5.7%)	0 (0%)
	Stage 1 b	20 (37.7%)	4 (7.5%)
	Stage 2 b	16 (30.2%)	5 (9.4%)
	Stage 3	14 (26.4%)	5 (9.4%)
Cancer cervix (N=56)	Stage 1 a	6 (10.7%)	0 (0%)
	Stage 1 b	21 (37.5%)	4 (7.1%)
	Stage 2 b	16 (28.6%)	0 (0%)
	Stage 3	13 (23.2%)	3 (6.5%)
GTN (N=5)	Stage 1 a	3 (60%)	0 (0%)
	Stage 1 b	2 (40%)	0 (0%)
Vulvar carcinoma (N=5)	Stage 2 b	1 (20%)	0 (0%)
	Stage 3	3 (60%)	0 (0%)
	Stage 4	1 (20%)	0 (0%)

There was significant relation between type of cancer and thrombocytosis. In which thrombocytosis was found in endometrial carcinoma, ovarian cancer and cancer cervix (Table 4).

Table (4): Correlation between thrombocytosis and type of cancer

Parameters	Thrombocytosis N=196	P-value
Type of cancer		
Endometrial carcinoma	**10(15.2 %)**	**0.04**
Leiomyosarcoma	**0**	
Ovarian cancer	**14 (26.4%)**	
Cancer cervix	**7 (12.5%)**	
GTN	**0**	
Vulvar carcinoma	**0**	

DISCUSSION

Our results revealed that, the mean age was 49.96 ± 14.9 years while the mean of parity was 2.9 ± 2.1, the mean BMI was 29.30 ± 14.1 kg/m^2, 42 patients with DM, 52 patients (26.5%) had HTN, 105 patients (53.6%) were rural, and 91 patients (46.4%) were urban. This is in agreement with **Gungor *et al.*** [14] who aimed to detect the incidence of thrombocytosis in females with EOT and to assess its relationship with clinical and pathological prognostic factor. They reported that age was 57.4 ± 3.8years. As well, **Lauby-Secretan *et al.*** [15] who studied the relationship between obesity and EC which is predominantly obvious for endometrioid EC, with relative risks of 1.5 for those with overweight, 2.5 for those with class 1 obesity, 4.5 for those with class 2 obesity and 7.1 for class 3 obesity.

Also, **Liao *et al.*** [16] who revealed an independent relationship between DM and the development of EC. Insulin resistance, hyperinsulinemia, hyperglycemia, inflammation and disturbance in the IGF-1 pathways could participate in carcinogenesis in diabetic subjects.

Our results showed that 66 patients (33.7%) had endometrial carcinoma with 10 patients (15.2%) had thrombocytosis, 11 patients (5.6%) had sarcoma, 53 patients (27.1%) had ovarian cancer with 14 patients had thrombocytosis (26.4%), 56 patients (28.6%) had cancer cervix with 7 patients had thrombocytosis (12.5%), 5 patients (2.5%) had GTN, and 5 patients (2.5%) had vulvar carcinoma regarding type of cancer. Similar to our study, **Takahashi *et al.*** [7] recorded that 7–41% of cases with EC complained from thrombocytosis with various cut-offs. Also, **Cohen *et al.*** [17] reported that thrombocytosis is more common in ovarian cancer in different studies, the prevalence of thrombocytosis ranges from 7% to 43%**.** As well **Cheng *et al.*** [11] recorded a positive relationship between thrombocytosis and poor outcome in terms of cancer cervix. Thrombocytosis was demonstrated to be accompanied by progressive stages, bulky disease, and positive pelvic LN.

Our findings reported that in endometrial carcinoma, 27 patients (40.9%) had stage 1 a with 8 of them (12.1%) had thrombocytosis, 29 patients (45.5%) had stage 1 b, 2 patients (4.5%) had stage 3 with all of them had thrombocytosis and 8 patients (9.1%) had stage 4. In sarcoma, 5 patients (45.1%) had stage 1 a and 6 patients (54.9%) had stage 4. In ovarian cancer, 3 patients (5.7%) had stage 1 a, 20 patients (37.7%) had stage 1 b with 4 of them (7.5%) had thrombocytosis, 16 patients (30.2%) had stage 2 b with 5 of them had thrombocytosis, and 14 patients (26.4%) had stage 3 with 5 of them had thrombocytosis. In cancer cervix, 6 patients (10.7%) had stage 1 a, 21 patients (37.5%) had stage 1 b with 3 of them (5.4%) had thrombocytosis, 16 patients (28.6%) had stage 2 b, and 13 patients (23.2%) had stage 3 with 2 of them had thrombocytosis. In GTN, 3 patients (60%) had stage 1 a, and 2 patients (40%) had stage 1 b. In vulvar carcinoma, 1 patient (20%) had stage 2 b, 3 patients (60%) had stage 3, and 1 patient (20%) had stage 4.

In agreement with our results, **Sharma and Singh** [10] found that 14 (18.2%) of 77 cases with EC demonstrated thrombocytosis. The median OS in patients with thrombocytosis was 7.0 ± 3.8 months. Data indicated that presurgical thrombocytosis among high-risk inner-city cases with stages III to IV EC is an independent prognostic indicator.

Also, **Sharma and Singh** [10] found that thrombocytosis was significantly associated with progressive stage and higher grade EOT, LN metastases, greater volume of ascites, and less optimal tumor cytoreduction with significantly shorter DFS and OS. **Cao *et al.*** [18] found that thrombocytosis before therapy was accompanied by a poor prognosis in cases with cervical cancer.

Lavie *et al.* [19] demonstrated that pretreatment thrombocytosis wasn't a prognostic indicator and that the pretreatment PLT counts of 201 females with vulvar cancer were correlated to the patient's age, stage, LN condition, histological type, and outcomes.

The correlation analysis in our results showed that thrombocytosis exhibited no correlations with stage, and type of cancer.

In agreement with our results, **Sharma and Singh** [10] revealed that thrombocytosis was significantly correlated with advanced stage and higher grade EOT.

In EC, the prevalence of thrombocytosis rises with increasing stage. In contrast with our results, **Gücer *et al.*** [20] revealed that thrombocytosis in cases with OC ranges from 22.4% to 62.5%. There were significantly higher ratios of thrombocytosis (PLT count > 400,000) in cases with stage III and IV than in those with stage I and II disease. Thrombocytosis wasn't correlated with grade, residual disease or advanced stage but cases with thrombocytosis did have a significantly worse prognosis compared to thrombocytosis free ones. Also, in progressive stage EC, while there was no statistical correlation between thrombocytosis and stage or pathology outcomes, such as histological type, grade.

CONCLUSION

There was significant relation between type of cancer and thrombocytosis. In which thrombocytosis was found in endometrial carcinoma, ovarian cancer and cancer cervix.

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REFERENCES

1. **Sałacki A, Wysokiński A (2015):** Reactive thrombocytosis resulting from frequent blood donations as an extremely rare cause of ST Segment Elevation Myocardial Infarction in the case of a 19-year-old male. Ann Agric Environ Med., 25 (4): 602–4.
2. **Rokkam V, Kotagiri R (2020):** Secondary thrombocytosis, In: StatPearls. StatPearls Publishing, Treasure Island (FL). https://www.ncbi.nlm.nih.gov/books/NBK560810/
3. **Rumi E, Cazzola M (2017):** Diagnosis, risk stratification, and response evaluation in classical myeloproliferative neoplasms. Blood, J Am Soc Hematol., 129 (6): 680–92.
4. **Muhammed Z, Alfatih M, Babiker A *et al.* (2022):** Reactive thrombocytosis with severe anemia and infection in a Sudanese patient: A case report. Ann Med Surg., 84: 104927. doi: 10.1016/j.amsu.2022.104927.
5. **Haemmerle M, Stone R, Menter D *et al.* (2018):** The platelet lifeline to cancer: challenges and opportunities. Cancer Cell, 33 (6): 965–83.
6. **Buergy D, Wenz F, Groden C *et al.* (2012):** Tumor–platelet interaction in solid tumors. Int J Cancer, 130 (12): 2747–60.
7. **Takahashi R, Mabuchi S, Kuroda H *et al.* (2017):** The significance of pretreatment thrombocytosis and its association with neutrophilia in patients with surgically treated endometrial cancer. Int J Gynecol Cancer, 27 (7): 1399-1407.
8. **Ye Q, Wu Z, Xia T *et al.* (2020):** Pre-treatment thrombocytosis predicts prognosis of endometrial cancer: A meta-analysis of 11 studies. Exp Ther Med., 19 (1): 359–66.
9. **Hufnagel D, Cozzi G, Crispens M *et al.* (2020):** Platelets, thrombocytosis, and ovarian cancer prognosis: surveying the landscape of the literature. Int J Mol Sci., 21 (21): 8169. doi: 10.3390/ijms21218169.
10. **Sharma D, Singh G (2017):** Thrombocytosis in gynecological cancers. J Cancer Res Ther., 13 (2): 193–7.
11. **Cheng J, Zeng Z, Ye Q *et al.* (2017):** The association of pretreatment thrombocytosis with prognosis and clinicopathological significance in cervical cancer: a systematic review and meta-analysis. Oncotarget, 8 (15): 24327-36.
12. **Nikolic O, Sousa F, Cunha T *et al.* (2021):** Vulvar cancer staging: guidelines of the European Society of Urogenital Radiology (ESUR). Insights Imaging, 12 (1): 131. https://doi.org/10.1186/s13244-021-01075-6
13. **Uysal A, Gultekin E, Taner C *et al.* (2013):** The impact of thrombocytosis on clinicopathological prognostic factors and survival in patients with vulvar cancer. Ginekol Pol., 84 (6): 1603. DOI: 10.17772/gp/1603
14. **Gungor T, Kanat-Pektas M, Sucak A *et al.* (2009):** The role of thrombocytosis in prognostic evaluation of epithelial ovarian tumors. Arch Gynecol Obstet., 279: 53–6.
15. **Lauby-Secretan B, Scoccianti C, Loomis D *et al.* (2016):** Body fatness and cancer—viewpoint of the IARC Working Group. N Engl J Med., 375 (8): 794–8.
16. **Liao C, Zhang D, Mungo C *et al.* (2014):** Is diabetes mellitus associated with increased incidence and disease-specific mortality in endometrial cancer? A systematic review and meta-analysis of cohort studies. Gynecol Oncol., 135 (1): 163–71.
17. **Cohen J, Tran A, Rimel B *et al.* (2014):** Thrombocytosis at secondary cytoreduction for recurrent ovarian cancer predicts suboptimal resection and poor survival. Gynecol Oncol., 132 (3): 556–9.
18. **Cao W, Yao X, Cen D *et al.* (2019):** Prognostic role of pretreatment thrombocytosis on survival in patients with cervical cancer: a systematic review and meta-analysis. World J Surg Oncol., 17: 1–10.
19. **Lavie O, Comerci G, Daras V *et al.* (1999):** Thrombocytosis in women with vulvar carcinoma. Gynecol Oncol., 72 (1): 82–6.
20. **Gücer F, Tamussino K, Keil F *et al.* (2004):** Thrombocytosis in gynecologic malignancies. Anticancer Res., 24 (3B): 2053–59.