Research Article

Clinicopathological of Pre-Operative Thrombocytosis in Epithelial Ovarian Cancer

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Abstract

Objective: To investigate the clinicopathological of preoperative thrombocytosis in patients with epithelial ovarian cancer at dr. Soedarso Regional General Hospital Pontianak.

Methods: A cross-sectional retrospective study was conducted over three months from January 2022 to March 2022, and bivariate analysis was performed using the Chi-Square test.

Results: A total of 28 subjects met the inclusion criteria, with 19 subjects had thrombocytosis (67.9%) and 9 subjects did not experience thrombocytosis (32.1%). Meanwhile, the results of the Chi Square Test showed a relationship between thrombocytosis and histopathological type in the subjects (p=0.036).

Conclusion: Preoperative thrombocytosis is associated with the histopathological type of epithelial ovarian cancer at dr. Soedarso Regional General Hospital Pontianak.

Keywords: epithelial ovarian cancer, histopathology, stage, thrombocytosis

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INTRODUCTION

Ovarian cancer remains a leading cause of death among gynecological malignancies. According to GLOBOCAN 2020, the global incidence of ovarian cancer reached 313,959 cases, resulting in 207,252 deaths. For instance, in the US, the risk of developing ovarian cancer stands at 1 in 70 women.[1] Especially in Indonesia, ovarian cancer ranks third in terms of cancer prevalence among women. This number is projected to increase significantly, with ovarian cancer accounting for 64.5% of deaths from cancer.[2,3] This number is predicted to increase significantly to 64.5% of deaths from ovarian cancer.[1]

Epithelial ovarian cancer (EOC) constitutes approximately 90% of all ovarian cancer cases across different races and ethnicities.[4] The most common and lethal type of EOC is High Grade Serous Carcinoma (HGSC).[5] In this case, the heterogeneity and rapid progression of ovarian cancer resulted in delayed and complex diagnosis cause poorer prognosis. As the stage increases, the 5-year-survival rate also deteriorates to below 30%.[6]

One of the studies regarding the detection of ovarian cancer that has been widely carried out is an increase in the number of platelets or thrombocytosis. This phenomenon can be seen in a variety of solid tumors, where the amount of elevated platelet may precede the diagnosis of malignancy. Malignant cells invade the physiological process of thrombopoiesis that promote the growth and survival of tumor, up to its metastasis. Cancer-associated thrombocytosis is correlated with reduced progression-free survival (PFS).[7,8]

Several studies have shown an association between pre-treatment thrombocytosis and the prognosis of ovarian cancer showing that pre-treatment thrombocytosis is an independent risk factor for the prognosis of patients with EOC or advanced ovarian cancer. In addition, pre-treatment thrombocytosis is also associated with

poor overall survival (OS) and PFS. In particular, pre-treatment thrombocytosis that increases tas the FIGO stage progresses has a very poor prognosis in stage III-IV patients compared to those in stage I-IV. Furthermore, a cohort study found that thrombocytosis is experienced in patients over 40 years of age, and is detected to be closely associated with carcinosarcoma and *clear cell* malignancies.[7-9]

Our hospital serves as the sole referral facility for patients suspected of cancer, including ovarian cancer, in West Borneo. Annually, the incidence of ovarian cancer is on the rise, presenting increasingly complex cases. This study was initiated in response to the necessity for a rapid, accessible, and cost-effective diagnostic and treatment approach for ovarian cancer.

METHODS

This cross sectional with retrospective study was conducted at dr. Soedarso Regional General Hospital Pontianak. We reviewed medical records of patients with suspected ovarian cancer at the Gynecology Oncology Polyclinic of dr. Soedarso RSUD hospital from 2017 to 2021, considering the number of cases and data limitations on hospital. The following criteria for our study were patients who have had their complete blood count checked before surgery, diagnosed with ovarian cancer after surgery, histopathological examination of the mass, and undergoing treatment at dr. Soedarso Regional General Hospital Pontianak. We excluded patient who were not examined or no complete blood results, multiple malignancies or infections from our study. We collect the data included age, parity, stadium, histopathology, CA-125, and platelet count. Meanwhile, this study was conducted for 3 months from January 2022 to March 2022. Of the 70 patients suspected of having ovarian cancer, 28 patients met the inclusion criteria set out in this study.

Thrombocytosis was an increase in the number of platelets exceeding 400,000 u/dL before treatment. The stages were classified according to the International Federation of Gynecology and Obstetrics System (FIGO) 2018. We divided the stages based on the severity, namely early stages (I and II) and advanced stages (III and IV). The division of histopathological type is based on WHO standard reference. After that, the Chi Square test was performed to find the relationship between thrombocytosis and the stage, as well as the type of histopathology. The test was carried out using SPSS *(Statistical Package for the Social Sciences)* 25. P values less than 0.05 were considered to be statistically significant. This study was approved by the ethical committee of dr. Soedarso Regional General Hospital Pontianak.

RESULTS

The baseline characteristics of the subjects are detailed in Table 1. We observed a predominance of subjects in advanced stages of FIGO (stages III and IV). High Grade Serous Carcinoma (HGSC) emerged as the most prevalent histopathological type, with 10 individuals (35.7%) diagnosed with this subtype. Moreover, the group of subjects exhibiting pre-operative thrombocytosis comprised 19 individuals (67.9%).

Table 1. Baseline Characteristics of Subjects

Variable	n (=28)	(%)
Age		
< 50	16	57.1
≥ 50	12	42.9
Parity		
0	5	17.9
1	16	57.1
>1	7	25.0
Stadium		
Early	7	25
Advanced	21	75
Histopathology		
High Grade Serous Carcinoma	10	35.7
Low Grade Serous Carcinoma	4	14,3
Mucinous	6	21.4
Clear cell	5	17.9
Endometrioid	3	10.7
CA-125 (U/mL)		
< 250	8	28.6
≥ 250	20	71.4
PLT (x103 u/dL)*		
≤400	9	32.1
>400	19	67.9

*PLT, platelet

Bivariate analysis was conducted on the variables of the preoperative platelet group using the Chi-Square test (refer to Table 2). The age variable showed a p-value of 1.000, while the parity variable resulted in a p-value of 0.258. Similarly, the stage variable showed a p-value of 0.646, and the CA-125 variable showed a p-value of 0.214. Notably, the histopathological variable demonstrated a significant association

with pre-operative thrombocytosis, with a p-value of 0.036 ($p<0.05$). The clinical implications of these findings are substantial, as higher histopathological findings correlate with increased pre-operative thrombocytosis. Moreover, pre-treatment thrombocytosis is indicative of disease progression, leading to higher FIGO stage advancements and ultimately indicating a very poor prognosis for patients with epithelial ovarian cancer.

Table 2. Result of Fisher Exact Test

Variable	Group		*P-Value*	Odds Ratio (95% CI)
	PLT >400 x 10^3 u/dL (n=19)	PLT ≤400 x 10^3 u/dL (n=9)		
Age				
< 50	11	5	1.000	0.909 (0.184-4.500)
≥ 50	8	4		
Parity				
0	5	0	0.258	
1	10	6		
>1	4	3		
Stages				
Early	3	4	0.646	1.875 (0.319-11.021)
Advanced	6	15		
Histopathology				
High Grade Serous Carcinoma	10	0	0.036	
Low Grade Serous Carcinoma	2	2		
Mucinous	3	3		
CC	3	2		
Endometrioid	1	2		
CA-125 (U/mL)				
< 250	7	1	0.214	0.214 (0.022-2.091)
≥ 250	12	8		

DISCUSSION

This study showed that subjects with pre-operative thrombocytosis were patients with advanced stages and types of HGSC. Bivariate analysis indicated that while the stages did not reach statistical significance ($p>0.05$), the histopathological test did ($p<0.05$). In addition, the results of this study did not show that preoperative thrombocytosis was correlated with other variables such as age, parity and CA-125 ($p>0.05$). Previous studies found same result.[10] Two studies showed that HGSC is the most common type, and its association with preoperative thrombocytosis exacerbates the disease and influences treatment outcomes.[8,11] However, a review of the literature studied from Ye et al stated that very few studies on the histopathological type of epithelial ovarian cancer with preoperative thrombocytosis were carried out, especially in the lethal type of HGSC.[7]

The results of this study indicate that the age group most affected by ovarian cancer is <50 years old. A study showed that age group is a predisposing factor in the growth of ovarian cancer. It is argued that age is associated with an increased number of ovulatory cycles, which are influenced by factors such as early menarche and late menopause. This is because the more the number of ovulation cycles, the more the process of cell mitosis that causes the inflammatory process due to the ovulation cycle. Therefore, it predisposes to the development of neoplastic cells.[12] Epithelial ovarian cancer (EOC) is considered a postmenopausal disease. Accordingly, previous studies have examined mean ages ranging from 50 to 79 years. However, age is not an independent prognostic factor.[13] The results of the research at Sanglah Hospital Denpasar, Dr. Cipto Mangunkusumo Hospital, and dr. Sardjito Hospital found an increase in the incidence of ovarian cancer as one gets older, with a peak incidence at the age of 41-50 years. However, the incidence decreases again at thereafter age. This is because the ethnic of Asian descent has a tendency to suffer from ovarian cancer at a younger age.[14,15]

The results in this study showed that parity presents the largest percentage of ovarian cancer cases. A study at RSUD H. Abdul Moeloek Bandar

Lampung showed the same results as this study.[16] Likewise, cohort studies in Europe and Sweden suggest that parity is not associated with survival in epithelial ovarian cancer (EOC).[17,18]

Advanced stages such as stages III and IV dominate in this study compared to the early stages, which is stage I. Some research at Sanglah Hospital Denpasar, H Adam Malik Hospital Medan, dr. Sardjito Hospital and Wahidin Sudirohusodo Hospital showed the same results, where stage III was the most common.[14,15,19,20] Correspondingly, conducted a study to examine the clinicopathological patterns and outcomes in patients with epithelial ovarian cancer (EOC) over a 35-year period (1985-2015) and showed the same results that stage III continues to be the most prevalent stage and shows a tendency to increase, although other stages also exhibit an upward trend.[5] Overall survival in patients with ovarian cancer tends to be low because 70% of patients are diagnosed first with an advanced stage, thus creating chemotherapy resistance.[21] In addition, high mortality is associated with epithelial and advanced ovarian cancer.[7]

More than half of the cases in this study had histopathological High Grade Serous Cancer (HGSC). In line with this study findings, a study Chang et al showed that the serous type was the most common around 43.3% and diagnosed at a more advanced stage about 82.8% of the total cases of the serous type.[22] A cohort study conducted from 1985 to 2015 showed that HGSC still ranks first as the most common histopathology, while mucinous decreased significantly over 35 years. Although, HGSC showed the lowest outcome at 5-year disease-specific survival (DSS), there was an increase in HGSC with an advanced stage resulting from a lack of awareness of the symptoms of ovarian cancer.[21]

CA-125 serum (cancer antigen 125) is one of the tumor markers used in initial screening of patients with a diagnosis of solid ovarian tumor which serves to monitor the outcome of chemotherapy in patients with epithelial ovarian cancer. Seventy-one percent (71%) of all study subjects had a CA-125 of 250 u/mL. CA-125 elevates in 50% of patients with stage I ovarian cancer and in 80-90% of patients with advanced ovarian cancer.[23] Hence, this finding is in line with this research.

Theoretically, preoperative thrombocytosis has a relationship with staging where the incidence of thrombocytosis increases as the FIGO stage progresses.[8] This theory may be related to the stage found in this study, where patients with pre-operative thrombocytosis were found to have stage III cases on average. Thus, the findings of this study confirmed the findings of studies stating that thrombocytosis was associated with metastases from ovarian cancer, and the incidence of thrombocytosis increases as the FIGO stage progresses.[7,8] Despite our study not demonstrating a direct relationship between stage and pre-operative thrombocytosis, the results of univariate analysis indicated a higher prevalence of advanced stages compared to early stages.

On the other hand, considering this research marks the first investigation conducted in West Kalimantan, it inevitably carries certain limitations. For instance, the small number of subjects or samples and the inadequate clinical data present limitations in this study. Therefore, future research focusing on the development of epithelial ovarian cancer should consider incorporating additional parameters that are easy to collect and obtain. Such studies could potentially be conducted even within primary health facilities, enabling early treatment initiation and thereby improving prognosis.

CONCLUSIONS

Pre-operative thrombocytosis have a relationship with histopathological type in epithelial ovarian cancer in Dr. Soedarso Regional General Hospital Pontianak.

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