

Research Article

The Role of Thrombocytosis as a Prognostic Factor for Epithelial Ovarian Cancer

Peran Trombositosis sebagai Faktor Prognostik pada Kanker Ovarium Jenis Epitelial

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Abstract

Objective: To determine whether thrombocytosis is a prognostic factor for epithelial ovarian cancer and its relationship with 3-year overall survival in epithelial ovarian cancer patients.

Methods: This study is a retrospective cohort study using medical record of patients with epithelial ovarian cancer registered in cancer registry of Oncology Division in Obstetrics and Gynecology Department, Dr. Cipto Mangunkusumo National General Hospital from January 2014 - July 2016. Data were collected when subjects were first until diseases outcomes identified in 3 years.

Result: Out of 220 subjects, 132 (60%) were patients with advanced stage epithelial ovarian cancer (stage II/III/IV). 94 (42.7%) subjects had thrombocytosis. Patients with advanced stage of disease had higher risk of having thrombocytosis than the ones with earlier stage ($p=0.005$; $OR=2.329$). Correlation between thrombocytosis and 3-year overall survival was known to be insignificant ($p=0.555$). There was shorter mean time survival between patients with thrombocytosis and the ones without but there was no significant difference in hazard ratio between the two groups ($p = 0.399$).

Conclusions: Thrombocytosis is not a prognostic factor in patients with epithelial ovarian cancer. There is also no significant difference of 3-year overall survival between patients with or without thrombocytosis.

Keywords: epithelial ovarian carcinoma, prognosis, thrombocytosis.

Abstrak

Tujuan: Membuktikan bahwa trombositosis sebagai faktor prognosis kesintasan pada pasien kanker ovarium jenis epitelial dan hubungannya terhadap kesintasan 3 tahun pasien kanker ovarium jenis epitelial.

Metode: Penelitian ini merupakan studi kohort retrospektif menggunakan data rekam medis pasien kanker ovarium epitelial yang terdaftar pada cancer registry Departemen Obstetri dan Ginekologi Divisi Onkologi Rumah Sakit Cipto Mangunkusumo pada tahun Januari 2014-Juli 2016. Pengamatan dilakukan saat subjek pertama kali didiagnosis akhir pengamatan selama 3 tahun.

Hasil: Didapatkan 220 subjek penelitian yang merupakan populasi terjangkau dan memenuhi kriteria inklusi dan eksklusi. Dari 220 subjek penelitian, 132 (60%) dari 220 subjek penelitian merupakan pasien dengan kanker ovarium stadium lanjut (Stadium II/III/IV). Trombositosis didapatkan pada 94 orang subjek penelitian (42,7%). Pasien dengan kanker stadium lanjut memiliki risiko trombositosis yang lebih tinggi dibandingkan subjek pada stadium awal ($p=0,005$; $OR=2,329$). Trombositosis secara statistik tidak bermakna pada kesintasan 3 tahun ($p=0,555$). Terdapat mean time survival yang lebih rendah pada pasien dengan trombositosis tetapi tidak ada perbedaan hazard ratio yang bermakna antara subjek dengan atau tanpa trombositosis ($p=0,399$).

Kesimpulan: Trombositosis bukan merupakan faktor prognostik pada pasien kanker ovarium jenis epitelial dan tidak terdapat hubungan antara trombositosis dan 3 tahun pada pasien dengan kanker ovarium jenis epitelial.

Kata kunci: karsinoma ovarium epitelial, prognosis, trombositosis.

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INTRODUCTION

Ovarian cancer is one of the most common cancers suffered by women along with breast, cervical, lung and rectal cancers. Epithelial ovarian cancer is the most deadly gynecological malignancy, representing 21,980 new cases in 2014 in the United States and about 14,270 (64.9%) of which outcome were death.¹ Only 30% of ovarian cancer patients can be diagnosed at an early stage, while the rest are already in an advanced stage.²

Cancer is a pathological condition that can be associated with thrombocytosis. This particular condition could be caused by the release of cytokines from several malignancies. Studies have shown that thrombocytosis in epithelial ovarian cancer is associated with increased levels of IL-6 in serum which will ultimately stimulate thrombopoiesis, therefore increasing thrombocyte production.³ Platelets would influence natural evolution of cancer through several mechanisms, namely protection against tumor cells and simultaneously produce several Growth Factors (GF) and enzymes such as lysophosphatidic acid, Metalloproteinase Matrix (MMP), thymidine phosphorylase, and vascular endothelial growth factor (VEGF) which play a role in angiogenesis, invasion and metastasis of tumor cells.^{4,5}

Thrombocytosis is associated with increased chance of recurrence for various cancer, including ovarian cancer (HR: 2.37; 95%CI: 1.82, 3.09).⁶ Previous researched have also studied that there is a linear relationship between thrombocytosis, stage of cancer, and decreased survival in patients with ovarian cancer.⁷ Growth factors and cytokines examination, while proven to be effective in determining the prognosis of cancer patients, remains to be costly for many countries, including Indonesia. Meanwhile, platelet examination is a routine blood test performed on patients, easy to do and relatively low cost compared to examination of growth factors and cytokines such as VEGF, PDGF and others.

This study aims to determine the relationship between thrombocytosis and 3-year survival of patients with epithelial ovarian cancer.

METHODS

An retrospective study was performed in National General Hospital Dr. Cipto Mangunkusumo on January 2014 to July 2019.

The study population were all epithelial ovarian cancer patients diagnosed between January 2014 and July 2016 and have completed appropriate treatment according to the procedure set. Patients with suspected sepsis, having another malignancy, or having incomplete medical record were excluded in this study. Consecutive sampling method was done in this study. Patients were then divided into thrombocytosis and non-thrombocytosis group. Thrombocytosis was defined as having thrombocyte in serum of more than 400.000 unit / dL. Baseline characteristics were analyzed and compared. Bivariate analysis between subjects' characteristics and thrombocytosis was done. Survival analysis using Kaplan-Meier was done to all subjects and overall survival between study groups were compared. Ethical clearance was issued from health research and ethical committee in Faculty of Medicine, Universitas Indonesia.

RESULTS

A total of 220 ovarian cancer patients had completed treatment in Dr. Cipto Mangunkusumo National General Hospital, therefore included in this study. Among those 220 subjects, 132 (60%) of whom were diagnosed with advanced ovarian cancer (stage II-IV), 94 (42.7%) of whom had thrombocytosis, 215 (97.7%) of whom had elevated CA-125 level, and 15 (6,8%) of whom died during the follow up period. Baseline characteristics of subjects can be found on Table 1.

Table 1. Baseline Characteristics of Subjects

Variables	Category	n	%
Age	≤ 50 years	97	44.1
	> 50 years	123	55.9
Thrombocytes	< 400.000 /dl	126	57.3
	≥ 400.000/dl	94	42.7
Staging	Early stage	88	40
	Advanced stage	132	60
	Stage II	35	15.9
	Stage III	77	35
Histopathology	Stage IV	20	9.1
	Serous	106	48.2
	Mucinous	42	19.1
	Endometrioid	23	10.5
	Clear Cell	47	21,4
Ascites	Transitional	2	0.9
	Not found	138	62.7
CA-125	Found	82	37.3
	Not found	138	62.7
CA-125	< 35 IU/L	5	2.3
	≥ 35 IU/L	215	97.7
Tumor Residue	< 1cm	131	59.5
	≥ 1cm	89	40.5
3-years survival	Positive	205	93.2
	Negative	15	6.8

In order to determine the involvement of other variables in determining thrombocytosis level in ovarian cancer patients, bivariate analysis between groups was done. Result of bivariate analysis in this study can be found in Table 2.

Table 1. Baseline Characteristics of Subjects

Variable	Study Groups		P-value	RR	CI 95%
	Thrombocytosis (N = 29)	Non-Thrombocytosis (N = 61)			
Age (y.o)			0.013	0.66	0.49-0.90
> 50	43 (19.5)	80 (36,4)			
< 50	51 (23.2)	46 (20.9)			
Ascites			< 0.001	1.86	1.38-2.50
Yes	50 (22.7)	32 (14.5)			
No	44 (20)	90 (42.7)			
CA-125			0.396	2.16	0.37-12.57
> 35 IU/L	93 (42.3)	122 (55.5)			
< 35 IU/L	1 (0.5)	4 (1.8)			
Stage			0.005	1.65	1.16-2.36
Advanced	67 (30.5)	65 (29.5)			
Early	27 (12.3)	61 (27.7)			
Residue (cm)			0.884	0.96	0.70-1.31
> 1	37 (16.8)	52 (23.6)			
< 1	57 (25.9)	74 (33.6)			

In order to compare overall survival rate of patients with and without thrombocytosis, survival analysis using Kaplan-Meier was done in this study. The Kaplan-Meier graph for this study can be found on figure 1.

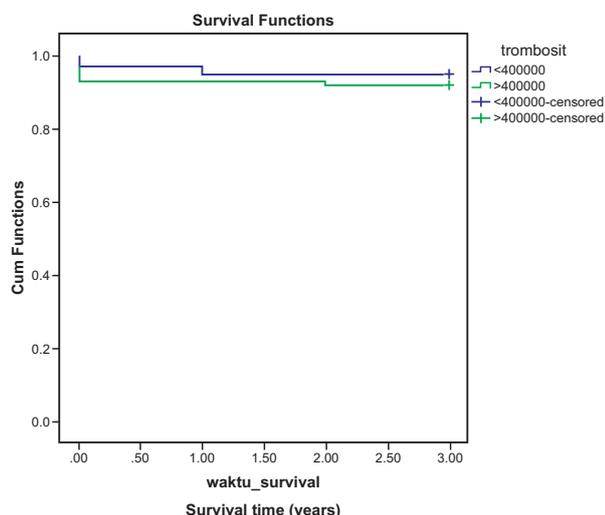


Figure 1. Kaplan-Meier Graph between Study Groups

In order to compare overall survival between groups, cox-regression analysis was done. It was found that there were no significant difference of survival time between study groups. (p = 0,555). The result of cox-regression analysis can be found on Table 3.

Table 3. Cox-regression Analysis of Study Groups

Variables	HR	P-value	95 % CI
Trombocyte level <400.000 /dl	1.548	0.399	0.561-4.269
≥ 400.000/dl			

DISCUSSION

In this study, it was found that patients with advanced cancer had a higher risk for thrombocytosis (p = 0.005; OR = 2.329). These results are similar to previous studies such as studies.³ In the mouse model, demonstrated an increase in hepatic thrombopoietin in response to excess tumor-derived interleukin-6 (IL-6) at higher tumor grading or advanced disease stage which then forms a positive feedback loop and promotes further tumor growth.³

Furthermore, thrombocytosis is known to have a relationship to overall survival (OS). In this study, researchers found that the presence or absence of thrombocytosis was not statistically significant in 3-years survival (p = 0.555). Further survival analysis showed a lower mean survival rate between the groups with thrombocytosis of 2.766 years compared to the group without thrombocytosis of 2.857 years. However, hazard analysis showed that thrombocytosis was not statistically significant to 3-years survival (p =

0.399). That thrombocytosis was not a significant prognostic factor in ovarian cancer patients.⁸ The results found in the study showed that thrombocytosis had a stronger correlation with other patient characteristics such as ascites and other hematologic abnormalities, especially anemia.⁸ Suggested that thrombocytosis was not a significant prognostic factor in patients with advanced stages. However, if the stage is stratified by early and advanced stages, thrombocytosis can be a significant prognostic factor in early stage patients.⁶

Differences in therapy given to patients with epithelial ovarian cancer in Indonesia can affect the prognosis and course of epithelial ovarian cancer, along with other influencing factors such as gene expression, chemotherapy response, and postoperative factors. Shown that different types of therapy given ($p = 0.011$), together with the stage of the disease, were significant prognostic factors for patient survival.⁹ Although the difference in therapy is hypothesized to have an influence on overall survival, there are not many other studies that have discussed the difference in therapy for survival of patients with epithelial ovarian cancer, so further research is still needed.

CONCLUSION

Thrombocytosis was not a prognostic factor of epithelial ovarian cancer patients' survival. There were no significant difference of survival between epithelial ovarian cancer patients with and without thrombocytosis.

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