Research Article

Preoperative Platelet-Lymphocyte Ratio as a Prognostic Factor of Epithelial Ovarian Cancer

Rasio Trombosit-Limfosit Pra Operasi sebagai Faktor Prognostik Epitel Kanker ovarium

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Abstract

Objective: To determine whether platelet-lymphocyte ratio can be a prognostic factor for epithelial ovarian cancer.

Methods: This study was a retrospective cohort with analytical design, conducted in the Department of Obstetrics and Gynecology of Prof. Dr. R.D. Kandou Manado General Hospital from January – November 2020. The subjects were all patients with epithelial ovarian cancer who met the inclusion and exclusion criteria. Data analysis was conducted with Chi-square test.

Results: 35 subjects were included in this study. Most subjects were 40-50 years and had a platelet-lymphocyte ratio of above 200. The mean platelet-lymphocyte ratio of the subjects with epithelial ovarian cancer was 244.663±130.0234. Chi-square test showed a significant association between platelet-lymphocyte ratio and the ovarian cancer relapse ($\chi2 = 14.464$ $p = 0.000$) with RR=4.0

Conclusion: There was a significant difference between platelet-lymphocyte ratio and the ovarian cancer relapse.

Keywords: epithelial ovarian cancer, inflammatory marker, platelet-lymphocyte ratio, prognosis.

Abstrak

Tujuan: Untuk mengetahui apakah nilai rasio platelet limfosit dapat menjadi faktor prognostik kanker ovarium epitel.

Metode: Penelitian ini merupakan kohort retrospektif dengan desain analitik di Departemen Obstetri dan Ginekologi RSUP Prof Dr. R.D. Kandou Manado dari Januari – November 2020. Subyek penelitian adalah seluruh pasien dengan kanker ovarium epitel yang memenuhi kriteria inklusi dan eksklusi. Analisa data dilakukan dengan uji Chi-square.

Hasil: Sebanyak 35 pasien diikutsertakan dalam penelitian ini. Mayoritas subyek berusia 40-50 tahun dan mayoritas memiliki rasio platelet limfosit diatas 200. Rerata rasio platelet limfosit pada subyek dengan kanker ovarium adalah 244.663±130.0234. Uji Chi-square menunjukan bahwa terdapat hubungan bermakna antara rasio platelet limfosit dengan kekambuhan keganasan ovarium ($\chi2 = 14,464$ $p = 0,000$) dengan RR=4.0

Kesimpulan: Terdapat hubungan bermakna antara rasio platelet limfosit dengan kekambuhan keganasan ovarium.

Kata kunci: kanker ovarium epitel, penanda inflamasi , prognosis, rasio platelet limfosit.

INTRODUCTION

Epithelial ovarian cancer accounts for 3% of all women cancers worldwide, and ranks third among the most common gynecologic cancers worldwide.[1] Primary cytoreductive surgery, followed by adjuvant chemotherapy, is still the gold standard of epithelial ovarian cancer.[2] As an advances and develompment of surgical and chemotherapy techniques, but the prognosis is still poor with a 40% 5-year survival rate. It is due to late stage of detection.[3]

The understanding of biomolecular properties could predict the patient outcome, many prognostic factors have been investigated especially regarding angiogenesis. Recently, several factors in angiogenesis of epithelial ovarian cancer are inflammatory markers or blood cells, have been studied. An increase in absolute platelet and lymphocyte counts or the platelet-lymphocyte ratio (PLR) has been reported and investigated as a prognostic factor in epithelial ovarian cancer. Furthermore, poor prognosis is found on elevated inflammatory markers in epithelial ovarian cancer patients.[4,5]

Several studies stated that an increased of PLR is associated with poor clinical and pathological features of cancer.[4,5] In epithelial ovarian cancer, preoperative thrombocytosis was associated with advanced or inoperable stages.[6] Several studies used PLR for a study of various type of cancer, namely colorectal, gastric, pancreatic, lung and epithelial ovarian cancers, to improve the prognostic function of platelets.[7] The limited study on PLR on epithelial ovarian cancer which limits its role as a prognostic factor, whereas another parameter, namely neutrophil-lymphocyte ratio, had been related with it.[4,5] Meta-analysis in 2014 from various types of cancer, shown that PLR was associated with advanced disease and poor survival from two studies on epithelial ovarian cancer.[4,5,7]

Due to this lack of study in Manado, so this study was done to evaluate the relationship of platelet-lymphocyte ratio as a prognostic factor of epithelial ovarian cancer on disease free survival (DFS), especially at Prof. DR. R. D. Kandou Central General Hospital, Manado.

METHODS

This study was a retrospective cohort study of epithelial ovarian cancer women confirmed by histopathology, conducted at the Department of Obstetrics and Gynecology Prof. DR. R. D. Kandou Central General Hospital, from January to November 2020. The sample was collected from medical record. This study was accepted by ethical clearance of Prof. DR. R. D. Kandou Central General Hospital, Manado.

All epithelial ovarian cancer women confirmed by histopatological examination, without any other patologic disease at the same time, without any disease which influence the platelet-lymphocyte ratio significantly (heart valve, autoimmune, blood abnormality disease), with a complete preoperative full blood count preoperative and operation report, and done a treatment at oncology department Prof. DR. R. D. Kandou Central General Hospital for one year, were met the inclusion criteria. Patients willing to participate in this study were asked to sign an informed consent. The exclusion criteria were unfollowed patient in the study period, uncomplete medical record, died due to Covid-19, and not willing to participate in the study. The number of participants were all of the epithelial ovarian cancer medical record at 2020 at Prof. DR. R. D. Kandou Central General Hospital, Manado.

The dependent variable was disease free survival (DFS) of epithelial ovarian cancer. The DFS was the length of survival without a signs or symptoms of the disease after a complete of primary treatment in one year, categorized by relapse and not relapse. The independent variables was platelet-lymphocyte ratio. The platelet-lymphocyte ratio was an absolute platelet count divided by absolute lymphocyte count, and the ratio was grouped by <200 and >200.

Data of platelet-lymphocyte ratio obtained and were collected, processed and analyzed using SPSS software 23rd version. The relationship of platelet-lymphocyte ratio and prognostic factor of DFS was assessed using chi-square test. The survival rate of ovarian cancer based on platelet-lymphocyte ratio was using risk estimation. The significance was used $p < 0.05$.

RESULTS

This study was conducted on 35 women with an epithelial ovarian cancer who met the inclusion and exclusion criteria and signed an informed consent for this study. The characteristics of the study subjects were shown in Table 1.

Table 1. Characteristics of Study Subjects

Characteristic	N	%
Age (years)		
< 40	7	20
40 – 50	15	42.9
> 50		37.1
Platelet-to-Lymphocyte Ratio (PLR)	13	
< 200	13	37.1
> 200	22	62.9
Menopausal Status		
Yes	14	40
No	21	60

Ovarian cancer incidence was more likely found on age of 40-50 years old (42.9%), then 50 years old (37.1%). The mean age of ovarian cancer was 47.57 years old. The platelet-lymphocyte ratio more than 200 was found on 21 ovarian cancer women (60.0%) than 14 (40.0%) women less than 200. The menopausal status from 35 subjects shown that 40% was menopause and the rest was not.

Table 2. The Relationship of Platelet-Lymphocyte Ratio Prognostic Factor and Disease-Free Survival

	Relapse		χ2*	RR	*P-value*
	Yes	No			
Platelet-to-Lymphocyte Ratio (PLR)			14.464	4.0	0.000
≥200 (n=21)	18	3			
< 200 (n=14)	3	11			

*using chi-square

In 21 epithelial ovarian cancer women with a PLR ≥200, 18 women had a relapse. In epithelial ovarian cancer women with PLR <200, 3 women had a relapse and 11 women did not. The chi-square test showed that there was a significant relationship between PLR and ovarian cancer relapse ($χ2$ = 14,464 p = 0.000) with RR=4.0.

Table 3 showed a distribution of PLR in ovarian cancer. The mean PLR in ovarian cancer women in this study was 244.663±130.0234.

Table 3. Mean Distribution of Platelet-to-Lymphocyte Ratio in Ovarian Cancer

	Ovarian Cancer (n=35)
Platelet-to-Lymphocyte Ratio (PLR)	
Mean	244.663
Median	223.655
Std Deviation	130.0234
Minimum	73.23
Maximum	812.08

DISCUSSION

The study was conducted on women with epithelial ovarian cancer. The age of 40-50 years old (42.9%) were the most common, followed by over 50 years old (37.1%). The mean age was 47.57 years old.

Epithelial ovarian cancer increased at the age of 40-49 years, then leveled off at the age of 50-59 years and decreased above the age of 60 years.[8] Based on data from Cancer Research UK, the average age of Caucasian women diagnosed with ovarian cancer is 63 years. Shen et al., in China reported that the mean age of epithelial ovarian cancer was 53 years (range, 17-79 years old), which is 10 years earlier than Caucasians.[9]

The PLR >200 was found in 22 ovarian cancer women (62.9%) and <200 was found in 13 women (37.1%) from this study. The PLR can be used as a predictive factor in various types of cancer. It plays an important role in the pathogenesis of the systemic inflammatory response and also associated with the prognosis of cancer.[10] Platelet counts increase due to the release of inflammatory mediators which stimulate megakaryocytes to produce more platelets. A PLR >200 has a significant association with a poor survival in advanced-stage cancer.[4] The advantage of using this ratio was affordable and easy to examine.[10]

From the 35 women, 40% were menopause, in this study. The incidence of epithelial ovarian carcinoma increases after menopause. Several epidemiological studies report that 30% of ovarian neoplasms occurring in postmenopausal patients are malignant, and only 7% of malignant ovarian neoplasms occurring before menopause.[8]

Two main theories have been proposed to explain the association between epithelial ovarian cancer risk and menopause, namely the persistent ovulation hypothesis and the gonadotropin stimulation theory. During the reproductive phase, the epithelial surface of the ovary will be injured due to the physiological process of ovulation. The wound will occur continuously, and the cell proliferation will heal the ovarian epithelium during the post-ovulatory phase. However, the mutation of proliferation leads to the formation of tumors. There is an increase in gonadotropin levels due to reduced ovarian follicles. Which causes an inflammatory response in the ovaries and will lead to tumor formation on the epithelial surface of ovarian cells.[8]

In 21 epithelial ovarian cancer women with a PLR >200, 18 women had a relapse. The epithelial

ovarian cancer women with a PLR <200 shown that 3 women had a relapse and 11 women did not. The chi-square test showed that there was a significant relationship between PLR and Ovarian Cancer Relapse (χ2 = 14.464 p = 0.000) with RR=4.0. The results of this study indicate a relationship between PLR with the relapse of ovarian cancer.

Tumor cells and the immune system interact in a complex manner. The immune system inhibits tumorigenesis, but promote inflammation through angiogenesis and immune cell evasion.[11] The tumor microenvironment activity is characterized by the presence of inflammatory markers such as platelets, lymphocytes and neutrophils.[12] Inflammation is crucial for tumor progression.[13] Leukocytes and platelets are secreted in large amounts due to inflammatory mediators such as cytokines and chemokines. Elevated PLR, NLR, and CRP are a sign of an increase inflammation due to the tumor itself or the host response.[14]

Inflammation plays a role in carcinogenesis and cancer progression. It contributes to the cancer capability by maintaining proliferation, angiogenesis, activation of the epithelial-to-mesenchymal transition, invasion, metastasis, and inhibitor of cancer cells death.[15] It is required in both early and late stages of tumorigenesis, as a result of a natural and adaptive immune response for eliminating cancer cells. However, cancer cells can escape from it and continue to grow. Chronic inflammation is a developmental risk factor. Several studies examine the relationship of cytokines and chemokines to cancer cells. In ovarian cancer, cytokines regulate the proliferation and survival of cancer cells.[11] Inflammation in ovarian cancer can be used as a predictor of its prognosis and response to therapy.[16]

The inflammatory response of neutrophil, lymphocytes, and platelets are an important factor in the tumorigenesis pathway. Platelet counts increase due to platelet-derived growth factor, platelet factor 4, transforming growth factor β, vascular endothelial growth factor and thrombospondin, for attachment of several cell types, including the surface epithelium of the ovary. In addition, its production in bone marrow stimulated by cytokines such as interleukin 6, TNF-α, and growth factors influenced by cancer cells, causing thrombocytosis.[17] Thrombocytosis in cancer is associated with poor survival.[18]

Platelets recruited by tumor cells can be used by cancer cells as a catalyst for the acceleration of tumor growth, angiogenesis, and metastasis processes. When the tumor volume exceeds a certain size (>1-2mm^3), the tumor begins to produce a new vascularization (angiogenesis) through the surrounding blood vessels, as a source of nutrients and oxygen for the tumor cells for survival and growth. Pro-angiogenic factors facilitate the process of angiogenesis by increasing vascular growth, vasodilatation, and increasing blood supply, which in turn accelerates tumor growth and metastasis.[19]

An increase in platelet count and a high PLR are indicators of poor prognosis in a several types of cancer.[12,20] Ovarian cancer women undergone a surgery, the PLR >300 had a poorer prognosis.[21] A meta-analysis showed that a high PLR before treatment had an overall survival and progression-free survival shorter. Patients with ovarian cancer had a higher PLR than benign ovarian masses.[22]

Previous clinical studies reported that an increase of NLR, PLR, neutrophil count, or platelet count was associated with poor clinical characteristics such as a high risk of relapse, aggressive tumor biology, and higher tumor progression in various types of cancer. A high PLR and CRP were associated with lower overall survival and DFS. The advantage of using inflammatory markers in ovarian cancer is easily obtained, inexpensive, and non-invasive using a laboratory data.[14]

The meta-analysis in 1250 ovarian cancer women reported that a higher PLR was strongly associated with lower overall survival, with a hazard ratio of 1.63. In addition, a high PLR has a lower progression free survival than a low PLR.[22] The PLR was a superior prognostic factor over the neutrophil ratio or other markers of the inflammatory response in the epithelial ovarian cancer women.[23]

However, the mechanism underlying the increase of PLR on ovarian cancer is not fully understood. It is associated by an increase of systemic inflammatory response. The lymphocyte count decreased due to the antitumor immune response, as a favorable condition for the tumor microenvironment.[22]

A reduced number of lymphocytes is an indicator of a reduced immune response, and correlated with a higher mortality in ovarian cancer than the control group or benign disease.[22] Lymphocytes kill cancer cells, inhibit the proliferation and migration of tumor cells.[18]

A low absolute lymphocyte count reduces the efficacy of therapy and the prognosis of ovarian cancer originating from epithelial, connective, or lymphoid tissue.[15] A high lymphocyte count and type 1 lymphocyte infiltration in tumor tissue are associated with a better prognosis in ovarian, colon, lung, and breast cancer. A low lymphocyte levels causes a weaken immune response to tumors.[22]

The other factors affect the prognosis of ovarian cancer are cancer pathology, molecular genetic factors, and cancer stage. Ovarian tumors are a heterogeneous, with a varied outcome. The heterogeneity of these tumors is characterized by its biological and molecular profile. In addition, the platelet counts can be influence not only by cancer cells but also the occurrence of acute or chronic infections or other inflammatory diseases and smoking habits.[19,24,25]

CONCLUSION

There was a significant relationship between platelet-lymphocyte ratio with a relapse of ovarian cancer, higher with ratio platelet-lymphocyte more than 200. There should be a further cohort study with a more sample and different prognostic parameter.

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