Research Article

High Random Blood Glucose Level before Surgery as a Risk Factor for Recurrent Event in Epithelial Ovarian Carcinoma

Kadar Gula Darah Sewaktu yang Tinggi sebelum Operasi sebagai Faktor Risiko Kejadian Residif pada Pasien Karsinoma Ovarium Tipe Epitelia

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Abstract

Objective: To investigate the high random blood glucose level as a risk factor for recurrent disease in EOC patient at Kariadi General Hospital.

Methods: Sixty six patients diagnosed as EOC in Kariadi General Hospital were divided into 2 groups: 30 patients with recurrent disease and 30 patients without recurrent disease after completing chemotherapy cycles. We analysed correlation between age of diagnosis, tumour mass location, Ca-125 level, histological subtype and random blood glucose level before surgery with recurrent disease.

Results: There is no significantly difference in age of diagnosis, tumour mass location and histological subtypes between two groups. However, recurrent EOC patients have higher Ca-125 level significantly than non-recurrent patients (327.8±250.5 vs 183.5±212.1 respectively; p = 0,01). Mean of random blood glucose level of recurrent patients is also higher than non-recurrent patients significantly (150.5 ±79 vs 110.8 ± 31.1 respectively; p = 0.006). Patient with random blood glucose level > 110 mg/dl have 3 times more likely to develop recurrence in EOC patient significantly with 95% CI.

Conclusion: The mean of random blood glucose level in recurrent EOC patients is significantly higher than non-recurrent EOC patients. Patient with random blood glucose level > 110 mg/dl have 3 times more likely to develop recurrence in EOC patient.

Keywords: cepithelial ovarian cancer, random blood glucose level, recurrent.

Abstrak

Tujuan: *Untuk membuktikan kadar glukosa darah sewaktu yang tinggi sebagai faktor risiko kejadian residif pada pasien karsinoma ovarium epitelial di RSUP dr. Kariadi.*

Metode: *Enam puluh pasien yang telah didiagnosis sebagai karsinoma ovarium epitelial di RSUP dr. Kariadi dibagi menjadi 2 kelompok: 30 pasien pada kelompok residif dan 30 pasien pada kelompok non-residif berdasarkan evaluasi setelah menyelesaikan siklus kemoterapi. Data yang dianalisis meliputi usia saat terdiagnosis, lokasi tumor, kadar Ca-125, subtipe histologi, kadar gula darah sewaktu (GDS) sebelum operasi dan hubungannya dengan kejadian residif.*

Hasil: *PTidak terdapat perbedaan yang bermakna dalam usia saat diagnosis, lokasi tumor dan subtipe histologis diantara kedua kelompok. Namun, kelompok pasien residif memiliki kadar Ca-125 yang lebih tinggi secara bermakna dibandingkan kelompok pasien non-residif (327,8 ± 250,5 vs 183,5 ± 212,1; p = 0,01). Rerata kadar GDS pada kelompok pasien residif juga lebih tinggi secara bermakna daripada kelompok non-residif (150,5 ± 79 vs 110,8 ± 31,1; p = 0,006). Pasien dengan kadar GDS > 110 mg/dl memiliki risiko 3 kali lipat untuk menjadi residif secara bermakna dengan tingkat kepercayaan 95%.*

Kesimpulan: *Rerata kadar GDS pada kelompok pasien residif lebih tinggi secara bermakna dibanding kelompok pasien non-residif. Pasien dengan kadar GDS > 110 mg/dl memiliki risiko 3 kali lipat untuk menjadi residif.*

Kata kunci: *kadar gula darah sewaktu, karsinoma ovarium epitelial, residif.*

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INTRODUCTION

Epithelial ovarian cancer is the fifth most common cause of death in women in America, and is the leading cause of death in gynecological malignancies.[1,2] In Indonesia, ovarian cancer ranks fourth of all malignancies. Epithelial ovarian cancer accounts for more than 90% of all malignancies in the ovary. About 70% of cases of ovarian cancer were diagnosed at an advanced stage, the 5-year survival rate is below 30%.[3-5] Recent clinical studies show that plasma glucose levels in cancer patients can be important prognostic indicators related to reduced survival life and recurrence in patients. In addition, hyperglycemia is thought to have an important role in triggering residual events in epithelial ovarian cancer through glucose transporter protein 1 (GLUT 1).[6,7] The objective of this study is to prove high blood glucose levels before surgery as a risk factors for recurrent events in epithelial ovarian carcinoma patients in Dr. Kariadi General Hospital.

METHODS

This is an observational study with case control research design. The sample of this study were 60 patients who had been diagnosed as epithelial ovarian carcinoma based on histopathological examination and hospitalized at Dr. Kariadi General Hospital Semarang, had undergone complete surgical staging or cytoreduction surgery, had completed the chemotherapy cycle and was willing to be the subject of research with informed consent. The sample will be divided into 2 groups, firstly the recurrent group which had recurrent disease based on the evaluation results after complete remission and secondly the non-recurrent group which had no recurrent disease based on the evaluation results were not found after remission. Data collection included patient age of diagnosis, tumor location, histological subtype, Ca-125 plasma level and random blood sugar level before surgery or treatment. The collected data will be analyzed by chi square test and Odds Ratio value were calculated for risk estimation.

RESULTS

In this study, we analysed 60 study subjects with 30 cases of recurrent epithelial ovarian carcinoma as a recurrent group and 30 cases of non-recurrent epithelial ovarian carcinoma as a non-recurrent group. Data of patient's characteristics in this study can be seen in table 1. In the recurrent group, the mean age of diagnosis patients was slightly higher than the non-recurrent group with a non-significant difference (50.8 ± 7.2 vs 49.3 ± 9.5 years). There were no differences in tumor location between the recurrent and non-recurrent groups where there were 23 unilateral cases (76.7%) and 7 bilateral cases (23.3%). The most histological subtypes of the recurrent group were endometrioid carcinoma types (33.3%), whereas in the most non- recurrent group were serous carcinoma types (40%), but there were no significant differences between the two groups. The mean level of Ca-125 in the recurrent group was significantly higher than in the non- recurrent group (327.8 ± 250.5 U / ml vs. 183.5 ± 212.1 U / ml).

Table 1. Characteristics of subjects

Characteristics		Group		*P-value*
		Control (N=30) Non Recurrent	**Case (N=30) Recurrent**	
Age (years old)		49.3 ± 9.5 Median: 47.5	50.8 ± 7.2 Median: 52	0.496[a]
Ca-125 Level (U/ml)		183.5 ± 212.1	327.8 ± 250.5	0.010[b]
Location	Unilateral	23 (76.7)	23 (76.7)	1.00[c]
	Bilateral	7 (23.3)	7 (23.3)	
Hitological	Serous Ca	12 (40.0)	7 (23.3)	
Subtype	Muscinous Ca	9 (30.0)	6 (20.0)	
	Endometrioid Ca	7 (23.3)	10 (33.3)	0.220[c]
	Clear Cell Ca	2 (6.7)	5 (16.7)	
	others	0 (0)	2 (6.7)	

The mean and median values of random blood glucose levels of recurrent epithelial ovarian carcinoma patients had significantly higher compared to random blood glucose levels of non-recurrent epithelial ovarian carcinoma (110.8 ± 31.1 vs. 150.5 ± 79).

Table 2. The Difference in Mean GDS Levels of Residual and non-Residual Ovarian Carcinoma Patients

	Control (N=30) Non Recurrent	Case (N=30) Recurrent	*P-value*
Random blood glucose levels (mg/dl)	110.8 ± 31.1	150.5 ±79	0.006**
Normality test	0.038*	0.001*	

When random blood glucose levels from both groups of patients were categorized into high and low random blood glucose levels with a cut-off value of 110 mg / dl, carcinoma patients with recurrent epithelial ovarian carcinoma with random blood glucose levels > 110 mg / dl were significantly more likely to have recurrent disease compared to patients who had random blood glucose levels <110 mg / dl. The OR value analysis of the relationship between random blood glucose levels and recurrent event in epithelial ovarian carcinoma patients is 3.00, which means patients with epithelial ovarian carcinoma who have random blood glucose levels more than 110 mg / dl have a 3.00-fold risk of being recurrent than those with random blood glucose levels less than 110 mg / dl. Level of significance shows p = 0.041 (p <0.05), so that at a 95% confidence level, OR values are considered significant or meaningful which means they can represent the entire population.

Table 3. Different Categories of GDS Levels in Patients with Residual and non-Residual Epithelial Type Ovarian Carcinoma

	Control (N=30) Recurrent	Case (N=30) Non Recurrent	OR	*P-value*
High Glucose Level (> 110 mg/dl)	20	12	3.000*	0.041*
Low Glucose Level (> 110 mg/dl)	10	18		

Based on the results of bivariate analysis, it appears that Ca-125 levels and high random blood glucose levels were significantly associated with recurrent events in epithelial ovarian carcinoma patients (p <0.05). High levels of random blood glucose are the most influential factor for the recurrent event, compared with the factor of Ca-125 levels, with a higher OR value. Patients with high levels of Ca-125 have a risk of being 1.003 times more likely to be recurrent than those with lower levels of Ca-125, whereas patients who have high levels of random blood glucose (more than 110 mg / dl) have a 3,445-fold risk of being recurrent than those with lower random blood glucose levels (less than 110 mg / dl).

Table 4. Results of Multivariate Analysis of Ca-125 Levels and GDS Levels with Residual Events in Epithelial Type Ovarian Carcinoma Patients

	P-value	OR	CI 95%	
			Lower	Upper
High Ca-125 Level	0.019	1.003	1.000	1.005
High Glucose Level	0.032	3.445	1.112	10.739

* = Uji *Logistic Regresion*

DISCUSSION

This study determined high random blood glucose levels as a risk factor for recurrent occurrence in patients with epithelial ovarian carcinoma, as well as other factors that influence it, which is age of diagnosis, location, levels of Ca-125 and histological subtypes. The age of diagnosis patients in both groups did not differ significantly (p> 0.05). This indicates that age does not affect the incidence of recurrent ovarian carcinoma in this study. In another study, it was found that the mean age of diagnosis patients with recurrent epithelial ovarian carcinoma was slightly higher than that of non-recurrent, with a median residual patient age: 61 years.8 These results are comparable to this study, where the median age of recurrent epithelial ovarian carcinoma patients is higher than the non-recurrent, with a median residual patient age: 52 years.

Similarly, the location of the tumor and the histological subtypes. In both groups, the location and histological examination were not

significantly different (p> 0.05). This indicates that the location of the tumor and histopathological subtype did not affect the incidence of recurrent ovarian carcinoma in this study. Another similar study showed that the most common histological subtype among those who experienced recurrent disease was clear cell carcinoma, whereas in this study it was found that the most common histological subtype in the recurrent group was endometrioid carcinoma.[8,9]

The results of the analysis of Ca-125 levels in both groups showed a significant difference. This shows that Ca-125 levels affect the incidence of recurrent ovarian carcinoma. This finding is consistent with other previous studies that concluded that in patients with recurrent ovarian cancer there was an increase in CA-125 levels. If CA-125 levels are above 35 U / mL, the clinician must have suspected recurrent event. An increase in CA-125 levels of 10 U / mL or an increase of 100% from the previous level is an accurate predictor of recurrent ovarian cancer. In another study, it was also stated that elevated serum CA-125 levels during follow-up can be used as a marker of recurrent event in epithelial ovarian carcinoma.[9,10]

Based on the analysis of the relationship between random blood glucose level and the incidence of recurrent epithelial ovarian carcinoma, we found that the mean random blood glucose levels in the recurrent epithelial ovarian carcinoma group were significantly higher than in the non-recurrent group. In addition, with a cut-off value of GDS 110 mg / dl, patients with random blood glucose levels > 110 mg / dl had a three-fold risk of developing recurrent event compared to patients with random blood glucose levels < 110 mg / dl. This shows that high level of random blood glucose influence and become a risk factor for recurrent event in patients with epithelial ovarian carcinoma. The results of this study are consistent with previous studies by Lambkin, et al where higher glucose levels were significantly associated with shorter survival times and patients with glucose levels of > 140 mg / dL had 2.48 times the risk of developing recurrent ovarian cancer. In addition to ovarian carcinoma patients, high blood glucose levels are also a risk factor for poor survival time and residual events in malignant cases in the head, neck, stomach and leukemia areas.[11-15]

Plasma glucose levels in cancer patients can be important prognostic indicators related to reduced survival and recurrence in patients. It is known that cancer cells have a significant increase in glycolysis compared to normal cells, and in general it has been shown that inside cancer cells has increased uptake and glucose metabolism is significant compared to normal cells. Hyperglycemia is thought to have an important role in triggering residual events in epithelial ovarian cancer through glucose transporter protein 1 (GLUT 1), the transmembrane protein responsible for glucose uptake. Increased expression of GLUT1 is associated with shorter survival times in ovarian cancer patients and predicts a shorter time for recurrence (DFI) in patients who achieve remission.[16-20]

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