Research Article

Clinical and Laboratory Predictors of Deep Vein Thrombosis in Ovarian Malignant Tumor

Prediktor Klinis dan Laboratorium dari Trombosis Vena Dalam pada Tumor Ganas Ovarium

Fitriyadi Kusuma, Christina Sitorus

Department of Obstetrics and Gynecology
Faculty of Medicine Universitas Indonesia/
Dr. Cipto Mangunkusumo Hospital
Jakarta

Abstract

Objective: To investigate the clinical and laboratory predictors of symptomatic deep vein thrombosis (DVT) in ovarian malignant tumor.

Methods: One hundred sixteen patients with suspected ovarian malignant tumor were recruited. Age, body mass index (BMI); D-dimer, fibrinogen, thrombocyte level, comorbid, tumor diameter, staging, distant metastasis, ascites, histopathology, length of surgery, blood loss and transfusion were recorded.

Results: Incidence of symptomatic DVT was 16.5% and 88.2% cases occurred before surgery. No case of symptomatic DVT during post-operative care was found. Predictors of DVT were distant metastasis (OR 28.99; 95% CI 3.83-219.52, BMI ≥ 22.7 kg/m^2 (OR 15.52, 95% CI 2.24-107.37), D-Dimer ≥ 1700 mg/ml (OR 13.30, 95% CI 2.40-73.84), advanced stage (OR 6.66; 95% CI 1.05-42.27), epithelial tumor (OR 6.5; 95% CI 0.34-125.75), tumor's diameter ≥ 18.25 cm (OR 2.36, 95% CI 0.48-11.54), and comorbidity (OR 2.49, 95% CI 0.53-11.66). Prediction score of DVT were score 3 for distant metastasis, BMI ≥ 22.7 kg/m^2, D-Dimer ≥ 1700 mg/ml, score 2 for advanced stage, score 1 for tumor diameter ≥ 18.25 cm, comorbid, epithelial tumor and score 0 for the absence of variables or its value less than the cut off. Total score ≥ 8 of 14 is the least score which has a good predictive value for DVT with AUC 0.92, 95% CI 0.86-0.92, probability 86.46%.

Conclusion: Distant metastasis and D-dimer are independently associated with the development of DVT in ovarian malignant tumor.

[Indones J Obstet Gynecol 2017; 5-3: 180-184]

Keywords: deep vein thrombosis, D-dimer, ovarian malignant, tumor predictor

Abstrak

***Tujuan**: Untuk mengetahui prediktor klinis dan laboratorium dari thrombosis vena dalam simptomatik pada tumor ganas ovarium.*

***Metode**: Seratus enam belas pasien yang diduga menderita tumor ganas ovarium direkrut ke dalam penelitian. Usia, indeks massa tubuh (IMT), kadar D-dimer, fibrinogen, trombosit, komorbid, karakteristik tumor (diameter, stadium, metastasis jauh, asites, histopatologi), lama pembedahan, jumlah perdarahan serta transfusi durante operasi di-dokumentasikan.*

***Hasil**: Insiden TVD simptomatik adalah 16,5% dan 88,2% kasus terjadi sebelum pembedahan. Tidak ditemukan kasus TVD selama perawatan pasca-operasi. Prediktor TVD adalah metastasis jauh (OR 28,99; 95% CI 3,83-219,52, IMT≥ 22,7 kg/m^2 (OR 15,52, 95% CI 2,24-107,37), D-dimer≥ 1700 mg/ml (OR 13,30, 95% CI 2,40-73,84), stadium lanjut (OR 6,66; 95% CI 1,05-42,27), tumor epithelial (OR 6,5; 95% CI 0,34-125,75), diameter tumor≥18,25 cm (OR 2,36, 95% CI 0,48-11,54), dan adanya komorbid (OR 2,49, 95% CI 0,53-11,66). Skor prediksi kejadian TVD adalah skor 3 untuk metastasis jauh, IMT ≥ 22,7 kg/m^2, kadar D-Dimer ≥ 1700 mg/ml, skor 2 untuk tumor stadium lanjut, skor 1 untuk diameter tumor ≥ 18,25 cm, adanya komorbid, tumor epitelial dan skor 0 jika tidak memiliki faktor prediktor atau nilai faktor prediktor kurang dari titik potong. Skor total ≥8 dari 14 adalah skor minimum yang masih memiliki nilai prediksi yang baik kejadian TVD dengan AUC 0,92, 95% CI 0,86-0,92 dan probabilitas 86,46%.*

***Kesimpulan**: Metastasis jauh dan D-dimer berkaitan secara independen dengan terjadinya DVT pada tumor ganas ovarium.*

[Maj Obstet Ginekol Indones 2017; 5-3: 180-184]

***Kata kunci**: D-dimer, prediktor, thrombosis vena dalam tumor ganas ovarium*

Correspondence: Christina Sitorus; achristina12@yahoo.com

INTRODUCTION

Patients who suffered from malignant ovarian tumor have high risks of developing thromboembolism. The incidence of deep vein thrombosis (DVT) malignant ovarian neoplasm varies from 5% to 29%.[1-5] Release of tissue and pro-coagulant factors by cancer cells may lead to coagulation activation and hyperviscosity[6] release of various cytokines by cancer cells could lead to endothelial injury. Several factors related to the treatment such as surgery and immobilization may cause venous stasis.[7,8] DVT has been associated with poor prognosis.[9] It is estimated that patients with DVT had a 2.2-fold increased risk in mortality compared to those without DVT. DVT is the source of pulmonary

embolism, a fatal condition that could lead to mortality.[10] Therefore, early detection of patients who are at high risk of DVT is crucial for proper prophylaxis.

METHODS

This was a prospective study of 116 subjects suspected with malignant ovarian tumor. The study was conducted at Dr. Cipto Mangunkusumo Hospital. The protocol of this research was approved by the Ethics Committee of Dr. Cipto Mangunkusumo Hospital. Pretreatment peripheral blood samples, D-dimer, fibrinogen levels were measured in all patients. Patients who had sign and symptoms of DVT underwent venous Duplex ultrasonography. The cut off level for each numerical variable as predictor of DVT was determined using RO analysis. The χ^2 test or Fisher Exact Test was used to evaluate the risk of DVT associated with each categorical variable. Multivariate logistic regression was performed to determine the strength of each variable as a predictor factor for DVT and create the prediction score of DVT in ovarian malignancy. A p-value less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS.

RESULT

Characteristics of the subjects

A total of 113 subjects were involved in this study. Thirteen patients were withdrawn (6 patients had benign ovarian tumor from histopathology and 7 patients had incomplete data. Characteristics of the subjects are shown in Table 1.

Incidence of deep vein thrombosis

Venous ultrasonography revealed DVT in 17 of 103 patients (16.5%) and 15 cases (88.2%) occurred before initial treatment for ovarian malignancy. No symptomatic DVT was observed during hospitalization with mean length of stay 8.8 days.

Table 1. Characteristic of the Subjects

Characteristics	TVD (+)	TVD (-)	Value p
Age (years)	50.35 ± 10.90	46.1 ± 12.05	0.250
BMI (kg/m^2)	23.31 ± 5.04	22.14 ± 3.80	0.278
Tumor's diameter	20.97 ± 9.28	17.47 ± 7.21	0.085
Length of surgery	4.5 ± 2.40	4.5 ± 1.75	0.998
Bleeding	1296 ± 1171	901 ± 1011	0.234
Transfusion	367.09 ± 450.604	279.81 ± 532.25	0.604
Thrombocyte (per mm^3)	342058.8 ± 125801.1	370732.6 ± 143790	0.446
D-Dimer (mg/ml)	3452.94 ± 3747.519	1172.74 ± 1847	0.025
Fibrinogen (mg/ml)			
Comorbid			
Yes	10 (58.82%)	36 (41.86%)	0.308
None	9 (52.94%)	50 (58.14%)	
Distant Metastasis			
Yes	8 (47.06%)	7 (8.14%)	0.0002
None	6 (35.3%)	79 (91.86%)	
Bilateral tumor			
Bilateral	7 (41.18%)	24 (27.91%)	0.566
Unilateral	11 (64.7%)	62 (72.09%)	
Ascites			
Yes	10 (0.58%)	38 (44.19%)	0.401
No	7 (41.18%)	48 (55.81%)	

Predictor factors and scoring of DVT

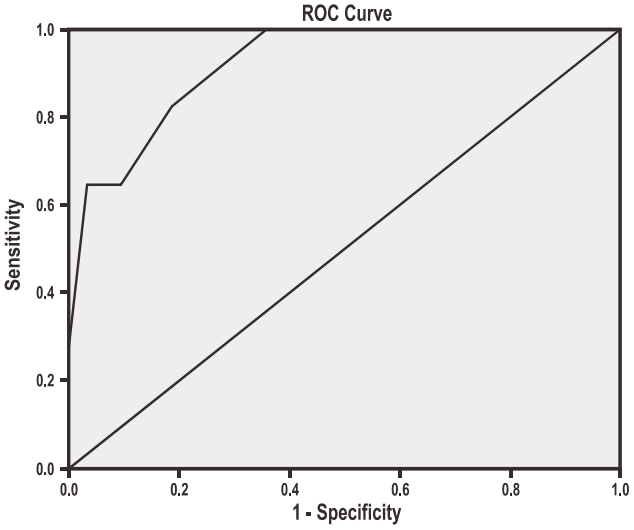
The cut off value for each numerical variable as a predictor of TVD was age ≥ 50 years, BMI ≥ 22.76 kg/m^2, tumor diameter ≥ 18.25 cm, thrombocyte count 326.500/mm^3, fibrinogen ≥ 399.7 mg/dl, D-dimer ≥ 1700 mg/ml. Through multivariate logistic regression with stepwise and backward selection, we generated the prediction model of DVT. The OR, CI and prediction value for each parameter of DVT were presented in Table 2. A total score ≥ 8 of 14 is the least score which still had a high prediction value of DVT with sensitivity of 64.7%, specificity of 90.7%, negative prediction value 92.86%, positive prediction value of 57.89%. This prognostic model had a good discrimination level with AUC 0.921 (95% CI 0.862-0.980) and good calibration with $p<0.05$ based on Hosmer and Lameshow analysis (Figure 1).

Table 2. The OR, CIs and Prediction Score of DVT in Ovarian Malignant Tumor

Variable	Adjusted OR	95% CI	Prediction Score
Distant Metastasis			
Yes	28.998	3.83-219.52	3
No			0
Body Mass Index			
≥ 22.76 kg/m^2	15.519	2.24-107.37	3
< 22.76 kg/m^2			0
D-dimer			
≥ 1700 mg/ml	13.305	2.39-73.84	3
< 1700 mg/ml			0
Stage of the tumor			
Advance stage (III and IV)	6,660	1.5-42.27	2
Early Stage (I and II)			0
Histopathology			
Epithelial tumor	6.500	0.34-125.75	1
Non epithelial			0
Tumor's diameter			
≥ 18.25 cm	2,359	0.48-11.54	1
< 18.25 cm			0
Presence of comorbidity			
Yes	2,495	0.53-11.66	1
None			0

Table 3. Sensitivity, Specificity, Positive and Negative Predictive Values at each Prediction Score of DVT. PPV, Positive predictive Value; NPV: Negative Predictive Value

Total score	Sensitivity (%)	Specificity (%)	PPV	NPV
1	100.0	2.3	16.83	100
2	100.0	5.8	17.35	100
3	100.0	19.8	19.77	100
4	100.0	31.4	22.37	100
5	100.0	45.3	26.56	100
6	100.0	64.0	35.42	100
7	82.4	81.4	46.67	95.89
8	64.7	90.7	57.89	92.86
9	64.7	96.5	78.57	93.25
10	41.2	98.8	87.5	89.47
11	29.4	100.0	100	87.75
12	11.8	100.0	100	85.15
13	5.9	100.0	100	85.15
14	0.0	100.0	100	84.16



Prediction model of DVT
AUC 0.92(CI 95%: 0.86-0.98)

Figure 1. Receiver Operator Curves for prediction of deep vein thrombosis

DISCUSSION

Ovarian malignancy is one of the tumors which have high incidence of symptomatic and asymptomatic DVT ranging from 5-35%. Our study found the incidence of symptomatic DVT of 16.5%. Factors related to cancer treatment such as surgery was shown to increase the risk of DVT by 2 to 5 fold, and most of DVT cases occurred within the first 2 week post-surgery.[11,12] In contrast with previous study, this study found that most of DVT cases (88.2%) occurred before initial treatment, and no DVT cases occurred during post-operative hospitalization with mean of length of stay of 8.8 days. Obstruction of the venous return of the lower extremities due to massive tumor within pelvic cavity, massive ascites leading to intravascular hypovolemic, massive cancer cells before any treatment which release massive tissue factor are the possible explanation for DVT occurrence before treatment.[4,13]

Numerous factors including advanced age[14-17], higher body mass index[3,15-17], presence of ascites[1-3,14], several specific histopathology subtypes[2,14], advanced tumor stage[3,15-18,] presence of metastasis[2,14], surgery[14], chemotherapy[1], and higher D-dimer and fibrinogen levels[4-5,12] were reported as predictors of DVT in malignant tumor. We found that prediction models derived from parameters including presence of distant metastasis, BMI, D-dimer level, tumor stage, tumor diameter, histology subtype and presence of comorbid was highly predictive of deep vein thrombosis in ovarian malignant tumor. Score 8 of 14 is the least score which still had a good prediction for DVT with an area under the receiver operator characteristics curve of 0.92. The application of prediction model may help to stratify individual risk of DVT which then can be used for selective prevention of DVT. Our study found that distant metastasis was the strongest predictor of DVT in ovarian malignant tumor, in accordance with previous study[2,14] followed by higher D-dimer level. Cut off the Dimer as predictor of DVT in our study was 1700 mg/ml with its area under curve of 0.76, sensitivity 79.2%, specificity 81.2%, NPV 42.86% and PPV 92.86%. Correlation of D-dimer level with DVT was extensively investigated and the cut off D-dimer as predictor for DVT found in our study was almost similar with cut off reported in previous study.[5,19] High D-dimer levels was reported associated with poor prognosis in cancer patients as it associated with more advanced stage and higher tendency for metastasis.[4-5,12,20] Higher BMI was another independent predictor of DVT in our study, which is in line with previous studies.[3,15-17] Advanced stage (stage III and IV) was another predictor of DVT in our study. Advanced stage was commonly associated with larger tumor size. As reported by previous studies, we found that larger tumor diameter[12] with cut off value of 18.25 cm caused a 2.8 fold increased risk of DVT.

Presence of other clinical disorders (comorbid) which influence any factor contributed in thrombus formation such as vascular injury, activate coagulation system or vascular stasis will increase the risk of DVT.[1,14] In our study, the presence of comorbidity increases the risk of DVT up to 1.77 fold. The most comorbidities found in our study were hypertension, diabetes mellitus, renal disease and cardiac disorder.

Our study has several limitations. Firstly, the evidence of DVT by Duplex ultrasonography was only confirmed in symptomatic patients therefore the incidence if DVT found in this case was only symptomatic DVT. Another weakness of our study is the small sample size. Further studies with larger sample sizes are required to be conducted in the future for a better understanding of the predictors of DVT in malignant ovarian tumors.

CONCLUSION

Distant metastasis and D-dimer are independently associated with the development of DVT in ovarian malignant tumor.

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