

# D-dimer level and Wells score in women undergone Lymphadenectomy in Gynecological Cancer to Assess Risk of Deep Venous Thrombosis

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## Abstract

**Background:** One of the most important prognostic indicators in cancer is the lymph node dissection. Lymphadenectomy considered as a risk factor for deep vein thrombosis in patients with gynecological malignancy who underwent surgery. D-dimer was used to detect deep vein thrombosis, thus, it's important to predict complications of post-operative Lymphadenectomy.

**Objective:** To predict the risk of deep venous thrombosis by used serum D-dimer and wells score after pelvic lymphadenectomy in gynecological cancer.

**Patients and method:** A cross sectional study conducted in Obstetrics and Gynecology/ ward in medical city, from 1<sup>st</sup>, January 2021 to 30<sup>th</sup>, Dec. 2021. A total number of 45 (22 endometrial, 12 ovarian and 11 cervical cancers).

**Results:** The mean±SD level of pre-operative D-dimer in patients with endometrial cancer was (423.2±123.9) while the mean±SD post-operative level was (987±125.1), the mean±SD level of pre-operative D-dimer in patients with ovarian cancer was (602±320.7) while the post-operative was (901.5±412), mean±SD level of pre-operative D-dimer in patients with cervical cancer was (339±157) while the postoperative was (1214±327), and the mean±SD level of pre-operative D-dimer in all gynecological cancers was (541±167) while the post-operative was (1016±302). The mean±SD of wells score of those who are likely to developed DVT (n=7) in pre-operative was (2.3±0.02) while for those who are unlikely to develop deep vein thrombosis (n=38) was (2.03±0.4) with statistically significant difference (p=0.04) while highly significant difference found in pre- and post-operatively between the group of deep vein thrombosis (p<0.001).

**Conclusion:** Highly significant increase of post-operative D-dimer in all gynecological cancer patients.

**Keyword:** D-dimer, Deep Vein Thrombosis, Gynecological Cancer, Lymphadenectomy, Wells Score

## Introduction:

One of the most important prognostic indicators in cancer is the lymph node dissection (LND). LND complications can occur like lymphedema. It is considered as a risk factor for deep vein thrombosis in patients with gynecological malignancy who underwent surgery. (1-3) Deep vein thrombosis is a blood clot that forms within the deep veins, usually of the leg, but can occur in the veins of the arms and the mesenteric and cerebral veins.(4) Depending on the relative balance between the coagulation and thrombolytic pathways, thrombus propagation occurs. Deep vein thrombosis is commonest in the lower limb below the knee and starts at low-flow sites, such as the soleal sinuses, behind venous valve pockets. (5-7) D- dimer can be used to detect deep

vein thrombosis. (8) Venous thromboembolism increased among patients suffering cancer; especially those with gynecological cancer. Many factors related to this relationship, as patient, cancer, and management. (9, 10) Wells score is a common procedure to detect risk for deep vein thrombosis, depending on risk factors only.(11, 12)

## Methods

A cross sectional study conducted in Obstetrics and Gynecology/ ward in medical city, from 1<sup>st</sup>, January 2021 to 30<sup>th</sup>, Dec. 2021. The study was approved by Iraqi Council for Medical Specializations and by Department of Obstetrics and Gynecology and a verbal consent was obtained from participants. Forty-five patients (22 with endometrial cancer, 12 with ovarian, and 11 with cervical cancer) who were admitted to the hospital, enrolled in the study; with inclusion criteria of patients suffering from gynecologic cancer with lymph node dissection. Exclusion criteria was patients with benign tumor, unfit for surgery, or lymphadenectomy was not done.

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Data were collected from patients by using a specially designed questionnaire which included:

1. Pre-operative: collected data included: (Age, BMI, stage and type of cancer, Modified Wells score, leg vein ultrasound, D-dimer measured [negative result (<500 ng/ml) ruling out deep vein thrombosis, and positive result ( $\geq 500$  ng/ml) is not diagnostic and indicates the need for further investigation].

2. 28 days post-operative: rescoring done by using modified Wells score, D-dimer measured and Doppler ultrasound for leg vein.

The analyses were performed using the Statistical Package for Social Sciences (SPSS; version 25.0). The *t*-test was used for continuous variables only while for categorical variables we used Chi-squared test to explore the differences between the groups. Unpaired *t*-test was applied to determine the differences between the means of independent groups. ROC was done to measure the validity test (sensitivity, specificity, NPV, PPV and the accuracy). Values were expressed as means $\pm$  SD. In addition, P values < 0.05 were considered statistically significant.

### Results

Mean $\pm$ SD age of patients with gynecologic tumor who had lymphadenectomy was 55.7 $\pm$ 8.3 years, while mean $\pm$ SD BMI was 25.2 $\pm$ 1.8 kg/m<sup>2</sup>. Cervical type found among 11 (24.4%) patients [9 (81.8%) were with stage I-II and 2 (18.2%) were with stage III-IV]. Endometrial type was found among 22 (48.9%) patients, [17 (77.3%) were with stage I-II and 5 (22.7%) were in stage III-IV]. On the other hand, ovarian type was found among 12 (26.7%) patients [5 (41.7%) were in stage I-II and 7 (58.3%) were in stage III-IV] Figure 1. Moreover, seven cases (15.6%) of deep vein thrombosis were detected 28 days post-operative (Figure 2).

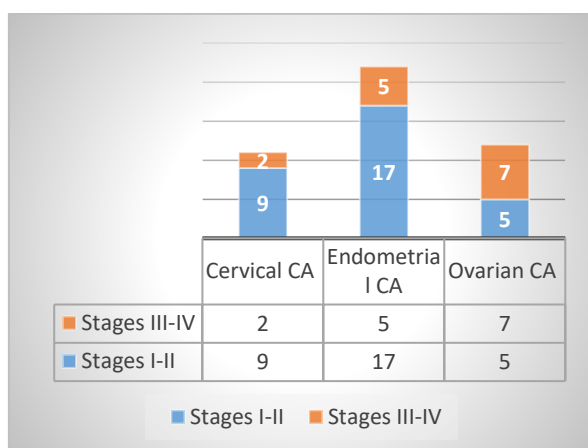


Figure 1: Patient's criteria according to the type and stage of the disease.

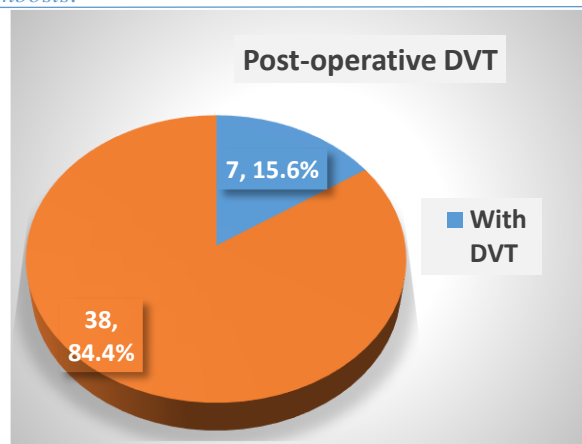


Figure 2: Post-operative cases of deep vein thrombosis among patients.

As shown in table 1, highly significant association was found between each of stage III-IV of endometrial cancer, and patients age >50 years with modified Wells score postoperatively, while cervical cancer is associated with modified Wells score preoperatively.

Table 1: Distribution of patients according to association between stage and type with mean Wells score in the studied groups pre- and post-operative

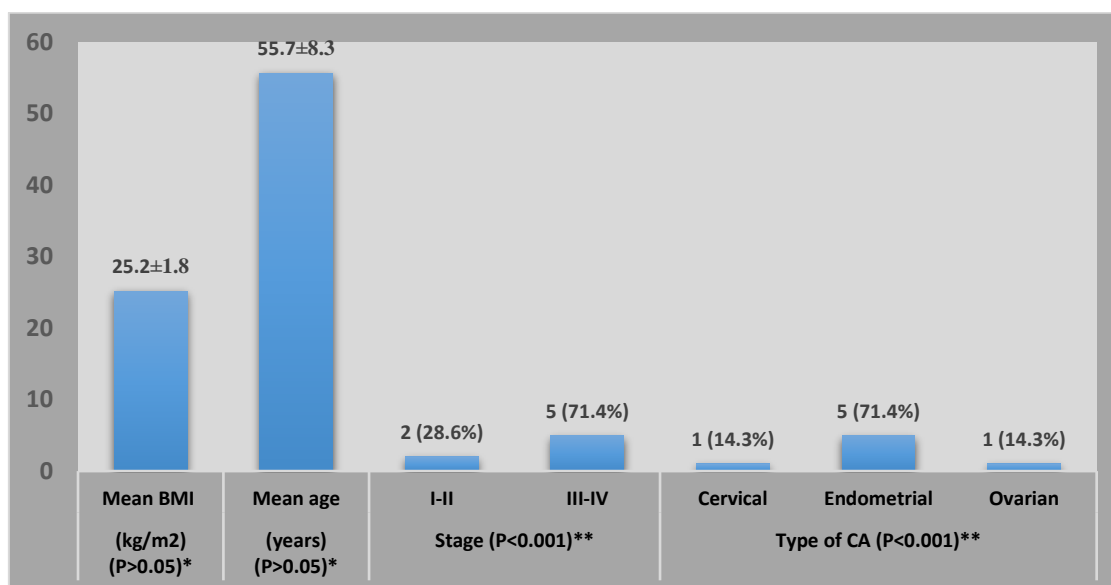
Variables		Modified Wells score (Mean $\pm$ SD)		P value
		Preoperative	Postoperative	
Stage	I-II	2.1 $\pm$ 0.3	2.28 $\pm$ 0.6	0.07
	III-IV	2.3 $\pm$ 0.04	2.8 $\pm$ 0.1	<0.001
Type	Endometrial cancer	2.3 $\pm$ 0.2	2.7 $\pm$ 0.01	<0.001
	Ovarian CA	1.8 $\pm$ 0.4	1.9 $\pm$ 0.3	0.1
	Cervical CA	2.2 $\pm$ 0.07	1.9 $\pm$ 0.02	<0.001
Age	<40 years (n=5)	2.19 $\pm$ 0.2	2.2 $\pm$ 0.3	0.8
	41-50 (n=10)	2.05 $\pm$ 0.06	2.06 $\pm$ 0.04	0.3
	>50 (n=30)	2.02 $\pm$ 0.01	2.04 $\pm$ 0.02	<0.001
BMI	Normal	2.2 $\pm$ 0.3	2.1 $\pm$ 0.8	0.4
	Overweight	2.19 $\pm$ 0.6	2.17 $\pm$ 0.2	0.8
	Obese	2.34 $\pm$ 0.2	2.29 $\pm$ 0.4	0.4

The mean $\pm$ SD level of D-dimer in pre-operative endometrial CA was (423.2 $\pm$ 123.9) while in post-operative was (987 $\pm$ 125.1) with highly significant difference (p<0.001), the mean level of pre-operative D-dimer in ovarian CA was (602 $\pm$ 320.7) while in post-operative was (901.5 $\pm$  412) with highly significant difference (p<0.001), mean $\pm$ SD level of pre-operative D-dimer in cervical CA was (339 $\pm$ 157) while in postoperative was (1214 $\pm$ 327) with highly significant difference (p<0.001), and the mean $\pm$ SD level of pre-operative D-dimer in all gynecological CA was (541 $\pm$ 167) while in post-operative was (1016 $\pm$ 302) with highly significant difference (p<0.001; Table 2).

**Table 2: Association between gynecologic tumor regarding mean D-Dimer in the studied groups pre- and post-operative**

Gynecologic CA	D-Dimer (ng/ml) (Mean±SD)		P Value
	Pre-operative	Post-operative	
Endometrial CA	423.2± 123.9	987±125.1	<0.001
Ovarian CA	602±320.7	901.5± 412	<0.001
Cervical CA	339±157	1214±327	<0.001
All Mean	541±167	1016±302	<0.001

As shown in figure 3; the mean±SD BMI of those who are likely to have deep vein thrombosis (n=7) was (25.2±1.8 kg/m<sup>2</sup>) with a range of 24-27 kg/m<sup>2</sup>, with mean±SD age (55.7±8.3) years ranged between (50-73) years, with no significant difference. Regarding to the stage of those who are likely to develop deep vein thrombosis, Stage III-IV was significantly higher than those in stage I-II. Moreover, endometrial cancer was more significant to those who are likely to develop deep vein thrombosis than other types of cancer in the study.



**Figure 3: Distribution of patients according to cancer features and post-operative deep vein thrombosis (n=7), \*Independent t test, \*\*Chi-squared test**

As shown in table 3, the mean±SD of Wells score of those who are likely to develop deep vein thrombosis (n=7) in pre-operative was (2.34±0.02) while for those who unlikely (n=38) was (2.03±0.4), with statistically significant difference (p=0.04), while no difference was found in post-operatively. Regarding D-dimer, highly significant difference was found in pre- and post- operatively between the groups of deep vein thrombosis (P<0.001).

**Table 3: Difference between deep vein thrombosis groups among Wells score and DVT in the studied group**

Variables		DVT likely (n=7)	DVT unlikely (n=38)	P value*
Wells score	Pre	2.34±0.02	2.03±0.4	0.04
	Post	2.41±0.04	2.3±0.4	0.4
D-dimer	Pre	872±247	285±98	<0.001
	Post	1102±511	176±82	<0.001

\*Independent t test, DVT= deep vein thrombosis

To detect validity test and area under curve for both D-Dimer and Wells score; ROC curve analysis was used as shown in table 4 & figure 4.

**D-Dimer:**

1. Pre-operative: Validity test to diagnose the deep venous thrombosis in gynecologic tumor patients at cut-off value of D-Dimer ≥ 1500 ng/ml

pre-operative to surgery showed that the sensitivity was (100%), specificity was (63%), NPV (100%), and PPV (39%); while accuracy was (83%).

2. Post-operative: the validity test to diagnose the deep venous thrombosis in gynecologic tumor patients at cut-off value of D-Dimer ≥ 1500 ng/ml pre-operative to surgery showed that the sensitivity was (93%), specificity was (23%), NPV (90%), PPV (21%) while accuracy was (67%); AUC=0.90 (which means it's a good predictor).

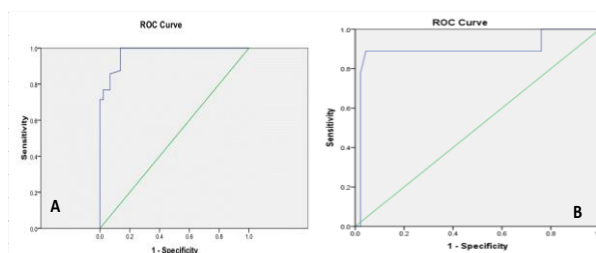
**Wells score:**

1. Pre-operative: Validity test to diagnose the deep venous thrombosis in gynecologic tumor patients at cut-off value of >2 scores of modified Wells score pre-operative to surgery showed that the sensitivity was (92.8%), specificity was (99.4%), NPV (98.4%), PPV (97.5%) while accuracy was (98.3%).

2. Post-operative: the validity test to diagnose the deep venous thrombosis in gynecologic tumor patients at cut-off value of >2 scores of modified Wells score preoperative to surgery showed that the sensitivity was (78.3%), specificity was (83%), NPV (80.2%), PPV (82%) while accuracy was (80%); AUC=0.90 (which means it's a good predictor)

**Table 4: Validity test of Wells score and D-Dimer to detect the deep vein thrombosis in gynecologic cancer**

		Sensi- tivity	Speci- ficity	NPV	PPV	Accuracy
<b>Wells score</b>						
> 2 score	Pre- operative	92.8%	99.4%	98.4 %	97.5%	98.3%
	Post- operative	78.3%	83%	80.2 %	82%	80%
<b>D-Dimer (ng/ml)</b>						
Cut off ≥ 1500 (ng/ml )	Pre- operative	100%	63%	100 %	39%	83%
	Post- operative	93%	23%	90	21%	67%



**Figure 4: ROC curve (AUC=0.9); A) for D-Dimer, B) for Wells score.**

**Discussion**

Deep vein thrombosis is a common complication of cancer patients and is a major cause of morbidity and mortality (13) D-dimer in endometrial, ovarian and cervical cancer was increased significantly post-operatively than that pre-operatively. This finding is in agreement with that found by Komatsu et al. (2014), except for the ovarian cancer in which the level of D-Dimer decreased post-operatively than pre-operative level with no significant difference. This difference may be attributed to collection of sample size differences between current and the previous study. (14) In the existing study the incidence of deep vein thrombosis was 7 (15.6%) cases in all gynecological cancer patients enrolled in current study, and the distribution of these cases was as follows: the incidence of deep vein thrombosis in endometrial cancer was (43.0%) of cases, while (28.5%) of cases presented with deep venous thrombosis in cervical CA and ovarian CA from all gynecological cancer patients. These findings were in agreement with a previous studies carried out by Matsuura Y et al. (2007) (15) and Bakhru A et al. (2013) (16) as they concluded that the incidence of deep vein thrombosis was found in 27.3% of patients with ovarian cancer. Also, in agreement with a previous two studies by Duska LR et al. (2010) (17) and Kodama J et al. (2010) (18) reported that incidence of deep vein thrombosis was found in 15–42% in ovarian carcinoma. However, it disagreed with Oranratanaphan S et al. (2015) that revealed the incidence of deep vein thrombosis presented in ovarian cancer comprising less than two-thirds of all gynecological cancers in his study. (19) Moreover, current study disagreed with Sakurai M et al. (2017) found that there was no difference in deep vein thrombosis rates in ovarian cancer patients (p>0.05).

(20) and disagreed with Uno K et al. (2007) who shown that deep vein thrombosis developed prior to treatment in less than half of patients with ovarian cancer. (21) In our study, the pre-operative value of D-Dimer at cut-off value of ≥ 1500 ng/ml showed that validity test to diagnose deep vein thrombosis in gynecologic tumor patients was with sensitivity of (100%), specificity of (63%), NPV of (100%), PPV of (39%) and accuracy (83%). This is in agreement with that mentioned in a previous study by Burgazli K et al. (2011)(22) and Kawaguchi R et al. (2012) (23) they revealed that D-dimer at cut-off level ≥0.5 mg/L is good predictor for the rate of deep vein thrombosis in elderly hospitalized patients, with excellent sensitivity (100%) and (41.8%) specificity.

**Regarding to Wells score in current study:**

Sensitivity in pre-operative was (92.8%), specificity (99.4%), NPV (98.4%), PPV (97.5%) and accuracy (98.3%). This was in agreement with Modi S et al. (2016) study, the Wells score was able to detect patients at risk of developing deep vein thrombosis with a specificity of 90 %, sensitivity of 67 %, positive predictive value of 31 %, and NPV of 98 % (24). Moreover, Silveira PC et al. (2016) study reported 91% sensitivity for Wells score to detect the deep vein thrombosis and 88% specificity. (25, 26). In our study, 7 (15.6%) asymptomatic patients were discovered with subclinical deep vein thrombosis by screening post-operation by lower limb Doppler study; which was approximated to other study which concluded that 10% of patients developed VTE within 30 days of initial surgery. (27) . Another study revealed that post-operative prevalence of deep vein thrombosis in gynecologic malignancy cases was five in 44 patients (11.4%). (28)

**Conclusion:**

Subclinical deep venous thrombosis was found in 7 (15.6%) cases of all gynecologic cancers. Pelvic lymph nodes dissection may be associated with subclinical deep venous thrombosis at 28 days post-operation in spite of standard thrombo-prophlyxis after surgery. Wells scoring pre-operatively was more accurate than D-dimer level in predicting subclinical deep venous thrombosis at 28 days post-operation.

**Authors' contributions:**

Dr. Safa Daud Sulman: writing the project, collecting data, writing draft, and research.  
Dr. Nawfal Azzo: supervisor, concept of the study, reviewing manuscript

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## مصل دي دايمر ونقاط ولز في المريصات اللواتي اجريت لهن استئصال العقد اللمفية الحوضية في الاورام النسائية

د.نوفل عزو: استشاري الامراض النسائية\استاذ في مستشفى بغداد التعليمي  
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### الخلاصة

**المقدمة:** إن سرطانات الجهاز التناسلي للأنتى - سبب مهم للإصابة بالسرطان والوفيات في جميع أنحاء العالم. تجلط الأوردة العميقة هو جلطة دموية تتشكل داخل الأوردة العميقة ، عادة في الساق . دي دايمر هو منتج ثانوي لعملية تجلط الدم وتفككه ويمكن قياسه من خلال تحليل عينة الدم .  
**هدف الدراسة:** تقييم الخثار الوريدي العميق باستخدام مصلى دي دايمر بالدم مع نقاط ولز بعد استئصال العقد اللمفية في الحوض في سرطان الجهاز التناسلي للمرأة .

**المرضى وطريقة العلاج:** تم إجراء دراسة مقطعية قائمة على الملاحظة في قسم أمراض النساء والولادة / مستشفى بغداد التعليمي ، مجمع مدينة بغداد الطبية ، بغداد ، العراق ، والتي أجريت على مدى سنة واحدة تبدأ من الأول من كانون الثاني (يناير) 2021 إلى نهاية ديسمبر 2021. العدد الإجمالي 45 (22 سرطان بطانة الرحم ، 12 سرطان مبيض ، 11 سرطان عنق الرحم) .

**النتائج:** كان متوسط مستوى دي دايمر قبل الجراحة في سرطان بطانة الرحم  $(123.9 \pm 423.2)$  بينما في ما بعد الجراحة كان  $(125.1 \pm 987)$  ، كان متوسط مستوى دي دايمر قبل الجراحة في سرطان المبيض  $(320.7 \pm 602)$  بينما كان في فترة ما بعد الجراحة  $(412 \pm 901.5)$  ، كان متوسط مستوى دي دايمر قبل الجراحة في سرطان عنق الرحم  $(157 \pm 339)$  بينما كان في فترة ما بعد الجراحة  $(327 \pm 1214)$  ، وكان متوسط المستوى قبل الجراحة كان دي دايمر في جميع أمراض النساء  $(167 \pm 541)$  بينما كان في فترة ما بعد الجراحة  $(1016 \pm 302)$  بينما وجد فرق ذو دلالة إحصائية بعد العملية. فيما يتعلق بـ دي دايمر ، تم العثور على فرق كبير للغاية قبل وبعد الجراحة بين مجموعات تقييم الخثار الوريدي العميق. متوسط نقاط ولس لأولئك الذين من المحتمل أن يصابوا بجلطات الأوردة العميقة في مرحلة ما قبل العملية كان  $(0.02 \pm 2.3)$  بينما بالنسبة لأولئك الذين من غير المحتمل أن يصابوا بجلطات الأوردة العميقة كان  $(0.4 \pm 2.03)$  مع وجود فرق معتد به إحصائياً  $(p = 0.04)$  بينما وجد فرق كبير ذو دلالة إحصائية قبل وبعد الجراحة بين مجموعة جلطات الأوردة العميقة.

**الاستنتاجات:** تبين ان نقاط ولز أكثر دقة من مصلى دي دايمر قبل العملية الجراحية وبعد ثمانى وعشرون يوماً من العملية الجراحية لتشخيص الخثره الوريديه العميقة المخفيه.

**الكلمات الافتتاحية:** تجلط الأوردة العميقة ، سرطان الجهاز التناسلي للمرأة ، معيار ويلز ، دي دايمر ، استئصال العقد اللمفية.