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A COMPARISON BETWEEN WELLS' SCORE AND MODIFIED DOPPLER ULTRASOUND IN THE DIAGNOSIS OF DEEP VENOUS THROMBOSIS OF THE LOWER LIMB

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ABSTRACT: The assessment of the probability of occurrence of deep vein thrombosis played a very important part in making a correct diagnosis and modified Wells' score is a widely used prediction rule for pre-test probability assessment. We aimed to evaluate the diagnostic accuracy of the modified Wells' score in the diagnosis of lower extremity deep vein thrombosis compared to Doppler ultrasound study. This is a cross-sectional study conducted in Baghdad Teaching Hospital from Jan 2017 till Dec 2017. Adults inpatients suspected of having lower-extremity deep vein thrombosis were included after taking verbal consents. Patients on antithrombotic treatment and those suspected to have pulmonary embolism were excluded. According to Wells' score; patients were divided into likely and unlikely groups. Lower extremity venous duplex ultrasound study was established. Correlation of Wells' score with DVT and its efficacy was analyzed using receiver operating characteristic curve. A total number of 113 patients were included; with a mean age of 40.6 ±, 12.7 years and males were 60 (53.1%). Based upon Wells' score, 45 (39.8%) patients were found to be likely to have DVT. Doppler ultrasound was positive for DVT in 48 (70.6%) patients of those who belong to the likely group with a statistically significant difference. The overall accuracy of Wells' score was 76.1%, and sensitivity was higher than the specificity. In this study; Wells' score demonstrated a high degree of accuracy. As an initial diagnostic tool; if we use Wells' score with a prior assumption; it has benefited as exclusion tool than a confirmatory test.

INTRODUCTION: Venous thromboembolic (VTE) disease is a major problem worldwide. Approximately 1.1 million (VTE) events occur each year across the EU, causing more than half a million deaths. In the US, (VTE) events (incident or recurrent, fatal and non-fatal) affect an estimated 900,000 people each year, with up to 300,000 deaths annually [1, 2].

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Risk Factors for Venous Thrombosis: They are primarily related to hypercoagulability, or due to immobilization and venous stasis. Independent predictors for recurrence include increasing age, obesity, malignant neoplasm, and acute extremity paresis. A significant risk is incurred by major orthopedic, abdominal, or neurologic surgeries. Moderate risk is promoted by prolonged bed rest; certain types of cancer, pregnancy, hormone replacement therapy, or oral contraceptive use; and other sedentary conditions such as long-distance plane travel [3].

Deep Vein Thrombosis: DVT of the lower extremity is subdivided into either distal or proximal vein thrombosis. Proximal-type is of greater importance clinically, since it is more commonly associated with serious, chronic disease (*e.g.*, active cancer, congestive failure, respiratory insufficiency, age >75), whereas distal thrombosis is more often associated with transient risk factors (*e.g.*, recent surgery, immobilization, travel) [4].

As a further example, over 90% of cases of acute pulmonary embolism (PE) are due to emboli emanating from the proximal, rather than the distal, veins of the lower extremities, and the mortality rate of proximal DVT is higher than that of distal DVT [5].

Clinical Examination: Given the high risk associated with proximal DVT that is not treated and the potential risk of anticoagulating a patient who does not have a DVT; an accurate diagnosis is essential which needs both clinical evaluation and objective testing. Testing approaches, including venography, venous ultrasonography, and D- dimer assay, have been developed. Venography is regarded as the gold standard for the diagnosis of DVT, but it is not suitable for routine examination because of its invasiveness and cost [6].

Compression Ultrasonography: A more direct approach to the diagnosis of DVT involves the use of compression ultrasonography [7]. The chronicity of the thrombus may be inferred from the echogenicity of the clot because older clots appear more echo dense [8].

Compression ultrasonography does not detect isolated thrombi in the iliac vein, and the results are limited in patients with deformities or a plaster cast, and routine compression ultrasonography needs to be repeated if the first test is negative and clinical suspicion is high [9].

Extended (Complete) Lower Extremity Ultrasound: One approach that may overcome these limitations of venous ultrasound involves imaging the entire venous system, including distal (*i.e.*, calf) veins, at the time of initial presentation (*i.e.*, whole leg ultrasonography) [10].

Addition of Pretest Probability (Wells' Score): Ultrasonography for DVT is most useful when the results are combined with an assessment of pretest probability. Wells' score for DVT (*i.e.,* Wells criteria for DVT) appears to be most commonly used [11, 12].

Objective: To evaluate the diagnostic accuracy of the Wells' score in the diagnosis of lower extremity DVT compared to Doppler ultrasound study.

MATERIALS AND METHODS:

Study Design and Sample: This is a cross-sectional observational study conductedover 12 months from Jan 2017 till Dec 2017. Adults (≥ 18 years) admitted to the medical ward in Baghdad Teaching Hospital / Medical city were included to this study based on clinical suspicion of lower extremity DVT depending on symptoms and signs of DVT (redness, pain, edema). After taking verbal consents from patients, data was collected by the same physician with standard questioner form informative about the name, gender, age, history of hypertension, diabetes, smoking, alcohol consumption, history of drug abuse like [amphetamine, ecstasy (MDMA)] and family history of DVT.

Exclusion Criteria: Ongoing antithrombotic treatment due to the already established diagnosis of DVT, Patients suspected to have a pulmonary embolism (dyspnea, tachypnea, and chest pain), and trauma patients.

TABLE 1: MODIFIED WELLS' SCORE [13]

Clinical feature	Points
Active cancer (treatment ongoing or within previous 6 m or palliative)	1
Paralysis, paresis or recent plaster immobilization of the lower extremity	1
Bedridden more than 3 days or major surgery within 4 weeks	1
Localized tenderness along the veins	1
Entire leg swelling	1
Calf swelling > 3 cm compared to the asymptomatic leg	1
Pitting edema (confined to symptomatic leg)	1
Collateral superficial veins (non- varicose)	1
Alternative diagnosis to DVT as likely or more likely	-2
Low probability (unlikely) <2	
High probability (likely) 2 or more	

Clinical assessment of DVT was done, and modified Wells' score was estimated and documented to calculate the clinical probability of DVT of lower extremities as (likely to have DVT if the score was 2 or more & and unlikely if the score was <2) as illustrated in the following **Table 1**.

Measurements: Doppler ultrasound examination was performed (by a radiologist) to all cases using (GE Healthcare, evolution) device. Ultrasonography of the lower extremity deep venous system was performed in the supine position, with the head of the bed raised 20° - 30°. The limb was externally rotated and slightly flexed at the knee. The transducer was placed transversely in the groin area to identify the common femoral vein and then was moved distally along the deep venous system, with a compression applied at 1-2 cm intervals. Compression of the veins within the adductor canal was sometimes difficult due to the deep course of the vein through the muscles. For the deep distal veins, the examination was made with the patient in a sitting position with the affected leg hanging over the side of the bed. The study protocol was approved by the ethical committee of the Arab Board council of Medicine.

Statistical Analysis: Discrete variables were presented using their number and percentage, the chi-square test was used to analyze the discrete variables (or Fisher exact test when chi-square was not valid; due to low sample size <20 and if 2 or more with an expected frequency is less than 5).

Two samples t-test was used to analyze the differences in means between two groups (if both follow a normal distribution with no significant outlier). Receiver operator curve (ROC) was used to find the validity of different parameters in separating active cases from control (negative cases) and area under the curve *i.e.* AUC and its P. value prescribed this validity (AUC ≥ 0.9 means excellent test, 0.8 - 0.89 means good test, 0.7 - 0.79 means fair test, otherwise unacceptable). The trapezoidal method was used to calculating the curve.

In a ROC curve, the true positive rate (Sensitivity) is plotted in function of the false positive rate (100-Specificity) for different cut-off points. Each point on the ROC curve represents a sensitivity/ specificity pair corresponding to a particular decision threshold. A test with perfect discrimination (no overlap in the two distributions) has a ROC curve that passes through the upper left corner (100% sensitivity, 100% specificity). Therefore, the closer the ROC curve is to the upper left corner, the higher the overall accuracy of the test (Zweig & Campbell, 1993).

Sensitivity: Probability that a test result will be positive when the disease is present (true positive rate).

Specificity: Probability that a test result will be negative when the disease is not present (true negative rate).

Positive Predictive Value: Probability that the disease is present when the test is positive.

$$PPV = \frac{sensitivity \times prevalence}{sensitivity \times prevalence + (1 - specificity) \times (1 - prevalence)}$$

Z: Probability that the disease is not present when the test is negative.

$$NPV = \frac{specificity \times (1 - prevalence)}{(1 - sensitivity) \times prevalence + specificity \times (1 - prevalence)}$$

Disease Prevalence: Whereas sensitivity and specificity, and therefore the ROC curve and positive and negative likelihood ratio are independent of disease prevalence, positive and negative predictive values are highly dependent on disease prevalence or prior probability of disease. Clinically, the disease prevalence is the same as the probability.

SPSS 20.0.0, Med Clac 14.8.1 software package was used to make the statistical analysis. A p-value of less than 0.05 was considered when appropriate to be significant.

RESULTS: As illustrated in table 2, a total of 113 patients were included in the study with a mean age of 40.6 ± 12.7 years ranging from (18 - 72) years, and male to female ratio was 1.13:1. Of the total sample, 42 (37.2%) were smokers, 27 (23.9%) had DM, 27 (23.9%) had hypertension, 12 (10.6%) were drug abusers, and 6 (5.3%) had a family history of DVT.

TABLE 2: DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PATIENTS

Variables	Value
Number	113
Age, mean ± SD* (range) years	40.6 ± 12.7 (18 – 72)
Gender, no. (%)	
Male	60 (53.1%)
Female	53 (46.9%)
Smoking, no. (%)	42 (37.2%)
Alcoholic, no. (%)	7 (6.2%)
Diabetes mellitus, no. (%)	27 (23.9%)
Hypertension, no. (%)	27 (23.9%)
Drug abuser, no. (%)	12 (10.6%)
Family history of DVT**, no. (%)	6 (5.3%)

SD*: Standard deviation, DVT**: Deep venous thrombosis

As illustrated in **Table 3**; based upon Wells' score, 45 (39.8%) patients were found to be unlikely to have DVT and 68 (60.2%) patients were found to be likely. Doppler ultrasound study was positive for DVT in 48 (70.6%) patients of those who belong to the likely group according to Wells' score compared to 7 (15.6%) from the unlikely group with a statistically significant difference.

TABLE 3: THE ASSOCIATION BETWEEN DOPPLER STUDY AND MODIFIED WELLS' SCORE

Wells' score	Doppler study		P. value
	No DVT (58)	DVT* (55)	
Unlikely to have DVT 45 (39.8%)	38 (84.4%)	7 (15.6%)	<0.001
Likely to have DVT 68 (60.2%)	20 (29.4%)	48 (70.6%)	

Chi-square test used. DVT*: Deep venous thrombosis.

As illustrated in **Table 4**; Wells' score showed a fair ability (since the AUC was between 0.7 - 0.79), and in our patients, the optimal cut point was above 1, this means that there is a high probability of DVT. To assess the validity of Wells' score, we found that the sensitivity (SN) was higher than the specificity (SP). So, as an initial diagnostic tool, Wells' score is better as a screening than a confirmatory test with an overall accuracy of 76.1%. The negative predictive value (NPV) was higher than the positive predictive value (PPV), this indicates that if we use Wells' score in conjugation with the prior assumption, it has benefited as exclusion tool than confirmatory.

TABLE 4: DIAGNOSTIC VALIDITY OF WELLS' SCORE USING ROC ANALYSIS

AUC	P value	Optimal cut point	SN %	SP %	Accuracy %	PPV %	NPV %
0.756	<0.001	>1	87.3	65.5	76.1	70.6	84.4

AUC: area under the curve, SN: sensitively, SP: specificity, PPV: positive predictive value, NPV: negative predictive value

As illustrated in **Table 5**; there was no statistically significant difference in the demographic variables and clinical characteristics of patients according to the presence or absence of DVT by Doppler study.

TABLE 5: ASSOCIATION BETWEEN VARIOUS PREDICTORS AND DOPPLER FINDINGS OF DEEP VEIN THROMBOSIS

Variables	No DVT	DVT	P. value
Number	58	55	-
Age (years), mean ± SD*	42.2 ± 11.8	39.0 ± 13.4	0.184
Gender, no. (%)			
Female	30 (56.6%)	23 (43.4%)	0.292
Male	28 (46.7%)	32 (53.3%)	
Smoking, no. (%)	21 (36.2%)	21 (38.2%)	0.828
Alcoholic	4 (6.9%)	3 (5.5%)	1.0
Diabetes mellitus, no. (%)	14 (24.1%)	13 (23.6%)	1.0
Hypertension, no. (%)	13 (22.4%)	14 (25.5%)	0.705
Drug abuser, no. (%)	6 (10.3%)	6 (10.9%)	0.922
Family history of DVT, no. (%)	5 (8.6%)	1 (1.8%)	0.207
Age was analyzed using an independent t-test.			
The rest of the variables were analyzed using either chi-square test or Fisher exact test.			

SD*: Standard deviation, DVT**: Deep venous thrombosis.

DISCUSSION: According to the results of this study; we found a highly accurate performance of Wells' score in assessing the clinical probability of DVT of the lower limbs. Before several years; Wells' score was evaluated in primary health care in a group of 1028 patient suspected of DVT of the lower limbs. Only patients with 4 or more points were qualified for further U/S evaluation. A valid score was obtained in 1002 patients (98%). In 500 patients (49%), with a score of 3 or less, 7 developed DVT within 3 months (incidence, 1.4% [95% CI, 0.6% to 2.9%]). A total of 502 patients

(49%) had a score of 4 or more; 3 did not have ultrasonography. Ultrasonography showed DVT in 125 patients (25%), for an overall prevalence in evaluable patients of 13% (125 of 1002) [14].

While Oudega and colleagues found that Wells' rule in combination with a D-dimer test was not safe for excluding DVT in primary care. The authors found a missed proportion of 2.9% and 2.3% missed cases, respectively [15]. Bernardi E and Camporese G found that patients with a high probability of DVT have over a 75% prevalence of DVT confirmed by tests whereas cases with a low pretest probability have a less than a 5% prevalence of DVT [16]. We obtained similar results in our study in cases with a high probability.

In our study; DVT was diagnosed by Doppler ultrasound in 15.6 % in cases within the unlikely group and 70.6% of the likely cases. This finding is almost similar to Hoţoleanu, Fodor D and Suciu O study which included 382 patients; where it was noticed that DVT was confirmed by Doppler ultrasonography in more than half of the cases; the highest percent of confirmed cases were in the patients with a high probability of DVT (70.58%) whereas the lowest percent was associated with the low clinical probability (14.63%) [17].

Our results suggest that the Wells' score risk stratification is sufficient in the diagnosis of DVT compared with the same result in the original Wells' study [18]. While in Silveira PC *et al.*, a cohort study of 1135 inpatient; it was found that Wells' score had a higher failure rate and a lower efficiency in the inpatient setting [19].

The mean age in our study was 40.6 ± 12.7 years while the average age in Mousa AY and Broce BAM study was 62.1 ± 16.3 years. In that study; females represented (55.7%) in our study it was (46.9%) [20].

From a G J Geersing *et al*., meta-analysis of 10002 patient's data from [13] study, there were no clinically important differences for the accuracy of the Wells' rule in males or females, or in patients presenting in primary or hospital care enabling a safe exclusion of DVT in these subgroups. The unlikely score (≤1) on the Wells' rule combined with a negative D-dimer test result can safely exclude DVT in about 1 in every 3 patients [21]. In a study done by N Sermsathanasawadi *et al*., DVT was confirmed in 26.4% and the modified Wells,' and the Constans score appears to be useful in the unselected population of outpatients and inpatients [22].

In a study of Hoţoleanu C *et al*., DVT was confirmed by Doppler ultrasonography in more than half of the cases; and the highest percent of confirmed cases were in the patients with a high probability of DVT (70.58%) whereas the lowest percent was associated with the low clinical probability (14.63%). These findings are similar to our findings [23].

In our study; the AUC was 0.756 while in Silveira PC *et al*., study; the AUC operating characteristics curve for the discriminatory accuracy of the Wells' score for risk of proximal DVT identified on lower-extremity venous duplex ultrasound studies was 0.60 [24]. It was (0.56) in Engelberger RP *et al.* [2] Although in our study; DM was not significantly associated with presence or absence of DVT by Doppler study, but Patients with diabetes who developed venous thromboembolism were more likely to suffer a complicated clinical course as found in Piazza G *et al.* [26] Han-liang H verified that hypertension could increase the development of DVT [27]. However, Wang *et al*., [28] reported that there was no statistically significant correlation between DVT and hypertension. Therefore, the controversial issue remains to be investigated.

CONCLUSION:

- Based on the results of this study, Wells' score demonstrated a high degree of accuracy.
- As an initial diagnostic tool; if we use Wells' score in conjugation with a prior assumption; it has benefited as an exclusion tool than a confirmatory test.
- Additional prospective studies in larger populations and measuring D- dimer are needed to validate the findings of the present study in a multicenter trial.

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