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ABSTRACT

***Background*: Deep Venous thrombosis (DVT) is difficult to diagnose. Pre-test probability rules used in screening for DVT have not been validated in an African population.**
***Objective*: Validation of the Wells Rule in African patients suspected to have DVT.**
***Design*: Descriptive cross sectional study.**
***Setting*: Moi Teaching and Referral Hospital (MTRH), a tertiary referral centre in Eldoret, Kenya**
***Subjects*: Adult patients presenting with suspected DVT had their pre-test probability of DVT calculated using the Wells rule before undergoing compression ultrasound imaging of their legs to confirm the diagnosis.**
***Results*: Ninety-seven (97) patients were enrolled between April 2010 and January 2011: median age 38 years (IQR: 31, 48); 71 (73%) women; and 40 (44%) were HIV-infected. DVT was confirmed in 78/81 (96%) of patients with high probability and 2/16 (12%) in those with low probability. Sensitivity of the Wells score was 0.975(95%CI 0.940,0.992) and specificity was 0.824 (95%CI 0.657, 0.902). Likelihood ratio for a positive test was 5.525(95%CI2.743, 10.097) and 0.030 (95%CI 0.009, 0.092) for a negative test. We found strong agreement between the Wells score and Doppler ultrasound findings with a Kappa value of 0.817 (95%CI 0.611, 0.915).**
***Conclusions*: The Wells Rule has good sensitivity, specificity and likelihood ratios in the preliminary diagnosis of DVT in African patients.**

INTRODUCTION

DVT affects an estimated 84 persons per 100,000 each year (1).While the incidence of DVT remains unchanged for men, it is increasing in older women (2). DVT prevalence studies show regional variation in the magnitude of the problem. The prevalence of proximal DVT was 3.17% in the general ward of a Netherlands Hospital, 0.10% at the Kaiser Permanente Hospitals in California, U.S.A and 0.18% in Assir Central Hospital in Saudi Arabia (3-5). No incidence or prevalence studies have been published from the Africa region.

Objective testing for DVT is essential because the symptoms of DVT are often nonspecific and clinical assessment alone is unreliable (6-9). Accurate diagnosis is important because patients with unrecognised (therefore untreated)proximal DVT may develop pulmonary embolism, whereas unjustified anti-coagulant therapy poses a risk for major bleeding (10, 11). In addition, a number of non-thrombotic disorders (for example, cellulitis, valve incompetence, lymphedema) mimic DVT (8).

The diagnosis of DVT in resource-limited countries is difficult because of shortage of diagnostic tests. The tools utilised in such settings for diagnosis of DVT are often limited to patient history and physical examination. Very few health care settings are able to process a rapid D-dimer test or a Doppler ultrasound. Based on results of the crude methods available, physicians must decide which patients to refer for additional, more burdensome and often costly tests.

Reported first in 1997 the Wells Rule, a clinical prediction rule used to determine the pre-test probability of DVT, is widely utilised in resource-rich settings(12).Reports from prospective validation studies using similar populations as the original study (patients with suspected DVT referred to a secondary outpatient care centre) confirm that the Wells score accurately stratifies patients into groups with high and low probability of DVT (13). However, applied to a slightly different population (patients in primary care settings), the Wells score was less accurate in making this prediction (14).These findings underscore

the importance of externally validating a clinical prediction rule to determine how well it performs in diverse patient populations and clinical settings, more so when used by non expert physicians. We therefore designed this study to validate the ability of the Wells Rule to determine the pre-test probability of DVT in an African population in a resource-limited setting.

MATERIALS AND METHODS

Ethical approval: We obtained approval to carry out the study from the Institutional Research and Ethics Committee (IREC) of Moi University School of Medicine (MUSoM) and Moi Teaching and Referral Hospital(MTRH). All patients provided written informed consent prior to enrolment into the study.

Study Design: This descriptive cross-sectional study was a diagnostic validation of the Wells Rule for DVT in a secondary health care setting using compression ultrasonography as the gold standard comparison.

Study site: We conducted the study at Moi Teaching and Referral Hospital (MTRH), a 500-bed referral center in Eldoret, Kenya. MTRH serves as a teaching hospital for Moi University School of Medicine.

Patients: We included patients ≥18 years with unilateral limb swelling suspected to be DVT. We excluded: 1) amputees with one lower limb; 2) patients with unilateral limb swelling clearly attributable to other etiologies (like fractures); and 3) patients already diagnosed to have DVT by Doppler ultrasound.

Case Definition: A case was defined as any male or female patient with unilateral lower limb swelling, measured as either an increase in thigh circumference of more than 2 centimeters at a point marked 20 centimeters below the anterior superior iliac spine or increase in calf circumference of more than 2 centimeters at a point marked 10 centimeters below the tibial tuberosity, both in comparison to the contralateral limb(15).

Clinical Procedures: We examined all patients in the anatomical position. The affected limb was designated the 'test' leg and the contralateral limb the 'control' leg. The thigh circumference was marked 20 centimeters below the anterior superior iliac spine and the calf circumference was marked at 10 centimeters below the tibial tuberosity. Assessment of tenderness along the deep venous system was done by firm palpation in the centre of the posterior calf, the popliteal space, and along the area of the femoral vein in the anterior thigh and groin. The same procedure was applied to the 'control' leg. After confirmation of clinically significant swelling and tenderness, the Wells scoring scale was applied to determine the probability of having DVT.

All patients had a Doppler ultrasound test. With the patient lying supine, the 'test' leg externally rotated and slightly flexed at the knee with a pressure cuff applied to the ankle, we examined the leg from the level of the inguinal ligament to the medial malleolus. Examination included the common femoral vein, superficial femoral vein, popliteal vein and all three deep calf vein sets. Compressibility of these veins was assessed at 2 – 3 centimeter intervals in the transverse plane. The presence or absence of impedance to venous flow was determined using duplex compression (Acuson Sequoia 512 sonographic imaging system). We used high-resolution linear array transducers with variable frequency (6–8 MHz) probes in all patients. This procedure was similarly applied to the 'control' limb. Non-compressibility of a segment of the veins was the sole criterion for diagnosis of DVT.

All patients had HIV tests using at least two rapid diagnostic assays using Determine HIV-1/2 ®(Inverness Medical Japan Co.Ltd) and SD Bioline HIV-1/2 3.0 (Standard Diagnostics Inc., Kyonggi-do, South Korea). When the result was indeterminate the Uni-goldRecombigen® HIV test (Trinity Biotech PLC. Bray, Co. Wicklow, Ireland) was performed as the tiebreaker diagnostic assay.

Statistical Analysis: We generated frequency tables for categorical variables and median for the continuous variables. We used the chi-square test to assess any association between categorical variables and presence of DVT. Where the cell counts were below 5 the Fishers' exact test was used in 2 by 2 tables. Sensitivity and specificity, Kappa statistic, positive and negative predictive value and likelihood ratios of the Wells score were determined using a two-way contingency table analysis.

RESULTS

We screened 120 patients with suspected DVT between April 2010 and January 2011. Of these, 23 patients were excluded from the study (19 declined to give consent and four were below 18 years). Of the 97 patients enrolled in the study, 71/97 (73%)were female and the median age was 38 years (IQR: 31, 48; Range: 18, 91). The large majority (80%) of patients was below the age of 55 years and most (81%) were farmers (Table 1).

Table 1
Socio-demographic characteristics of patients with suspected DVT

Characteristic	Frequency N=97 (%)
Female	71 (73)
Marital status	
Married	68 (70)
Single	19 (20)
Separated / widowed	10 (10)
Education	
None	11 (11)
Primary	78 (80)
Secondary	7 (7)
Tertiary	1 (1)
Age (years)	
≤ 24	9 (9)
25 – 34	32 (33)
35 – 44	28 (29)
45 – 54	8 (8)
55 – 64	7 (7)
≥65	13 (13)
Occupation	
Farmer	79 (81)
White collar	8 (8)
Unemployed	10 (10)
Point of Admission	
Surgical	19 (20)
Medical	55 (57)
Obs / Gyne	23 (23)

DVT was confirmed in 80 / 97(82%) patients. Majority (53 / 80(88%) of these patients were aged between 25 and 44 years. Nine(9%) patients were less than 24 years and 13 (14%) were >65 years. Overall, 40 / 97 (41%) patients were HIV-infected, 35 with DVT and five without. Majority (58%) of patients with confirmed DVT had it on their left leg. Three subjects (4%) had DVT in both legs.

Among the nine criteria of the Wells score, localised tenderness in the deep vein system and swelling of the entire leg were the most common presentations (96% and 94% respectively). Provided in Figure 1 are the other clinical signs demonstrated and their frequencies of occurrence.

The most common alternative diagnoses in those without DVT were cellulitis (5 / 17; 29%); incompetent veins (4 / 17; 24%); lymphedema (4 / 17; 24%); Kaposi's sarcoma (2 / 17; 12%); arteriovenous malformation (1 / 17; 6%). We were unable to establish a diagnosis in 1 / 16 (6%) patient without DVT. Risk factors in patients confirmed to have DVT included use of oral estrogen pills in 35 / 80 (44%); pregnancy in the last six months in 17 / 80(21%); recent injury or surgery in 11 / 80 (14%); paralysis or immobilisation in 10 / 80 (13%); and cancer in 6 / 80 (8%). Seven (9%) patients had no clear identifiable risk factor for DVT.

Wells score: Of the 97 study participants, 81 (84%) scored ≥2 and were stratified as highly likely to have DVT. The remaining 16 (16%) patients scored ≤1 and stratified unlikely to have DVT (Figure 2). Of the 81 patients in the highly likely group, 78 (96%) had DVT confirmed by Doppler ultrasound. In the less likely group only 2 / 16 (12%) had DVT. The prevalence of DVT was thus high in the highly likely group as compared to the less likely group ($p<0.001$).

The sensitivity of the Wells score in this study was 0.975 (95%CI 0.940, 0.992) and specificity was 0.824 (95%CI 0.657, 0.902). The positive predictive value was 0.96 (95%CI 0.928, 0.979);the negative predictive value was 0.875(95%CI 0.70, 0.96) and; the negative likelihood ratio was 0.03 (95% CI 0.009, 0.092). We found strong agreement between the Wells score and Doppler ultrasound findings with a Kappa value of 0.817(95%CI 0.611, 0.915).

Figure 1
Frequency of each criterion of the Wells Rule among the subjects suspected to have DVT

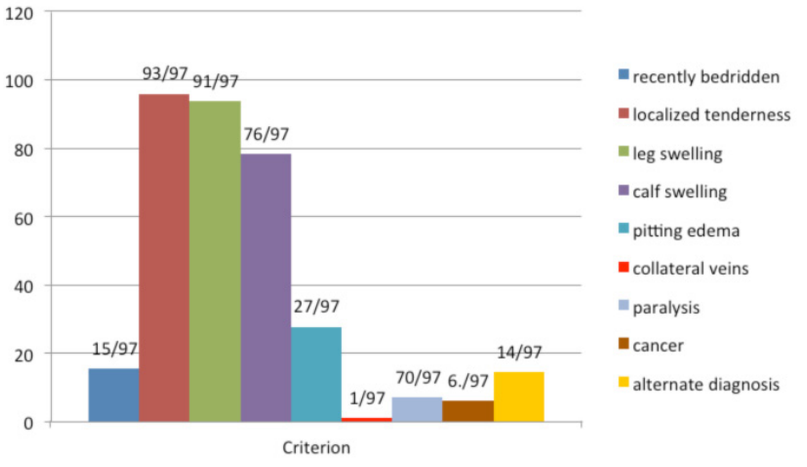
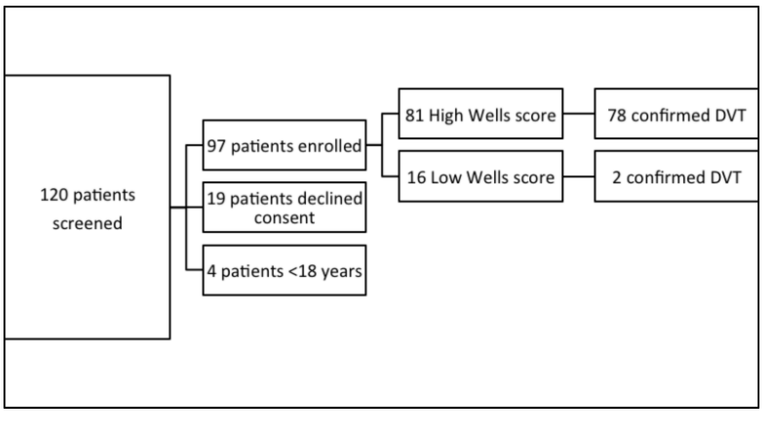


Figure 2
Wells probability score and confirmed diagnosis of DVT in an African patients suspected of DVT



DISCUSSION

To our knowledge, this is the first validation study of the Wells Scoring Rule for DVT in African patients. The prevalence of DVT in our "high" pretest probability group was higher than reported by Wells *et al*. (96% versus 75% respectively) (12).The difference may be explained by the fact that Wells originally trichotimised results into low, moderate and high probability groups while we dichotomised our patients into "less" and "highly" likely probability groups. We found a prevalence of 12.5% among those ranked low probability, which was higher than Wells' prevalence (3%) but similar to the prevalence in several other studies (14, 16,17). We postulate that the different clinical setting and patient population account for the variance in outcome in the low probability groups. Overall, the prevalence of DVT was higher in the "highly" likely group as compared to the "less" likely group ($p<0.001$). This study therefore demonstrates that risk stratification was successful and can be a valuable tool in the context of a diagnostic pathway.

While the gender distribution in this study was similar to many other reported studies (females >males), our patients were younger than those from resource-rich settings (median age 38years versus 57- 66 years respectively)(1-3,6-17).This finding is probably a reflection of our population demographics with most people in the 20-40 years age group (18). Another explanation could be that the cumulative effect of co-morbidities (like cancer, frequent surgeries and hospitalisations) is greater in ageing populations who are proportionately more in resource-endowed settings. Susceptibility to thrombosis induced by pregnancy and puerperium and the use of combined oral contraceptives may explain the preponderance of females to develop DVT.

Infection with HIV is a major health problem globally (19). We found 35/80(44%) patients with

DVT were HIV-infected compared to 5/17 (29%) in the group without DVT (p<0.001). Despite this highly statistically significant difference in HIV prevalence between the two groups, we are unable to make any inferences because our study was not powered to look for this association.

Study Limitations: We used Doppler ultrasound to diagnose DVT and despite its excellent sensitivity and specificity, there still lies some intra-observer and inter-observer variability. The gold standard test, the venogram, was not used due to lack of fluoroscopy to view filling defects. This study did not measure D-dimer levels, which is a useful 'rapid point of care' test in ruling out venous thrombo-embolism especially in the low probability group. (20). Prior history of DVT was added to the recent modification of the Wells score and earns the patient one point during assessment. This study did not use the modified Wells criteria because the parameter of 'recurrent DVT' was difficult to validate objectively in our setting since patients were not certain of their diagnosis. Compounding this is the absence of integrated medical records between local hospitals that would have enabled us access patient past medical records, if any. The paucity of epidemiological studies on DVT in Africa made it difficult to infer the appropriate sample size (based on the prevalence of DVT). Finally, the finding of an association between HIV and DVT may not hold true since our sample size was not derived based on HIV prevalence in the sampled population.

In conclusion, the management of patients with suspected DVT based on pretest clinical probability stratification followed by ultrasound is valid in our setting. The strategy of applying Wells score will reduce the need for unnecessary ultrasound testing in those with low Wells score.

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