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Clinical utility of the modified Wells score in combination with the D-dimer assay in the prediction of deep venous thrombosis in a local population

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Clinical utility of the modified Wells score in combination with the D-dimer assay in the prediction of deep venous thrombosis in a local population

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DECLARATION

I, Matthew Goodier, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine (Diagnostic Radiology) in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

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(Candidate)

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ABSTRACT

Clinical prediction scores such as the modified Wells score have proved useful to determine the likelihood for the presence of lower limb deep venous thrombosis (DVT). Infection with HIV may affect the validity of this approach in the South African context. This study of 230, mostly inpatients, of which 40% were HIV positive, confirms the validity of the modified Wells score in a South African population with a high HIV seroprevalence. The score was found to be most accurate when performed within 48 hours of initiation of anticoagulation therapy and when combined with D-dimer assay result. The more widespread utilisation of this score, especially in conjunction with the D-dimer assay as part of a diagnostic algorithm will make investigation of DVT simpler and more cost effective. A diagnostic algorithm previously proven to be cost effective is suggested for adoption in local clinical practice as well as a basis for future research.

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ABBREVIATIONS

ARV	Antiretroviral
CHBH	Chris Hani Baragwanath Hospital
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CT	Computed Tomography
CMV	Cytomegalovirus
DVT	Deep vein thrombosis
ELFA	Enzyme-linked fluorescence assay
ELISA	Enzyme-linked immunosorbent assay
HIV	Human Immunodeficiency virus
HIT	Heparin-induced thrombocytopenia
HJH	Helen Joseph Hospital
LMWH	Low molecular weight heparin
MR	Magnetic resonance
MRI	Magnetic resonance imaging
PE	Pulmonary embolism
PISA-PED	Prospective investigative study of acute pulmonary embolism diagnosis
ROC	Receiver operated characteristic
TB	Tuberculosis
QALY	Quality-adjusted life year
UK	United Kingdom
US	Ultrasound
VDU	Venous Doppler ultrasound
VTE	Venous thromboembolism

1 INTRODUCTION

1.1 BACKGROUND

Deep venous thrombosis (DVT) of the lower limbs is a common condition which affects a significant proportion of the South African population each year.[1] Prompt and accurate diagnosis of DVT is important to avoid the potentially fatal complication of embolization to the pulmonary arterial circulation.[2] Signs and symptoms of DVT, such as leg pain and swelling, are non-specific, occurring also in other conditions such as congestive cardiac failure, cellulitis and chronic venous insufficiency. This makes it difficult to diagnose DVT based on clinical signs and symptoms alone.

Prediction scores based on clinical findings have proved useful to determine the likelihood for the presence of DVT.[1] Several such scores exist but the Wells score is the oldest and most widely known of these.[3] The Wells score, unlike other prediction scores, does not rely on the results of special investigations such as arterial blood gases, chest x-ray or electrocardiograph. The Wells score initially designed stratified patients into 3 groups (high, intermediate and low risk).[1] More recent work by Wells has simplified the test into a dichotomised version indicating whether DVT is likely versus unlikely.[1] This modified version was the one used in this study and will be referred to as the 'modified Wells Score'.

Raised levels of D-dimer in the blood may indicate the presence of a deep vein thrombosis. The D-dimer is a product produced in the blood during fibrinolysis. The levels of D-dimers in the blood rise in the presence of an intravascular thrombus, e.g. DVT. Raised levels are, however, nonspecific in making the diagnosis of DVT and may be present in pregnancy, liver

disease, malignant conditions and systemic inflammatory conditions.[5] The D-dimer assay is thus sensitive but not specific for the presence of a DVT. The major clinical utility of the D-dimer is that due to a high negative predictive value, a negative test is considered to effectively exclude the presence of a DVT in non-pregnant outpatients with no co-morbid illnesses.[7]

In several studies validating the Wells score, a combined approach of using Wells scoring and D-dimer assay was found to be even more accurate in the exclusion of the condition in low-risk patients.[3, 6, 8, 9] It has been shown that this approach is cost effective as a significant number of patients do not need to be referred for a confirmatory venous Doppler ultrasound (VDU).[1]

Due to the limited resources available in the public health care sector, it is important that the viability of adopting such cost and labour saving strategies be investigated for the South African context. There are, moreover, other unique differences between the local setting and the situation in which previous studies validating the combined Wells score and D-dimer were carried out. Medical professionals in South Africa work in a high human immunodeficiency virus (HIV) seroprevalence setting. The relationship between HIV and vascular disorders such as DVT is complex but HIV has been established to increase the risk of DVT as well as influencing the results of the D-dimer test.[4, 10] HIV patients have generalised suppression of their immune systems as well as a reduced ability to mount an inflammatory response. Although this has not been specifically studied previously, the clinical presentation of DVT in HIV positive may differ from that in HIV negative patients.

This in turn may affect the accuracy of clinical prediction scores such as the Wells score in the local setting.

The study reported on here sought to investigate the validity of the modified Wells Score in combination with the D-dimer assay in predicting the risk for deep vein thrombosis in a local population of patients referred for VDU. The study is unique due to the high proportion of HIV positive patients included. It included both inpatients and outpatients and relied on the referring doctor to assess the patient's modified Wells score which accurately reflects how these tests would be applied in clinical practice.

1.2 STUDY OBJECTIVES

1. To determine the diagnostic performance of the modified Wells Score and D-dimer assay in a patient sample from three public hospitals in Johannesburg (Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), Chris Hani Baragwanath Hospital (CHBH) and Helen Joseph Hospital (HJH))
2. To investigate any effect of HIV positivity on the accuracy of these tests

2 LITERATURE REVIEW

2.1 INTRODUCTION

In this chapter, the latest literature regarding deep vein thrombosis, clinical prediction scores in general and the Wells score in particular are reviewed, the D-dimer assay, the relationship of HIV to deep venous thrombosis and strategies, particularly their cost effectiveness, in the investigation of suspected deep venous thrombosis are also discussed.

2.2 DEEP VENOUS THROMBOSIS

Deep venous thrombosis is a common condition with clinically significant DVT occurring in about 100 per 100,000 people annually.[11] Although no specific epidemiological data is available from South Africa, DVT is a commonly encountered health problem in local hospital practise.

The pathophysiology of deep venous thrombosis has been related to the 'Virchow triad' of abnormal venous blood flow, usually due to stasis, vessel wall abnormality or damage, and abnormalities in the blood constituents such as platelets and the factors involved in the coagulation and fibrinolytic pathways resulting in a predisposition to develop a DVT or venous thromboembolism (VTE).[12] Causes of venous stasis include prolonged bed rest or immobilisation of the limbs, e.g. casts for fracture treatment. Hypercoagulable states are found in patients who have risk factors including recent major surgery or trauma, pregnancy, liver disease, nephrotic syndrome and active cancer, as well as certain drugs such as oral contraceptives.[11, 13, 14] Institutionalised patients i.e. hospitalised patients or patients resident in nursing homes are also at increased risk of DVT.[15]

Common symptoms of DVT include limb pain and swelling. Physical examination may show unilateral oedema, warmth, and dilation of superficial veins. All these features are non-specific and may occur in cellulitis, ruptured Bakers cyst, muscular injury, Achilles tendonitis or rupture.[1, 16]

The most dangerous complication of DVT is embolization into the pulmonary arterial system with resultant increased pulmonary arterial vascular resistance mainly due to hypoxic vasoconstriction which may result in right heart failure. Additional pathophysiological sequelae are increased total alveolar dead-space as well as ventilation perfusion mismatches.[2] The mortality rate for clinically significant pulmonary embolism varies according to the size of the embolism or 'clot burden'. For massive pulmonary embolism the mortality rate is between 30-60% in the acute setting.[17] Non-massive pulmonary embolism has a lower mortality rate however these patients are at risk of recurrent thromboembolism if the risk factors for the initial thromboembolic event persist.[18, 19]

Initial therapy for deep venous thrombosis usually involves either unfractionated heparin or low molecular weight heparin (LMWH) such as enoxaparin sodium. The ease of administration and efficacy of LMW heparin has made this the preferred anticoagulant for the treatment of DVT.[20] LMWH can be administered subcutaneously, has a longer biologic half-life, dosing is fixed, laboratory monitoring is not required and some adverse effects of unfractionated heparin, such as thrombocytopenia, are less likely.[21, 22]

Whilst the prompt initiation of anticoagulation therapy with heparin is important to reduce risk of clot propagation and embolization, such therapy has potentially severe adverse such as haemorrhage and thrombocytopenia. Approximately 2% of patients experience major bleeding within the first 3 months of therapy.[23] The estimated fatality rate for each episode of major bleeding is 13%.[23] Prolonged heparin therapies also places patients at risk of heparin-induced thrombocytopenia (HIT).[22] Because of these complications associated with anticoagulation therapy, prompt and accurate diagnosis of DVT is important in clinical practise to limit the need for commencement of treatment for suspected DVT until its presence can be ruled out.

2.3 D-DIMER

D-dimer is a fibrin degradation product which is produced as a result of fibrinolysis of a thrombus. It consists of two covalently cross-linked D-regions of adjacent fibrin monomers that cannot be further lysed by the fibrinolytic enzyme plasmin.

Blood assay for D-dimer levels is a commonly used diagnostic test which has a high sensitivity for deep vein thrombosis but lacks specificity since elevated levels may also be the result of other conditions such as pregnancy, liver disease, malignancy and inflammatory conditions (including chronic HIV infection).[4] The major current clinical usage of this test is in screening patients for the presence of thrombotic conditions, mainly deep venous thrombosis and pulmonary embolism. The D-dimer assay has been shown to have a high negative predictive value in the evaluation of patients with suspected DVT.[7] A review by

Stein concluded that: “For excluding PE or DVT, a negative result on quantitative rapid ELISA is as diagnostically useful as a normal lung scan or negative duplex ultrasonography finding”.[24]

There are many types of D-dimer assay, both quantative and semi-quantative. These fall into three main types: enzyme-linked immunosorbent assay (ELISA), latex agglutination assays and whole-blood agglutination.[5] The performance of the D-dimer test varies depending on the type of test.[24, 25] Different tests vary in terms of different sizes of fibrin degradation products that can be detected, the anti-D-dimer monoclonal antibodies from different assays recognize different epitopes, and discrepancies can exist in the assay format, calibration standards, and instrumentation.[5] Assays may be defined as high or medium sensitivity[8] and there is no standardisation as to the cut-off values for a positive test. Test-specific cut off values are thus used. The sensitivity of D-dimer tests considered to have good analytical performance is above 95% and specificity above 40%.[26] In a recent review examining performance of various D-dimer assays in current use,[5] the following findings were presented: ELISA and enzyme-linked fluorescence assay (ELFA), the microplate ELISA and the automated quantitative turbidimetric assays (such as the INNOVANCE, STA-LIATEST D-DI and D-DIMER PLUS assays utilised in this study) have a higher sensitivity than the whole-blood agglutination assay (95% compared with 85%), but a lower specificity (50% vs 70%). The major advantage of the whole-blood agglutination assay is that it is a qualitative test which is readily available and fast to perform and thus is the test commonly used in the emergency department setting.

The local laboratories of the three hospitals which provided data for this study use three different types of latex-agglutination tests for D-dimer assays from different manufacturers. Thus CMJAH laboratory uses the STA-LIATEST D-DI D-dimer test manufactured by Stago, CHBH uses D-DIMER PLUS manufactured by Siemens and HJH laboratory uses the INNOVANCE D-dimer assay manufactured by Siemens. These are all latex agglutination immunoturbidimetric assays with high sensitivity. They are the most commonly used D-dimer assays produced commercially for use in clinical practice as they can be done rapidly and are sensitive. ELISA tests are the gold standard type of test but are not easy to use in practice as they are time consuming, require batching, which is expensive, and are more suitable for research applications. However, latex agglutination assays, such as the immunoturbidimetric assay, have been shown to have equivalent diagnostic performance to D-dimer ELISA tests.[27]

2.4 WELLS CLINICAL PREDICTION SCORE

Individual clinical signs and symptoms are of limited value in the diagnosis of DVT. Results of a large meta-analysis [1] showed that the likelihood ratio for most individual signs and symptoms of DVT is close to 1 (see Table 1):

Table 1 Likelihood ratios of various clinical signs and symptoms of deep venous thrombosis (in meta-analysis by Goodacre, 2006)

CLINICAL FEATURE	NUMBER OF STUDIES	Likelihood ratio (LR) (95% confidence interval (CI))
Calf pain	12	1.08 (0.96 – 1.20)
Calf swelling	13	1.34 (1.14 – 1.53)
Past history of DVT	9	2.54 (1.79 – 3.61)
Malignancy	17	2.61 (2.03 – 3.36)
Recent immobilisation	14	1.93 (1.63 – 2.28)
Recent surgery	14	1.72 (1.35 – 2.19)
Obesity	4	1.02 (0.75 – 1.38)
Difference in calf diameter	7	1.76 (1.43 – 2.18)

Homan's sign	11	1.40 (1.18 – 1.66)
Warmth	11	1.31 (1.08 – 1.60)
Tenderness	12	1.18 (1.06 – 1.32)
Erythema	6	1.30 (1.02 – 1.67)
Oedema	10	1.18 (0.99 – 1.41)
		Modified from Goodacre, 2006

The study concluded that, if taken individually, only malignancy and a past history of DVT were useful in ruling in the diagnosis of DVT.

Thus, because of nonspecific clinical symptoms and signs and the major implications of missing the diagnosis of DVT, objective clinical prediction scores have been developed to assist clinicians in determining the clinical probability of DVT.

The Wells score is one of the oldest and most commonly used objective clinical prediction scores for the presence of DVT.[8] The Hamilton score is a recently devised six item score whose performance in a single study compared favourably with the Wells score.[28] This test has not been nearly as extensively evaluated as the Wells score. Other scores relying on clinical variables only are the Kahn score, a four item score, and the St Andre score which is a six item score.[29, 30] In the limited number of studies conducted using these scores, performance of the Kahn score and St Andre score performance proved inferior to the Wells score.[29] Other scores, namely the Geneva score and the Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISA-PED) score exist.[31] These, however, include results of special investigations such as arterial blood gas in the former and chest x-ray in the latter.

The Wells score is based on only traditional risk factors such as recent surgery and malignancy as well as findings on clinical examination (see Table 2).

Table 2 Modified Wells score. The modified Wells score is a score out of 9 based on risk factors such as recent surgery and malignancy as well as findings on clinical examination.

MODIFIED WELLS SCORE[5]	
RISK FACTOR	**POINTS**
Active cancer (patient receiving treatment for cancer within the previous 6 months or currently receiving palliative treatment)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for 3 days or more, or **major surgery** within the previous 12 weeks requiring general or regional anaesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than that on the asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting oedema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previously documented deep-vein thrombosis	1
Alternative diagnosis at least as likely as DVT	-2
	Score > or = 2 DVT likely; score < 2 DVT unlikely

As individual clinical features of DVT have been found to have a low positive predictive value of about 15% and since no single clinical risk factor or finding of clinical examination is sufficiently sensitive and specific for deep venous thrombosis,[32] the combination of these into a prediction score has proven to be useful in clinical practice. The score initially designed stratified patients into 3 groups as follows (see Table 3):

Table 3 Original Wells score stratification. The score stratified patients into 3 groups.

SCORE	RISK GROUP
<0	Low
1-2	Intermediate
>2	High

More recent work by Wells has simplified the test into a dichotomised version indicating whether DVT is likely versus unlikely[6] (see Table 4). The dichotomised version of the Wells score was used in this study and will be referred to as the 'modified Wells Score":

Table 4 Modified Wells score stratification. The modified score was simplified and stratified patients into 2 groups.

SCORE	RISK GROUP
<2	Low clinical probability
>=2	High clinical probability

This has effectively raised the cut-off of a significant Wells score result, increasing the specificity while decreasing the sensitivity. This was found to be advantageous and safe as long as the test was used together with a D-dimer assay.[6] Other stratification methods have been used for example , combining the high and intermediate probability groups.[33]

The Wells score has been extensively validated in outpatient centres for patients with low clinical probability of DVT in hospitals in Canada, Europe and the United states.[8, 34] The studies carried out during the development and subsequent validation of the test were conducted mainly on outpatients. However two studies conducted on hospitalised patients

showed that the Wells score was accurate in these populations also.[3, 30] Pregnant women were not included in the majority of these studies.

The value of an objective prediction score has been questioned. In the PIOPED study,[35] physicians used clinical judgment alone to categorize their clinical suspicion of pulmonary embolism (PE) as high, intermediate, or low and some studies have found that doctors subjective assessment of DVT risk is comparable to the performance of objective clinical prediction rules.[36] However, in this study, the assessing physicians were more experienced with the clinical evaluation of DVT than is generally the case in the local setting, where the evaluation of the patient is often the responsibility of interns or junior medical officers, especially in the initial emergency setting. Although no studies assessing the differences in accuracy of clinical assessment for DVT could be found, it is possible that the accuracy of junior doctor's clinical evaluation may be inferior to that of the doctors participating in the abovementioned study and may be assisted by the use of an objective measure such as the Wells score.

2.5 VENOUS DOPPLER ULTRASOUND

VDU is the most widely utilised test in the investigation of patients with suspected DVT. This is mainly because conventional venography is painful, invasive and utilises potentially harmful iodinated contrast material. Venography may induce DVTs in up to 2% of patients.[37] Venography is also not technically possible in 10% of patients due to difficulties in vein cannulation related to obesity or excessive swelling.[31]

VDU has several limitations. VDU is generally dependent on the operator's skill and experience. VDU cannot reliably distinguish between acute and chronic thrombus (which does not need treatment). It is important to define the terms "proximal" and "distal DVT". "Proximal" DVT generally refers to thrombus occurring in the popliteal vein or femoral veins whereas "distal DVT" refers to thrombus occurring in the calf veins.

Sensitivity is reduced for thrombi in the pelvic and calf veins and in the presence of extensive subcutaneous oedema or obesity. However, a sensitivity and specificity of up to 96% and 97% respectively for proximal DVT on meta-analysis compared with venography have made VDU the imaging of choice for venous thrombosis.[1, 38] VDU is somewhat less sensitive for DVT that is isolated to calf veins with sensitivities of 41 – 75% reported, depending on the techniques used.[1] In current practice, VDU is considered the most useful widely available test and the decision to treat the patient relies on the result of the VDU.

Performance of a VDU is not standardised. Several manoeuvres such as adequacy of venous compression, phasicity of Doppler waveform and response to augmentation manoeuvres, such as manual distal calf compression, may be utilised as evidence for or against the presence of venous thrombus. Practice also varies in terms of the examination of calf veins because the presence of an isolated calf vein thrombus has only a very low risk for pulmonary embolism. A calf vein thrombus may, however, progress distally into the larger veins of the thigh, and thus most authorities recommend follow-up VDU to detect clot propagation and to ascertain any need for treatment. Many practitioners in the local setting do not routinely evaluate the calf veins.

Emergency venous Doppler to exclude deep venous thrombosis is not widely available due to resource constraints and the prioritisation of other imaging studies and more emergent conditions after hours. These resource constraints refer primarily to staff availability and equipment availability after hours. Usually only 1 or 2 registrars are on duty at any specific time and the ultrasound equipment available after hours is often of low technical quality particularly pertaining to the Doppler capabilities of the machine. VDU are often delayed for 48 hours or even longer after presentation. Current practice is to initiate anticoagulation therapy in those with a reasonably high clinical suspicion of DVT while waiting for a VDU to be performed. For outpatients this usually means admission to hospital to await the VDU.

2.6 OTHER MODALITIES

Several other modalities are currently available in the investigation of DVT. These include plethysmography, computed tomographic (CT) venography and magnetic resonance (MR) venography. These modalities have been shown to be useful but are either not widely accessible (as in the case of plethysmography), are expensive (as in the case of MRI) or involve ionising radiation (as in the case of CT). For these reasons, in most institutions, these modalities are only utilised if the findings of the VDU are equivocal. They are not widely utilised in the local setting of this study and thus will not be discussed further.

2.7 COMBINED APPROACH

In a large study,[6] combining the modified Wells score with D-dimer assay resulted in a negative predictive value of 99.1% for the presence of DVT. Using this approach, 218 of 562

patients with suspected DVT avoided unnecessary VDU. The finding was confirmed in a comprehensive systematic review of 14 studies involving more than 8000 patients using the Wells clinical prediction rule, of which 11 of the studies looked at the combined Wells score and D-dimer approach.[8] The overall prevalence of DVT in this meta-analysis was 19%. The pooled sensitivity, specificity, and negative LRs of D-dimer testing in the low clinical probability group were 88%, 72%, and 0.18%.[8] The LRs for a normal result on a high sensitive D-dimer assay among patients with low clinical suspicion were 0.10.[8] The authors concluded that diagnostic accuracy for DVT improves when the clinical probability is estimated before diagnostic tests are performed.[8] Furthermore, the Wells score test in combination with D-dimer assay has the potential to identify patients for whom lower limb ultrasonography is unnecessary.[8] This is based on results from the above meta-analysis which found that the combination of a negative D-dimer result and a low or moderate clinical probability estimate created a probability estimate after testing for DVT of less than 1%.[8] This approach has also proved accurate and cost effective in specific patient populations such as cancer patients in a Canadian hospital.[9] The viability of adopting such cost and labour saving strategies in the South African context should be investigated.

2.8 COST EFFECTIVENESS AND THE USE OF STRUCTURED ALGORITHMS IN DVT INVESTIGATION

The major advantage of structured investigative algorithms in medical practice is to improve care by advocating evidence-based, clinically effective practices to clinicians who may not be aware of the latest evidence.[39, 40, 41] Further advantages include cost reduction, standardization of practice, and reduction of medical liability.[40] The purpose of such

guidelines for clinical practice, according to Shiffman,[39] "…are meant to provide a vehicle for facilitating consistent, effective, and efficient medical practice with the overall goal of improving health outcomes and reducing inappropriate care."

No clinical guidelines or standard algorithms related to the investigation of DVT are in widespread use in the Johannesburg hospitals. Although no clinical audit of practice in the investigation of DVT has been published, many patients with suspected DVT are sent for VDU. This is because it is readily available, cheap and accurate first-line modality. These patients may or may not have had a D-dimer blood test prior to VDU with the decision to obtain the test being at the discretion of the clinician.

The combination of clinical probability scoring, D-dimer blood testing and VDU into diagnostic algorithms have been shown by several studies to be a highly cost effective strategy.[1, 42, 43] A recent large meta-analysis investigating clinical and cost-effectiveness of all non-invasive tools used in the diagnosis of deep vein thrombosis examined multiple algorithms in use in hospitals throughout the United Kingdom (UK).[1] As part of this study, a postal survey of UK hospitals was performed to determine current practice in the work-up of DVT. The cost-effectiveness analysis determined the net benefit of using each algorithm in terms of the cost per quality-adjusted lifeyear (QALY).[1] This study identified the diagnostic algorithm used by Wells in his 2003 study as being the most cost effective algorithm which utilised modalities widely available in the United Kingdom's National Health Service (NHS) (Well scoring, D-dimer and above leg VDU) (Figure 1):

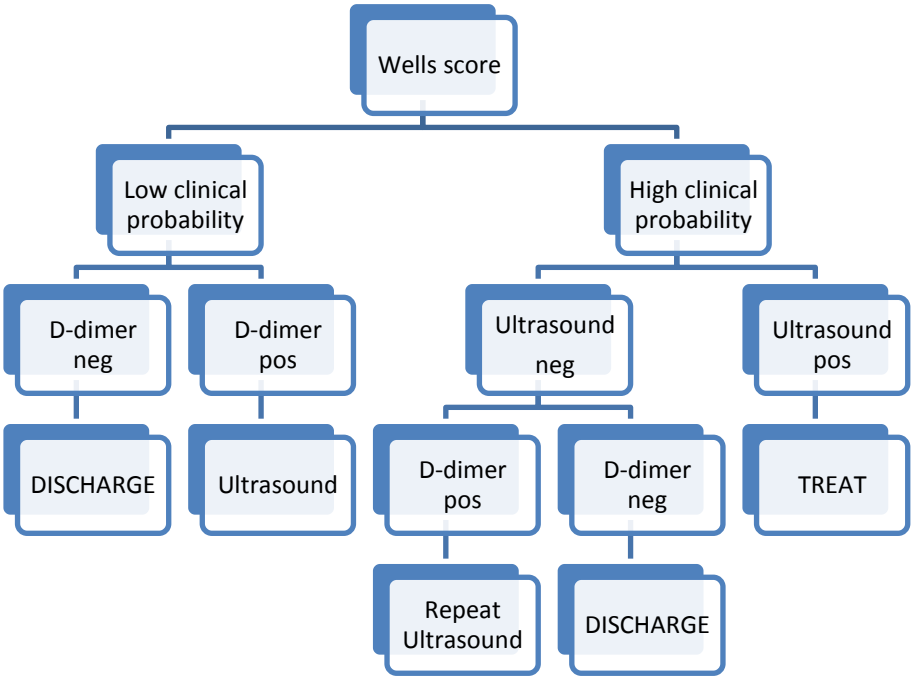


Figure 1 The diagnostic algorithm used by Wells in his 2003 study. This was the most cost effective algorithm which utilised modalities widely available in the United Kingdom's National Health Service (NHS)

This algorithm compared favourably with costs incurred when a strategy of routine VDU for all patients with suspected DVT is followed[1] as summarised below (see Table 5):

Table 5 Costs incurred per 1000 patients for algorithm of ultrasound for all DVTs compared to selected ultrasound according to the Wells algorithm

	Cost of investigations (£) / 1000 patients	**Cost of treatment and complications of non-treatment (£) / 1000 patients**	**Total cost (£) / 1000 patients**
VDU for all	59 364	196 536	255 900
Selected VDU & Wells Algorithm	47 527	168 556	216 082

This analysis concluded that, for the same health benefit, up to £39 818 (equivalent to R445 962 at the time of writing) could be saved per 1000 patients. While the report commented

that the use of repeat VDU scanning in patients with an initially negative VDU did identify additional patients with false negative VDU , it was more expensive and thus the incorporation of repeat VDU scanning would depend on the amount available for the additional health benefit.[1]

Although the cost-effectiveness data can by no means be directly applied to the local situation, in general terms it is likely that the relative costs of the various modalities and algorithms tested in the abovementioned cost-effectiveness analysis are probably similar in this country. More specifically, availability of diagnostic tests and the most commonly utilised tests (i.e. VDU and D-dimer assay) appear to be the same as those utilised most commonly in this country. Precise data on practise patterns and cost effectiveness for our setting will only be available once a similar cost effectiveness analysis has been performed by our Department of Health.

The study reported here sought to determine whether the modified Wells score is valid in the local setting. Potential benefits of such a study include validation of the modified Wells score in a local setting as well as assistance in designing cost-effective protocols for appropriate investigation of suspected DVT in this setting.

2.9 EFFECTS OF HIV

To date the Wells score has not been validated in the South African setting which differs from settings where previous studies have been conducted in terms of being characterised

by a high HIV seroprevalence. The overall prevalence of HIV in the general population in South Africa is estimated to be 17.8% and in Gauteng 16.6%.[44]

There appears to be no studies validating the Wells score in such a high HIV seroprevalence setting nor do any previous studies record data on the HIV status of the participants. It is possible that factors such as high HIV seroprevalence may affect the validity of this test locally. This effect may be significant as HIV seroprevalence in hospitalised patients is expected to be substantially higher than the general population.[45, 46]

Infection with the human immunodeficiency virus has been shown to increase the risk for lower limb DVT via a number of mechanisms as recently reviewed by Eyal and Veller.[47] These include lower levels of natural blood anticoagulants such as Protein S[48], Protein C[49], and Heparin co-factor II[50], higher levels of procoagulant factors such as von Willebrand's factor and endothelial cell dysfunction due to direct infection with HIV. In the limited number of studies done overseas to quantify the additional risk, the incidence of DVT in HIV infected individuals was found to be highly variable, between 0.19% and 18%.[51] This is still substantially higher than the general population which has an annual incidence of approximately 0.05%.[52] Despite this, previous large investigations of the epidemiology of and risk factors for DVT in other settings do not include a study of the role of HIV because the numbers of HIV patients in the institutions publishing these papers is small.[11, 13]

In HIV, DVT risk may increase with lower CD4 counts[53] and certain opportunistic infections such as cytomegalovirus (CMV) and tuberculosis (TB).[54] There is also evidence for a possible

additional risk in patients on treatment regimens including protease inhibitors and rifampicin.[55] In a high HIV seroprevalence setting the incidence of HIV-related DVTs is expected to be high. In a recent publication presenting data from Charlotte Maxeke Johannesburg Academic Hospital, 11 out of 13 (84%) of patients with DVTs were HIV infected.[56]

HIV patients are known to have reduced immune responses mainly due to CD4+ T-cell depletion as well as dysregulation of the immune system.[57] The presentation of other conditions such as meningitis[58] and pulmonary tuberculosis[59] is known to be atypical in HIV positive patients in whom these conditions may be more chronic or indolent than in immunocompetent patients. No studies have been done comparing the clinical presentation of HIV-associated DVT with DVT in HIV negative patients. HIV may result in a reduced sensitivity of the Wells score as it partly relies on clinical examination findings of inflammation such as the degree and extent of leg swelling.

HIV infection may also affect the accuracy of the D-dimer assay. HIV is also known to result in systemic endothelial dysfunction. This has been shown to be associated with increased levels of traditional markers of systemic inflammation including the D-dimer levels.[4] In this context, the D-dimer level has actually been proposed as an independent marker of increased risk of adverse cardiovascular events in HIV positive patients.[10] Because of these factors, the D-dimer test may have reduced positive predictive value in this group of patients. This is unlikely to influence the negative predictive value of the test.

2.10 SUMMARY

Clinical prediction scores such as the Wells score have proved useful to determine the likelihood for the presence of lower limb deep venous thrombosis (DVT). In several previous studies validating the Wells score, conducted in developed countries such as Canada, France and the United States, a combined approach using Wells scoring and D-dimer assay were found to reliably exclude DVT in low-risk patients. This study was undertaken in part because it is possible that infection with HIV may affect the validity of this approach in the South African context. No clinical guidelines or standard algorithms related to the investigation of DVT are in widespread use in the Johannesburg hospitals. The combination of clinical probability scoring, D-dimer blood testing and VDU in diagnostic algorithms have been shown by several studies to be a highly cost effective strategy. The viability of adopting such cost and labour saving strategies in the South African context should be investigated. The study reported here sought to determine whether the modified Wells score is valid in the local setting. Potential benefits of such a study include validation of the modified Wells score in a local setting as well as assisting in designing cost-effective protocols for appropriate investigation of suspected DVT in this setting.

3 MATERIALS AND METHODS

3.1 STUDY POPULATION

The study reported on here was a prospective study of a combined sample of inpatients and outpatients with clinical signs and symptoms of lower limb deep vein thrombosis who were referred for VDU. Data collection commenced on 2/6/2010 and concluded on 27/10/2010. The study was performed in three of the hospitals served by the University of the Witwatersrand Radiology Department: Chris Hani Baragwanath Hospital Helen Joseph Hospital and Charlotte Maxeke Johannesburg Academic Hospital.

All non-pregnant patients 18yrs or older were eligible for inclusion. The study sample was limited to a convenience sample (a sample where the patients are selected at the convenience of the researcher). This is because there was limited access to patients mainly because participation was contingent on the agreement of both referring clinicians and patient.

3.2 SAMPLE SIZE

The prevalence of DVT in patients referred for venous Doppler was estimated to be 35%. A sensitivity of 95% and confidence limits of 5% were required so a minimum sample size of 209 was aimed for. This was calculated according to the following formula for sample size estimation for a required sensitivity:[60]

Desired sensitivity (SN) = 95%

Confidence interval (W) = 5%

Expected Prevalence (P) = 35%

z is a constant = 1.96

$$N = (z^2 \times (SN(1-SN))/W^2/P)$$

= 209 patients

3.3 MEASUREMENTS TOOLS

Three major measurement tools were used: a data collection form, D-dimer assay and a VDU.

3.3.1 Data Collection Form

A brief form regarding each patient whose data was included was completed by the referring clinician (see Appendix 2). The information recorded included the following:

- Patient demographic data:
    - name
    - age
    - hospital number
    - referring doctor and referring doctors telephone number;

- Clinical data:
    - D-dimer assay result (if available)
    - HIV status (if known) and whether the patient was on antiretroviral medication
    - Pregnancy status
    - Whether patients had been on therapeutic anticoagulation therapy for longer than 48hours before ultrasound
    - Information required to calculate the modified Wells score.
- VDU result

3.3.2 D-dimer

Each patient had the results of their D-dimer assay recorded, if available. The relevant local laboratories of the three hospitals which formed the sites for the study used three different D-dimer assays as indicated in the table below:

Table 6 The D-dimer assays in use in the relevant local laboratories of the three hospitals

HOSPITAL	TEST
CMJAH	STA-LIATEST D-DI (Stago)
CHBH	D-DIMER PLUS (Siemens)
HJH	INNOVANCE (Siemens)

The above are latex agglutination immunoturbidimetric assays. Immunoturbidimetric assays have been shown to have equivalent diagnostic performance to D-dimer ELISA tests.[27] A positive assay is defined as greater than 500 µg per litre for the INNOVANCE and STA-LIATEST D-DI tests and greater than 250 µg per litre for the D-DIMER PLUS (information obtained from respective test package inserts). For standardisation purposes, in the relevant laboratories, the result is divided by a factor of 2. Thus in this study, the result is considered positive if the D-dimer value is greater than 250 µg per litre for patients from any of the three hospitals (Elise Schapkaitz, Consultant Haematologist, personal communication).

3.3.3 Venous Doppler

For each patient a VDU was performed by a sonographer, radiology registrar or radiology consultant. The vein segments routinely examined extend from the common femoral vein to the popliteal vein with examination of the calf veins performed by some operators but

not others. Protocol for performance of the tests was not standardised but all of the ultrasound machines used could perform pulsed wave Doppler as well as colour Doppler.

3.4 DATA COLLECTION

In order to facilitate data collection, the heads of the departments of Medicine, Surgery and Emergency Medicine were informed of the study prior to its commencement via email and their co-operation was requested (see Appendix 3). These departments are responsible for the majority of requests for VDU. A brief presentation to inform the radiology department of the study took place during a regular case presentation meeting. Specifically, Ms Z Holland (CMJAH) and Dr A Bera (CHBH), who are responsible for ultrasound in their respective hospitals, as well as the registrars doing their ultrasound blocks in the three hospitals, were approached for their co-operation.

The data collection process was conducted in two ways. In the first instance, the data collection form together with the consent form was made available in the respective ultrasound departments, with copies being distributed in advance to all clinicians who showed a willingness to participate.

When booking the VDU, clinicians were informed about the study and encouraged to participate. If they agreed, they were supplied with the data collection form and consent form. The data collection form and consent form were completed before booking the patient, the completed forms being stapled to the radiological request form. Once the patient came for the venous Doppler study, the data collection form was detached and the

radiologist or sonographer indicated on the form whether the test was positive or negative. The form was then placed in a designated collection box. In order to maintain confidentiality, the section of the form with the patients name and other identifying data was separated from the section with the patient's blood results, clinical findings and ultrasound result. The forms were linked by a numerical code known only to the researcher. Supplies of the forms were replenished on a weekly basis.

In addition, as far as was logistically possible, the statistics books for ultrasound were examined on a daily basis to find inpatients that had been missed by the first process. These patients were found in the wards and their data added to the study provided they met the inclusion criteria and gave informed consent. The modified Wells score and clinical information was recorded by staff from the radiology department. In all cases, recruited patients signed an informed consent form (see Appendix 1).

The study was an open study and the operator performing the VDU study was not blinded to the Well's score or the D-dimer result.

In order to assure the quality of the data, every few days the data collection forms were checked for completeness and any missing or unclear data was, as far as possible, clarified with the referring doctor. All outstanding D-dimer results were followed up with the respective laboratories, using the patients' hospital numbers as recorded on the forms. In cases where data could not be completed, forms had to be discarded.

The study concluded when a sufficient amount of data had been obtained. As mentioned above, this was estimated to be at least 209 patients. The final number included was 230. Ideally the sample size would have been larger in order identify if small differences between subgroups were statistically significant. However, the study had to be terminated due to time constraints.

3.5 DATA ANALYSIS

Data was entered on a spreadsheet and basic descriptive statistical analysis was performed using Microsoft Excel (see Appendix). The online calculator OpenEpi (Dean AG, Sullivan KM, Soe MM. OpenEpi: Open Source Epidemiologic Statistics for Public Health, Version 2.3.1. http://www.openepi.com)[61] was used to calculate the measures of test diagnostic performance including the ROC curves for the modified Wells score and D-dimer tests and the likelihood ratios for components of the modified Wells score and HIV positivity. The t-test was used to compare the age of the group of patient with DVT and the group without. The chi-squared test (two-tailed, Yates corrected) was used to compare the gender and outpatient or inpatient status of the group of patient with DVT and the group without as well as the DVT prevalence in HIV positive, negative and unknown groups. The ANOVA test was used to compare the mean ages between HIV positive, negative and unknown groups. The agreement between the modified Wells score and the reference standard (VDU) was determined using the McNemar test and the Cohen Kappa test.

3.6 ETHICAL CONSIDERATIONS

Although the study required recording of potentially sensitive information such as HIV status, the data was collected and stored in a confidential manner. No HIV testing was performed, as the patient's known status was recorded. Blood was also not taken for D-dimer estimation as the patients known result was recorded. Thus, no additional invasive testing was undertaken. VDU was performed as usual. Overall, the study had a minimal impact on the normal workflow of the ultrasound departments.

A brief information sheet explaining the study was provided to the participants (see Appendix 1). Informed consent was obtained in all cases before the patients were enrolled in the study. Although the study subjects were not expected to benefit directly from participation in the study, results were expected to make a positive contribution to medical knowledge regarding deep venous thrombosis in the local setting and may make the investigation process for patients presenting with this condition in the future more efficient.

Approval for this study from the University of the Witwatersrand Ethics Committee was obtained and the ethical clearance certificate (M10213) was issued on 16/04/2010 (see Appendix 4).

3.7 SUMMARY

The study reported here was a prospective study in a combined sample of inpatients and outpatients from three Johannesburg teaching hospitals in order to determine the diagnostic performance of the modified Wells score and D-dimer assay using VDU as a reference standard test. Three major measurement tools were used: a data collection form, D-dimer assay and a VDU. Basic descriptive statistical analysis was performed using Excel. The online calculator OpenEpi was used to calculate the measures of test diagnostic performance. Approval for this study from the University of the Witwatersrand Ethics Committee was obtained.

4 RESULTS

4.1 DEMOGRAPHICS

A total of 230 patients were included in the study. Six patients could not be included as they had not completed the consent form. Five patients could not be included because they were pregnant. Two patients could not be included because they were underage. This left 230 patients for analysis. The mean age of included patients was 44.8 (SD 16.0, range 18-89); 107 (46.5%) were male and 123 (53.5%) were female.

Patients were recruited from Chris Hani Baragwanath (113 patients, 49%), Charlotte Maxeke Johannesburg Academic Hospital (96 patients, 42%) and Helen Joseph Hospital (21 patients, 9%). The sample comprised 173 (75.3%) inpatients and 57 (24.8%) outpatients (see Figure 2):

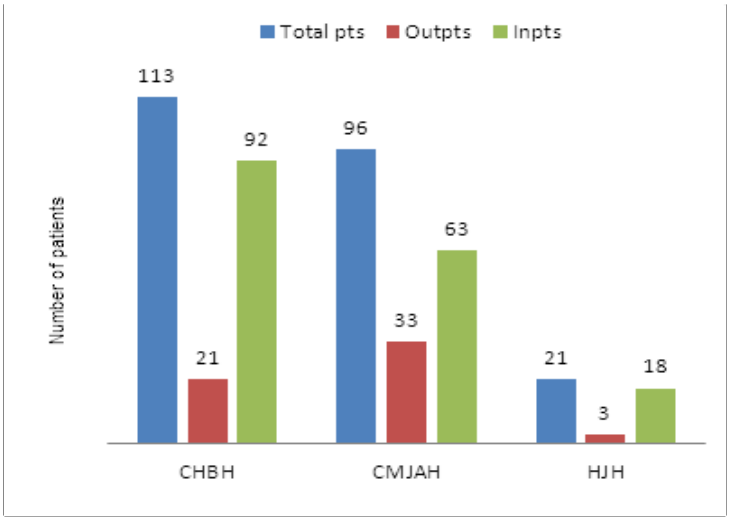


Figure 2 Numbers of in- and outpatients from the three hospitals

Of the total, 96 patients (42.6%) had DVT and 134 (58.3%) did not. Other characteristics of the study population are summarised below (see Table 7):

Table 7 Summary of various characterstics of the study population

	Total	**DVT Present**	**DVT absent**	***p***
Study population	230	96 (41.7%)	134 (58.3%)	n/a
Mean age (SD)	44.8 (16.0)	39.7 (12.5)	48.1 (17.8)	0.00005 (t-test)
Sex				0.447 (chi^2)
Male	107 (46.5%)	48	59	
Female	123 (43.5%)	48	75	
Outpatients	57 (24.8%)	15	42	0.01 (chi^2)
Inpatients	173 (75.3%)	81	92	

The age of the patients with DVT was significantly lower than the patients without DVT. Significantly more inpatients had DVT's in comparison to outpatients.

4.2 D-DIMER

In total, 146 (63%) patients had D-dimer results recorded. Of these 122 (84%) were positive and 24 (16%) were negative.

4.3 HIV

In total, the HIV results of 188 (81.7%) of the patients were recorded. Of these 188, 92 (49%) were positive, 96 (51%) were negative. Of the HIV positive patients, 46 were on ARV's and 46 were not on ARV's. 30 of the 46 patients (65.2%) on ARV's had DVT compared to 25 of the 46 patients (54.3%) who were not on ARV's. There was not a statistically significant

association between the DVT rate between the patients on ARV's and those not on ARV's (p = 0.2985).

Other demographic characteristics of the HIV positive and negative study groups are summarised below (Table 8):

Table 8 Demographic characteristics of the HIV positive and negative groups

	HIV positive	**HIV negative**	**HIV unknown**	***p***
Patients	92 (40.0%)	96 (41.7%)	42 (18.2%)	
Mean age (SD)	36.0 (11.6)	49.8 (16.0)	51.4 (17.8)	0.0012 (ANOVA)
Sex				0.087 (chi^2)
Male	46	48	13	
Female	46	48	29	
Outpatients	13	25	19	0.00052
Inpatients	79	71	23	(chi^2)
DVT				0.000024
Present	56	29	10	(chi^2)
Absent	36	57	32	

Of note, statistically significantly more HIV positive patients had DVT's in comparison to HIV negative patients. The HIV positive group was also statistically significantly younger than the HIV negative patient group. Statistically significantly more inpatients were HIV positive compared to negative and unknown groups.

4.4 WELLS SCORE

The most frequent modified Wells score items present were an alternative diagnosis (n=118), clinical examination findings such as calf swelling (n=121), pitting oedema (n=105),

entire leg swelling (n=94) and localised tenderness in the distribution of the deep venous system (n=74). The most frequent item related to the clinical history was being bedridden for 3 days or more or recent surgery (n=51). The frequency of all findings on the modified Wells score for all patients are summarised below (see Figure 3):

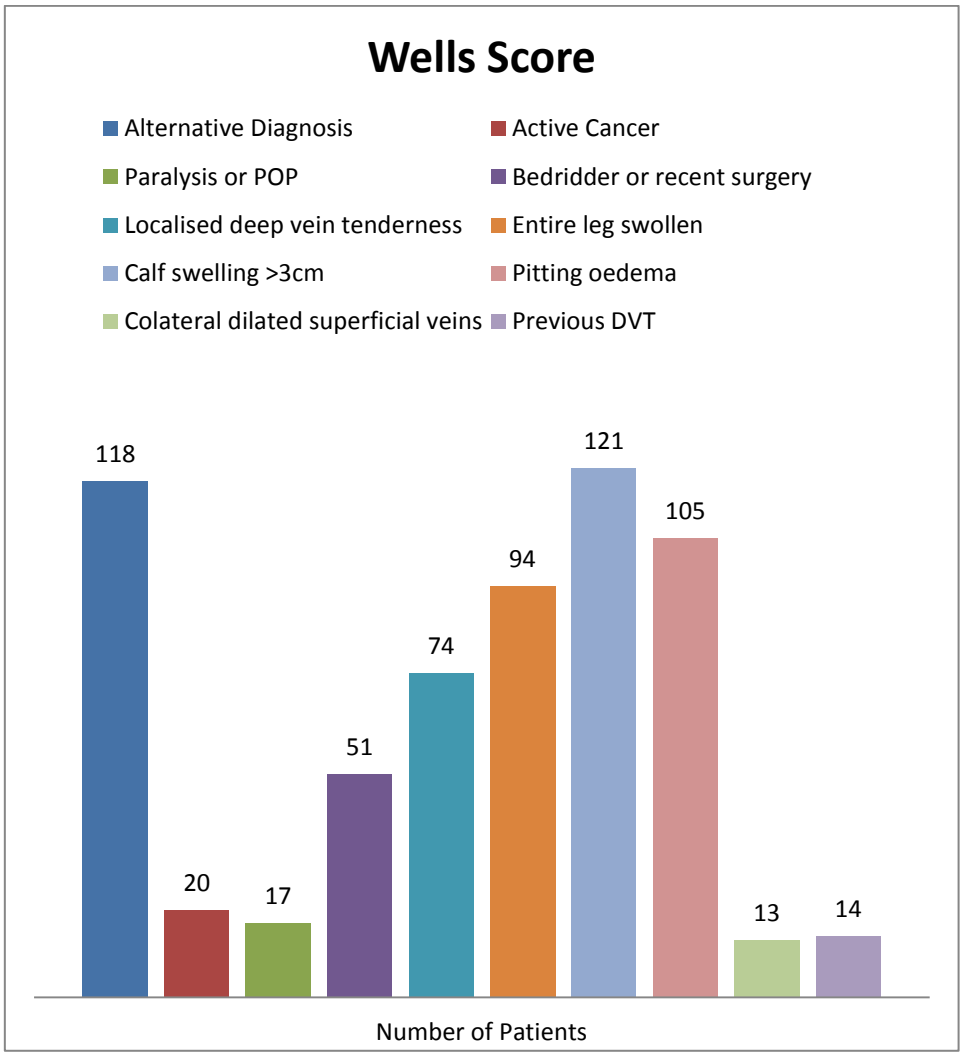


Figure 3 Frequency of findings on the modified Wells score for all patients

Total values of the modified Wells score ranged from -2 out of 9 to 6 out of 9. The mean score was 1.19 (SD 1.9). The distribution of the modified Wells scores for all patients is summarised below (see Figure 4):

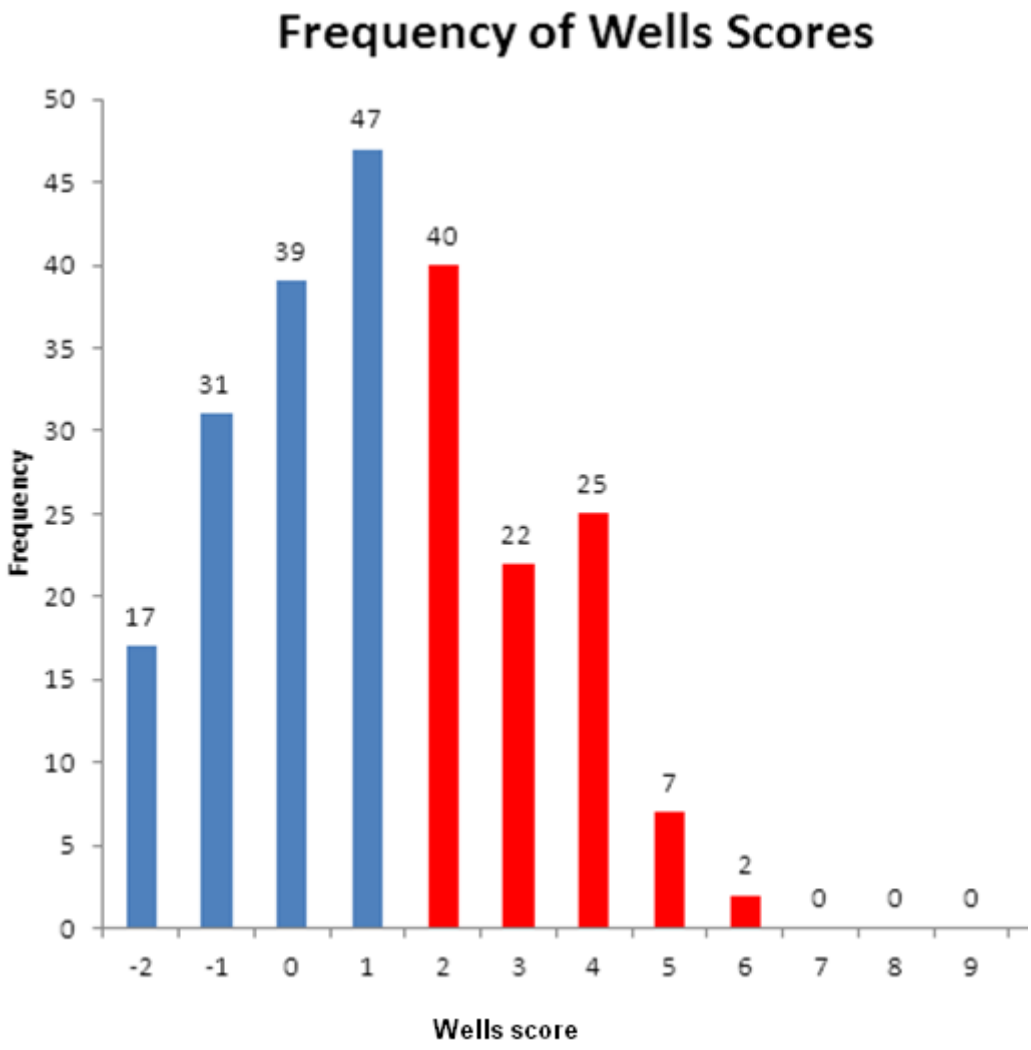


Figure 4 Histogram of the distribution of the modified Wells scores for all patients (n=230)

4.5 EVALUATION IN ANTICOAGULATED PATIENTS

Of the total of 230 patients, 184 (80%) were not on any anticoagulation treatment or had modified Wells score evaluation within 48 hours of initiation of anticoagulation and 46 (20%) were evaluated more than 48 hours after initiation of anticoagulation (see Figures 5 & 6).

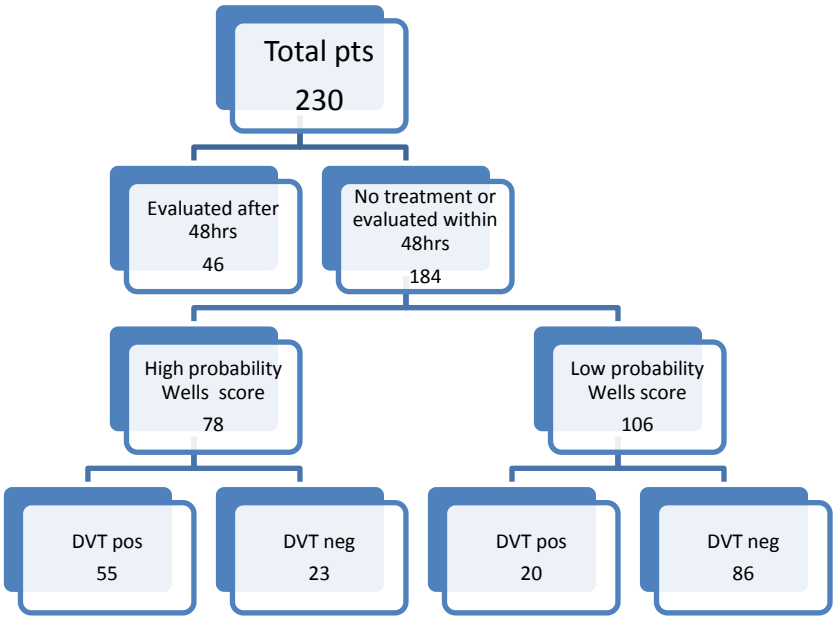


Figure 5 Summary of modified Wells score and Ultrasound findings in the group of patients not on anticoagulation treatment or evaluated within 48 hours of initiation of anticoagulation

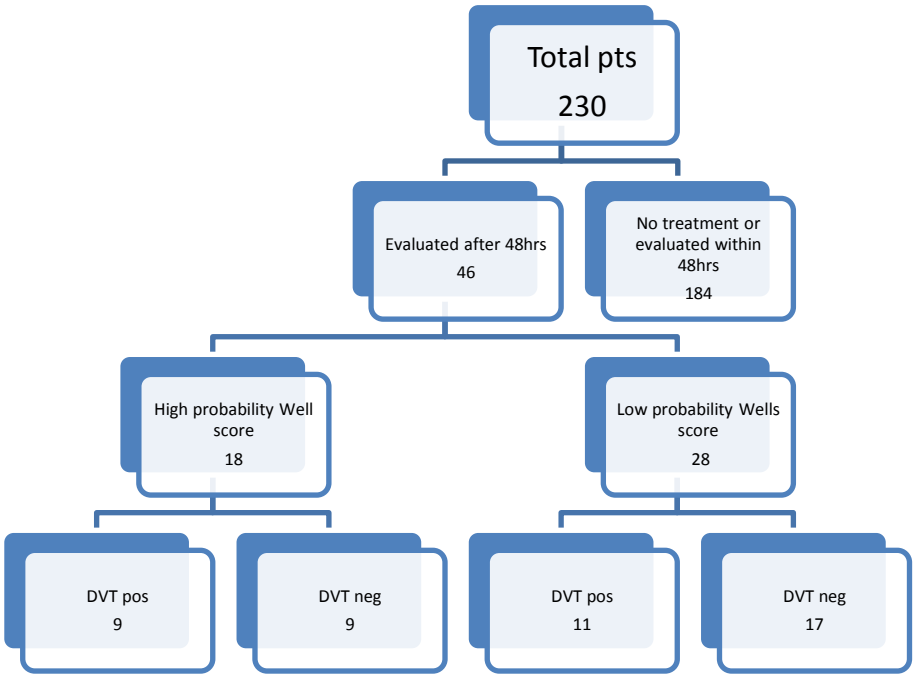


Figure 6 Summary of modified Wells score and Ultrasound findings in the group of patients evaluated after 48 hours of initiation of anticoagulation

Performance of the modified Wells score as a diagnostic test in all patients (see Table 9) and the two subgroups (see Table 11 & 12) are summarised below. Note that the terms "high clinical probability" and "low clinical probability" refer to the modified Wells score stratification. The tables of results include likelihood ratios for the individual parameters of the modified Wells Score (see Table 10). The overall performance of the modified Wells score in comparison to VDU was determined by means of a 2x2 table. The level of agreement between the modified Wells score and VDU was determined with the McNemar test and the Cohen Kappa. (See Table 12)

Table 9 Modified Wells score performance in all patients. Note that the terms "High clinical probability" and "Low clinical probability" refer to the modified Wells score stratification.

	DVT PRESENT	DVT ABSENT	TOTAL
HIGH CLINICAL PROBABILITY	**64**	**32**	**96**
LOW CLINICAL PROBABILITY	**32**	**102**	**134**
	96	**134**	**230**

Parameter	Estimate	Lower - Upper 95% CIs
Sensitivity	66.67%	(56.76, 75.29)
Specificity	76.12%	(68.24, 82.55)
Positive Predictive Value	66.67%	(56.76, 75.29)
Negative Predictive Value	76.12%	(68.24, 82.55)
Diagnostic Accuracy	72.17%	(66.05, 77.57)

Table 10 Likelihood ratio for the Wells score parameters in all patients

Modified Wells Score Parameters	**Likelihood Ratio for a positive finding**	**95% CIs**
Alternative diagnosis	0.5886	(0.5214 - 0.6645)
Cancer	0.4653	(0.0003255 - 665.1)
Paralysis, paresis or recent plaster immobilisation	0.7614	(0.004744 - 122.2)
Bedridden for longer than 3 days	1.57	(1.202 - 2.051)
Localised tenderness along deep venous system	2.736	(2.434 - 3.075)
Entire leg swollen	1.804	(1.669 - 1.95)
Calf swelling >3cm compared to asymptomatic side	2.123	(2.021 - 2.23)
Pitting oedema confined to the symptomatic limb	2.179	(2.046 - 2.321)
Dilated collateral superficial veins	2.233	(0.1019 - 48.94)
Previous documented DVT	2.513	(0.2068 - 30.52)

The only parameters significantly associated with the presence of DVT were being bedridden for longer than 3 days, localised tenderness along deep venous system, swelling

of the entire leg, calf swelling >3cm compared to asymptomatic side and pitting oedema confined to the symptomatic limb.

The variables of cancer, paralysis, paresis or recent plaster immobilisation, dilated collateral superficial veins and a previous documented DVT did not have a statistical significant association with the presence of DVT.

The presence of an alternative diagnosis equally likely than DVT was significantly negatively associated with the presence of DVT.

The performance of the modified Wells score was significantly worse in the subgroup when the score was evaluated after 48 hours of anticoagulation therapy. Because recommendations will be based on application of the score within 48 hours, *further analyses excluded patients evaluated after this time.*

Table 11 Modified Wells score performance in patients evaluated after 48 hours of initiation of anticoagulation

	DVT PRESENT	**DVT ABSENT**	**TOTAL**
HIGH CLINICAL PROBABILITY	**9**	**9**	**18**
LOW CLINICAL PROBABILITY	**11**	**17**	**28**
	20	**26**	**42**

Parameter	Estimate	Lower - Upper 95% CIs
Sensitivity	45%	(25.82, 65.79)
Specificity	65.38%	(46.22, 80.59)
Positive Predictive Value	50%	(29.03, 70.97)
Negative Predictive Value	60.71%	(42.41, 76.43)
Diagnostic Accuracy	56.52%	(42.25, 69.79)

Table 12 Modified Wells score performance in patients on no anticoagulation treatment or evaluated within 48 hours of initiation of anticoagulation treatment

	DVT PRESENT	DVT ABSENT	TOTAL
HIGH CLINICAL PROBABILITY	**55**	**23**	**78**
LOW CLINICAL PROBABILITY	**20**	**86**	**106**
	75	**109**	**184**

Parameter	Estimate	Lower - Upper 95% CIs
Sensitivity	73.33%	(62.37, 82.02)
Specificity	78.9%	(70.32, 85.51)
Positive Predictive Value	70.51%	(59.62, 79.48)
Negative Predictive Value	81.13%	(72.65, 87.44)
Diagnostic Accuracy	76.63%	(70.01, 82.16)
Cohen's kappa (Unweighted)	0.5191	(0.3747 - 0.6635)
McNemar p-value	0.6473	

In patients on no anticoagulation treatment or evaluated within 48 hours of initiation of anticoagulation, there was moderate agreement between the modified Wells score and the VDU as determined by the Cohen Kappa test (as per Landis and Koch magnitude guidelines) and the McNemar test showed no significant difference between the tests.

The prevalence of DVT in high clinical probability patients on no anticoagulation treatment or evaluated within 48 hours of initiation of anticoagulation was 70.51% (95% CI = 59.58 - 79.52) and low clinical probability patients was 18.87% (95% CI 12.48 - 27.43).

DVT prevalence increased for each increasing value of modified Wells score. When the modified Wells score was -2 the prevalence was 0.00% compared to a prevalence of 100% at a modified Wells score of 6. The prevalence of DVT for each value of the modified Wells score is summarised below (see Figure 7):

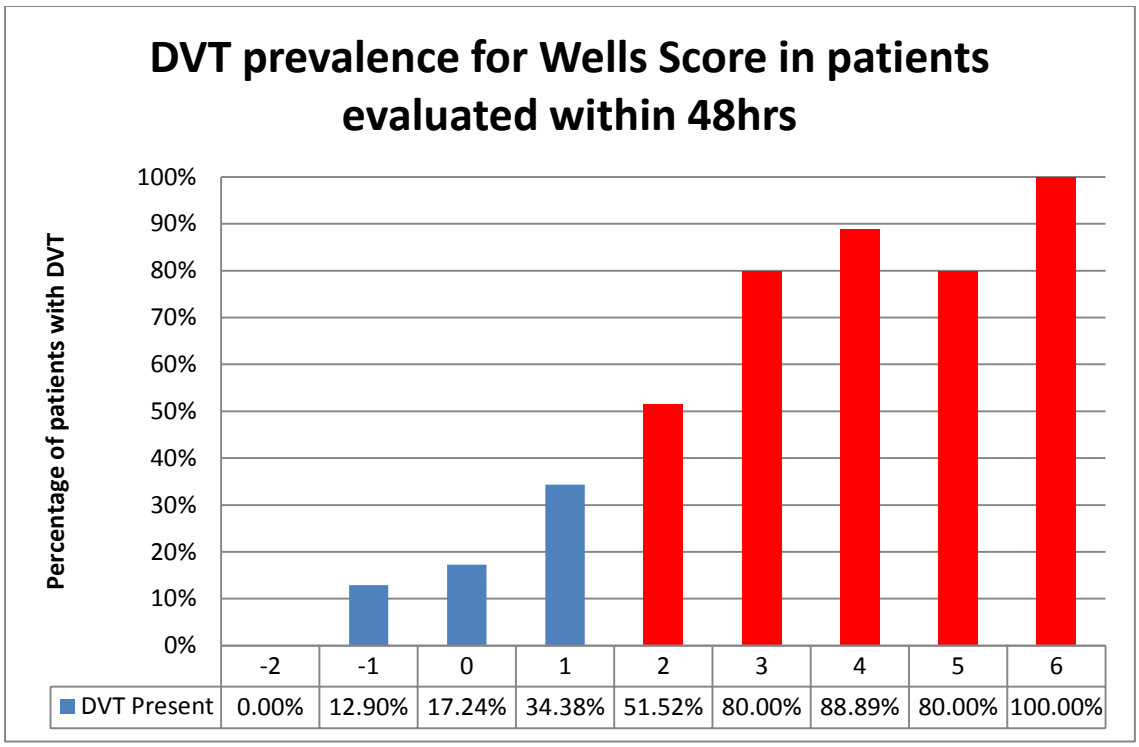


Figure 7 Graph demonstrating prevalence of DVT for each value of the modified Wells score. Higher values of the modified Wells score are associated with higher frequencies of DVT. The blue bars indicate patients with low clinical probability and the red bars indicate patients with high clinical probability.

A Receiver Operated Characteristic (ROC) curve for the modified Wells score was calculated to investigate the relationship between test sensitivity and specificity. The cut-off value of <2 as 'low clinical probability' and >=2 for 'high clinical probability' is shown below (see

Figure 8). Please note that this is included just for illustrative purposes and is not equivalent to the statistically optimum cut off value.

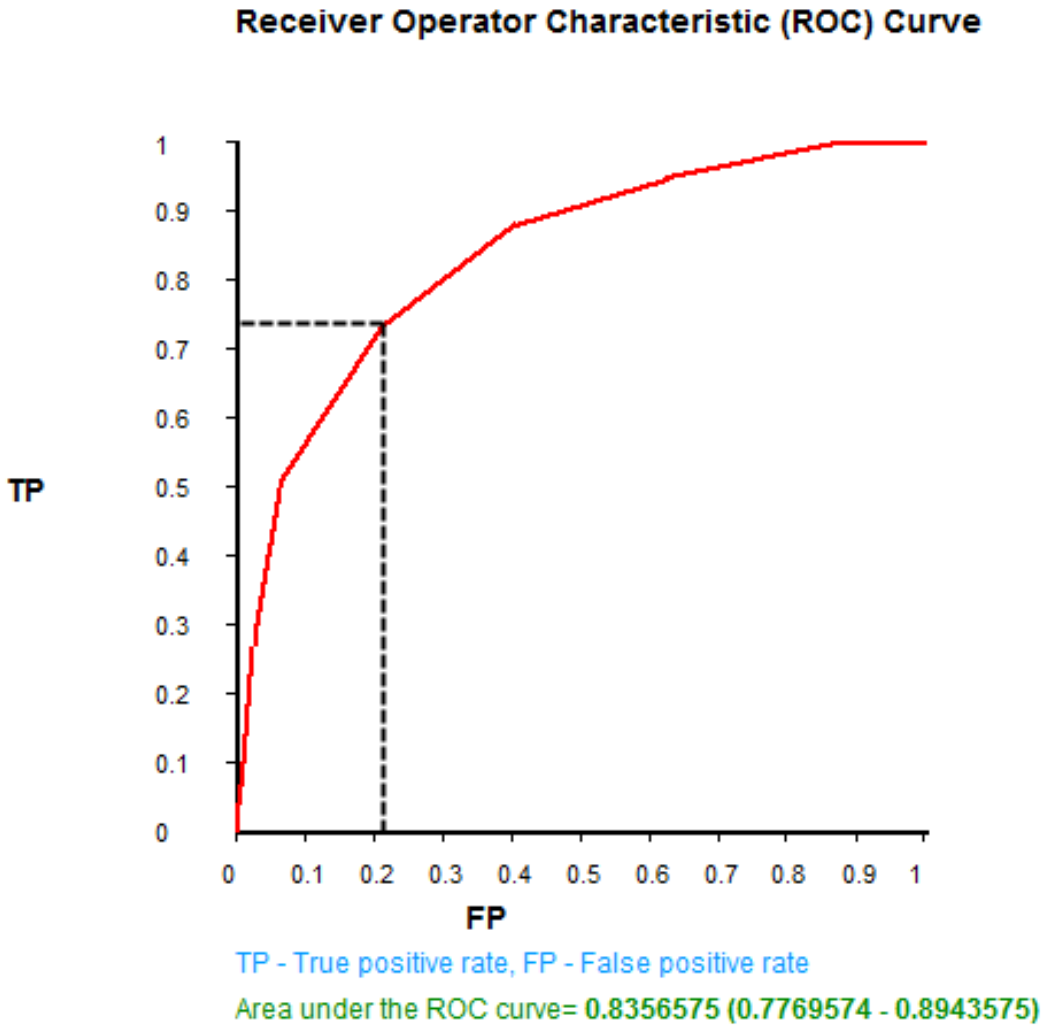


Figure 8 ROC curve for modified Wells score performance in patients on no anticoagulation treatment or evaluated within 48 hours of initiation of anticoagulation treatment. The sensitivity and specificity for a cut-off value of 2 is shown (-------). Please note that this is not equivalent to the statistically optimum cut off value.

4.6 INPATIENTS VS OUTPATIENTS

Of the 184 patients on no anticoagulation treatment or evaluated within 48 hours of initiation of anticoagulation treatment, 51 were outpatients and 133 were inpatients. 14 (27.5%) of the outpatients had a DVT and 61 (45.9%) of the inpatients had a DVT. The

performance of the Wells score in the inpatient and outpatient subgroups are summarised below (see Tables 13 & 14):

Table 13 Modified Wells score performance parameters for all inpatients on no anticoagulation treatment or evaluated within 48 hours of initiation of anticoagulation treatment

Parameter	Estimate	Lower - Upper 95% CIs
Sensitivity	73.77%	(61.56, 83.16)
Specificity	79.17%	(68.43, 86.95)
Positive Predictive Value	75%	(62.77, 84.22)
Negative Predictive Value	78.08%	(67.32, 86.03)
Diagnostic Accuracy	76.69%	(68.82, 83.07)

Table 14 Modified Wells score performance parameters for all outpatients on no anticoagulation treatment or evaluated within 48 hours of initiation of anticoagulation treatment

Parameter	Estimate	Lower - Upper 95% CIs
Sensitivity	71.43%	(45.35, 88.28)
Specificity	78.38%	(62.8, 88.61)
Positive Predictive Value	55.56%	(33.72, 75.44)
Negative Predictive Value	87.88%	(72.67, 95.18)
Diagnostic Accuracy	76.47%	(63.24, 86)

The performance of the test between in and outpatient groups was not different.

4.7 EFFECT OF HIV

Of the 188 patients with recorded HIV results, 92 (48.9%) were positive and 96 (51.1%) were negative. The DVT prevalence in HIV positive patients was 60.87% and in HIV negative patients 31.25%. 30 of the 46 patients (65.2%) on ARV's had DVT compared to 25 of the 46

patients (54.3%) who were not on ARV's. There was not a statistically significant association between the DVT rate between the patients on ARV's and those not on ARV's (p = 0.2985).

The performance of the modified Wells Score in HIV negative and positive patients is summarised below (see Tables 15 & 16) (Patients evaluated after 48hrs of initiation of anticoagulation treatment are not included).:

Table 15 Modified Wells score performance parameters for all HIV negative patients on no anticoagulation treatment or evaluated within 48 hours of initiation of anticoagulation treatment

	DVT PRESENT	**DVT ABSENT**	**TOTAL**
HIGH CLINICAL PROBABILITY	**21**	**14**	**35**
LOW CLINICAL PROBABILITY	**2**	**42**	**45**
	24	**56**	**80**

Parameter	**Estimate**	**Lower - Upper 95% CIs**
Sensitivity	87.5%	(69, 95.66)
Specificity	73.68%	(61.02, 83.35)
Positive Predictive Value	58.33%	(42.2, 72.86)
Negative Predictive Value	93.33%	(82.14, 97.71)
Diagnostic Accuracy	77.78%	(67.58, 85.46)

Table 16 Modified Wells score performance parameters for all HIV positive patients on no anticoagulation treatment or evaluated within 48 hours of initiation of anticoagulation treatment

	DVT PRESENT	DVT ABSENT	TOTAL
HIGH CLINICAL PROBABILITY	**29**	**5**	**34**
LOW CLINICAL PROBABILITY	**13**	**24**	**37**
	42	**29**	**71**

Parameter	Estimate	Lower - Upper 95% CIs
Sensitivity	69.05%	(53.97, 80.93)
Specificity	82.76%	(65.45, 92.4)
Positive Predictive Value	85.29%	(69.87, 93.55)
Negative Predictive Value	64.86%	(48.76, 78.17)
Diagnostic Accuracy	74.65%	(63.45, 83.32)

The negative predictive value of the modified Wells score in HIV negative patients was significantly greater than in HIV positive patients. Otherwise, no performance parameter was significantly different between HIV positive and negative groups.

It was hypothesised that because HIV positivity is an independent risk factor for the presence of DVT in the studied population, the addition of HIV to the modified Wells score would be likely to result in a more accurate score. The modified Wells score was then calculated including HIV positivity as an additional score of 1. This new score was now out of 10 and the cut off for the high clinical probability group was > or equal to 3 and the low clinical probability group was <3. The performance of this score including the presence of HIV is summarised below (see Table 17):

Table 17 Performance parameters of modified Wells score including HIV as an additional score of 1 for all patients on no anticoagulation treatment or evaluated within 48 hours of anticoagulation using cut off of >=3 for high clinical probability and <3 for low clinical probability

Parameter	Estimate	Lower - Upper 95% CIs
Sensitivity	71.21%	(59.36, 80.73)
Specificity	89.41%	(81.09, 94.33)
Positive Predictive Value	83.93%	(72.19, 91.31)
Negative Predictive Value	80%	(70.86, 86.81)
Diagnostic Accuracy	81.46%	(74.51, 86.85)

A receiver operator characteristic curve for this new score was generated with the cut-off used indicated (Figure 9). Please note that this is included for illustrative purposes and is not equivalent to the statistically optimum cut off value.

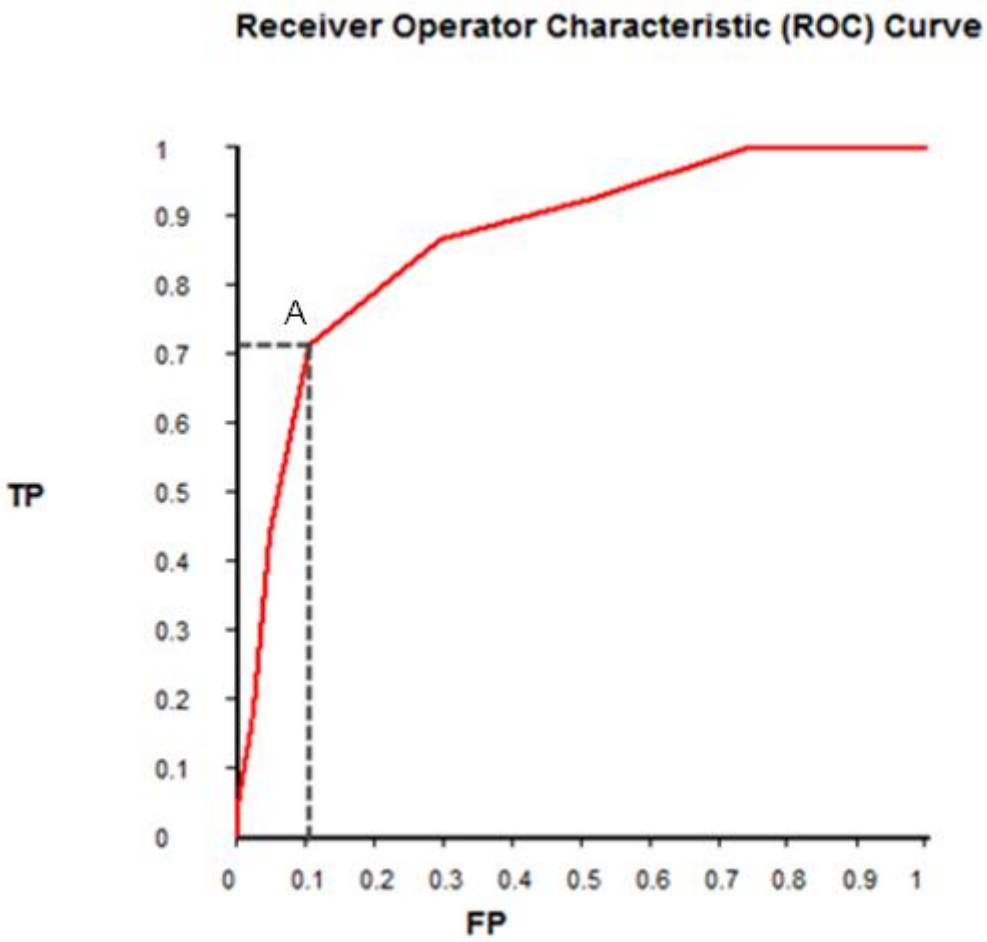


Figure 9 ROC curve for modified Wells score performance in patients on no anticoagulation treatement or evaluated within 48 hours of anticoagulation. The sensitivity and specificity for the new cut-off value of 3 is shown (point A). Please note that this is not equivalent to the statistically optimum cut off value.

This was compared to the original modified Wells score. The ROC curve plots show that for the new test specificity was improved with a small decrease in sensitivity (see Figure 10):

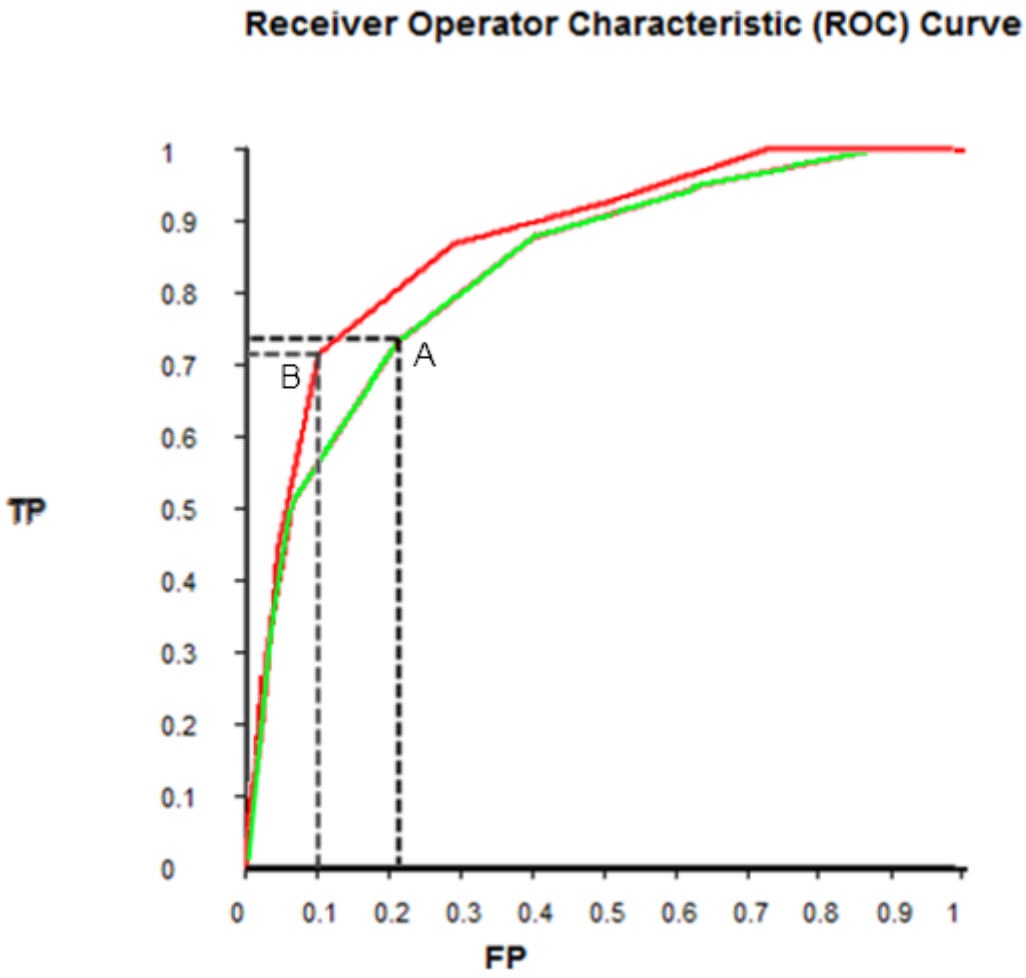


Figure 10 Comparison of ROC curves for modified Wells score performance including (red curve) and not including (green curve) HIV as a criterion in patients on no antigoagulation treatement or evaluated within 48 hours of anticoagulation. The sensitivity and specificity for the cut-off values are shown (points A and B). The ROC curve plots show that for the new test specificity was improved with a small decrease in sensitivity

4.8 PERFORMANCE OF D-DIMER

The overall sensitivity of the D-dimer test was 96.36% (95% CI = 87.68% to 99%) and specificity 29.09% (95% CI = 18.77% to 42.14%). The diagnostic performance of the D-dimer test is summarised below (see Table 18) (Patients evaluated after 48hrs of initiation of anticoagulation treatment are not included):

Table 18 D-dimer performance parameters for all patients on no anticoagulation treatment or evaluated within 48 hours of initiation of anticoagulation treatment

	DVT PRESENT	DVT ABSENT	TOTAL
D-DIMER POSITIVE	**53**	**39**	**92**
D-DIMER NEGATIVE	**2**	**16**	**18**
	55	**55**	**110**

Parameter	Estimate	Lower - Upper 95% CIs
Sensitivity	96.36%	(87.68, 99)
Specificity	29.09%	(18.77, 42.14)
Positive Predictive Value	57.61%	(47.41, 67.2)
Negative Predictive Value	88.89%	(67.2, 96.9)
Diagnostic Accuracy	62.73%	(53.41, 71.19)

The performance of the D-dimer in the low clinical probability Wells score group of patients is summarised below (see Table 19) (Patients evaluated after 48hrs of initiation of anticoagulation treatment are not included):

Table 19 D-dimer performance parameters for low clinical probability patients on no anticoagulation treatment or evaluated within 48 hours of initiation of anticoagulation treatment

	DVT PRESENT	DVT ABSENT	TOTAL
D-DIMER POS	13	32	45
D-DIMER NEG	0	11	11
	13	43	56

Parameter	Estimate	Lower - Upper 95% CIs
Sensitivity	100%	(77.19, 100)
Specificity	25.58%	(14.93, 40.24)
Positive Predictive Value	28.89%	(17.73, 43.37)
Negative Predictive Value	100%	(74.12, 100)
Diagnostic Accuracy	42.86%	(30.77, 55.86)

It should be noted that the sensitivity and negative predictive value of the D-dimer test in the group of patients with low clinical probability Wells scores were both 100%.

4.9 PERFORMANCE OF COMBINED APPROACH

The diagnostic performance of a combination of the modified Wells score and the D-dimer blood test for patients that had the D-dimer blood result is summarised below (see Table 20) (Patients evaluated after 48hrs of initiation of anticoagulation treatment are not included):

Table 20 Combined Wells score and D-dimer performance parameters for all patients on no antigoagulation treatment or evaluated within 48 hours of initiation of anticoagulation treatment

	DVT PRESENT	DVT ABSENT	TOTAL
HIGH CLINICAL PROBABILITY and/or D-DIMER POSITIVE	**55**	**44**	**99**
LOW CLINICAL PROBABILITY and D-DIMER NEGATIVE	**0**	**11**	**11**
	55	**55**	**110**

Parameter	Estimate	Lower - Upper 95% CIs
Sensitivity	100%	(93.47, 100)
Specificity	20%	(11.55, 32.37)
Positive Predictive Value	55.56%	(45.74, 64.95)
Negative Predictive Value	100%	(74.12, 100)
Diagnostic Accuracy	60%	(50.66, 68.67)

Of particular note is that no false negative results were obtained resulting in a test sensitivity and negative predictive value of 100%.

4.10 SUMMARY

The age of the patients with DVT was significantly lower than the patients without DVT. Significantly more inpatients had DVT's in comparison to outpatients. Similarly, significantly more HIV positive patients had DVT's in comparison to HIV negative patients.

There was moderate agreement between the modified Wells score and VDU (the reference standard test) as determined by the Cohen Kappa test. The McNemar test showed no significant difference between the tests.

The modified Wells score was found to be significantly less accurate in patients evaluated after 48 hours of anticoagulation treatment. Diagnostic accuracy of the modified Wells score was very similar between the inpatient and outpatient groups although the number of patients included in the outpatient group was small. Diagnostic accuracy was not significantly different in HIV negative and HIV positive patient groups. However the modified Wells score in HIV negative patients has a significantly higher negative predictive value.

The D-dimer blood test had good sensitivity but poor specificity. HIV positivity was an independent risk factor for the presence of a DVT. Using HIV positivity as an additional criterion to the modified Wells score thus can result in improved diagnostic accuracy (due to improved specificity at the cost of a slight reduction in sensitivity).

The performance of the Wells score combined with the D-dimer assay had very high sensitivity with no false negative results.

5 DISCUSSION

5.1 DISCUSSION OF FINDINGS

Patients with DVT's were significantly more likely to be HIV positive and were significantly younger. This was thought to be due to the higher rate of HIV positivity amongst young people generally in our population. In the South African population, the HIV prevalence is highest in those ages 25-29 with a significant drop-off with increasing age.[44] Similarly, the significantly increased rate of DVT amongst inpatients was thought to be explained by the higher rates of HIV positivity in this group.

The diagnostic performance of the modified Wells score in patients evaluated after 48 hours of anticoagulation was significantly worse. This was mainly due to an increased false negative rate resulting in a decreased sensitivity. This is expected since the clinical signs in patients on prolonged anticoagulation therapy will resolve, resulting in a lower modified Wells score.

The modified Wells score performed reasonably well as a screening test. There was moderate agreement between the tests as determined by the Cohen Kappa test (as per Landis and Koch magnitude guidelines) and the McNemar test showed no significant difference between the tests. Although this study supports the conclusion that the modified Wells score could never be used as a stand-alone test to exclude DVT given its negative predictive value of only 81%, its performance was comparable to that obtained by other studies. More importantly is its performance when combined with a the D-dimer test which has a very high negative predictive value.

The modified Wells score performance was very similar between in- and outpatients. The group of inpatients had slightly higher sensitivity, specificity and positive predictive value and a lower negative predictive value than the outpatients but none of these differences were statistically significant. The overall accuracy of the test between inpatients and outpatients was very similar. The results are somewhat surprising as inpatients are expected to have more co-morbid illnesses and have a higher pretest probability of DVT which should decrease specificity of the score. The finding is likely to be due to the limited sample size, especially given the small group of outpatients included.

The modified Wells score was slightly less accurate in HIV positive patients as compared to HIV negative patients. This was mainly due to a lower negative predictive value. This reduction is possibly due to the reduced inflammatory response that is present in these patients. The sensitivity of the modified Wells score in HIV negative patients was also greater than in HIV positive patients. This difference did not reach statistical significance. Despite this, the findings do suggest that the Wells score is accurate enough to be valid in a population with a high HIV seroprevalence. Addition of HIV as one of the modified Wells score criteria improved test specificity and accuracy and should be considered when making use of the test in a high HIV seroprevalence setting.

Overall, the D-dimer blood test showed a high sensitivity but a low specificity. This low specificity is expected since D-dimer specificity is expected to be lower in populations with a

high prevalence of comorbid illnesses such as that of this study population which included a high percentage of inpatients and HIV positive patients.

The combined test had an excellent sensitivity and negative predictive value and no patient who had received no anticoagulation treatment or who had been evaluated within 48 hours of initiation of anticoagulation treatment with a negative combined test was found to have a DVT. Although this group of patients was small, the finding suggests that this approach is useful in assisting to exclude a DVT in our population. The small size of this group also highlights the underutilisation of the D-dimer test in our setting. Overall only 147 of the 230 (63.9%) patients included in the study had D-dimer results available. More importantly, considering that the D-dimer has been previously found to be most useful in outpatients, only 23 of the 57 (40.4%) of the outpatients in this study had D-dimer blood test performed. The small size of this group also may have an impact on the cost-effectiveness of this approach. Whether this is truly a cost-effective approach in both in- and outpatients is a topic for future studies.

5.2 STUDY LIMITATIONS

5.2.1 Inadequate statistical power / small sample size

The patients included in the study represented only a small proportion of the total VDUs performed in the three departments during the data collection period. A conservative estimate of the total number of VDUs performed is 50 per week. This means an estimated 800 patients were done during the study period and thus the study population represents approximately 25% or less of total VDU studies performed. The small number of patients enrolled as a proportion of total VDUs may be due to several factors. Firstly, the study was

based on voluntary participation of the referring doctor and did not work with a consecutive sample. Secondly, anticoagulation for longer than 48 hours was an initial exclusion criterion. Data on these patients was not collected until two months into the study, thus resulting in a smaller sample for this group of patients. Finally, because of limited access to emergency ultrasound for deep vein thrombosis (for example, over weekends), a significant number of potential participants were placed on therapy before referral for ultrasound.

Analysis of the different subgroups also suffers from a lack of statistical power due to a number of patients who had no D-dimer or HIV result available as well as the small number of outpatients included in the study. This reflects the local practice since currently a relatively low number of patients have D-dimer assays prior to VDU. Although this test is readily available in the local setting, there are no protocols promoting its use.

A number of patients who had been on anticoagulation treatment for more than 48 hours were included in the study. This was mainly to confirm the hypothesis that the modified Wells score would be less accurate in this group of patients since their clinical signs may have resolved. Once this group was excluded from the statistical analysis, only 184 patients remained in the study.

It is possible that ARV medications may influence the risks of DVT in HIV positive patients. In the study there was a trend for more DVTs in patients on ARVs however this association was not statistically significant. Had the sample size been larger, the difference in DVT rates

between the groups could have reached statistical significance. This could be an interesting issue to examine in further studies with greater sample sizes.

5.2.2 Bias

There was a somewhat higher proportion of patients who were positive for DVT in the study than expected as compared to the results of previous studies. Wells has a quoted prevalence of 15%.[8] An informal pilot retrospective record review was conducted prior to commencement of formal data collection indicated prevalence of 35% amongst all patients coming for VDU. This is somewhat lower than the prevalence of DVT in the formal study of 41.7%. This is probably due to an increased likelihood of clinicians including patients for whom they have a high clinical suspicion for DVT.

Although other studies[6, 8, 34] validating the modified Wells score and D-dimer test were conducted almost exclusively on low-risk outpatients, this study included both in- and outpatients. There was, in fact, a bias toward including predominantly inpatients. This is because inpatients were more likely to have positive studies and in the event of forms being incompletely filled in during the day or not included by the staff in sonar, it was only inpatients who could be found and their information obtained. Forms of outpatients with incomplete data had to be discarded.

Patients are more likely to have D-dimer blood tests already taken if they are inpatients. This could have resulted in more false positives since the D-dimer test is known to be non-

specific and inpatients are more likely to have positive D-dimer tests due to other conditions such as systemic inflammation, liver disease etc.

5.2.3 Not blinded

Because the study information form was completed before VDU was performed, the information reflected on the form such as D-dimer level and modified Wells score result was not hidden from the operator performing the sonar. This could possibly have led to bias in interpretation of the VDU. Conversely, in the cases where the study information form was completed after the VDU was performed, the doctor assessing the modified Wells score was not blinded to the result of the VDU. Again, the potential for bias exists.

5.2.4 Limited comparability to previous studies

In order to enable ease of comparison, the study was designed to be as similar as possible to previous studies which have investigated the validity of the modified Wells score.[8] Unfortunately due to logistical reasons and limited resources available, this study did differ in several respects from previous studies.

Ideally, the study should have been confined to outpatients. However, both in- and outpatients were included in this study. The major reason for this was that in all three departments, far fewer outpatients are referred for VDU than inpatients. Outpatients were also more difficult to enrol in the study. If only outpatients had been included then the sample size would have been far smaller. Nevertheless, there were advantages obtained from the inclusion of both in- and outpatients since this did allow for assessment of

modified Wells score and D-dimer test performance in inpatients in our local context and did allow for a comparison between in- and outpatients.

In addition, the study included patients who were assessed more than 48 hours after initiation of anticoagulation therapy. The reason for this was that it seemed to be of value to examine modified Wells score and D-dimer test performance in patients referred for VDU after being on therapy for more than 48 hours, since this is a relatively common occurrence in our setting due to the limited availability of emergency sonar for this indication.

5.2.5 Use of VDU as a reference standard test

Contrast venography is generally considered to be the reference standard for DVT. In comparison to venography, VDU has a good sensitivity for proximal DVT but a lower sensitivity for calf vein thrombi. The accuracy of VDU is also considered to be dependent on the operator. In this study, operators were often inexperienced radiology registrars. The VDU protocol used in the study was not standardised and many operators may only have examined the venous segments above the knee. Details of the VDU report were not recorded on the data collection sheet. These would include whether a proximal or distal DVT were present and the level of confidence of the findings of the report. Both these variables would have affected the accuracy of the result and thus would have usefully been included.

In several other studies examining the Wells score, these limitations were addressed either by confirming the finding with venography[3] or by conducting a follow-up VDU in 1-2 weeks[8], although in general these are not cost effective strategies in clinical practice.[1] Neither of these strategies were utilised in this study since performing additional venograms and calling patients back for additional VDU studies were not logistically feasible. This may have resulted in some false positive or negative results. Nevertheless, the yield of positive finding for repeat sonography in other studies is only 0-2%,[1] which would not have made a significant difference to the results in this study. Repeat sonography and venography are also not commonly utilised diagnostic strategies in routine practice in the local setting.

5.2.6 Non standardisation of technique of Wells score assessment

The modified Wells score was assessed by a range of clinicians with variable levels of clinical experience of DVT as well as variable levels of familiarity with the modified Wells score. No training in application of the modified Wells score was provided. Although, because of this, the process was not standardised, it does represent conditions similar to those in which the Wells score would be utilised in clinical practice.

5.2.7 Non standardisation of definition of HIV result

Because no blood tests were taken as part of the study (due to logistical constraints), in most cases the HIV status of the patients included in the study was determined based on blood testing taken previously. If no recent blood result was available then the HIV status that the patient reported verbally was used. It was left to the discretion of the clinician as to what constituted a recent negative test and whether they considered the verbal report of

HIV status as reliable. In questionable cases they were advised to record the status as unknown. Thus the HIV status recorded was subject to inaccuracies related to unreliability of patients verbal reporting of their status. This is anticipated to result in some underreporting of positive status. Patients may also have been recorded as being HIV negative based on a previous test but may have subsequently contracted HIV, resulting in misclassification of this group of patients.

5.2.8 Non-generalisable results

No control group was included in the study. As a result, the findings may not be generalisable to other settings.

5.3 RESULTS IN COMPARISON TO PREVIOUS STUDIES

5.3.1 Demographics

This study suggests that the population with DVT is significantly younger locally compared to previous studies conducted internationally. The mean age of 44.8 years in this study is younger than any study included in Goodacre's meta-analysis, in which mean ages ranges from 45 to 68 years with a median of 60 years.[1] The mean age of patients with DVT was even younger (39.7 years). This may be considered to be due to the high number of young HIV positive patients present in our hospital system. In the current study the mean age of the HIV positive group was 36.0 years compared to the HIV negative group which was 49.8 years.

5.3.2 Wells score

A notable aspect of previous studies examining diagnostic performance of the Wells score is the heterogeneity of results. The following ROC plot (modified from the meta-analysis by Goodacre, 2006)[1] shows the variability in the results of Wells score performance and includes the result of the current study (see Figure 11):

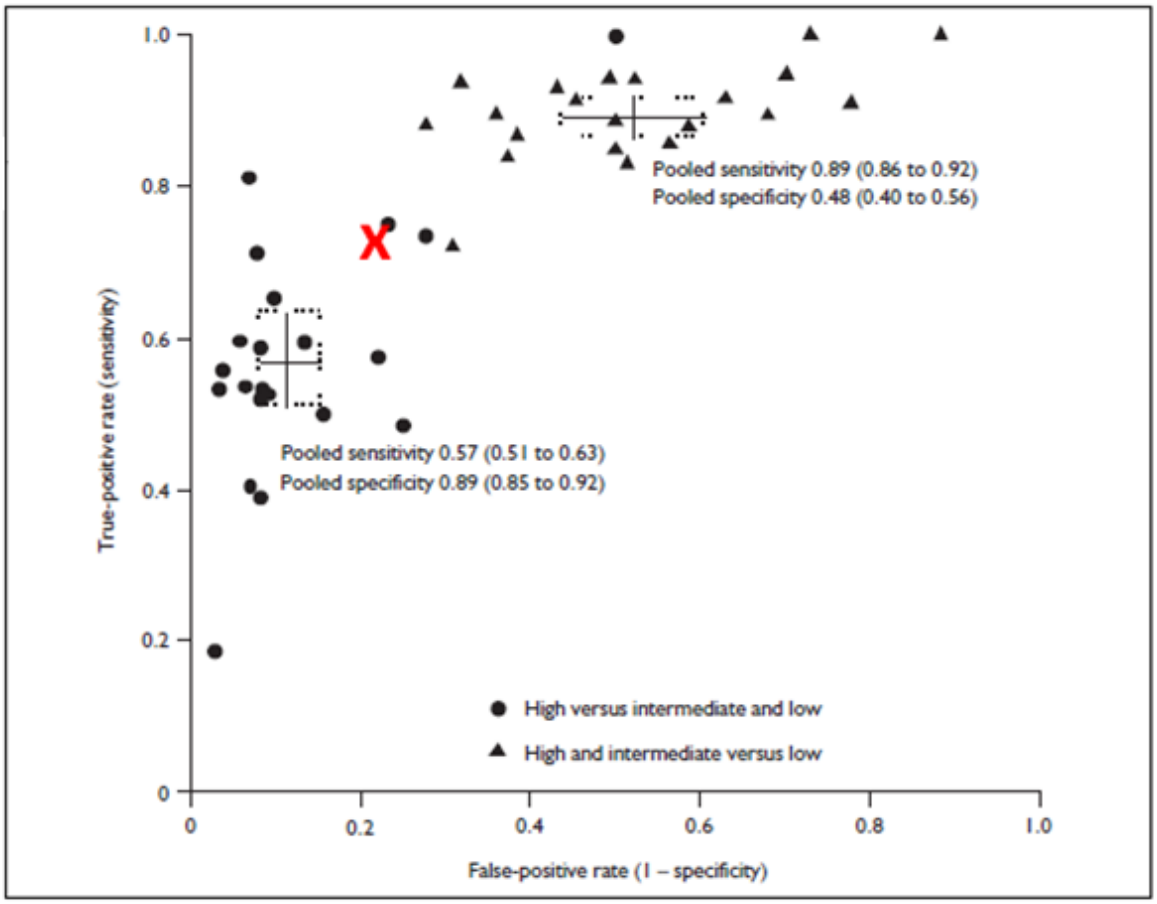


Figure 11 ROC plot (modified from Goodacre, 2006) shows the variability in the results of Wells score performance included in the meta-analysis compared to the result of the current study which is indicated with an "X"

Note: The studies included in the meta-analysis are different as they used the original Wells score which stratified patients into high / intermediate / low categories. This study used the dichotomous form of the score which explains the intermediate sensitivity and specificity demonstrated in the ROC plot.

It is important to emphasise that the current study contained mainly inpatients. Only two large studies have examined the performance of the Wells score in inpatients. Both showed similar performance of the Wells score to this study. In the study by Wells et al, the Wells score showed a prevalence of DVT of 76% / 19.7% / 10.0% in the high, intermediate and low probability groups.[3] In the study by Constans et al the prevalence of DVT was 51% / 19% / 9% in the high, intermediate and low probability groups.[30] The current study showed a prevalence of DVT of 70.5% / 18.9% in the high and low probability groups, respectively. In both studies the overall prevalence of DVT was lower (24.2% and 28.0% respectively) than in this study (41.7%).

5.3.3 D-dimer

Previous studies examining the diagnostic performance of the D-dimer assay show variable results due to differences in the assay used and the criteria for inclusion in the study. The following ROC plot (modified from Goodacre, 2006) shows the variability in the results of D-dimer assays included in the meta-analysis by Goodacre (this table is for latex tests only) and includes the results from the current study (See Figure 12):

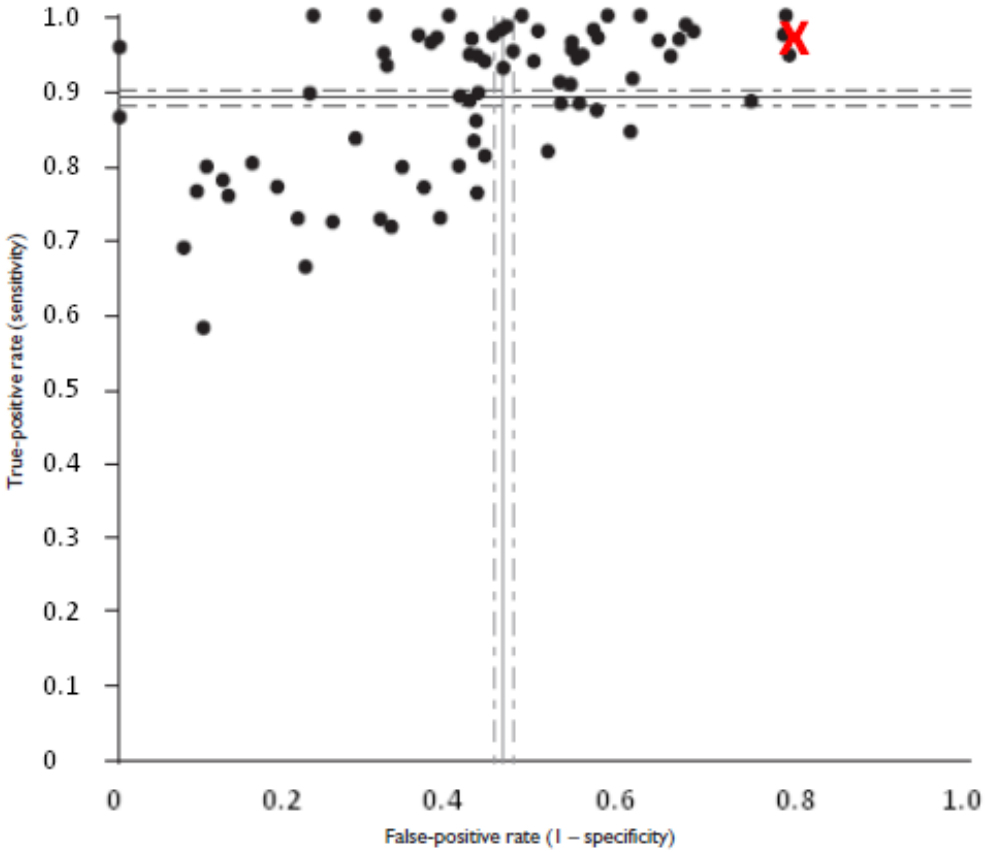


Figure 12 ROC plot (modified from Goodacre, 2006) shows the variability in the results of D-dimer performance included in the meta-analysis compared to the result of the current study which is indicated with an "X"

Data from the meta-analysis by Goodacre show pooled sensitivity of 94% and specificity of 45% for all included studies. Data from my study shows a similar sensitivity but a much lower specificity. The lower specificity is not surprising as the study population contained mostly inpatients, who are more likely to have raised D-dimer levels for other reasons including HIV infection.

5.4 CONTRIBUTION OF THE STUDY AND PROPOSED FURTHER RESEARCH

Despite methodological limitations, the results of the study suggest that the modified Wells score is a robust and practical tool for the investigation of suspected DVT in the local setting. During the study, modified Wells score assessments and VDUs were conducted in many ways under similar conditions to how these would be performed in everyday clinical practise in our setting. For example, most modified Wells score assessments were completed by junior doctors and VDUs by radiology registrars or sonographers.

No patients with a negative combined test were found to have DVT which is in keeping with the results of previous studies and suggests that combining these tests may be useful to exclude the presence of a DVT. This study may not be seen to be sufficiently large to base recommendations that VDU is unnecessary for patients with low clinical probability Wells scores and negative D-dimers and further studies should be undertaken to investigate this group of patients. A potential significant contribution to current practice may be to consider a negative combined test as a reasonable basis for withholding potentially harmful therapy until the condition can be definitively excluded by VDU.

A particularly important finding of this study is that the D-dimer assay may be underutilised in local practice. Overall only 147 of the 230 (63.9%) patients included in the study had D-dimer results available. More importantly, considering that the D-dimer has been previously found to be most useful in outpatients, only 23 of the 57 (40.4%) of the outpatients in this study had D-dimer blood test performed.

The study found no DVT in 11 patients with low pre-test probability scores and a negative D-dimer; however, 50 patients with negative modified Wells scores did not have D-dimers taken. It is in this group of patients that a finding of a negative D-dimer may have made a venous Doppler unnecessary had it been taken.

Based on the study findings, a diagnostic algorithm including the modified Wells score and D-dimer assay should be further investigated for local use. An example of such an algorithm is that suggested by Wells (See Figure 13):

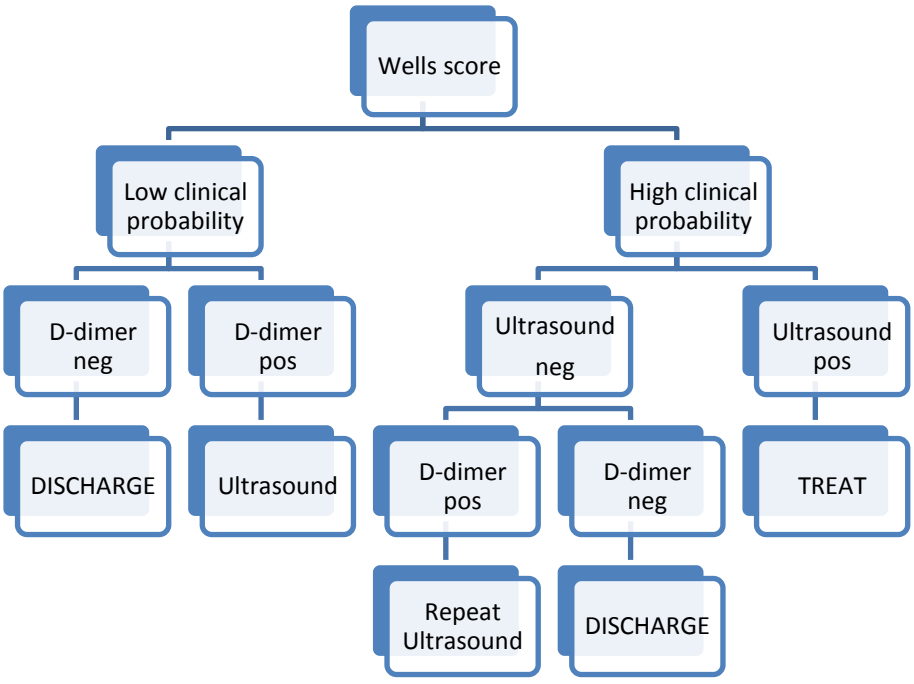


Figure 13 An example of a diagnostic algorithm (as per Wells, 2003) that may be used as a basis for future research

Future studies should determine the safety, accuracy and cost-effectiveness of the proposed approach in the local setting. Such studies could examine the utility of a repeat VDU in patients with initially negative VDU in order to confirm the accuracy of the initial VDU in our

practice. It is currently uncertain what the true accuracy is in local practice and whether a repeat VDU in clinically high risk patients, especially if the D-dimer test is positive, may not also be useful. This study did not record data on the patient's CD4 counts or the details of the antiretroviral therapy that the patients were receiving. The association of CD4 count and ARV therapy with DVT risk could be looked at in future studies with larger sample sizes.

Future studies should also attempt to address some of the methodological limitations present in this study. Requiring that a D-dimer be taken prior to inclusion in the study will increase the group of patients with negative combined tests in order to give a more accurate idea of the true negative predictive value of this combined approach in this group of patients.

5.5 SUMMARY

Despite several methodological limitations including inadequate statistical power, bias, lack of blinding, non-standardisation of VDU technique and potential inaccuracies in reporting of HIV status, the results of this study are consistent with the findings of previous studies and may support the validity of the modified Wells score and D-dimer assay in a South African population with a high HIV seroprevalence. Due to the abovementioned methodological limitations, further research is needed. Making use of a new score which uses HIV positivity as an additional criterion to the Wells score may result in improved diagnostic accuracy.

The more widespread utilisation of the modified Wells score, especially in conjunction with D-dimer assay as part of a diagnostic algorithm will make investigation of this condition simpler and more cost effective. A diagnostic algorithm previously proven to be cost effective is suggested for adoption in local clinical practice as well as a basis for future research. Future research could examine the effect of CD4 count and ARV drugs on the risk for DVT as well as investigating the most cost-effective approach for DVT investigation in South Africa.

6 CONCLUSION

The results of this study confirm the validity of the modified Wells score in a local South African population with a high HIV seroprevalence. The widespread adoption of such a score will help to stratify patients risk for DVT and is especially of value for clinicians inexperienced in assessing patients with DVT.

The score was found to be significantly less accurate in patients evaluated after 48 hours of anticoagulation treatment. As expected, this was mainly due to a reduction in test sensitivity. Further data analysis in this study thus excluded this group of patients. Diagnostic accuracy of the modified Wells score was very similar between the inpatient and outpatient groups, although the number of patients included in the outpatient group was small.

This is the first study to validate the modified Wells score in a high HIV seroprevalence setting and is the first to examine the effect of HIV on test accuracy. Diagnostic accuracy was found to be slightly better in HIV negative than in HIV positive patients although this difference was not statistically significant. HIV positivity was an independent risk factor for the presence of a DVT. Using HIV positivity as an additional criterion to the modified Wells score can thus result in improved diagnostic accuracy (due to improved specificity at the cost of a slight reduction in sensitivity).

The D-dimer blood test performed as expected with good sensitivity but poor specificity. As previous studies have shown the main clinical utility of the D-dimer test is that a negative test essentially excludes the presence of DVT in low risk patients. In this study also, the combination of modified Wells score and D-dimer blood testing identified all patients with DVT if this approach was applied only to patients evaluated within 48 hours. The only two false negatives were present in the group of patients evaluated after 48 hours. Of note was the large number of patients, especially outpatients, with low clinical probability modified Wells scores who did not have D-dimer results available, suggesting that the D-dimer is underutilised in the group of patients that would benefit most from its use.

This study should be seen as a basis for future research. Specifically, the accuracy and viability of utilisation of a diagnostic algorithm using the modified Wells score and D-dimer assay should be investigated since this strategy may have the potential to significantly reduce costs which is highly desirable in our setting.

7 APPENDICES

1 Informed consent form

INFORMATION DOCUMENT AND CONSENT FORM:

Clinical utility of the modified Wells Score in combination with the d-Dimer assay in the prediction of Deep Vein Thrombosis in a local population.

Hello, my name is Matthew Goodier and I am doing research on the causes of deep venous clotting (blood clots in the veins of the leg) as part of my MMed thesis. Research is just the process to learn the answer to a question. I am inviting you to take part in this research study to help us learn more about what may cause a deep vein clot to happen.

As part of the study, you will be asked a few questions about your medical history and the circumference of your leg will be measured by your doctor. This should take about 10 to 15 minutes. The results of two of your blood tests: HIV and the d-Dimer test, which tests how your blood is clotting, will be recorded, as will the result of the ultrasound test of your leg. No new blood tests will be performed as part of the study. It is important for you to know that all personal information that is recorded as part of the study will remain confidential and will not be published. If we do publish the results of the study, you will remain completely anonymous.

Although you will not be benefiting directly by participating in the study, you will be helping us to learn more about deep vein clotting and the tests we do to diagnose it. This will help us to treat other patients more effectively in the future.

It's your choice whether or not you decide to participate in the study. If you do not wish to participate this will not affect your hospital treatment in any way. You can also change your mind at anytime about participating in the study.

CONSENT:

I have read and understood the information above and agree to participate in the study

_____ _____

(Participant) (Witness)

_____

(Date)

If you require further information feel free to contact me:

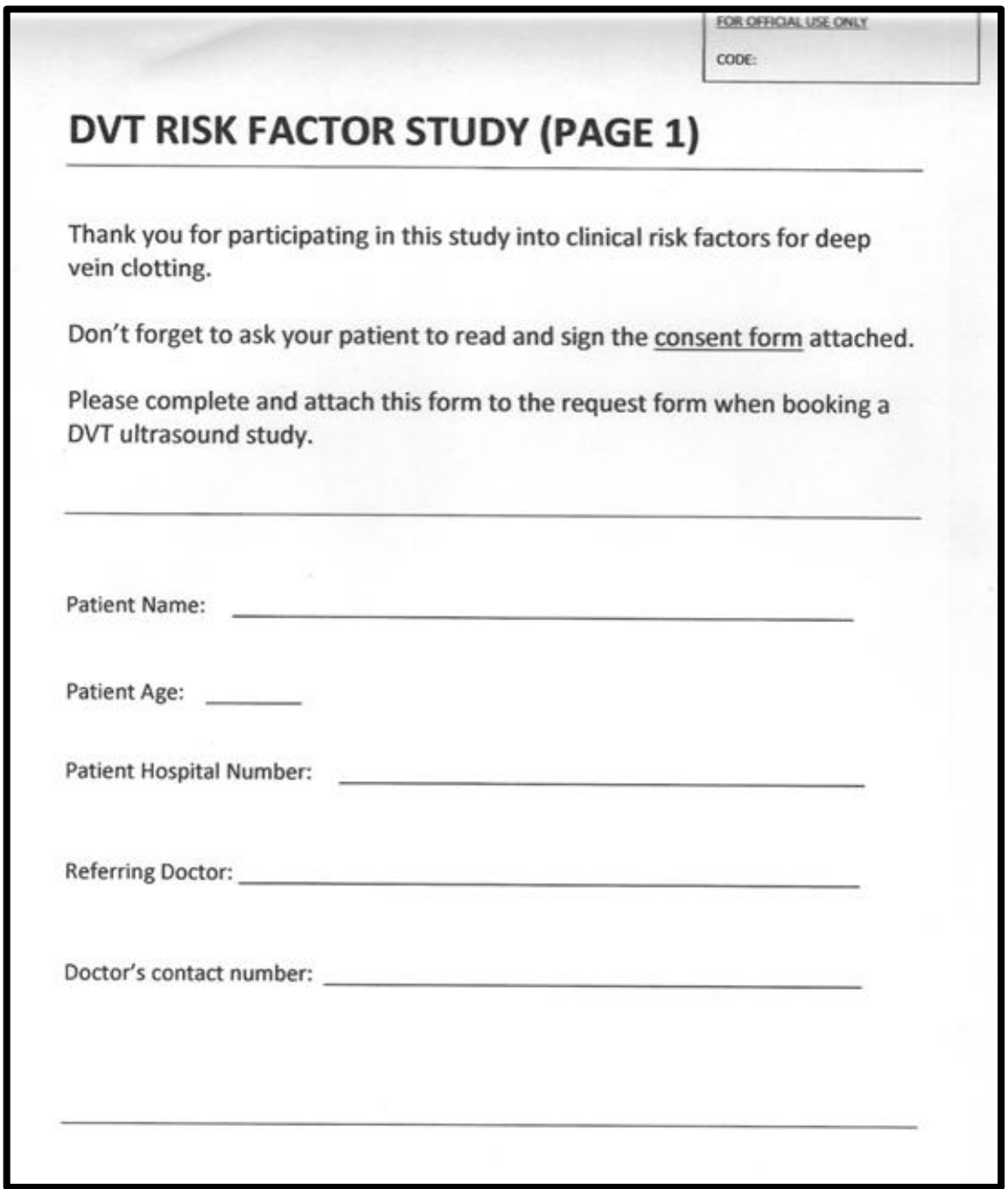
Dr Matthew Goodier
Radiology Registrar
Charlotte Maxeke Johannesburg Academic Hospital Radiology Department
Tel: 011 4893500
Cell: 0844968165

If you wish to report a complaint / problem related to this study please contact:

Human Research Ethics Committee Chairperson:

- **Professor Peter Cleaton-Jones: Tel:(011) 7172301**

2 Data collection sheet



FOR OFFICIAL USE ONLY

CODE:

DVT RISK FACTOR STUDY (PAGE 1)

Thank you for participating in this study into clinical risk factors for deep vein clotting.

Don't forget to ask your patient to read and sign the consent form attached.

Please complete and attach this form to the request form when booking a DVT ultrasound study.

Patient Name: _____

Patient Age: _____

Patient Hospital Number: _____

Referring Doctor: _____

Doctor's contact number: _____

FOR OFFICIAL USE ONLY
CODE:

DVT RISK FACTOR STUDY (PAGE 2)

SECTION A (FOR REFERRING DOCTOR)

Please put a ring around the correct option:

D-DIMER RESULT:	POS	NEG
Is the patient an:	OUTPATIENT	INPATIENT
Patient HIV status:	POSITIVE	NEGATIVE / UNKNOWN
On ARV's:	YES	NO
Pregnant	YES	NO
On therapeutic anticoagulants for > 48 hours	YES	NO
Is an alternative diagnosis (e.g. CCF, cellulitis, lymphoedema) at least as likely as deep-vein thrombosis?	YES	NO

RISK FACTOR	X
Active cancer (patient receiving treatment for cancer within the previous 6 mo or currently receiving palliative treatment)	
Paralysis, paresis, or recent plaster immobilization of the lower extremities	
Recently bedridden for 3 days or more, or **major surgery** within the previous 12 wk requiring general or regional anaesthesia	
Localized tenderness along the distribution of the deep venous system	
Entire leg swollen	
Calf swelling at least 3 cm larger than that on the asymptomatic side (measured 10 cm below tibial tuberosity)	
Pitting oedema confined to the symptomatic leg	
Collateral superficial veins (non-varicose)	
Previously documented deep-vein thrombosis	

SECTION B (FOR SONOGRAPHER / RADIOLOGIST)

Ultrasound Result:	DVT PRESENT	NO DVT

ONCE SONAR RESULT IS RECORDED - PLEASE SEPARATE FORMS AND PLACE IN RED BOXES PROVIDED. THANK YOU.

3 Letter to the Department Heads

To who it may concern

Dear Sir / Madam

Re: DEEP VEIN THROMBOSIS (DVT) ULTRASOUND STUDY

Over the first few months of 2010, I will be conducting a research project in the ultrasound departments of the following hospitals: Baragwanath ,Charlotte Maxeke Johannesburg Academic and Helen Joseph. The purpose of the study is to investigate the diagnostic performance of the modified Wells clinical prediction score alone and in combination with d-Dimer assay in the investigation of lower limb deep vein thrombosis. We feel that validating this clinical score in the local population will provide clinicians with a valuable tool to improve confidence in making a clinical diagnosis of deep vein thrombosis and will facilitate referrals to the ultrasound department.

I am asking for your department's co-operation in order to make this study possible. What is required is firstly that each patient being referred for venous ultrasound be asked to consent to their participation in the study. In addition a short data sheet (provided by the ultrasound department) should be completed with demographic information, the Wells score and the patient's d-Dimer result and attached to the request form before the study is booked . The completion of the form is estimated to take about 5 minutes. We emphasise that no ultrasound will be refused or delayed in order to enrol the patient in the study.

Your co-operation is appreciated. If you have any queries or comments please feel free to contact me.

Dr Matthew Goodier
Registrar
Department of Diagnostic Radiology
Charlotte Maxeke Academic Hospital
Cell: 0844968165
E-Mail: goodiermatt@gmail.com

4 Ethics committee clearance document

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Matthew Goodier

CLEARANCE CERTIFICATE	**M10213**
PROJECT	Clinical Utility of the Modified Wells Score in Combination with the d-Dimer Assay in the Prediction of Deep Vein Thrombosis in a Local Population
INVESTIGATORS	Dr Matthew Goodier.
DEPARTMENT	Diagnostic Radiation
DATE CONSIDERED	26/02/2010
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 16/04/2010 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Prof V Mngomezulu

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

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