Evaluation of the Modified Wells Score in predicting Venous Thromboembolic disease (VTE) in patients with Tuberculosis (TB) or Human Immunodeficiency Virus (HIV) in a South African (SA) setting

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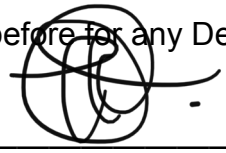
A research report submitted to the faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the degree of Master of Medicine, Johannesburg 2022

DECLARATION

I Dr Tweedy Keokgale declare that this Original Research Report is my own, unaided work. It is being submitted for the Degree of Master of Medicine in the branch of Internal Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any Degree or examination at any other University.



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DEDICATION

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ABSTRACT

Background

There is paucity of data on the Modified Wells Score (MWS) utility on patients with venous thromboembolism (VTE) in a South African setting where there is a high burden of Human immunodeficiency virus (HIV) and Tuberculosis (TB). This study analyses the performance of this score in HIV/TB infected patients compared to non-infected patients.

Objectives

Assess the performance of the MWS as an additional risk factor for VTE in hospitalised patients with a high burden of HIV/TB infections.

Methods

A retrospective cross sectional cohort analysis of the utility of the MWS in 156 HIV/TB infected and non-infected adult patients diagnosed with VTE on Compression Ultrasonography (CUS) or Computed Tomography Pulmonary Angiography (CTPA) in a medical inpatient setting over six months. Patients with HIV and/or TB were assessed as having an additional risk factor (1 point for each) and this was compared to the MWS. A McNeymar's paired sample chi- squared test was used to compare the sensitivity of this score against the MWS.

Results

Of the 156 patients with VTE who were enrolled, HIV was the commonest risk factor (42.31%) with TB accounting for 10.90% of cases. When the MWS adjusted for HIV/TB was used, the sensitivity increased from 25% to 100% for the HIV-/TB+ category, it increased from 77.36% to 98.11% in the HIV+/TB- category and increased from 84.62% to 92.95% in the HIV+/TB+ category. These differences were statistically significant at p-value <0.05 in all categories.

Conclusion

The MWS performs better when HIV/TB infectivity are included as additional risk factors in the score.

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NOMENCLATURE

AFB	Acid Fast Bacilli
ANOVA	Analysis Of Variance
ART	Anti Retroviral Treatment
CD_4	Cluster Of Differentiation 4
CHBAH	Chris Hani Baragwanath Academic Hospital
CKD	Chronic Kidney Disease
CMV	Cytomegalovirus
CTPA	Computed Tomography Pulmonary Angiography
CUS	Compression Ultrasonography
DVT	Deep Vein Thrombosis
ELISA	Enzyme Linked Immunosorbent Assay
HIV	Human Immunodeficiency Virus
HREC	Human Research Ethics Committee
LAM	Lipoarabinomannan
MAC	Mycobacterium avium complex
MWS	Modified Wells Score
NHREC	National Health Research Ethics Council
PACS	Picture Archiving and Communication System
PAI1	Plasminogen activator inhibitor 1
PI	Principal Investigator
PI'S	Protease inhibitors
PJP	Pneumocystis Jerovicii pneumonia
PLHIV	People Living with Human Immunodeficiency Virus
PE	Pulmonary Embolism
ROC	Receiver Operation Curve
SA	South Africa
SBH	Sebokeng Regional Hospital
SD	Standard Deviation
TB	Tuberculosis
TNF	Tumor necrosis factor
USA	United States Of America
VL	Viral Load
V/Q	Ventilation Perfusion Scan

VTE	Venous Thromboembolism
WHO	World Health Organization

CHAPTER 1

1.1- Introduction and Literature review

The Modified Wells Score (MWS) has been validated in determining the probability for venous thromboembolic disease (VTE) in multiple studies in high income countries with low prevalence of Human immunodeficiency virus (HIV) and Tuberculosis (TB) (1-3). These infectious diseases do not appear as independent risk factors in the MWS. This prediction score is based on non-invasive clinical parameters that are derived from history and examination of patients with VTE; each clinical parameter is allocated points that are added together to calculate the MWS, see Appendix 3 and 4. South Africa (SA) has a high prevalence of both HIV and TB (4) and the clinical utility of the MWS within this such an environment has not been critically evaluated with HIV/TB as an additional risk factor.

Deep vein thrombosis (DVT) and/or pulmonary embolism (PE) are collectively known (VTE) (5), VTE is the abnormal formation of clots in the venous system from an acquired or hereditary cause (6). The diagnostic approach to a patient with VTE includes the use of the MWS and D-dimer testing (1). In 1997, the Wells Score was developed as a nine-component clinical prediction rule for DVT, with two points being deducted if an alternative diagnosis to DVT is at least as likely. This gives a possible score range of -2 to 8. There are three risk categories: high (=>3points), intermediate (1- 2 points) and low (<1) (7, 8). In 2003, a further component that is, previously documented DVT, was added to the original Wells score, while the duration of surgery was increased from 4 to 12 weeks (1). This gives a possible score of -2- 9. This version of the MWS reduced the risk categories from three levels (low, intermediate, high) to two: likely (2 points or more) and unlikely (less than 2 points) (1). In 1998, a seven component clinical prediction rule was developed for PE: points are based on criteria in the history and on examination giving a possible score range of 0-12.5 with a score of >6 predicting a high risk for PE, a score of 2-6 an intermediate risk and a score <2 predicting a low risk (8, 9). In 2000, the Wells score for PE was further revised reducing the number of risk categories to just two as for DVT; likely = (>4 points) and unlikely = (<4 points) (8, 10).

Compression Ultrasound (CUS) for DVT and Computed Tomography Pulmonary Angiography (CTPA) for PE can safely be withheld in patients who are unlikely to have VTE according to the MWS and a normal D-dimer (2, 3). Patients who have a high MWS

need a confirmatory CTPA or CUS for PE and DVT respectively. The MWS is the most widely used score for VTE (4, 11) but lacks validation in a South African context with a high prevalence of HIV and TB infection. (12-14) However, neither is part of the pretest probability score. Furthermore, within the South African context, HIV and TB infection are commonly regarded as two of the most important contributors to the rising numbers of VTE's (15). The current mortality associated with VTE in SA is approximately 20 000 deaths per annum (15). Three quarters of these deaths occur in medically ill patients (16) but the true prevalence of VTE in SA is unknown (17).

1.2- Etiology of VTE

PE refers to a blockage of a major vessel in the lungs due to a thrombus (18). DVT is often the precursor of a PE, and is found in 70% of patients with PE (19). VTE is associated with significant morbidity and mortality from cardiac and pulmonary complications, hence the importance of an early diagnosis (13). Virchow's triad describes three factors that contribute to the development of VTE: hypercoagulability; stasis; and endothelial injury (20). The two most important categories of VTE risk factors are patient and procedure.

Patient related risk factors include: age >60 years, history of VTE, immobility, underlying malignancy, pregnancy, estrogen therapy in the form of contraception and hormonal therapy, smoking, congestive heart failure, obesity, hereditary thrombophilic states, inflammatory bowel disease, nephrotic syndrome especially with chronic renal failure (CKD), HIV/TB, and autoimmune diseases including anti-phospholipid syndrome (16, 21, 22).

Procedure related risk factors include duration of procedure, degree of tissue damage especially orthopaedic, degree of immobility following surgery and the nature of the surgical procedure (16).

1.3- VTE and HIV

There is a high burden of HIV in SA, with an estimated prevalence in 2018 of 7.52 million people, of whom about 62% are on treatment, significantly below the target set by the World Health Organization (WHO) (23, 24). Although increasing age is a risk factor for

VTE, the median age for VTE is about 40 years in a South African setting, potentially due to the high prevalence of HIV in this age group (22, 25). Moodley et al. reports a median age of 40 years in HIV-infected VTE patients. HIV contributes to the development of a hyper-coagulable state that predisposes to a two to tenfold increase in VTE versus the uninfected (13). In people living with HIV (PLHIV), there is disruption of the normal balance of coagulation factors with an increase in pro-thrombotic proteins such as von Willebrand factor and a reduction in naturally occurring anticoagulants such as protein S and protein C (26). While most abnormal coagulation factors improve after starting antiretroviral therapy (ART), the coagulopathy fails to normalise completely (27). PLHIV also have higher levels of the lupus anticoagulant, homocysteine, anti-cardiolipin and anti-phospholipids antibodies than the general population; these also contribute to a pro-thrombotic state (26). In addition HIV may directly damage vascular endothelium rendering the vessel wall pro-thrombotic (13).

Similarly, opportunistic infections (oi's) including cytomegalovirus (CMV), pneumocystis jerovicii45 pneumonia (PJP) and mycobacterium avium complex (MAC) have been associated with VTE (13). Furthermore, antiretroviral drugs such as the Protease inhibitors (PIs) promote thrombosis via an effect on the metabolism of thrombotic proteins in the liver (13). A systemic literature review of 13 studies between 1991 and 2007 reported an annual incidence of VTE of between 0.19 - 7.73% in PLHIV per year (13). Low CD_4 cell counts and malignancy are reported as other important risk factors for VTE (11).

1.4- VTE and TB

According to the 2018 World Health Organization's (WHO) Global Report approx.322 000 South Africans contracted TB in 2017 (28). A 2010-2011 study from the Dr. George Mukhari Academic Hospital (Pretoria) reported a 47% prevalence of TB in patients with VTE (29). In an audit of VTE in a Johannesburg hospital, the prevalence of HIV was 50% and that of TB, 30% (22). Awolesi et al. reported a similarly high prevalence of 51.85% and 35.80% for HIV and TB respectively in their cohort of patients in KwaZulu-Natal (25). Indeed these researchers point out that TB is the commonest 'oi' of PLHIV, associated with an increased risk for VTE. (25) TB induces a pro-thrombotic state via the production of cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6), that render vascular endothelium thrombogenic. HIV interferes with the production of hepatic

coagulation factors in the liver increasing factor VIII, fibrinogen and plasminogen activator inhibitor 1(PAI1), and reducing antithrombin and protein C levels (12, 30, 31). The causal relationship between TB and VTE is also demonstrated in the improved pro-thrombotic state a month after initiating TB therapy and the introduction of rifampicin that induces the hepatic coagulation protein synthesis and increases the risk of thrombosis (31, 32).

1.5- Diagnosis of VTE

See Appendix 1 for diagnostic algorithm for suspected VTE (5). Evidence-based literature supports the practice of determining clinical probability (33). Patients with a high MWS (>=2 for DVT and >=5 for PE) are subjected to gold standard testing with CUS and CTPA for DVT and PE respectively (see appendix 1), if the score is low, blood is drawn for D-dimers (8).

Multiple studies have shown that VTE can safely be ruled out by low probability MWS and a normal D-dimer test (1-3). A normal D-dimer level is 0-0.25mg/l (34) however, if a patient is older than 50 years an adjusted D-dimer must be used (age multiplied by 10ng/ml) as D-dimers levels increase with age (35). If the D-dimers levels are elevated the patient is subjected to a gold standard confirmatory test (Appendix 1).

1.6- Accuracy of the Wells Score

Wells *et al* previously published studies reporting the incidence of pulmonary embolism to be 5-8% and 39% to 41% in the unlikely and likely groups for MWS respectively (10). For DVT, Wells *et al* when evaluating the 3 level Wells score 3%, 17% and 75% of the patients with low, moderate and high pretest probability respectively had DVT (7). Subsequently, multiple studies have confirmed the accuracy, efficiency and sensitivity of the Wells score with published sensitivity of 92% by Rabab *et al* and 95% by Amit Bahia for PE and 76.1% sensitivity for DVT (36-38). Modi *et al* reports a specificity, sensitivity, positive predictive value, negative predictive value of 90%, 67%, 31% and 98% respectively for DVT using the 3 level score. In the 2 level score, sensitivity, specificity, positive predictive value and negative predictive value were 100%, 36%, 9% and 100% respectively (39). Lucassen *et al* reported a meta-analysis with a sensitivity of 84% and specificity of 58% with the 3 level score (40) while with the 2 level score the sensitivity and specificity was 60% and 80%

respectively for PE while Bahia *et al* reported a specificity of only 27% (36). A prospective validation study by Wolf *et al* found Kappa values for Wells criteria to be 0.54 and 0.72 for the 3 level and 2 level scorings respectively (41). H'Ng *et al* reported for DVT the 2 level Wells score to have a specificity of 57.74% and sensitivity of 78.57% (42) approximating that to the MWS by Subramaniam *et al* which showed 75% sensitivity and 55% specificity (43). Agreement between a positive Wells score and radiological results for VTE was significant in Owaidah *et al's* study showing sensitivity of 88%, specificity of 55%, positive predictive value of 26% and negative predictive value of 96% (34). Given the above literature, the true sensitivity and specificity of the Wells score is unclear since the studies were all done under different settings and permutations (outpatient, trauma, emergency department, inpatient) and some studies assessed the 'old' 3 level score while other studies assessed the 2-level MWS.

1.7- Wells criteria use in HIV/TB

There is no data that validating the MWS in countries with a high burden of HIV and TB. MWS has been validated with traditional risk factors in high income countries (1, 44). Given the high burden of HIV/TB in SA there is a concern that the MWS might not perform as well as it does in assessing probability of VTE in a non-HIV/TB population as compared to the HIV/TB infected patients.

Considering the poor sensitivity of D-dimers as a rule-in test in the face of HIV/TB co-infection, should we consider HIV/TB an additional risk factor for the MWS? This is being hypothesized in SA as many studies have shown that the commonest cause for VTE is HIV/TB (22, 25, 29, 45). A recommendation by Mampuya *et al*. suggests that doctors working in a primary setting should be trained in the prompt diagnosis and early management of VTE (45). Both Mampuya *et al*. and Awolesi *et al.* conclude that a scoring system that includes HIV/TB should be considered in the South African setting so that gold standard tests are ordered promptly without awaiting D-dimers if the MWS probability is high (25, 45). Their studies showed that the MWS diagnostic accuracy is improved when using a score which includes HIV/TB as independent risk factors.

CHAPTER 2- Methodology

2.1- Research question

To assess the accuracy of the Modified Wells Score in HIV and TB infected patients in a South African cohort of inpatients as compared to the findings of the current published accuracy of this prediction rule.

2.2- Objectives

I- Compare the gold-standard imaging confirmed on CUS and CTPA positive result for VTE to the Modified Wells Score.
ii- Compare the performance of this prediction rule in a cohort of patients with the following permutations:
HIV negative and TB negative (control) vs

- HIV positive and TB positive OR
- HIV positive and TB negative OR
- HIV negative and TB positive

iii- Compare the performance of the Modified Wells Score with a score that includes HIV/ TB as additional risk factors. A score of 1 each will be allocated for HIV and TB.

2.3- Research Design

This study was a retrospective cross sectional cohort analysis of 156 adult patients who were diagnosed with VTE at Chris Hani Baragwanath Academic Hospital and Sebokeng Regional Hospital to determine the predictability of the Modified Wells Score. Adult patients with confirmed VTE on CUS or CTPA were included. Patients were excluded if VTE was diagnosed by ventilation perfusion scan (V/Q), if they had unconfirmed HIV status, pregnant patients and surgical patients were also excluded.

2.4- Data collection

Data collection was performed by the principal investigator (PI) via face-to-face interaction. Patients were recruited over a period of six months. Patient records were reviewed to

complete the data sheet (Appendix 2), Appendix 3 and 4 (MWS). History and examination were performed by the PI to ascertain the clinical features that appear in the MWS, TB had to be definitively diagnosed as per:

1. GeneXpert (nucleic acid amplification test for mycobacterium tuberculosis and rifampicin sensitivity) on sputum, pleural fluid, ascitic fluid, cerebrospinal fluid, bronchial washings or other specimens
2. Acid fast Bacilli (AFB) on specimen
3. Compatible histology, i.e., granulomas with caseous necrosis
4. Urinary antigen detection of lipoarabinomannan (LAM)
5. Culture of TB with or without drug sensitivity
6. Compatible abdominal sonographic findings i.e. lymphadenopathy, abdominal lymph nodes and intra- abdominal fluid
7. Patients that are screened negative as per Gauteng Hospital protocol were treated as negative for TB since further testing was not required.

2.5- Data Analysis

The information obtained from the data sheet was entered into an Excel® spreadsheet. Data was then exported to Stata version 15 a software program for further analysis. The demographic and clinical characteristics of all patients were recorded. Categorical variables were described using frequencies and percentages. A bar graph was used to explore age distribution in patients with VTE. Patients with VTE were categorized into 4 groups, (i) HIV Negative and TB Negative (ii) HIV Negative and TB Positive (iii) HIV Positive and TB Negative and (iv) HIV Positive and TB Positive. Fisher's exact test was used to compare differences in sensitivity of the MWS to correctly assign a positive VTE status across the 4 patient categories.

The overall sensitivity of the MWS, the adjusted MWS (HIV and/or TB) and D-dimers to correctly assign a positive VTE status was estimated using proportions with logit-transformed 95% confidence intervals. The McNemar's paired sample chi-squared test was used to compare the sensitivity of each score against the MWS.

Patients were further categorized into cases (HIV positive and/ or TB positive) and controls (HIV negative, TB negative). Differences in age, gender, MWS and D-dimers in cases and

controls were explored. The Student's T-test for comparison of means was used to compare normally distributed continuous variables (age, MWS), the Wilcoxon rank-sum test for equality of medians was used to compare D-dimers which was not normally distributed and Pearson's Chi-squared test was used to compare proportions by gender.

Mean MWS and the median D-dimers for each patient category are presented. Analysis of variance (ANOVA) was used to compare mean MWS across patient categories. The Kruskal-Wallis equality-of-populations rank test was used to compare the median D-dimers by patient category.

2.6- Ethics

Ethics approval was obtained from Wits Research Ethics Committee (HREC Medical), Ref Number M190680. Permission for the use of patient records and patient interview was obtained from the Clinical Head of Department of Internal Medicine and the Chief Executive Officer/Superintendent/Clinical Manager of the two hospital (CHBAH and SBH). The research proposal was submitted for approval by National Health Research Ethics Council (NHREC), Ref number GP201910001.

CHAPTER 3- RESULTS

Table 3.1: Summary of the characteristics, D-dimer scores and Modified Wells Scores of patients included in this study with Venous Thromboembolic disease (n=156)

CHBAH- (n=137)

SBH- (n=19)

	n	(%)	Mean (SD)	Median (IQR)
Demographic features				
Age at presentation (years)			51.54 (17.91)	
<20	3	1.92		
20-29	13	8.33		
30-39	33	21.15		
40-49	26	16.67		
50-59	25	16.03		
60-69	28	17.95		
70-79	17	10.90		
≥80	11	7.05		
Gender				
Male	43	27.56		
Female	113	72.44		
Clinical Features				
HIV				
Negative	90	57.69		
Positive	66	42.31		
TB				

Negative	139	89.11		
Positive	17	10.90		
Type of VTE				
DVT	121	77.56		
PE	31	19.87		
DVT and PE	4	2.56		
Risk factors for VTE				
HIV/TB	52	33.33		
Metabolic syndrome	36	23.08		
Malignancy	17	10.90		
Unknown/None	14	8.97		
Bedridden/Immobility	9	5.77		
Autoimmune disease	5	3.21		
Hormonal contraceptive use	5	3.21		
Sepsis/Infection	5	3.21		
Other	5	3.21		
Smoking	4	2.56		
Congestive heart failure	2	1.28		
CKD	2	1.28		
Patient Category				
HIV Negative, TB Negative	86	55.13		
HIV Negative, TB Positive	4	2.56		
HIV Positive, TB Negative	53	33.97		
HIV Positive, TB Positive	13	8.33		

D dimers score				2.89 (1.18 - 5.80)
Modified wells score				4 (3 - 5)

Key to Table 3.1: HIV- Human immunodeficiency virus, TB- Tuberculosis, VTE- Venous thromboembolism, DVT- Deep vein thrombosis, PE- Pulmonary embolism, CKD- Chronic kidney disease, IQR- Inter quartile range, SD- Standard deviation, n- Number, CHBAH- Chris Hani Baragwanath Academic Hospital, SBH- Sebokeng Regional Hospital.

Table 3.2: Comparison of Cases and Controls (n=156)

	HIV Negative, TB Negative (Controls)	HIV and/or TB positive	P Value*
Age *Mean (SD)*	58.13 (18.65)	43.46 (13.10)	**<0.0001***
Gender *N (%)*			
Male	22 (51.16)	21 (48.84)	
Female	64 (56.64)	49 (43.39)	0.539
Modified Wells Score *Mean (SD)*	4.37 (1.60)	3.91 (1.35)	0.055
D-dimers *Median (IQR)*	2.69 (1.12- 5.8)	3.02 (1.2- 6.12)	0.692

Key to Table 3.2: *- Statistically significant, n- Number, SD- Standard deviation, IQR- Inter quartile range, HIV- Human immunodeficiency virus, TB- Tuberculosis,

Table 3.3: Comparison of the overall sensitivity of the MWS vs the adjusted MWS. For HIV/ TB as additional risk factors.

Scores	MWS (95% CI)	Comparison Group (95% CI)	Difference (95% CI)	McNemar's Chi-squared test P-value
MWS vs MWS+HIV only	83.33 (76.66-86.43)	91.02 (85.36-94.63)	7.69 (2.86-12.51)	0.0005*
MWS vs MWS + TB only	83.33 (76.66-86.43)	85.90 (79.45-90.56)	2.56 (0.56-5.68)	0.0455*
MWS vs MWS + HIV + TB	83.33 (76.66-88.43)	92.95 (87.66-96.07)	9.61 (4.35-14.88)	0.0001*

Key to Table 3.3:*- Statistically significant, HIV- Human immunodeficiency virus, TB- Tuberculosis, MWS- Modified Wells Score, CI- Confidence interval, P value- Probability value.

Table 3.4: Sensitivity of the Modified Wells Score, before and after adjustment for HIV and/ or TB

Patient Category	Modified Wells Score N (%)	Modified Wells Score Adjusted for HIV+ only (+ 1) N (%)	Modified Wells Score adjusted for TB+ only (+1) N (%)	Modified Wells Score Adjusted for HIV+ & TB+ (+1 +1) N (%)	Total
HIV Negative, TB Negative	77 (89.53)	77 (89.53)	77 (89.53)	77 (89.53)	86
HIV Negative, TB Positive	1 (25.00)	1 (25.00)	4 (100.00)	4 (100.00)	4
HIV Positive, TB Negative	41 (77.36)	52 (98.11)	41 (77.36)	52 (98.11)	53
HIV Positive, TB Positive	11 (84.62)	12 (92.31)	12 (92.31)	12 (92.31)	13
Overall	130 (83.33)	142 (91.03)	134 (85.90)	145 (92.95)	156

Key to Table 3.4: HIV- Human immunodeficiency virus, TB- Tuberculosis VTE- Venous thromboembolism, Positive +, Negative -.

Table 3.5: Sensitivity of the Modified Wells Score in Patients with HIV and/or TB vs Controls

Patient Category	Modified Wells Score N (%)	Modified Wells Score Adjusted for HIV+ only (+1) N (%)	Modified Wells Score adjusted for TB+ only (+1) N (%)	Modified Wells Score Adjusted for HIV+ & TB+ (+1 +1) N (%)	Total
HIV Negative, TB Negative/Not indicated (Controls)	77 (89.53)	77 (89.53)	77 (89.53)	77 (89.53)	86
HIV and/or TB positive	53 (75.71)	65 (92.86)	57 (81.43)	68 (97.14)	70

Key to Table 3.5: N- Number, + Plus, HIV- Human immunodeficiency virus, TB- Tuberculosis,

Table 3.6: Logistic regression comparison of cases and controls

	Unadjusted		Adjusted Odds Ratio (95% CI)	
	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
Age	0.95 (0.93 – 0.97)	**<0.001***	0.96 (0.93 – 0.98)	**0.001***
Gender				
Male	Reference		Reference	
Female	0.80 (0.40 – 1.62)	0.539	0.87 (0.34 – 2.21)	0.762
Modified Wells Score	0.81 (0.65 – 1.01)	0.058	0.89 (0.65 – 1.22)	0.459
D-dimers	1.00 (0.99 – 1.02)	0.695	1.02 (0.97 – 1.07)	0.416

Key to Table 3.6: *- Statistically significant HIV- Human immunodeficiency virus, TB- Tuberculosis VTE- Venous thromboembolism + Positive, - Negative

Cases were significantly younger than controls mean (SD) 43.46 (13.10) vs 58.13 (18.65), p<0.0001. There were no significant differences in the mean MWS, median D-dimers and gender in cases and controls.

Table 3.7: Summary of the CD4 and viral load results obtained for patients with VTE in this study

	N	%	Median (IQR)
HIV Prevalence in VTE Patients (N=156)			
Negative	90	57.69	
Positive	66	42.31	
CD_4 count in HIV+ patients (N=66)			
CD_4 count done	62	93.93	
CD_4 count not done	4	6.06	
CD_4 Count, cells/µL (N=62)			
<200	32	51.61	
200 - <350	3	4.84	
350 - <500	7	11.29	
>500	20	32.26	
Overall Median CD_4 (IQR)			184 (74- 540)
Viral Load, copies/ml (N=63)			
Virally suppressed	41	65.08	
Not suppressed	22	34.92	
Overall Median VL (IQR)			61 (0- 23100)
Virally suppressed/ CD_4 > 200	26	41.27	

Key to Table 3.7: N- Number, HIV- Human immunodeficiency virus, TB- Tuberculosis VTE- Venous thromboembolism, IQR- Interquartile range, VL- Viral load, CD4- Cluster of differentiation

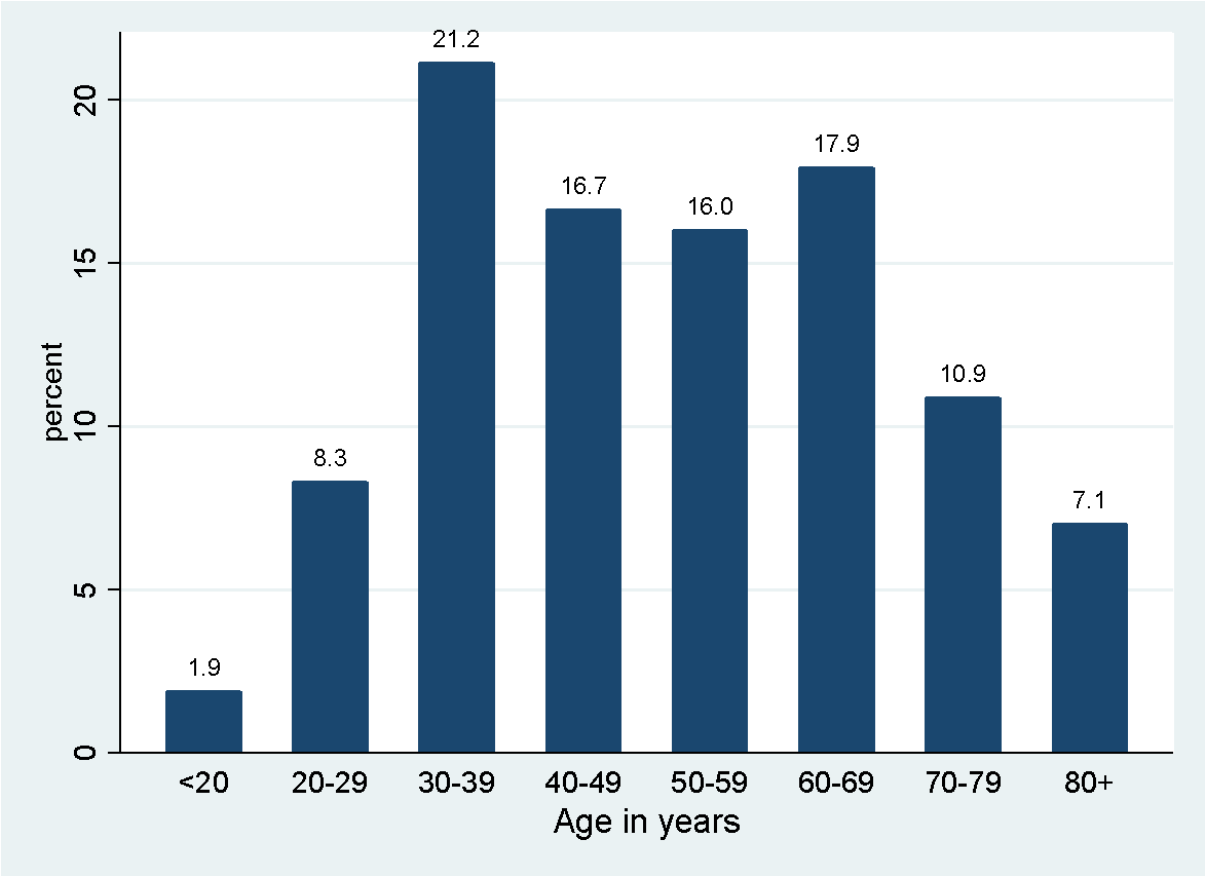

Figure 3.1: Distribution of age in patients with Venous thromboembolism

The distribution of age in patients with confirmed VTE had two peaks, 30-39 age group and 60-69 age group.

CHAPTER 4- DISCUSSION

4.1- Incidence and demographics

156 patients were enrolled in this study (Table 3.1), 72.44% of the patients were female (Table 3.1), in keeping with previous VTE studies demonstrating a female predominance (25, 45, 46). Stats SA reports that women are more likely to attend health care facilities earlier than men which explains the female predominance (23), other factors that could account for this is the use of oral contraception, hormone replacement therapy and pregnancy, which are proven risk factors for VTE (21, 22).

We report a prevalence of 42.31% HIV positive patients with VTE in our study (Table 3.1), with the current general HIV prevalence in South Africa reported at 13.1% in 2018 (23, 47). This increased prevalence of VTE supports the hypothesis that HIV is a major risk factor for VTE in the South African context (29). An audit by Louw *et al*. reported an HIV prevalence of 84% in patients with VTE (12).

Of the 66 that tested HIV positive, 21 had other risk factors (excluding TB) (31.8%) (5-metabolic syndrome, 7-malignancy, 2- sepsis, 2- previous central lines, 2 combined oral contraception, 1-long distance travel, 1 smoker, 1-end stage renal disease), 13 had concomitant TB, 4 had TB alone without HIV. The only control was between non-HIV/TB infectivity and HIV/TB infectivity, it was difficult to find patients who had HIV/TB only, 31.8% of them had other risk factors so indeed we don't know in those patients if the risk factor for VTE was HIV/TB or other.

The prevalence of VTE in patients that tested positive for TB in this study was 10.90% (Table 3.1). This prevalence is also much higher than the national prevalence of active TB reported to be 0.043% (322000) in South Africa in 2017. A study at George Mukhari Academic Hospital reported a 47% prevalence of TB in patients with VTE (29).

In a one year audit of patients with VTE at a Johannesburg hospital, the prevalence of HIV was 50% and that of TB was 30% (22), with a similar finding by Alowesi *et al*. in a Kwazulu Natal study that reported a prevalence of 51.85% and 35.80% for HIV and TB respectively. These findings are discordant with the current study where we report a prevalence of

42.31% for HIV and only 10.90% for TB (Table 3.1). The reasons for this discrepancy are not clearly evident from the data analyzed, however some of the reasons might be the time period of data collection, the setting of the study and the exclusion of patients where a Ventilation Perfusion scan (V/Q scan) was used to diagnose VTE. Another explanation could be the introduction of the antiretroviral programme that has seen some improvement over the years with more patients getting treated earlier than before. However, Mampuya *et al.* demonstrated a TB prevalence of 12.4% (45), similar to the findings in this study. For patients diagnosed with TB, the low prevalence of VTE in this study as compared to some of the other South African studies could be because of the strict inclusion criteria in which only patients with a confirmed laboratory diagnosis of TB were included in the analysis.

4.2- Distribution of age in patients with VTE

The distribution of age in our study has two peaks as shown in Figure 3.1 (age 30-39 and 60-69). Advancing age is a risk factor for thrombosis in the developed world but the mean age of HIV infected patients at the time of VTE is 40 years (47). In our study we demonstrated almost the same trend, patients with HIV/TB were significantly younger than controls (non-infected): mean age 43.46yrs (SD 13.10) vs 58.13yrs (SD 18.65); $p<0.0001$ (Table 3.2) this is possibly due to the high prevalence of HIV/TB in the younger population (age-15-49) (23).

4.3- Performance of the MWS with gold standard imaging

The MWS performed well, proving that it can be validated in a South African setting, of the 156 patients in the study, 130 patients were classified as high probability according to the MWS for VTE (83.33%), this is almost comparable to the published accuracy of 92% and 95% for PE and 76.1% for DVT (36-38). This finding supports the diagnostic algorithm of immediate imaging in the high probability patient as a confirmatory investigation (7, 9). Our study also showed that the MWS has utility in the South African context since the MWS performance was the same in HIV/TB infected patients as compared to non-infected patients (Table 3.2 and Table 3.4), the mean MWS for controls and cases was 4.37 and 3.91 respectively (p value- 0.055) hence the difference was not statistically significant.

4.4- Performance of the MWS in the following categories:

I: HIV-/TB- (control)

II: HIV+/TB+ or HIV-/TB+ or HIV+/TB-

Evidence based literature supports the use of clinical probability scores to improve diagnostic algorithms. The MWS is one of the most validated and widely used scores (10). Multiple studies have been done to analyse the sensitivity, specificity and accuracy of the MWS. In a comparison of the Wells score and doppler ultrasound in the diagnosis of DVT, the Wells score showed a sensitivity of 76.1% (38). For PE the Wells score showed a sensitivity of between 92% to 95% when compared to CTPA (36)(37). It needs to be noted however that the accuracy of the Wells score and its sensitivity is not clear because the studies that have been done are very heterogenous in regards to the patient population selection and the setting in which the score was applied. This study was performed on medical inpatients with confirmed VTE on either CTPA or CUS. One of the studies that was similar to our study is by Owaidah *et al.* but they used the 3 level score and they reported a sensitivity of 88% and specificity of 55% for DVT/PE combined (34), whereas our study showed a 83.33% sensitivity for DVT/PE (Table 3.4) which is comparable even though we used different scores. In another study by Rabab *et al.* they demonstrated a 92% sensitivity in inpatients with PE using the MWS (37).

There is no data in the literature that assesses the accuracy of the MWS in a South African setting.

In our study we report an average sensitivity of 83.33% for PE and/or DVT in all categories (Table 3.4). There were statistically significant differences in the sensitivity of the adjusted MWS by patient category (p value <0.05 in all categories) (Table 3.3). Sensitivity of the score for HIV-/TB- patients was 89.53%. For HIV+/TB- patients the sensitivity was lower at 77.36%, for HIV+/TB+ patients, the sensitivity was 84.62%, lower than the control group and the published accuracy mentioned above. Lastly, for the group HIV-/TB+ the sensitivity was only 25% (Table 3.4).

This clearly shows that the score under performs in HIV/TB infected patients. The reason for this could be that HIV and/or TB aren't included in the score as independent risk factors while there is actually a high burden of those two diseases in SA. Table 3.3 clearly shows

the significance of including HIV/TB as additional risk factors, Furthermore, there is no data that confirms the validation of the MWS in SA while it has been well validated in high income countries with traditional risk factors (25, 45). Nonetheless, it is hypothesised in multiple studies in SA that the commonest risk factor for VTE is HIV/TB (44, 48) and indeed in our study the commonest risk factor was HIV at 42.31%, TB at 10.90% which is third after HIV and Metabolic syndrome respectively (Table 3.1).

4.5- Performance of the MWS with a score that includes HIV/TB as additional risk factors

Mampuya *et al*. and Awolesi *et al.* concluded in their studies that a scoring system that includes HIV/TB should be considered in a South African setting so that gold standard tests are ordered promptly without awaiting D- Dimers in the event that the probability is low according to the MWS (25, 45). This is particularly important because D-dimers are a poor rule in test when they are positive (1), and the studies by Mampuya *et al*. and Awolesi *et al.* showed that the MWS diagnostic accuracy is improved when using a score that includes HIV/TB as independent risk factors.

In our study we report a similar outcome, when the MWS is adjusted to include HIV and or TB (+1 for each), the sensitivity increased from 25% to 100% for the HIV-/TB+ category, it increased from 77.36% to 98.11% in the HIV+/TB- category and increased from 84.62% to 92.95% in the HIV+/TB+ category. The differences were all statistically significant at p-value of <0.05 for all categories (Table 3.3). The implications of the under-diagnosis using the unadjusted MWS has significant implications in that we are potentially missing VTE in HIV/TB infected patients, does this mean the adjusted MWS can also be applied in HIV/TB low prevalent countries? Could the addition of HIV/TB as additional risk factors even in high-income countries be something to be considered? (Appendix 5).

Addition would improve the predictability in those countries as well however since the prevalence is low it is unclear if the change would be statistically significant since the commonest cause of VTE in those countries isn’t HIV/TB and its rather malignancy which is already included in the MWS.

The improved diagnostic accuracy of the MWS adjusted for HIV/TB means we can now rely less on D-dimers to diagnose VTE and rely more on the adjusted MWS as a pretest probability score. The current diagnostic algorithm used for VTE recommends that if the MWS is low and VTE is still suspected one has to do a D-dimer, if D-dimer is positive only then can one request imaging. However, we report that in the event of a patient who has HIV/TB, an additional score of 1 (HIV or TB only) or 2 if both are positive can allow the clinician to order imaging promptly without a D-dimer if the MWS is assessed as “likely” for VTE. This can potentially save more lives as we can diagnose patients quicker which will lead to faster treatment. In a primary health care setting this will allow patients to be transferred quicker to referral hospitals and potentially save money that might needlessly have been spent on D-dimers in the HIV/TB patient cohort where the D-dimer results are not always immediately available have a poor sensitivity and a poor positive predictive value.

4.6- VTE correlation with CD_4 count

It has been shown that the lower the CD_4 count the greater the chance of having VTE (13, 49). Explanations for this is that patients are more prothrombotic at lower CD_4 counts (13, 49). In our study we report the same trend (Table 3.7), of the 66 patients that tested positive for HIV and had a confirmed VTE, 62 had CD_4 count recorded and 51.61% had a CD_4 count less than 200 cells/μL (median=184; IQR = 74-540). Viral load suppression did not help with prediction of VTE in our study because 65.08% of the patients with a measured viral load had levels that were suppressed (Table 3.7). This is in keeping with Bibas *et al* study that showed that there is no correlation between viral suppression/non-suppression and thrombotic phenomenon.

4.7- Strengths

A modified MWS which includes HIV and/or TB in the scoring system is inexpensive, fast and it is a score that could potentially alter the prediction model when diagnosing VTE in a HIV/TB high burden setting.

4.8- Limitations

Colleague referrals and weekly screens were the method of identifying patients. This could have impacted on the number of patients included into the study with confirmed VTE for the period of data collection.

Most patients did not have MWS recorded in files, so the investigator retrospectively calculated the score in confirmed cases, which could have introduced bias to this study.

TB cases enrolled for the study had to have a microbiological confirmation of tuberculosis.

VTE patients diagnosed with VQ Scan were not enrolled in the study as this method of confirmation is not universally regarded as a gold standard for the diagnosis of PE and this could have decreased the patient recruitment number as well.

4.9- Recommendations

For easier data collection we recommend that the Principal investigator make use of Department of Radiology to identify all patients with a confirmed VTE diagnosis.

Before data collection we suggest an algorithm for the diagnosis of VTE be made available to admitting doctors so that all patients can have their MWS's recorded to avoid bias by the investigator. We recommend the use of the MWS as it has been well validated and usefulness confirmed in this study.

Based on the results,
I- We recommend that a score that includes HIV/TB infection as additional independent risk factors be considered with further studies over a longer period of time to obtain an improved analysis.
II- We recommend that studies be performed to assess if thrombo-prophylaxis should be considered in all HIV/TB infected patients.
III- We recommend that a consideration is made to include all TB cases in the study regardless of method of diagnosis.

CHAPTER 5- Conclusion

The MWS has not been validated in a South African setting where there is a high burden of HIV/TB. This study has shown that the MWS is reliable in the South African context, however, its accuracy is improved when adjusted to include HIV and or TB as additional independent risk factors.

CHAPTER 6- References

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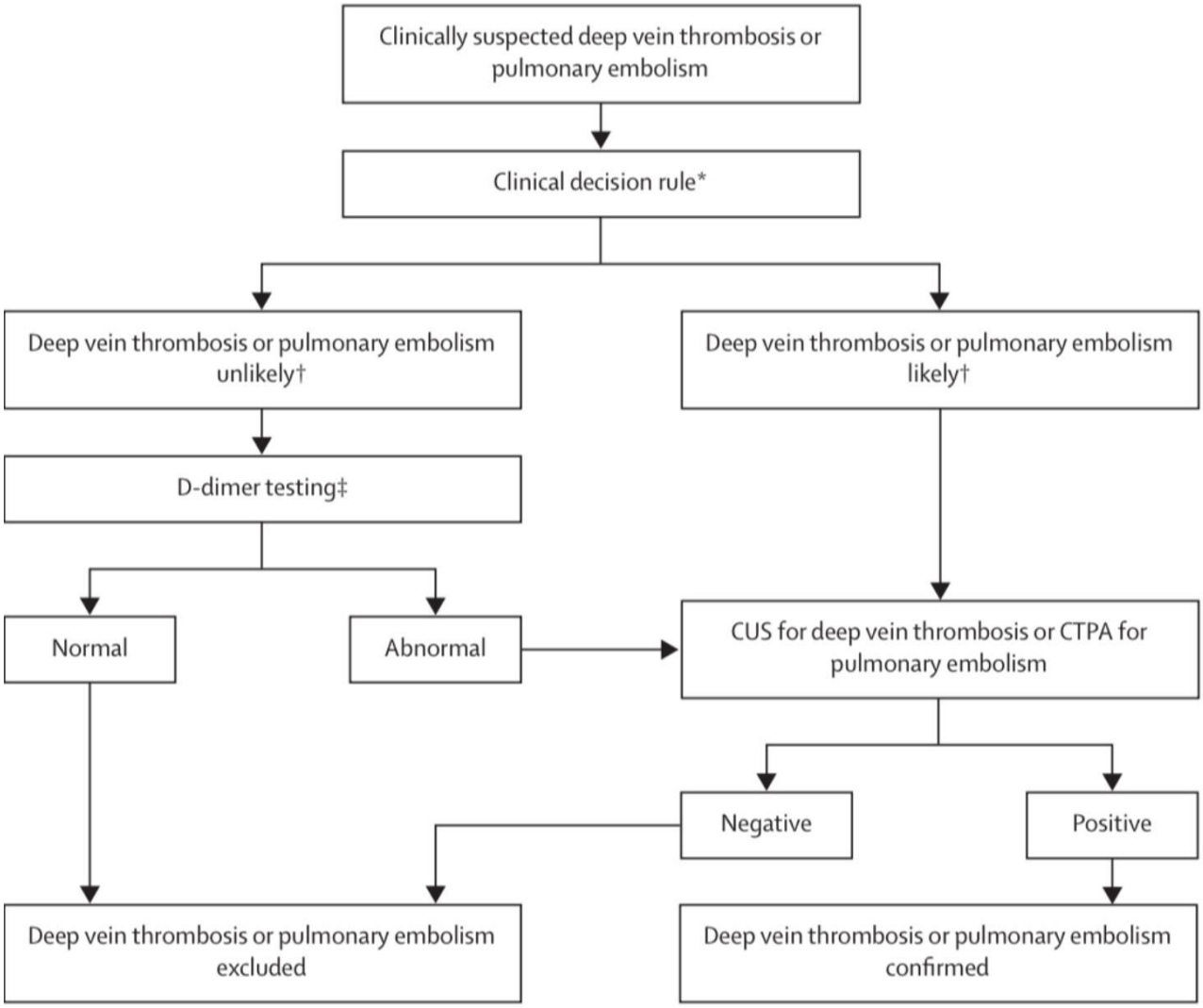
CHAPTER 7- APPENDICES

Appendix 1- Diagnostic algorithm for suspected VTE (5)



Appendix 2 Data Collection Info Sheet

Evaluation of the Modified Wells Score in predicting venous thromboembolic disease (VTE) in patients with tuberculosis (TB) or human immunodeficiency virus (HIV)

Candidate no……..

Name……

File number……..

Age (years)……

Gender- Female ☐

Male ☐

HIV Status- positive ☐

Negative ☐

Unknown ☐

CD4 (cells/ul)……

VL (copies/ml)……..

TB STATUS
positive ☐

Negative ☐

Unknown ☐

TB diagnosis- culture ☐

Urine LAM ☐

GXP sputum ☐

GXP other ☐

OTHER, eg, AFB, Auramine ☐

Risk factor other than HIV/TB

Common risk factor	TICK
Malignancy	
Immobile for 3 days or more	
Surgery pass 12 weeks for DVT or 4 weeks for PE	
OTHER-eg combined oral contraceptives, Recent long distance travel, etc	

Modified Wells Score……..

Site of VTE (DVT-left or right? Or PE?)…….

Duplex doppler ultrasound results…….

CTPA results……..

D-Dimer results (mg/l)……

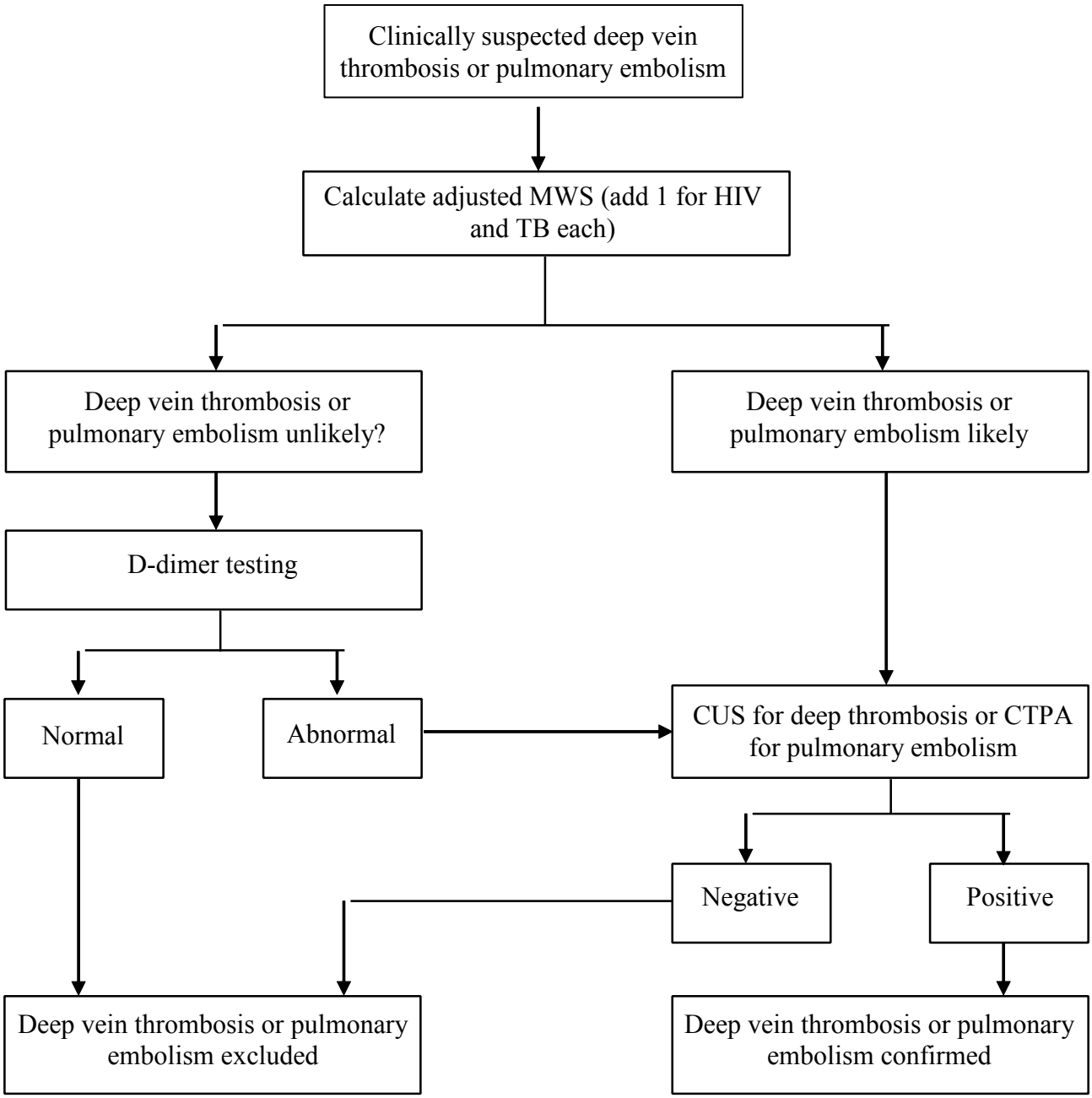
Appendix 3: Wells Score for DVT (1).

MODIFIED WELLS SCORE FOR DVT		
RISK FACTOR	POINTS	Tick
ACTIVE CANCER (patient receiving treatment for cancer within the previous 6 months or currently receiving palliative	1	
PARALYSIS, PARESIS, OR RECENT PLASTER IMMOBILISATION 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	
LOCALISED TENDERNESS along the distribution of the deep venous system	1	
ENTIRE LEG SWOLLEN	1	
CALF SWELLING at least 3cm larger than that on the asymptomatic side(measured 10cm 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 less than 2- DVT UNLIKELY	
Total		

Appendix 4: Wells score for PE (4).

Risk factor	Score	Tick
An alternative diagnosis is less than PE	3	
Heart rate >100	1.5	
Immobilisation for =>3 days or surgery in the previous four weeks	1.5	
Previous DVT/PE	1.5	
Hemoptysis	1.0	
Malignancy	1.0	
Clinical symptoms of DVT (leg swelling, pain with palpitation)	3	
TRADITIONAL CLINICAL PROBABILITY ASSESSMENT (WELLS CRITERIA)		
High	>6	
Moderate	2-6	
Low	<2	
SIMPLIFIED CLINICAL PROBABILITY ASSESSMENT (MODIFIED WELLS SCORE)		
PE likely	>4	
PE unlikely	<=4	
Total		

Appendix 5: Diagnostic algorithm for suspected VTE with adjusted MWS for HIV/TB



VTE- Venous thromboembolism, CUS- Compression ultrasonography,
CTPA, Computed tomography pulmonary angiography.

Appendix 6: Study Information Sheet

Evaluation of the Modified Wells Score in predicting Venous Thromboembolic Disease (VTE) in patients with Tuberculosis (TB) or Human Immunodeficiency Virus (HIV).

Hello, my name is Dr Tweedy Keokgale, I'm doing research on the use of a tool called 'Modified Wells Score', it's used to predict the possibility of a patient having a clot in the legs or chest, clots can be caused by a lot of things like cancer, HIV, TB, oral contraceptives just to name a few.

The study involves the doctor asking you questions about your illness and examining you, this will include in addition me reviewing your medical notes in particular your HIV and TB status, this will be kept confidential.

The examination involves measuring of the size of your leg as well to see how much the swelling is. The above is just the things specific to the study but a general examination of the relevant system will be done as well.

I am therefore inviting you to be part of the study which will help me complete my MMed thesis. Research or study is just a process of collecting data or information to help us try to answer a question. Even though you won't be benefiting anything directly from this study, you'll however be helping us to understand the use of the score better. Your name will be kept anonymous.

This is how the study will be conducted.

1-You'll present to hospital as per usual with any complaint, information sheet and consent form will be given to you by me or the treating doctor at that particular time if you happen to present with symptoms and signs suggestive of venous thromboembolic disease, you'll be given time to read the info sheet and sign the consent, the treating doctor with do a

normal examination like in any other patient, specific to VTE includes measuring the size of your leg swelling and routine examination of the relevant systems. The treating doctor will then order some bloods (D-Dimers if score is not suggestive of VTE, HIV test) with your consent of course. Alternatively the treating doctor will book a sonar of the leg or a scan of the chest if the score is suggestive of VTE. This is a 1-7 day process including waiting times for scans and treatment of VTE in the ward. After all this I will then visit you in the ward to check for your results which will take less than 5minutes.

2- Procedures involved in the study are not specific to the study, these procedures are routine things that you'll get even if you were not involved in the study- these include HIV test, TB test if you have a cough or signs and symptoms that would warrant a TB investigation, duplex doppler ultra sound (DD US) of your swollen leg-this is a gold standard for diagnosing DVT, computed tomography of the pulmonary artery (CTPA)-This is a gold standard for diagnosing pulmonary embolism and bloods including a D-Dimer-This is a degradation product of fibrin which reflects ongoing activation of Haemostatic system in this case a clot or thrombus.

3- Blood will be taken from your arm or groin under aseptic technique with minimal pain, this will take 2-5minutes, sonar of the leg will take 15-30mins on average, CTPA will take 15-30mins to execute but the report can take up to a day or two.

4- A hardcopy questionnaire will be used by the treating doctor to ask your history e.g if you have been bedridden recently. You'll not be filling the questionnaire yourself.

5- Questions you will be asked include the following

Any recent immobilisation or recent admission or fracture.

Any active cancer

Any known HIV OR TB

Any coughing blood, pain with palpitations or previous history of VTE

This will take less than 5minutes of your time.

Blood as mentioned already will be taken, but only about 4 teaspoon size once only (test specific to the study) on arrival to hospital.

6- Risks involved in the study are the same as those you face from any other medical condition, risks of taking blood include pain and risk of prolonged bleeding, risk of a CTPA involves renal failure and allergic reaction to the contract but this happens only in less than 5 % of cases.

7- BENEFITS OF THE STUDY; There is no direct benefit to be in the study but it will give us a better understand of the score so that it can benefit those patients that come once the study is complete and the data is interpreted.

8-PARTICIPATION IS VOLUNTARY; Participation is voluntary, refusal will not result in any penalty or loss of any treatment. You are allowed to discontinue participation at any time and you can choose that your data not be used for the study unless you consent for the data to be retained.

8- REIMBURSEMENTS; You will not benefit financially from the study.

9-CONFIDENTIALITY; Normally personal information will be treated in the strictest confidence and will only be available to me or my supervisors. The only exceptions which are rare is information to be disclosed to human research ethics committee of the university in the event that you lay a complaint.

10- If results are published the data will be secured for two years or 6 years if no publication. After that data will be discarded accordingly.

11- OUTPUTS- This will be discussed with the participant if they are available so that they can appreciate the work they’ve been involved in and how this will help patients in the future.

CONTACT DETAILS OF HUMAN RESEARCH ETHICS COMMITTEE (HREC) ADMINISTRATOR AND CHAIRPERSON

For complaints/problems

This study has been approved by the HREC medical of the University of Witwatersrand Johannesburg (“committee”). A principal function of this Committee is to safeguard the rights and dignity of all human subjects who agree to participate in a research project and the integrity of the research.

If you have any concern over the way the study is being conducted please contact the Chairperson of the Committee who is Professor Clement Penny, who may be contacted on the telephone number 011 717 2301, or email on clement.Penny@wits.ac.za. the telephone numbers for the committee secretariat are 0117172700/1234 and the email addresses are zanily.ndlovu@wits.ac.za and rhulani.mukansi@wits.ac.za

Thank you for reading this Study Information Sheet.

For further enquiries contact

Dr Tweedy Keokgale

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Appendix 7: Participant Informed Consent Sheet

Evaluation of the Modified Wells Score in predicting Venous Thromboembolic Disease (VTE) in patients with Tuberculosis (TB) or Human Immunodeficiency Virus (HIV).

1- I have been given a Participant Information Sheet which explains the nature and processes involved in this study which is attached.

2- I was given time to read it or had it read to me in a language I'm most comfortable with.

3- I was given time to ask questions and found answers in the information sheet and what the intended outcomes will be.

4- I fully understand why the study is being done and what the intended outcomes will be.

5- I know that they will be no immediate benefit to me, should I agree to participate I know I wont be receiving any payment, also I know the participation won't cost me anything but time.

6- I understand that even if I consent to participate at the beginning, I can always withdraw at a later stage and won't have to give reasons why, if that happened, any data collected about me for the purposes of the study would immediately be discarded unless I've given consent for the data to be kept.

7- I have been given a range of contact details, listed below. If I require further information or become concerned about any aspect of this study I'm free to speak to any of these contacts.

Name of participant……

Witness……

Date……

For further enquiries contact

Principal investigator

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Appendix 8 MMed Timing: Tweedy Keokgale

	March 2018	April 2018	May 2018	June 2018	July 2018	Aug 2018	Sep 2018	Oct 2018	Nov 2018	Dec 2018	Jan 2019	Feb 2019	Mar 2019	Apr 2019	May 2019	Jun 2019	Jul 2019	Aug 2019	Sep 2019	Oct 2019	Nov 2019	Dec 2019
Literature review																						
Preparing protocol																						
Ethics application																						
Collecting data																						
Data analysis																						
Writing up research report																						

	Jan 2020	Feb 2010	March 2020	April 2020	May 2020	June 2020	July 2020	Aug 2020	Sep 2020	Oct 2020	Nov 2020	Dec 2020
Collecting data												
Data analysis												
Writing up research report												

Writing up research report	Jan 2022	Feb 2022	March 2022									