

**CLINICAL PRESENTATION AND DIAGNOSTIC WORK  
UP OF SUSPECTED PULMONARY EMBOLISM IN A  
DISTRICT HOSPITAL EMERGENCY CENTRE SERVING  
A HIGH HIV/TB BURDEN POPULATION**

By

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## **Dedication**

This research project is dedicated to my mother Cvetanka Bulajic for her endless support, understanding and guidance during this time.

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## List of abbreviations

ABG	Arterial Blood Gas
AIDS	Acquired Immunodeficiency Syndrome
CDR	Clinical Decision Rule
COPD	Chronic Obstructive Pulmonary Disease
CT	Computed Tomography
CTPA	Computed Tomography Pulmonary Angiography
CUS	Compression Ultrasonography
CXR	Chest X-ray
DVT	Deep Venous Thrombosis
ECG	Electrocardiography
ELISA	Enzyme-linked Immunosorbent Assay
EMPEROR	Emergency Medicine Pulmonary Embolism in the Real World Registry
ESC	European Society of Cardiology
HAART	Highly Active Anti-retroviral Therapy
HICs	High-income countries
HIV	Human Immunodeficiency Virus
HS d-dimer	High Sensitivity d-dimer
ICOPER	International Cooperative Pulmonary Embolism Registry
LITE	Longitudinal Investigation of Thromboembolism Etiology
LMICs	Low- and middle- income countries
MDCT or MD-CTPA	Multi-Detector Computed Tomography Pulmonary Angiography
mSv	mili-Sievert (unit of ionizing radiation dose)
NPV	Negative Predictive Value
OR	Odds Ratio
PE	Pulmonary Embolism
PERC	Pulmonary Embolism Rule-out Criteria
PIOPED	Prospective Investigation of Pulmonary Embolism Diagnosis
PPV	Positive Predictive Value

RBBB	Right Bundle Branch Block
RV	Right ventricle
SSPE	Sub-segmental Pulmonary Embolism
TB	Tuberculosis
US	United States
V/Q scan	Ventilation/Perfusion Scan
VTE	Venous Thromboembolism
WHO	World Health Organization

## **PART A: LITERATURE REVIEW**

## **Introduction**

Pulmonary embolism is a condition with a variable clinical presentation and a high rate of morbidity and mortality if untreated. Risk stratification and diagnostic work up are well known in high-income countries (HICs), but little is known about the presentation and prevalence of PE in a population with a high HIV/TB burden.

This study aims to describe the clinical presentation and diagnostic work up of suspected Pulmonary Embolism (PE), a broad literature review was undertaken in order to compile all the evidence for the diagnostic strategy for PE. Firstly, a non-systematized review was conducted on the clinical presentation and diagnostic strategy for PE to obtain good background knowledge. This was followed by a focused literature search in Medline and Africawide (as outlined below in Methods) on the association of Human Immunodeficiency Virus (HIV) and Tuberculosis (TB) with Pulmonary Embolism (or Venous Thromboembolism).

The diagnosis of PE is difficult and therefore we needed to examine the evidence for clinical signs and symptoms, bedside investigations and imaging modalities such as CT Pulmonary Angiography (CTPA). As it is not possible, cost effective or safe to perform CTPAs on all patients with suspected PE(1), the assessment of clinical probability (clinical decision rules) is important and we looked for literature supporting its use. Furthermore, diagnostic algorithms, which improve the work up of PE were explored, as this details when and what investigations are needed.

It is unknown how patients are currently being risk stratified or worked up for PE in our district hospital emergency centre. It is also unknown whether clinical decision rules are being used. Also unstudied is the prevalence rate of HIV and TB in a population diagnosed with PE in our setting.

TB and HIV are common conditions in our patients and have not historically been seen as risk factors for PE. However, it is known that both conditions induce a hyper-coagulable state. We sought to determine the prevalence of HIV and TB in our study population — even though at this stage it is not clear if these are risk factors. If so, increased vigilance, detection and treatment could potentially improve prognosis in cases of PE.

Subsequently, the literature review is broad, attempting to look at the diagnosis of PE holistically. By educating ourselves on the most up to date evidence, we can use it to assess the diagnostic management of patients in our setting and find ways to improve it.

### **Methods (search strategy)**

A literature search was done on Medline (viaPubmed) and Africawide databases.

#### *Terminology for Search 1: MeSH search in Medline (Pubmed)*

1# 'Pulmonary embolism' [MeSH] OR 'Venous thromboembolism' [MeSH]

AND

2# 'HIV infections' [MeSH]

1# 'Pulmonary embolism' [MeSH] OR 'Venous thromboembolism' [MeSH]

AND

3# 'Tuberculosis' [MeSH]

Filters: humans, adults 19+years

#### *Terminology for Search 2: keyword search for new articles in 2016 in Medline*

'Pulmonary embolism' OR 'Venous Thromboembolism'

AND

'HIV' OR 'Human Immunodeficiency Virus' OR 'AIDS' OR 'Acquired Immunodeficiency Syndrome'

'Pulmonary embolism' OR 'Venous Thromboembolism'

AND

'TB' OR 'Tuberculosis'

Filters: humans, adults 19+years, publication dates: 2016

Terminology for Search 3: keywords in Africawide

'Pulmonary embolism' OR 'Venous Thromboembolism'

AND

'HIV' OR 'Human Immunodeficiency Virus' OR 'AIDS' OR 'Acquired Immunodeficiency Syndrome'

'Pulmonary embolism' OR 'Venous Thromboembolism'

AND

'TB' OR 'Tuberculosis'

**History**

Pulmonary embolism (PE) could be regarded as a quintessential diagnosis in medicine.(2) The complexity of this diagnosis is the subject of many trials and articles. Prasad et al. tells the story of PE, from historically being an almost universally fatal condition diagnosed post mortem, to a treatable one following the introduction of anticoagulation in the first half of the 20<sup>th</sup> century. In the era of CT Pulmonary Angiography, it has become over-diagnosed.(2) Due to the latter, the incidence of PE in high-income countries (HICs) had doubled while the mortality rate remained the same. However, in low and middle-income countries (LMICs) little is known about the incidence and subsequent morbidity of PE. South Africa is classified as an upper middle-income country.(3)

Pulmonary embolism is a potentially fatal disease with a widely variable clinical presentation. It occurs when thrombus, arising from the deep veins of the lower legs or iliac vessels breaks off and travels into the pulmonary circulation where it blocks off a pulmonary artery or its branches.

Significant morbidity and mortality is associated with untreated PE.(4)

Venous thromboembolism (VTE) is an umbrella term that includes Deep Venous Thrombosis (DVT) and Pulmonary Embolism (PE).

## **Disease Burden**

The true incidence of Pulmonary Embolism is difficult to establish in the general population. The incidence rate is thought to be between 0.5 to 2 per 1000 person-years in HICs.(5, 6) In the United States (US) the incidence rate was 112.3 per 100 000 population.(7) For South Africa, no data on incidence rates could be found in the literature. Mortality rates attributed to diseases of the pulmonary circulation (2525 deaths in 2014)(8) include deaths from PE, but greatly underestimate the burden of disease.

Autopsy studies have shown gross emboli in 1.5 to 30% of routine autopsies.(9) It is probable that autopsy data overestimate the incidence of PE by detecting asymptomatic cases, whereas reliance on clinical diagnosis probably underestimates the incidence. (10)

The Longitudinal Investigation of Thromboembolism Etiology (LITE) found a higher incidence of VTE in older males(5), while other studies saw higher rates in women below the age of 55, but also in older men.(11, 12) The incidence also rises markedly with age in both sexes, with pulmonary embolism accounting for most of the increase.(12)

PE is the most common cause of vascular death after myocardial infarction and stroke.(13) The mortality rate at 3 months for PE was reported at 15.3% by the International Cooperative Pulmonary Embolism Registry (ICOPER).(14) The 28-day case fatality rate varies between 10-15% (5, 6), while the mortality rate for untreated PE can be as high as 30%.(5, 10)

Even in patients treated for PE, they appear to be four times as likely to die of recurrent thromboembolism compared to patients treated for DVT.(15) 40-50% of patients with DVTs develop PE, which may be asymptomatic. However in 10%, the occurrence of PE may be fatal, and very often it goes clinically unrecognized.(16)

In studies from the US, both incidence and mortality rates are higher in African Americans compared to Caucasians.(11, 17)

## Pathophysiology of thromboembolism

Virchow's triad, proposes that venous thrombosis is the result of at least one of three etiological factors:(18)

- hypercoagulability
- alterations in blood flow (stasis)
- endothelial injury or dysfunction

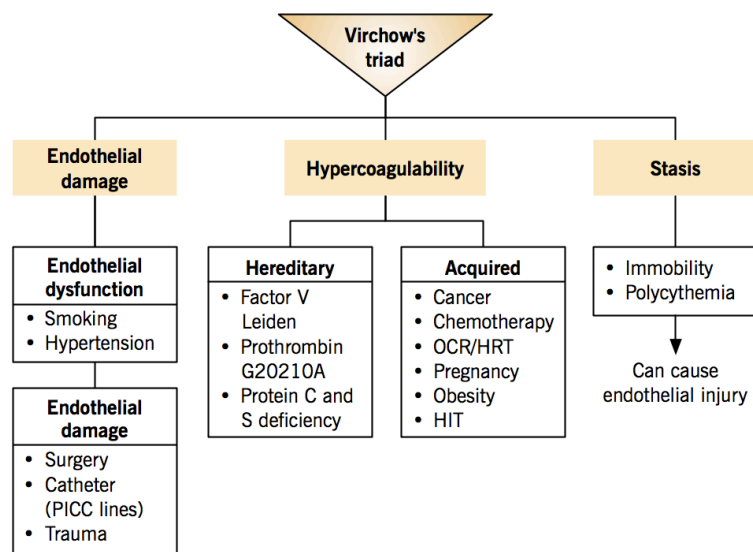


Figure 1: Virchow's triad

Reproduced from Tapson VF. Acute Pulmonary Embolism. N Engl J Med 2008; 385(10):1037-52.

### Risk factors

The latter pathophysiologic mechanisms underlie the risk factors for VTE and between 75-96% of patients with VTE have at least one risk factor.(18) The risk also increases with the number of risk factors present.

However, PE can occur in the absence of any risk factors and the proportion of idiopathic or unprovoked PE was 20% in the ICOPER study.(14)

Risk factors, or otherwise known as predisposing factors, for VTE were previously classified into hereditary and acquired. VTE is currently regarded as the interaction between patient-related and setting-related risk factors.(13)

See Table 1.

Many risk factors are known to be associated with VTE, but as illustrated in Table 1, the odds ratio for some risk factors is higher than for others. The latter is more useful for predicting which patients will benefit from prophylactic anticoagulation than for the diagnosis of PE. However, a clinician's knowledge of the odds ratio's could help to guide their implicit assessment of suspected PE.

<b>Predisposing factor</b>	<b>Patient-related</b>	<b>Setting-related</b>
<b>Strong predisposing factors (odds ratio &gt;10)</b>		
Fracture (hip or leg)		✓
Hip or knee replacement		✓
Major general surgery		✓
Major trauma		✓
Spinal cord injury		✓
<b>Moderate predisposing factors (odds ratio 2–9)</b>		
Arthroscopic knee surgery		✓
Central venous lines		✓
Chemotherapy		✓
Chronic heart or respiratory failure	✓	
Hormone replacement therapy	✓	
Malignancy	✓	
Oral contraceptive therapy	✓	
Paralytic stroke	✓	
Pregnancy/postpartum		✓
Previous VTE	✓	
Thrombophilia	✓	
<b>Weak predisposing factors (odds ratio &lt;2)</b>		
Bed rest >3 days		✓
Immobility due to sitting (e.g. prolonged car or air travel)		✓
Increasing age	✓	
Laparoscopic surgery (e.g. cholecystectomy)		✓
Obesity	✓	
Pregnancy/antepartum	✓	
Varicose veins	✓	

Table 1: Predisposing factors for venous thromboembolism

Reproduced from: Torbicki A, Perrier A, Konstantinides S, Agnelli G, Galie N, Pruszczyk P, et al. Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). *European heart journal*. 2008;29(18):2276-315.

## **Pathophysiology of Pulmonary Embolism**

Pulmonary embolism results from the embolization of a thrombus from the deep venous system of the legs or iliac vessels. Single or multiple emboli travel via the inferior vena cava to the right side of the heart and depending on the size, cause obstruction at different levels of the pulmonary circulatory tree.

Acute PE primarily causes haemodynamic consequences, but also impairs gaseous exchange. The former is only seen when 30-50% of the pulmonary vascular bed becomes occluded by emboli.(16) The resulting increase in pulmonary vascular resistance (pulmonary hypertension) causes an increase in right ventricular (RV) afterload and may lead to ventricular dilatation and failure.

Increased RV pressure and the resultant bulging of the interventricular septum contribute to left ventricular diastolic dysfunction and this can lead to hypotension, cardiogenic shock or syncope.(16) If the right ventricle cannot match the increase in pressure, then cardiac arrest can occur subsequent to pulseless electrical activity or asystole.

The severity of the clinical deterioration is related to the size of obstruction (of the pulmonary vasculature), the duration over which the obstruction occurs and the patient's pre-existing cardiovascular state.(21) A patient with pre-existing cardiopulmonary disease or decreased cardiovascular reserve does not have sufficient compensatory mechanisms and this may adversely impact the prognosis.(14)

The effect of acute PE on the respiratory system is hypoxaemia through different mechanisms including ventilation perfusion mismatch (relative over perfusion of the non-embolized areas) and low mixed venous oxygen saturation (due to reduced cardiac output).(21) Distal areas of the lung that are affected by embolus may become infarcted and result in pulmonary haemorrhage, which present as pleuritic chest pain and haemoptysis. Table 2 illustrates the pathophysiological abnormalities and their corresponding clinical features.

<b>1 Pathophysiological consequences and corresponding clinical features of pulmonary embolism</b>	
<b>Pathophysiological consequences</b>	<b>Clinical features (% of patients with feature)</b>
<i>Haemodynamic</i>	
Reduced cardiac output	Palpitations (20%) Tachycardia (40%) Hypotension (5%)*
Increased pulmonary vascular resistance	
Vascular obstruction	Pulmonary hypertension — loud P2 (25%)
Neurohumoral agents	Right ventricular dilatation and hypokinesis (50%)
Pulmonary artery baroreceptors	Tricuspid regurgitation; neck vein distension (10%) Right ventricular failure (30%)
<i>Respiratory</i>	
Alveolar hyperventilation	Fever (15%) Cough (10%)
Reflex stimulation of irritant receptors	Chest pain (60%): pleuritic (40%), substernal (15%)
Increased airways resistance	Tachypnoea (60%)
Bronchoconstriction	Hypocapnia (80%); dyspnoea (60%)
Reduced pulmonary compliance	Respiratory alkalosis (90%) Raised hemidiaphragm (30%); rales (20%)
Lung oedema	Consolidation; pleural effusion (40%)
Lung haemorrhage	Haemoptysis (10%) Atelectasis (30%)
Loss of surfactant	
Ventilation–perfusion mismatch causing suboptimal gas exchange	
Increased alveolar dead space	Hypoxaemia: chest pain/loss of consciousness (80%)
Right-to-left shunting	Cyanosis (15%)
*Major pulmonary embolism may cause circulatory failure and cardiac arrest.	

Table 2: Pathophysiology and clinical features of pulmonary embolism

Reproduced from Lee CH, Hankey GJ, Ho WK, Wikelboom JW. Venous thromboembolism: Diagnosis and management of Pulmonary Embolism. MJA 2005;182(11):569-574.

## **Clinical features**

No isolated clinical sign or symptom is sensitive or specific enough to diagnose PE.(22) The two most common symptoms of PE are chest pain and shortness of breath.(4) However these are also known to be the two most common symptoms presenting to emergency centres.(23) Many symptoms of PE also mimic those of other cardiopulmonary diseases such as congestive heart failure and COPD. The clinical diagnosis of PE is difficult as PE spans the spectrum of medical presentations from asymptomatic to cardiovascular collapse and death.(4)

Table 2 illustrates a full list of clinical features as well as their percentage of occurrence.

Landmark studies such as the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED I and PIOPED II trials) investigated the clinical presentation of PE. The most common symptoms were sudden onset of dyspnoea and pleuritic chest pain. The most common signs were tachypnoea and tachycardia.(24) In the PIOPED II trial, calf pain, oedema or tenderness was found to be the number one factor differentiating patients with pulmonary embolism from those without.(25)

Concern was raised that these trials included only patients who were already identified by physicians for suspected PE and also did not include the very ill or patients who died immediately.(22) Therefore they do not represent the typical patient presenting to an emergency centre. Another concern is that in the PIOPED II trial, of those with confirmed PE on CT Pulmonary Angiography (CTPA), 18% had a low probability clinical assessment.(24)

Traditionally the clinical symptoms were grouped into 3 syndromes of presentation:(25, 26)

1. syndrome of pulmonary infarction (pleuritic chest pain with or without haemoptysis)
2. syndrome of isolated dyspnoea
3. syndrome of circulatory collapse (syncope or systolic blood pressure of 80mmHg or less)

The percentages of each syndrome occurring, according to PIOPED II, were 41%, 36% and 8% respectively. However 14% of patients did not fit into any of the above syndromes.(25)

The above syndromes and the clinical features mentioned only serve to suggest the presence of PE and to alert the clinician to investigate the possible diagnosis.

In a systematic review and meta-analysis by West, et al. data were examined to estimate the value of individual clinical features for the diagnosis of PE. They used pooled likelihood ratios and found syncope (2.38), shock (4.07), thrombophlebitis (2.20), current DVT (2.05), leg swelling (2.11), sudden dyspnoea (1.83), active cancer (1.74), recent surgery (1.63), haemoptysis (1.62) and leg pain (1.60) to be features that slightly increase the probability of PE. Of the above, all were statistically significant ( $p < 0.001$ ) except for shock, leg swelling and leg pain. Decreasing the probability, are absence of dyspnoea (LR 0.521 and  $p < 0.001$ ) and tachypnoea (LR 0.561 and  $p = 0.312$ ). They concluded that no feature in isolation could be used to rule in or rule out PE.(27)

Large registries such as the ICOPER (14) also reported on the clinical presentation of PE but it did not differentiate between in- and out-patient populations.

Therefore, the EMPEROR study undertook to describe the clinical characteristics of PE in patients presenting to emergency centres. The most common risk factors or co-morbidities found were: hypertension, obesity, recent hospitalization and active malignancy. Dyspnoea, chest pain and extremity swelling suggesting DVT were found to be the most common presentations. No differences in vital signs were detected between the PE positive and PE negative groups.(28)

In a study done by Courtney et al. the objective was to determine the predictive value of clinical features (including history) in a sample of symptomatic emergency centre patients. They prospectively investigated both previously validated (explicit) variables and well as those not part of prediction scores (implicit) i.e. those that clinicians believed to be important clinical predictors of PE. They found strong associations for previously validated variables: history of past VTE, unilateral leg swelling, recent surgery, oestrogen use, oxygen saturation less than 95% and active cancer. Of interest is that they found that non-cancer related thrombophilia, pleuritic chest pain and family history of VTE increased the probability of PE, which are variables that are not part of existing prediction rules.(29)

In a recent review article by Kline and Kabrhel, the following were found to be risk factors for PE in a population presenting to emergency centres:(30)

- older age, surgery requiring intubation, new use of oral contraceptives, prior unprovoked VTE and limb immobilization

Clinical features included:

- Symptoms of recent unexplained dyspnoea, pleuritic chest pain and haemoptysis increase the probability
- Signs of tachycardia (>100bpm), low pulse oximetry saturation (<95%) and leg swelling or pain increase the probability, while wheezing on chest auscultation decreases the probability
- Tachypnoea and syncope are less predictive features

In addition, there is no current evidence that smoking, obesity, travel or family history of VTE increases the probability of PE in the symptomatic emergency room patients.(30) The frequency of PE diagnosis is also determined by the age and comorbid condition of the population that is served by the emergency centre.(5, 12) Classification of the clinical presentation of PE into the categories of 'acute minor', 'acute massive' and 'subacute massive' correlates size and acuity of PE with the clinical presentation.(31)

However, newer guidelines such as the European Society of Cardiology (ESC), use a different classification system based on the risk of early mortality associated with PE and categorizes patients into low-, intermediate- and high-risk.(16) The above classification is used for prognostication of PE patients rather than for clinical diagnosis.

## **Bedside investigations**

### *Chest Xray*

The chest X-ray (CXR) is clinically useful for exclusion of diseases that could mimic PE such as pneumonia, left heart failure, pneumothorax or pleural effusion.(22) However PE could co-exist with these conditions.(31)

The most common CXR findings include an elevated hemi-diaphragm, atelectasis, consolidation or pleural effusion (usually only costophrenic blunting).(22) However,

the CXR may be normal. Moreover, a normal CXR in a patient with severe acute dyspnoea and no wheezing should raise suspicions of a PE.(31)

None of these CXR findings are sensitive or specific. More specific but less sensitive signs are Hampton's hump (a wedge shaped, pleural based pulmonary opacity) and Westermarck' sign (relative oligoemia) but these are rare.(4) In the ICOPER study, cardiomegaly was found to be the most common abnormality on CXR (27%), but it did not correlate with echocardiographic signs of right ventricular hypokinesis.(32)

### *Electrocardiography (ECG)*

The ECG in PE may be normal; or show abnormalities such as sinus tachycardia, non-specific ST and T wave changes, signs of right heart strain or even atrial arrhythmias such as atrial fibrillation.(33) Evidence of right ventricular strain could include P *pulmonale*, T wave inversion in leads V1-V4, QR pattern in V1, incomplete RBBB, S1Q3T3 pattern, or rightward shift of the QRS axis.(34)

In a study in EC patients, findings of acute pulmonary hypertension (right ventricular overload) on ECG, were found more frequently in patients who had PE compared to those that did not have PE.(35) The most frequent ECG findings were abnormalities of the ST segment and T wave.(22)

Rodger, et al. analysed ECGs of patients with suspected PE and found that only two findings were statistically significant: tachycardia and incomplete RBBB, albeit only marginally more frequently found in patients with PE.(34)

S1Q3T3 was historically thought to be specific for PE, but was found not to occur more in patients with PE compared to patients without PE who were initially suspected to have PE.(34)

The conclusion is that ECG findings have limited diagnostic utility in patients with suspected PE.(34) It is more useful in suggesting alternate diagnoses such as acute myocardial infarction or pericarditis.(4)

### *Arterial blood gas (ABG)*

ABG findings could include hypoxaemia and hypocapnia with respiratory alkalosis due to compensatory hyperventilation.(36)

Low PaO<sub>2</sub> (arterial oxygen pressure) in patients with suspected PE can be an adjunct in the diagnostic assessment, however patients with PE and no other cardiopulmonary disease could still have normal PaO<sub>2</sub> measurements.(22)

20% of patients with PE have normal PaO<sub>2</sub> levels and a normal A-a gradient (alveolar-arterial oxygen gradient).(37) Therefore hypoxaemia is a poor discriminator between those that do and do not have PE.(37)

Despite the above, any unexplained hypoxaemia or sudden change in A-a gradient increase the likelihood of PE.(4)

### *Compression ultrasonography (CUS) for Deep Venous Thrombosis (DVT)/PE*

Bilateral lower limb compression venous ultrasonography (CUS) for detecting proximal DVT has a sensitivity over 90% and a specificity of 95%.(38)

In suspected PE, the diagnosis of a proximal DVT with CUS, obviates the need for further testing for PE prior to anticoagulation.(39) CUS was found to have a 95.5% concordance with CT venography and the advantage of no exposure to radiation.(40)

In a prospective outcome study, proximal DVT detected by CUS was found to have a high specificity for the presence of PE on MD-CTPA (99%) but a low sensitivity (39%).(39) The use of CUS in PE is valuable in patients with contraindications to CTPA or if the CTPA is indeterminate or negative in patients with a high pre-test probability.(41)

## **Approach to Diagnosis**

The current evidence-based approach to the diagnosis of PE is a non-invasive sequential use of different modalities:

- clinical probability assessment (by means of clinical gestalt or validated clinical decision rule), followed by
- D-dimer and/or
- Imaging: MD-CTPA

Prior to exploring the above modalities it is important to note the types of studies used in accumulating evidence for PE diagnostic research.

Accuracy studies are for establishing the characteristics of a diagnostic test (sensitivity and specificity) by comparing the test results with a reference/ gold standard.

Outcome studies are for evaluating the patient outcome when employing a certain diagnostic test or strategy in clinical decision-making.

In the field of PE, the outcome measurement is the rate of venous thromboembolic events (DVT or PE) during a 3-month follow-up period in patients left untreated by anticoagulants.(16) The reference for comparison is the rate of DVT or PE in patients left untreated after a negative conventional pulmonary angiogram, which is around 1–2%.(42)

### *Clinical probability assessment and Clinical Decision Rules*

As previously stated, no single symptom or sign or feature on bedside investigation is sensitive or specific enough for the diagnosis of PE.(22) A combination of these variables however, made either implicitly (i.e. by the clinician's knowledge) or explicitly (by using a prediction score or clinical decision rule (CDR)) can be used to classify patients into risk categories in an increasing order of probability of PE,(16) i.e. their pre-test probability can be calculated.

Clinical or physician 'gestalt' relates to the clinicians' use of their own knowledge, experience and judgment to produce an unstructured estimate of the pre-test probability.(4)

Explicit assessment by use of a prediction or Clinical Decision Rule (CDR) can be made using the Wells or Revised Geneva scores, which have both been prospectively tested and validated.(4) Comparison of gestalt to the two above mentioned CDRs has found similar predictive accuracy in emergency centre patients.(43)

Gestalt may allow for flexibility of clinical judgment and doesn't require recall of all the variables in a CDR, however reduced accuracy has been described in inexperienced clinicians.(44) The use of a CDR offers a consistent and reproducible approach to calculating pre-test probability. However a study found that only 68% of emergency physicians were familiar with a CDR and only used it in 50% of cases.(44)

With regards to choice of CDR, one possible limitation of the Well's score is the inclusion of 'alternative diagnosis more likely than that of PE'.(45) This is a subjective criterion that carries a major weight in the score and therefore cannot be standardized.(46)

To obviate the standardization problems, the revised Geneva score was derived from patients admitted to emergency wards for clinically suspected PE.(47) This score has been validated in prospective studies and found to have similar performance to the Wells score.(48, 49)

Both rules have been simplified so that each criterion carries the same weight (i.e. 1 point). (See Table 3) Studies have validated the simplified scores and found no decrease in diagnostic accuracy.(50, 51)

The Prometheus study compared both the original and simplified version of the Wells and revised Geneva scores and found similar performance and safety when combined with D-dimer testing.(52)

Wells rule			Revised Geneva score		
Items	Original	Simplified	Items	Original	Simplified
Previous PE or DVT	1.5	1	Previous DVT or PE	3	1
Heart rate > 100/min	1.5	1	Heart rate 75-94/min	3	1
			Heart rate $\geq$ 95/min	5	2
Surgery or immobilization < 4 weeks	1.5	1	Surgery or fracture within 1 month	2	1
Hemoptysis	1	1	Hemoptysis	2	1
Active malignancy	1	1	Active malignancy	2	1
Clinical signs of DVT	3	1	Unilateral lower limb pain	3	1
Alternative diagnosis less likely than PE	3	1	Pain on lower limb deep vein palpation and unilateral edema	4	1
			Age > 65 years	1	1
Clinical probability			Clinical probability		
Low	< 2		Low	0-3	
Intermediate	2-6		Intermediate	4-10	
High	> 6		High	$\geq$ 11	
PE unlikely	$\leq$ 4	$\leq$ 1	PE unlikely	$\leq$ 5	$\leq$ 2
PE likely	> 4	> 1	PE likely	> 5	> 2

Table 3: Original and simplified Wells and revised Geneva Scores

Adapted from Huisman MV, Klok FA. Diagnostic management of acute deep vein thrombosis and pulmonary embolism. *Journal of Thrombosis and Haemostasis*. 2013; 11:412-22.

The use of the above CDRs allows the clinician to classify patients into different clinical probability categories that correspond to the prevalence of PE:(46)

- low (5-10% prevalence of PE)
- intermediate (20-30%)
- high (60-80%)

Both rules have also been dichotomized and this results in the classification into two categories: PE unlikely or PE likely.(45, 51) This two level scheme will be discussed further under the heading *Combination of pre-test probability assessment and D-dimer testing*.

Furthermore, the use of the calculated pre-test probability can help the clinician to:(4)

- safely exclude PE (see PERC rule)
- determine if investigation for PE needs to be initiated
- determine which investigation is needed (by following a diagnostic algorithm)
- determine which patients would benefit from treatment with anticoagulation prior to the completion of diagnostic tests

## PERC rule

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### (A) The Pulmonary Embolism Rule-out Criteria (PERC) rule

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Age < 50 years  
Pulse < 100 bpm  
Pulse oxymetry > 94%  
No unilateral leg swelling  
No hemoptysis  
No surgery or trauma within 4 weeks  
No prior deep vein thrombosis or pulmonary embolism  
No oral hormone use

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Table 4: PERC rule

Adapted from Hugli O, Righini M, Le Gal G, Roy PM, Sanchez O, Verschuren F, et al. The pulmonary embolism rule-out criteria (PERC) rule does not safely exclude pulmonary embolism. *Journal of thrombosis and haemostasis* : JTH. 2011;9(2):300-4.

Patients must meet all 8 criteria to be identified as PERC negative.

The PERC criteria were developed to rule out PE in a subset of patients with suspected PE but deemed to be very low risk.(53) A multicentre prospective study in EC patients found that the combination of pre-test probability of less than 15% (as assessed by clinician gestalt) and PERC negative criteria reduce the probability of VTE to less than 2%.(54)

However, new data suggests that the PERC criteria alone cannot safely rule out PE in a population with a low pre-test probability and a relatively high prevalence of PE (Specificity 33.2% and NPV 93.6% for the PERC rule).(55)

## *D-dimer*

D-dimer is a degradation product of cross-linked fibrin, and its concentration is elevated in the bloodstream in VTE due to the simultaneous activation of fibrin generation and lysis.(56)

D-dimers can be measured by a large variety of assays. In a systematic review, the sensitivity of ELISA (enzyme-linked immunosorbent assay) and quantitative rapid ELISA for D-dimer testing in suspected PE were superior to the semi-quantitative latex

agglutination and whole blood agglutination assays.(57) The latter two are termed moderately sensitive assays compared to the ELISA assays which are highly sensitive.(57)

The ELISA essays have been shown to be more than 95% sensitive in acute VTE (with a cut-off value of 500mcg/l or ng/ml). (46) Therefore D-dimer testing can be used to rule out PE in combination with low or moderate pre-test probability. In patients with a high pre-test probability, D-dimers should not be measured as they are very rarely normal and have a false negative rate in up to 9.3%.(58)

The specificity for D-dimer testing in VTE is low. Even though the D-dimer is a very specific test for fibrin, false positive results can occur as fibrin is produced in a wide variety of disease states including: infection, recent surgery, cancer, pregnancy and trauma.(4) Therefore the positive predictive value (PPV) of D-dimer is very low.(16)

D-dimer concentration also increases with age and therefore age-adjusted D-dimer values have been studied. The most common formula to determine D-dimer threshold is age x 10ng/ml. It is reasonable and safe to use this to rule out PE in patients above the age of 50 with low and intermediate pre-test probability.(59) A multicentre management study found that the use of age-adjusted D-dimer, with a simplified Wells or revised Geneva score of <4, had a very low VTE rate (0.3%) on 3 month follow up.(60)

*Combination of pre-test probability and D-dimer testing*

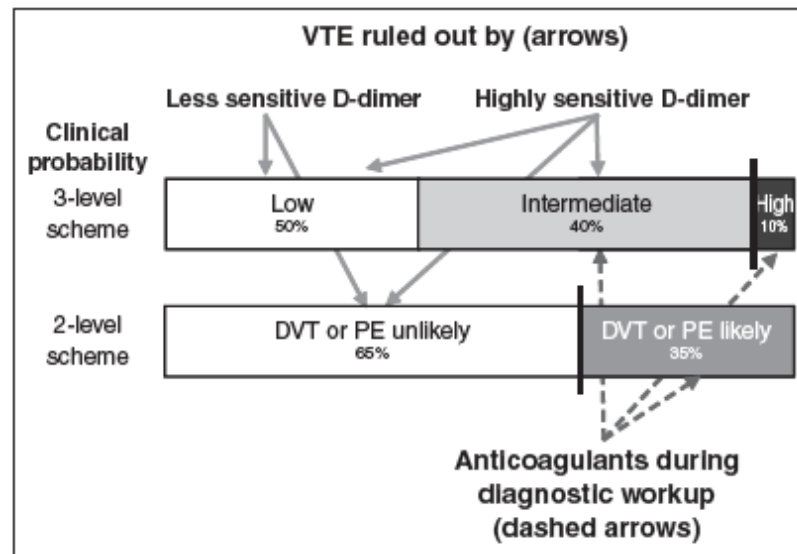


Figure 2: Clinical probability schemes

Adapted from Bounameaux H, Perrier A, Righini M. Diagnosis of venous thromboembolism: an update. *Vascular medicine*. 2010;15(5):399-406

Clinical probability can be shown as a three-level or two-level scheme. It allows PE to be ruled out in 'low and intermediate' or 'unlikely' categories (using a highly sensitive D-dimer) or in the 'low' or 'unlikely' categories (using a less sensitive D-dimer assay).(46)

Several systematic reviews and meta-analyses have concluded that PE can be ruled out in patients with a combination of a non-high or unlikely clinical probability (using any of the validated CDRs or clinical gestalt) and a normal highly sensitive D-dimer test result.(61-63)

Lucassen et al. recommend the use of standardized CDRs because gestalt has a lower specificity, but the choice of a particular rule and d-dimer test are dependent on both prevalence and setting.(63) Bounameaux and colleagues advise the use of the revised Geneva score in populations with a PE prevalence of more than 20%, as this score was derived and validated in such populations.(46)

## *CTPA*

MD-CTPA (Multi-Detector Computed Tomography Pulmonary Angiography) is the imaging modality of choice for the investigation of suspected PE. (4)

The CT can be done within 4-6 seconds of injection of intravenous contrast and the diagnosis is made by identification of filling defects in the contrast-enhanced pulmonary arteries.(56)

CT technology has advanced from single detector to multi-detector scanners, which have a two-dimensional array of detector elements (i.e. multiple, parallel rows of detectors).(64) This allows multiple slice acquisition simultaneously and increases the speed of CT imaging. MDCT refers to CT scanners capable of acquiring 2 or more slices(64), with 512 and 640-slice scanners now on the market. Sensitivity (as well as technical parameters) of the test increase with increasing slice capability and currently CT scanners with less than 16 detector rows (16 slice) cannot be advocated for CTPA.(65)

The PIOPED II investigators reported higher sensitivity of using CT Angiography with venography compared to angiography alone.(66)

However, only 4-slice CT scanners were used then and the addition of venography significantly increased the radiation dose with only a modest improvement in negative predictive value. In a systematic review and meta-analysis by Mos, et al., a technically adequate MDCT scan (alone) for suspected PE in an emergency centre population, irrespective of pre-test probability, had a sensitivity and specificity of 90%.(67)

Currently the use of MDCT as a single imaging modality has a 3-month VTE rate of <2%. Evidence for this comes from the Christopher Study Investigators that saw a VTE rate of 1.3% in patients with a positive D-dimer (or 'likely' clinical probability) and negative MDCT.(68) Also Righini et al, compared the use of D-dimers and MDCT with the addition of compression ultrasonography of the lower limbs (CUS) and found a 3-month VTE rate of 0.3% in both groups.(48)

The advantages of MD-CTPA include a binary positive or negative result.(41)

Historically, Pulmonary Angiography was the gold standard, however it was invasive, as it needed right heart catheterization. V/Q (Ventilation/Perfusion) scanning needs nuclear medicine facilities and has many indeterminate test results especially in

patients with an abnormal chest X-ray, prior cardiopulmonary disease or the elderly.(4) As seen in the PIOPED I trial, a high probability V/Q scan has a sensitivity of 41% and a specificity of 97%.(69) However most results fall into the low or intermediate scan probability categories, which need additional imaging to confirm the diagnosis.

The advantage of MD-CTPA over V/Q scanning includes faster acquisition time, higher-contrast images, availability, useful as a sole diagnostic test and detects alternative diagnoses.(4, 70) MD-CTPA also has a much lower frequency of inconclusive results than V/Q scanning (0.9-3.0 vs 28-46%).(56)

The value of CTPA in establishing alternative diagnoses in patients scanned for suspected PE has been questioned.

In one study, findings to support alternative diagnoses were found in 43% of scans. These diagnoses however only had a therapeutic consequence for a few patients.(71) In a multicentre study of emergency centre patients with suspected PE, the most common non-PE finding on CTPA was a pulmonary infiltrate suggesting pneumonia.(72) Hall et al., investigated the relevance of incidental findings and found that CTPAs ordered on EC patients were twice as likely to find an incidental pulmonary nodule or adenopathy than PE.(73) These would prompt either further investigation or follow-up, but their clinical significance is questionable.

The above evidence supports the view that CTPA should be used to confirm or exclude PE and not to find alternative diagnoses.

Disadvantages of MD-CTPA include a radiation dose of 10-20 mSv, which could increase the lifetime risk of fatal cancer.(41) Higher radiation doses (up to 80 mSv) have been reported and this is a significant breast radiation dose.(74)

Contrast complications include life threatening anaphylactoid reactions, local tissue damage due to extravasation and contrast-induced nephropathy. Therefore CTPA may be contraindicated in patients with contrast allergy or renal insufficiency.(4)

CTPA has limited value in pregnant patients due to radiation dose and high non-diagnostic rate.(4) Cost and availability of radiological expertise could also limit its

use. Other disadvantages are a 6-10% false positive rate in low-risk populations as well as technically inadequate images in up to 10% of scans.(41)

The question has arisen about what to do in patients with an intermediate or high clinical probability who have indeterminate CTPAs. One approach could include a follow-up V/Q scan or alternatively bilateral lower limb venous compression ultrasonography (CUS).(41) If CUS is performed in the emergency room and found to be negative on repeat exam in 3-7 days, VTE can be safely excluded.(41)

Even though MD-CTPA has a high enough negative predictive value, studies have raised the concern that MD-CTPA alone may not be reliable for excluding PE in patients with a high clinical probability.(75, 76) Even though the yield for additional bilateral venous ultrasonography is low(75), it can be useful in the latter situation where there is a discrepancy between clinical probability and CT result.

In patients with suspected PE, who have clinical features of deep vein thrombosis (DVT), if venous ultrasonography is diagnostic, it precludes the need for lung imaging to diagnose PE.(77) This could be beneficial in patients with contra-indications to CTPA. However, negative bilateral proximal lower-limb ultrasonography has a sensitivity of 30% and a specificity of 57% for PE.(48) Therefore a negative DVT ultrasound cannot rule out PE.

In summary, the following table includes the Best Practice Advice from the American College of Physicians with regards to the use of CT and the corresponding evidence.(78)

Clinical Situation	Basis for Imaging Action (Reference)
<b>Immediate CT</b>	
Hemodynamically unstable, with suspected PE* High pretest probability of PE	Risks of inaction outweigh risks of CT Incidence of PE 19%-28% even with a D-dimer level <500 ng/mL (7, 74)
<b>Defer CT until after D-dimer result</b>	
Intermediate pretest probability Low pretest probability and PERC > 0	Low incidence of PE (<1.1%) if D-dimer level <500 ng/mL (41-43)
<b>No CT or D-dimer test</b>	
Low pretest probability and PERC = 0	Incidence of PE <1% (47)
<b>Begin with lower-extremity venous ultrasonography</b>	
Patients with symptoms of DVT and PE	Similar treatment will be pursued without exposing the patient to the risks of radiation or intravenous contrast

Table 5: Clinical situations and suggested imaging strategies

Adapted from: Raja AS, et al. Evaluation of Patients With Suspected Acute Pulmonary Embolism: Best Practice Advice From the Clinical Guidelines Committee of the American College of Physicians. *Ann Intern Med* 2015;163(9):701-11.

With the increasing availability of MD-CT scanners, concern has grown for its overuse and the associated risk of harm secondary to radiation and unnecessary expense. In a US study, the use of CTPA imaging for suspected PE rose 14-fold between 2001 and 2008.(79) Reasons for this could be widespread availability and increased sensitivity; but also a practice known as defensive medicine in which clinicians order the test to mitigate their risk of missing the diagnosis and avoiding liability.(80)

The yield of CTPA for PE (or CTPA positivity rate) in EC patients differs widely and studies since 2001 have reported rates of between 5.7% and 37%.(81) Only 3 studies had rates above 20%, however these followed an ideal work up of patients instead of actual clinical practice. Although there is no ideal CTPA positivity rate, some investigators have suggested that a rate of less than 10% reflects CTPA overuse.(81)

In a prospective observational study on the appropriateness of CTPA use in EC patients, one third of CTPAs performed for suspected PE were avoidable. The study's authors recommend the use of diagnostic protocols or guidelines to lower the number of inappropriate CTs.(1)

#### *Sub-segmental Pulmonary Embolism (SSPE)*

The increased sensitivity of newer MD-CT scanners has led to a phenomenon of 'overdiagnosis', i.e. the increased detection of small, isolated sub-segmental emboli. A quarter of CT scans reported sub-segmental pulmonary emboli, however when reviewed by a second radiologist, in half of the cases, there was no agreement.(41)

A meta-analysis revealed the rate of detection was twice as high when MDCT was used (9.4% vs 4.7% for single slice CT scanners).(82) However, the same study found no difference in mortality or 3-month VTE risk for patients left untreated and therefore a hypothesis was made that sub-segmental pulmonary embolism (SSPE) could be clinically unimportant.

Den Exter and colleagues challenged this hypothesis with their findings that symptomatic SSPE mimics more proximal PE with regards to risk profile and short-term clinical course.(83) Also, compared to patients without PE, SSPE was associated with a higher incidence of recurrent VTE and mortality.(83)

With regards to the controversy of anticoagulation for SSPE, a Cochrane review in 2014 found no randomized controlled trials to provide evidence for the effectiveness and safety of anticoagulation versus no therapy(84).

In an international survey, thrombosis experts recommend anticoagulation of isolated SSPE in symptomatic patients, in those with active cancer, prior PE, ongoing PE risk (immobility or indwelling catheter) or elevated D-dimer.(85)

European Society of Cardiology (ESC) guidelines recommend an individualized approach depending on benefit/risk ratio of anticoagulation and presence of DVT.(16) Findings of an ongoing prospective management study (NCT 01455818) on the safety of withholding anticoagulation in SSPE should be available after June 2017.(86)

### *Diagnostic algorithms*

The use of a validated diagnostic algorithm has been found to lower healthcare costs and also decrease complication risk.(56)

A simple diagnostic algorithm, as proposed by the Christopher Study Investigators, uses a clinical decision rule to work out the pre-test probability and classifies patients into 'PE unlikely' and 'PE likely' categories (using the dichotomized rule).(68) The algorithm is then followed to determine if the patient needs D-dimer testing or multi-detector CTPA.

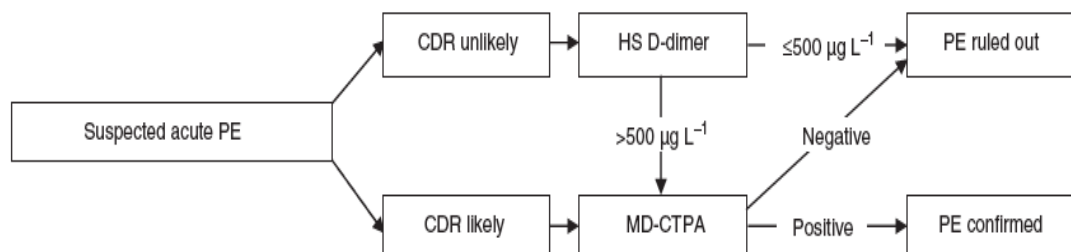


Figure 3: Diagnostic algorithm

Figure adapted from Huisman MV, Klok FA. Diagnostic management of acute deep vein thrombosis and pulmonary embolism. *Journal of Thrombosis and Haemostasis*. 2013; 11:412-22.

This algorithm makes use of high sensitivity D-dimer (HS D-dimer) and Multi-detector CT Pulmonary Angiography (MD-CTPA). The use of this algorithm allowed management decisions to be made in 98% of patients with suspected PE and avoided CT scans in 30%.(56)

Kline and Kabrhel, in a recent article, set out an algorithm combining clinical probability testing, PERC rule, D-dimer and MD-CTPA as well as V/Q scanning. (See Appendix 1)

Despite the overwhelming evidence to support the use of diagnostic algorithms, adherence in clinical practice is poor.(87) All of the algorithms begin with pre-test probability testing, however in one Canadian record review, pre-test probability was only documented in 64% of cases in which D-dimer tests had been done for suspected VTE.(87)

In a European study, the routine practice for diagnosing PE differed substantially from evidence based guidelines. ECs without written diagnostic algorithms were found to be an independent risk factor for inappropriate work-up. Furthermore, in 40% this was also related to clinicians not adequately making pre-test probability part of their decision-making.(88)

## **HIV and TB**

According to the World Health Organization (WHO), South Africa is a high-HIV, high-TB burden country.(89) The importance of these two conditions in the diagnosis of PE is two-fold. Firstly, symptoms and signs associated with HIV infection (and its opportunistic infections) and/or TB are similar to the clinical presentation of PE e.g. dyspnoea, haemoptysis, tachypnoea. This means that the clinical suspicion of PE could be forgone in favour of the more common diagnoses in our setting. Secondly, both HIV and TB can induce a hyper-coagulable state (and increase the risk of VTE), which will be examined in the separate headings below.

### HIV and VTE

The official South African National HIV Survey reported the prevalence rate of HIV in adults aged 15-49 at 18.8% in 2012.(90) The 2015 mid-year statistics estimate was 16.6% for the same age group.(91)

The UNAIDS estimate for 2013 for the same age group is 19.1%.(92)

The importance of these figures relate to the relationship between HIV and the risk of venous thromboembolism (VTE).

HIV infection has been recognized as a pro-thrombotic condition and an association with VTE has been reported by a large number of studies, mostly done in the pre-HAART era. These studies estimated an overall increase in the risk of VTE in HIV-infected patients to be 2-10 fold higher than in the general population.(93). A systematic review done in 2005, found mostly retrospective cohort studies that reported the incidence of VTE in HIV positive patients ranging from 0.19 to 7.63%.(94) In a large study of hospitalized patients with HIV analysed from 1999 to 2005, the incidence of VTE was 1.7% and the relative risk was higher in HIV-infected compared to non-HIV patients (1.21).(95)

A more recent US study evaluated the risk of DVT/PE in HIV infected patients by calculating Odds Ratios (OR) while adjusting for age and found a 43% increase in the OR for developing PE, 10% increase for developing DVT and 40% increase for developing a PE or DVT over the 9 year period of the study.(96) The latter authors suggested that based on their data, emergency physicians should consider VTE part of

the differential diagnosis of an HIV-patient that presents with dyspnoea and without traditional risk factors. (96)

In another US study, HIV-infected veterans were compared with prospectively matched HIV negative controls, and found to have a 33% increased incidence of a first venous thromboembolism.(97) The increased incidence in HIV patients remained significant even after adjusting for confounding factors such as malignancy and use of central venous catheters.(97)

For African populations, a Kenyan study reported a 10.9% prevalence rate of HIV in a group of PE patients.(98) In South Africa, the incidence of VTE in HIV-infected patients is unknown, however they were found to have abnormal markers of coagulation. The markers improved after the initiation of HAART, but were still significantly different than that of non HIV-infected controls. This showed evidence of a persistent haemostatic disturbance.(99)

The haemostatic changes that occur in HIV infection cause a generalised hypercoagulable state and this could explain the increased risk for VTE.(94) There is an increase in pro-coagulant factors and a decrease in anticoagulant factors. The underlying mechanism for these changes are a direct triggering of the immune system by the HIV, as well as the stimulation of common pathways of the coagulation system and inflammatory response.(100)

Other risk factors for patients infected with HIV are being younger than 50 years old, presence of concomitant infections (e.g. cytomegalovirus), low CD4 counts (<200/mm<sup>3</sup>), or a diagnosis of AIDS (Acquired Immunodeficiency Syndrome).(101)

A recent case control study found similar findings to the latter and no significant differences in antiretroviral exposure, plasma HIV viraemia or other traditional risk factors. (102) Hospitalization in the last 3 months was also found to be an independent risk factor in HIV patients (OR 13, CI 6.4-27).(103)

The association between increased VTE risk and the use of Protease Inhibitors as part of HAART has been inconsistent in various studies and the evidence to support this is limited.(94)

The risk of VTE in HIV infected patients is a combination of risk factors related to HIV and traditional risk factors.(93)

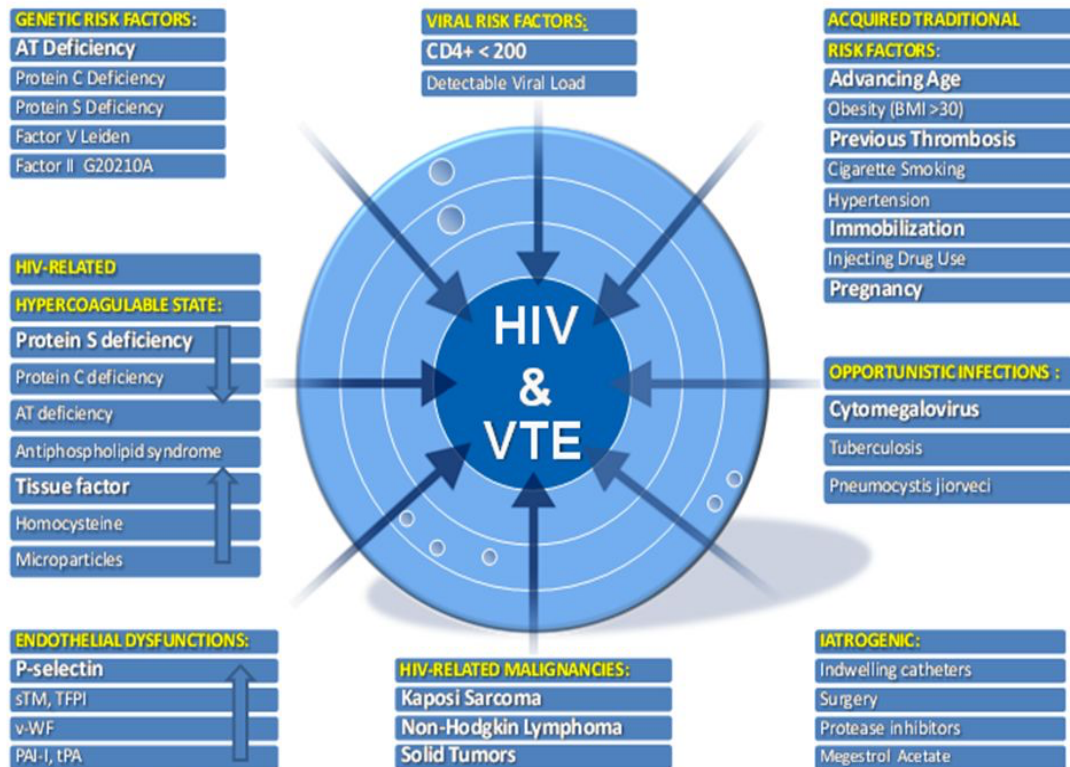


Figure 3: Multi-factorial aetiology of HIV-related venous thromboembolism  
 Reproduced from: Bibas M, Biava G, Antinori A. HIV-Associated Venous Thromboembolism. Mediterranean journal of hematology and infectious diseases. 2011;3(1):e2011030

### TB and VTE

The WHO Global TB Control Report 2015 estimated the South African TB prevalence rate at 696/100 000 and an incidence rate of 834/100 000.(89) The prevalence of HIV infection in TB patients is 61%.(89)

Tuberculosis induces a transient hypercoagulable state by various mechanisms. Active pulmonary tuberculosis induces haemostatic changes: thrombocytopenia, increased levels of fibrinogen and factor VIII, decreased anti-thrombin III and Protein C levels, that result in activated coagulation and inhibited fibrinolysis.(104, 105)

Other mechanisms include stasis secondary to venous compression by enlarged lymph nodes or immobility from severe respiratory disease.(105)

Literature for the association between TB and venous thrombosis, usually presenting as lower limb DVT, has been documented in a number of case reports or case series. In a retrospective study in South Africa in the 1980s, the prevalence of DVT was 3.4% in TB patients within the first two weeks of anti-TB treatment.(106) However DVT was not always objectively confirmed in this study and patient co-morbidities were unknown. Studies in other countries reported incidences of VTE in TB patients of 0.6% (Italy) (107), 0.7% (Israel) (108)and the largest database reported an incidence of 2.07% (US)(109).

A recent South African study reviewing the risk factors for DVT found that in patients with confirmed DVT: 64.4% were HIV-infected, 56.5% had TB and 43.3% were co-infected. (110)

Adults with active tuberculosis have a greater risk of VTE than those without (Odds ratio 1.55, [95% CI 1.23-1.97],  $p < 0.001$ ) and the mortality is greater in those with active TB and VTE.(109)

One retrospective review found that more than half of TB patients diagnosed with VTE had no apparent risk factor except for the TB.(111)

Most TB patients developed VTE in-hospital while not on thromboprophylaxis. Interestingly, none of those patients were immobile or severely ill and were admitted only for initiation and monitoring of anti-TB treatment. Also very few had other co-morbidities. Therefore the authors suggest that thrombo-prophylaxis should be considered for all hospitalized TB patients irrespective of the level of respiratory illness.(111)

Even though the haemostatic changes secondary to TB improve during the first month of treatment (105), Rifampicin may increase the risk of VTE due to effects on the cytochrome p450 system and anticoagulant hepatic proteins. (112) Higher doses of warfarin may be needed to maintain a therapeutic INR for treatment of concomitant VTE. Studies in countries with a high prevalence of TB, have also recommended that TB should be considered as an independent risk factor and included in the risk evaluation for VTE.(113)

## **Summary of literature review**

Pulmonary embolism, a manifestation of venous thromboembolism, has a widely variable clinical presentation and therefore is difficult to diagnose.

Its incidence rate is difficult to determine as it may be overestimated by autopsy studies and underestimated by clinical diagnosis. Significant morbidity and mortality is associated with untreated PE and the mortality rate may be as high as 30%.

The risk factors for PE all have underlying mechanisms relating to abnormalities of the components of Virchow's triad. Risk factors are divided into patient and setting related factors, which have different odds ratios. Risk is increased by an increasing number of risk factors although idiopathic PE can occur i.e. in which there is no identifiable risk factor.

No single symptom or sign is sensitive or specific enough to diagnose PE. Chest pain and shortness of breath are the two most common symptoms. Factors found to be increase the probability of PE in an EC population are symptoms of unexplained dyspnoea, pleuritic chest pain and haemoptysis, while signs include tachycardia, low oxygen saturation and leg swelling or pain.

Bedside investigations such as Chest X-ray, ECG and arterial blood gas could show features that suggest PE, but again no single finding or abnormality is sensitive or specific enough to rule in or rule out PE.

Combinations of risk factors and symptoms/signs have been made into validated Clinical Decision Rules used for estimating the pre-test probability of PE. Examples such as the Wells and revised Geneva score have been simplified, and perform as well as the original scores and are comparable to clinical gestalt. Depending on the pre-test probability (low, intermediate or high) patients then receive the appropriate investigation. Dichotomized rules have re-arranged the categories into 'PE unlikely' and 'PE likely'.

Patients deemed to have a very low probability (<15%), can be ruled out using the PERC rule. Low and intermediate probabilities need a highly sensitive D-dimer assay to rule out PE. Those with a positive D-dimer need confirmatory testing with CTPA. High probabilities do not need D-dimer testing and should proceed immediately to CTPA.

The current focus of diagnostic research is to identify the patients in whom PE can be excluded without the need for invasive testing. Therefore there is a need for a standardized approach. Diagnostic algorithms combining clinical probability assessment with D-dimer testing or imaging with CTPA have been shown to decrease costs and complications.

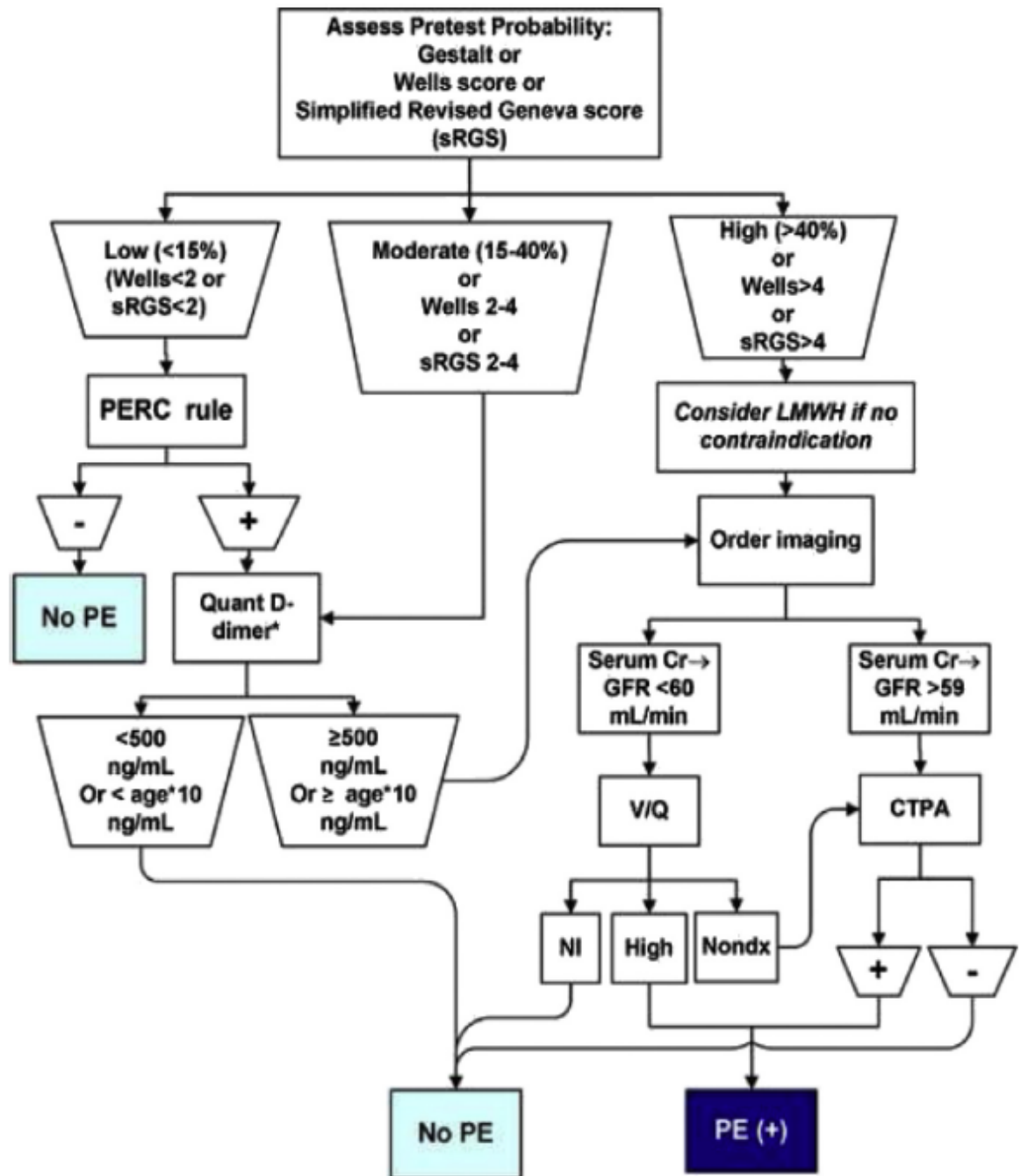
MD-CTPA has many advantages including fast acquisition, quality imaging, use as a sole diagnostic test, and less inconclusive results than V/Q scanning. Any discrepancies between CTPA result and pre-test probability can be followed up by repeat compression ultrasonography. In fact, in patients with suspected PE with signs of DVT, positive compression ultrasonography precludes the need for imaging for PE and anticoagulation can be started immediately.

The increasing availability and sensitivity of CTPA has led to overuse of this modality and is associated with a risk for harm due to radiation and increased cost. Also, 'overdiagnosis' has been seen with the detection of small sub-segmental pulmonary emboli (SSPE) whose significance has been debated. Currently trial results are awaited regarding the safety of withholding anticoagulation in SSPE.

HIV and TB are diseases that predispose the patient to a hyper-coagulable state. Numerous studies have shown that both are associated with a higher risk of VTE. Also, anticoagulation prophylaxis should be considered in hospitalized patients with HIV and or TB.

## Appendices:

### Appendix 1



Reproduced from: Kline JA, Kabrhel C. Emergency Evaluation for Pulmonary Embolism, Part 2: Diagnostic Approach. The Journal of emergency medicine. 2015;49(1):104-17

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**PART B: ARTICLE**

# **CLINICAL PRESENTATION AND DIAGNOSTIC WORK UP OF SUSPECTED PULMONARY EMBOLISM IN A DISTRICT HOSPITAL EMERGENCY CENTRE SERVING A HIGH HIV/TB BURDEN POPULATION**

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<sup>a</sup> Acquisition, analysis and interpretation of data, literature review, drafting of article

<sup>b</sup> Design of study, review of research proposal including submission to ethics, revision of literature review, revision of article

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# **CLINICAL PRESENTATION AND DIAGNOSTIC WORK UP OF SUSPECTED PULMONARY EMBOLISM IN A DISTRICT HOSPITAL EMERGENCY CENTRE SERVING A HIGH HIV/TB BURDEN POPULATION**

## **Abstract (315 words)**

### **Introduction**

The diagnosis of Pulmonary Embolism (PE) is challenging to make and is often missed in the Emergency Centre. The true incidence of PE in South Africa is unknown. The diagnostic work-up of PE has been improved by the use of Clinical decision rules (CDRs) and CT Pulmonary Angiography (CTPA) in high-income countries. Currently used CDRs have not been validated in the South African environment, where HIV and TB are highly prevalent. Both conditions are known to induce a hyper-coagulable state.

### **Methods**

This study was a retrospective chart review of patients with suspected PE who had CTPAs performed between October 2013 and October 2015 at Mitchell's Plain Hospital, South Africa. Data were collected on demographics, presenting symptoms and signs, vitals, bedside investigations, HIV and TB status, use of CDRs and CTPA result. A Revised Geneva Score was calculated retrospectively and compared to the CTPA result.

### **Results**

The median age of patients with confirmed PE was 45 years and 68% were female. The CTPA yield for PE in our study population was 32%.

The most common presenting complaint was dyspnoea (83%), followed by cough and chest pain. 29% of patients also had clinical features of DVT. No sign or symptom was observed to be markedly different in those with confirmed PE compared to those without. Among patients with confirmed PE, 37% were HIV positive and 52% had current TB. The retrospective revised Geneva Scores correlated poorly with the CTPA results.

## Discussion

PE remains a diagnostic challenge. Worldwide, the use of CDRs has shown to improve the utilization of CTPA. In our study, the retrospectively calculated CDR was not predictive of PE in a population with a high prevalence of HIV and TB. Emergency physicians should be cautious when making a clinical probability assessment of PE in this setting. However, further studies are needed to determine whether HIV and TB could be independent risk factors for PE.

## **Introduction**

Pulmonary embolism (PE) is a potentially fatal disease with a widely variable clinical presentation. The true incidence of PE is difficult to establish in the general population. In high-income countries (HIC) the incidence rate is estimated to be 0.5 to 2 per 1000 person years.(1, 2) In low-to-middle income (LMIC) countries such as South Africa no reliable data is available on the incidence of PE. Undiagnosed and therefore untreated PE is associated with significant morbidity and mortality.(3) The mortality rate for untreated PE can be as high as 30%.(1, 4)

The use of Clinical Decision Rules (CDRs) and increased availability of CT Pulmonary Angiography (CTPA) have improved the diagnostic work-up of PE. However, the currently used CDRs have never been validated in the South African environment, in which both HIV and TB are highly prevalent. Both of these conditions are known to induce a hyper-coagulable state, which is a risk factor for venous thromboembolism (VTE).(5, 6) VTE is a term that encompasses both Deep Venous Thrombosis (DVT) and Pulmonary Embolism (PE).

This study aimed to describe the clinical presentation and diagnostic work up of patients who presented to a district hospital's emergency centre in South Africa with a suspected PE. Secondly, the study sought to determine whether CDRs were being used by clinicians, for assessment of pre-test probability, prior to requesting CTPAs. Revised Geneva scores were calculated retrospectively and compared to the CTPA result. The study also sought to determine the prevalence of HIV and TB in the sample population with confirmed PE.

## **Methods**

This retrospective chart review was done at the emergency centre of Mitchell's Plain Hospital in Cape Town, South Africa. Mitchell's Plain Hospital is a district level hospital with 230 beds. The 24-hour emergency centre (EC) sees 3500 patients per month. The decision to send patients for CTPA is made on morning ward rounds, when patients who are deemed to be at high risk of having a PE are presented to the Emergency Medicine consultant. It was not known whether CDRs were used or documented, or whether decisions were made by clinical gestalt alone.

CTPA scans are only available on site from 8am to 4pm, on weekdays. After-hours or on weekends, patients with high clinical probabilities are anti-coagulated while awaiting CTPA. If unstable, patients are anti-coagulated and sent to the tertiary hospital for CTPA. A 16-slice multi-detector CT Scanner is used for CTPA and is reported on by the in-house radiologist.

The study population included all patients over the age of 18, who had CTPAs performed for suspected PE at Mitchell's Plain Hospital over a period of 24 months (October 2013 up to October 2015).

Patients were excluded if they had CTPAs performed for other indications (e.g. thoracic trauma), repeat CTPAs (in patients already diagnosed with PE on initial CTPA), chronic PE or if the patients' electronic notes and/or physical folder could not be found. 160 patients met the inclusion and exclusion criteria; due to missing patient notes the final sample size was 127.

Data collection was performed using 3 databases: radiological imaging from the local Picture Archiving and Communication System (PACS), electronic patient notes from Enterprise Content Management (ECM) and laboratory data from the National Health Laboratory Service (NHLS). Initially, patients who had CTPAs within the study period were identified on PACS. These patients' emergency centre and in-patient notes were traced on ECM and data was collected and entered onto a pre-designed excel spreadsheet.

Individual patient data were coded with an independent study number and patient identifiers were not entered on the data collection spreadsheet. Collected data included: demographics, risk factors and previous medical history, vitals, signs and symptoms, and findings on physical examination. Results of bedside investigations such as ECG and arterial blood gases were included if found. The NHLS database was used to obtain laboratory parameters such as D-dimer, HIV result, CD4 count or results of TB investigations. It was also noted whether a CDR was documented in the patient notes and a retrospective CDR (Revised Geneva score) was calculated for each patient from the collected data. (See Appendix B)

This study was approved by the University of Cape Town, Human Ethics Research Committee (Ref 762/2015) and the Western Cape Provincial Government.

## Results

### *Patient demographics*

See Table 1

**Table 1** Patient Demographics

Demographic	PE suspected (whole sample) n=127	PE confirmed (CTPA +ve) n=41
Mean age, yrs	43	45
Age > 65 yrs	10%	1%
Female sex	72%	68%

### *Risk factors and comorbid conditions*

Except for recent hospitalization (36%), age >65 years (10%), post-partum (10%), previous VTE (6%), and immobilization (5%), there were very few individual risk factors in our study population with suspected PE (< 2%). Some risk factors such as family history of VTE, oestrogen use and smoking were very poorly documented in patient notes.

In patients with confirmed PE on CTPA, 68% had one or more co-morbidities, compared to 80% in those without PE.

46% of patients with confirmed PE had current or previous lung pathology e.g. active TB, previous TB, TB bronchiectasis or COPD.

### *Symptoms and signs*

The most prevalent vital sign abnormalities on presentation were tachycardia, tachypnoea and hypoxaemia. (See Table 2)

Patient-reported dyspnoea was the most common presenting symptom (83%), followed by cough and chest pain. Less than 40% of patients reported a sudden onset of symptoms. No symptom or sign was observed to be markedly different between patients with confirmed PE and those without PE.

Physical examination revealed 'clear' or no findings on chest examination in 33%, but clinicians documented signs of pulmonary hypertension in 25% of patients with PE.

Twenty eight patients with suspected PE and leg pain/swelling suggesting DVT also received compression ultrasonography. Fifteen patients were diagnosed with DVT of which twelve also had PE confirmed on CTPA. This means that in our sample of PE patients 29% presented with clinical signs of DVT.

See Table 2 for comparison of vital signs and clinical features between patients with confirmed PE and those with no PE.

**Table 2** Vital signs and clinical features on presentation

Features	Confirmed PE (n=41)	No PE (n=86)
<b>Vitals in EC</b>		
Tachycardia (>94bpm)	33 (80%)	65 (76%)
Heart rate (mean)	114 ±19	109 ± 23
Tachypnoea (RR>20)	29 (71%)	50 (58%)
Hypoxaemia (Sats<95%)	19 (46%)	38 (44%)
Saturation (mean)	90% ± 12	93% ± 7
Hypotension (SBP<90mmHg)	2 (5%)	7 (8%)
<b>Symptoms</b>		
Cough	21 (51%)	46 (53%)
Dyspnoea	34 (83%)	71 (83%)
Chest pain	17 (41%)	52 (60%)
Chest pain (pleuritic)	15 (37%)	42 (49%)
Sudden onset of symptoms	16 (39%)	30 (35%)
<b>Signs</b>		
Chest: crackles	21 (53%)	43 (50%)
Chest: wheezes	10 (25%)	12 (14%)
Chest: clear	13 (33%)	32 (37%)
Pulmonary Hypertension	10 (25%)	22 (26%)
Leg pain and/or swelling suggesting DVT	15 (37%)	13 (15%)

### *Bedside investigations*

The most common abnormalities on ECG in patients with confirmed PE were sinus tachycardia (68%), T wave inversion in the precordial leads (51%) and non-specific ST segment or T wave changes (43%). The only statistically significant abnormality was T wave inversion in leads III and V1, which was present in 35% of those with PE vs 18% without PE (p value = 0.04).

With regards to arterial blood gas measurements, there were very small differences in PaO<sub>2</sub>, PaCO<sub>2</sub>, and oxygen saturation between patients with confirmed PE and no PE, not reaching statistical significance.

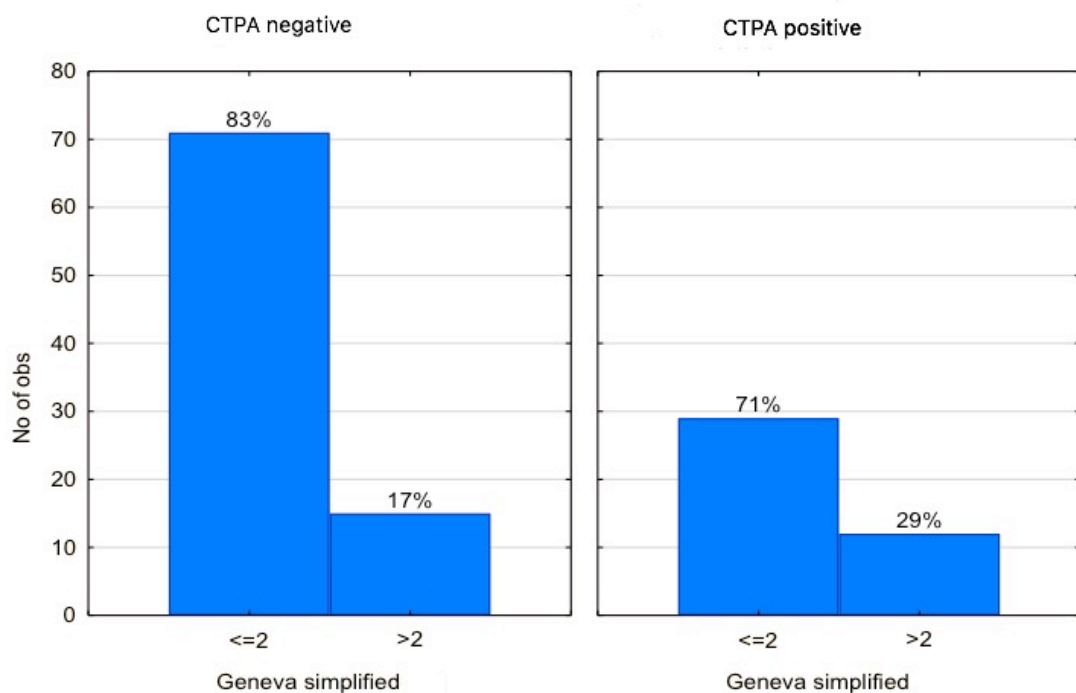
### *Use of pre-test probability or CDRs*

The Wells score was documented in the notes in only 13% of patients with suspected PE. The Revised Geneva Score was not documented in any of the notes.

### *Retrospectively calculated Revised Geneva Score (RGS)*

The simplified dichotomized Revised Geneva Score categorizes patients into 'PE likely' (score >2) or 'PE unlikely' (score ≤ 2). This was calculated retrospectively on the collected data and found to have very poor correlation with the CTPA result.

**Figure 1** Correlation: Revised Geneva Score vs CTPA



In our study population the RGS had a sensitivity of 63%, specificity of 54%, positive predictive value of 44% and a negative predictive value of 71%.

55% of the Revised Geneva scores were =2, which is just below the cut-off point for the dichotomized rule.

#### *CTPA positivity rate*

The CTPA yield for PE in our study population was 32% (n=41).

The anatomic positions included saddle emboli, left and right main pulmonary arteries/lobar arteries/segmental arteries and sub-segmental arteries. In 61% of positive CTPAs, the pulmonary embolism was found simultaneously at different levels and/or included both lungs. Only 3 patients (7.3%) had purely sub-segmental emboli.

#### *D-dimer measurement*

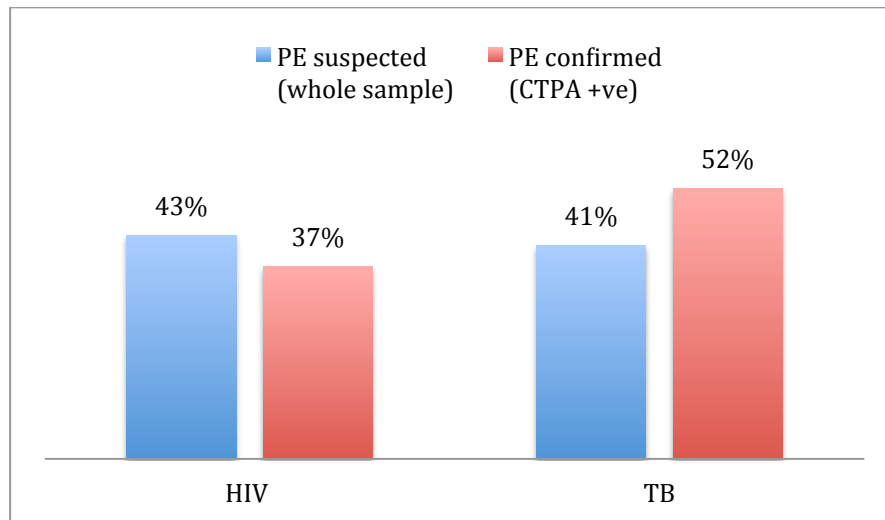
D-dimer testing was performed in 21 patients (17%). The level was above the cut-off value (>500ng/ml) in 76%. Ordering of D-dimer tests did not correlate with documented CDR score (Wells) or retrospective CDR score (Revised Geneva).

#### *HIV and TB*

In our study population (patients with suspected PE), the prevalence of HIV was 43% and that of TB was 41%. (See Figure 2) It must be noted that 20% of HIV results were missing from the data (either not done or not documented) and in 42% of patients the TB status was unknown (no laboratory testing done).

Among those patients with confirmed PE, 37% were HIV positive and 52% had current TB. See Figure 2

**Figure 2** Prevalence of HIV and TB in suspected PE vs confirmed PE



Of the 52% (13 patients) with current TB and PE, 12 patients also had previous TB and 8 of those had been diagnosed with TB bronchiectasis.

The prevalence of having both HIV and TB was 35% in the study population.

31% also had documented previous TB.

CTPA positivity rate in patients with suspected PE and known HIV or TB:

In HIV positive patients with suspected PE, the CTPA was positive in 30% (compared to 36% in HIV negative patients).

In patients with active TB and suspected PE, 43% had confirmed PE on CTPA (compared to 27% in TB negative patients).

## Discussion

For South Africa, no data on the incidence of PE could be found in the literature.

It is a condition that remains undiagnosed, untreated and leads to significant morbidity and mortality. Mortality data from Statistics SA in 2014 found 2525 deaths 'attributable to diseases of the pulmonary circulation'.(7) This number includes deaths from PE but grossly underestimates the burden of disease.

### *Patient demographics*

In our study population, the mean age at diagnosis of PE was 45 years and only 1% was over the age of 65. This could be related to the total life expectancy in South Africa, which was 62.5 years at the 2015 mid-year population estimate.(8)

### *Clinical features*

The most common clinical presentations in our study were shortness of breath, cough and chest pain. This is congruent with what has been found in studies in HICs where the two most common symptoms of PE are chest pain and shortness of breath.(3) These are also known to be the two most common symptoms presenting to emergency centres around the world.(9)

The clinical diagnosis of PE is difficult as it spans a spectrum of medical presentations, from asymptomatic to cardiovascular collapse and death.(3)

In our study population, no sign or symptom was observed to be significantly different between patients with confirmed PE and those without. A systematic review and meta-analysis by West, et al. concluded that no feature in insolation could be used to rule a PE in or out.(10)

Although tachycardia, tachypnoea and hypoxaemia were the most frequent vital sign abnormalities in our patients with confirmed PE, they were similarly frequent in those without PE. Even in the multi-centre US study, no differences in vital signs were detected between the PE positive and PE negative groups.(11) A possible explanation is that patients presenting with a significant cardio-respiratory complaint will all have some degree of tachycardia, tachypnoea and lower oxygen saturation. This also presents the problem of looking at vital signs in patients with co-morbidities and suspected PE.

Many symptoms of PE also mimic those of other cardiopulmonary diseases such as congestive heart failure and chronic obstructive pulmonary disease (COPD).(3) In our study, 68% of confirmed PE patients had one or more co-morbidities and 46% had current or previous lung pathology. In South Africa, there is also a higher burden of infectious diseases (pneumonia, TB) with a steady rise in lifestyle-associated diseases such as congestive cardiac failure and COPD.

The EMPEROR study, which described the clinical presentation of PE in patients presenting to multiple emergency centres in the United States (US), found dyspnoea, chest pain and extremity swelling suggesting DVT to be the most common presentations.(11)

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We found DVT in 15 of 28 patients with suspected PE and leg pain/swelling suggesting DVT, by compression ultrasonography. Of the 15 patients diagnosed with DVT, 12 also had PE confirmed on CTPA. This means that in our sample of PE patients 29% presented with clinical signs of DVT. This may be lower than documented in other studies, but in our setting compression ultrasonography for DVT is not routine practice in patients with suspected PE, and was only performed if DVT was also suspected clinically.

*Bedside investigations*

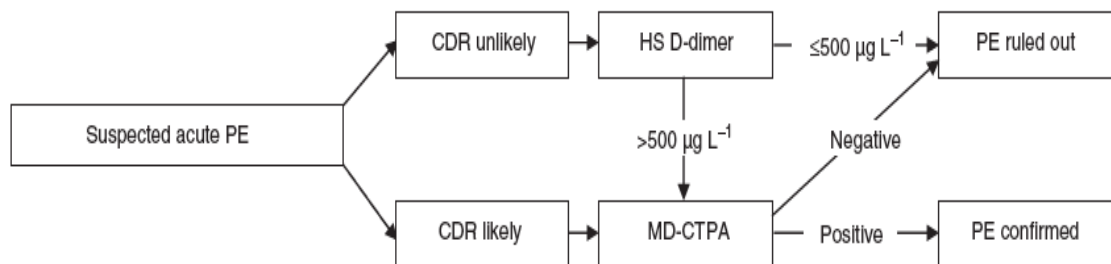
Only one ECG feature: T wave inversion in lead III and V1 was statistically significant, although it was only present in 35% of patients with confirmed PE.

Arterial blood gas measurements did not offer any extra information to help differentiate between PE and no PE.

*Approach to diagnosis: CDR, D-dimer and CTPA use*

The current evidence based approach to the diagnosis of PE is a non-invasive sequential use of different modalities: clinical probability assessment (by use of clinical gestalt or CDR), followed by D-dimer measurement or CTPA. These have been combined into a diagnostic algorithm. See Figure 3.

**Figure 3** Diagnostic algorithm for Pulmonary Embolism



(PE: Pulmonary Embolism, CDR: Clinical Decision Rule, HS D-dimer: High-Sensitivity D-dimer, MD-CTPA: Multi-detector CT Pulmonary Angiography)

Figure adapted from Huisman MV, Klok FA. Diagnostic management of acute deep vein thrombosis and pulmonary embolism. *Journal of Thrombosis and Haemostasis*. 2013; 11:412-22.

The use of a validated diagnostic algorithm has been found to lower healthcare costs and also decrease complication risk.(12) However, despite the overwhelming evidence to support the use of diagnostic algorithms, adherence in clinical practice even in HICs is poor.(13) In our setting no written diagnostic algorithm or guideline exists.

As seen in our study, only 13% of patients with suspected PE had a documented clinical probability assessment by a CDR (Wells score). It appears that most of our patients deemed to be high risk enough to be sent for CTPA, were dependent on the clinicians' unstructured estimate of their pre test probability (i.e. clinical gestalt).

The most commonly known CDRs are the Wells score and Revised Geneva score. We retrospectively calculated the revised Geneva score as it only includes objective criteria(14). (See Appendix B) The purpose of the clinical probability assessment is to categorise the patient into pre-test probability categories: 'PE likely' (score >2) or 'PE unlikely' groups (score ≤ 2) by using the dichotomized Revised Geneva score in this example.(15) The categories correlate with the patient's estimated risk of PE and guide the next step in the diagnostic algorithm.(16) (See Figure 3)

In our study population, the score had a sensitivity of 63% and specificity of 54%. These compare poorly with the sensitivity and specificity values described by Lucassen, et al. in a meta-analysis to be 91% and 37%, respectively.(17) In our study, 71% of patients with confirmed PE (CTPA positive) would have been incorrectly categorized as 'PE unlikely' using the RGS. Therefore, if the decision to scan in our population was based on the RGS, CTPA would have not been performed and 71% of PEs would have been missed.

MD-CTPA (Multi-Detector Computed Tomography Pulmonary Angiography) is the imaging modality of choice for the investigation of suspected PE. (3)

In HICs, the increased availability and advancing technology of CT scanners has led to overuse of this modality (14-fold increase in the US).(18) This is associated with an increased risk of harm due to radiation and unnecessary expense. A study evaluating the appropriateness of CTPA use in emergency centre patients found that one third of CTPAs performed for suspected PE were avoidable; and recommended the use of diagnostic protocols or guidelines to lower the number of inappropriate CTs.(19)

In LMICs, such as South Africa, CTPA is often only available at large tertiary hospitals and some secondary-level hospitals. Its use is also limited by cost and radiological expertise. It would make sense that the implementation of diagnostic algorithms/guidelines in our setting would improve the utilization of a scarce and costly resource.

The CTPA positivity rate in our study population was 32% (n=41).

International studies performed since 2001 reported that the yield of CTPA in emergency centre patients differs widely and produced rates of between 5.7% and 37%.<sup>(20)</sup> Only 3 of those studies had rates above 20%, however these followed an ideal work up of patients instead of actual clinical practice.<sup>(20)</sup>

A recent study concluded that adhering to a diagnostic protocol increased the yield of CTPA and reported a yield of 29.6%.<sup>(21)</sup>

The high yield in our study could be explained by the fact that only patients who were clinically assessed as high risk for PE were sent for CTPA, even though a few could have been missed as there was no diagnostic protocol.

#### *HIV and TB*

According to the World Health Organization (WHO), South Africa is a high-HIV, high-TB burden country.<sup>(22)</sup> The 2015 mid-year statistics estimate for the prevalence of HIV in adults aged 15-49 was 16.6%.<sup>(8)</sup> The WHO Global TB Control Report 2015 estimated the South African TB prevalence rate at 696/100 000 and the prevalence of HIV infection in TB patients at 61%.<sup>(22)</sup> The importance of these figures relate to the relationship between HIV, TB and the risk of venous thromboembolism (VTE).

In our study population, the prevalence of HIV and TB was high, at 43% and 41% respectively, even though as many as 20% of patients had not been tested for either, or that test not documented.

HIV infection has been recognized as a pro-thrombotic condition and a number of studies have estimated an overall increase in the risk of VTE in HIV-infected patients to be 2-10 fold higher than in the general population.<sup>(5)</sup>

Although prolonged hospitalization and traditional risk factors play a role, examination of risk factors in HIV positive patients revealed an increased risk in patients younger than 50 years old, the presence of concomitant infections (e.g. cytomegalovirus), low CD4 counts (<200/mm<sup>3</sup>), or a diagnosis of AIDS (Acquired Immunodeficiency Syndrome).<sup>(23)</sup>

A Kenyan study reported a 10.9% prevalence rate of HIV in a group of PE patients.(24) In South Africa, the incidence of PE in HIV-infected patients is unknown. However, a study reviewing the risk factors for DVT found that in patients with confirmed DVT, 64.4% were HIV-infected, 56.5% had TB and 43.3% were co-infected. (25) The above compares to our study in which patients with confirmed PE, 37% were also HIV-infected, 52% had TB and 35% were co-infected.

Tuberculosis also induces a hyper-coagulable state and adults with active tuberculosis have an increased risk of VTE.(6) One review found that more than half of TB patients diagnosed with VTE had no apparent risk factor except for the TB.(26) Our study showed that in patients with active TB and suspected PE, 43% had confirmed PE on CTPA (compared to 27% in TB negative patients). This shows that TB patients in whom the clinical suspicion of PE was high, had confirmed PE in more than 40% of cases. This illustrates the importance of not discarding PE as a diagnosis in patients with active TB.

### *Limitations*

This retrospective chart review was subject to limitations concerning missing data. The lack of data influences the analysis and interpretation of the results of our sample. As the sample population was drawn from patients that had been sent for CTPA, it includes a higher than average risk population. It is therefore not representative of the undifferentiated emergency room population.

The study design and limited data only allowed for simple statistics and multivariate analysis could not be carried out. Therefore no causative relationships could be determined and we could not carry out hypothesis testing.

### **Conclusion**

Our results show a high prevalence of HIV and TB in patients with confirmed PE. Both diseases are known to induce hyper-coagulable states and increase the risk of VTE. However, neither form part of any validated Clinical Decision Rules. In this population, the currently available CDRs may not have assisted in diagnosing a PE. Emergency physicians should be cautious when making a clinical probability assessment of PE in a population with a high prevalence of HIV and TB. PE is a high morbidity/ high mortality diagnosis and future studies need to address the current limitations of

available CDRs and their utilization in a high prevalence population. Further research is also needed to determine whether HIV and TB could be independent risk factors for PE.

### **Dissemination of results**

Results from this research were presented to the medical staff of the Emergency Centre of Mitchell's Plain Hospital, as part of a presentation at their academic morning session.

### **Conflict of interest**

The authors declare no conflict of interest

### **Authors contribution**

BB carried out the acquisition, analysis and interpretation of data; the literature review, and drafting of the article.

TW designed the study, reviewed the research proposal and facilitated submission to ethics, revised the literature review and revised the article.

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## **PART C: ADDENDA**

## GUIDE FOR AUTHORS

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### INTRODUCTION

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Continued on next page

<b>Results</b>		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
<b>Discussion</b>		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
<b>Other information</b>		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).



**UNIVERSITY OF CAPE TOWN**  
**Faculty of Health Sciences**  
**Human Research Ethics Committee**



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13 October 2015

**HREC REF: 762/2015**

**Dr T Welzel**  
Surgery  
Division of Emergency Medicine  
J46.56  
Old Main Building

Dear Dr Welzel

**PROJECT TITLE: CLINICAL PRESENTATION AND DIAGNOSTIC WORK UP OF SUSPECTED PULMONARY EMBOLISM IN A DISTRICT HOSPITAL EMERGENCY CENTRE SERVING A HIGH HIV/TB BURDEN POPULATION (MMed candidate B Bulajic)**

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

**Approval is granted for one year until the 30<sup>th</sup> October 2016.**

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: [www.health.uct.ac.za/fhs/research/humanethics/forms](http://www.health.uct.ac.za/fhs/research/humanethics/forms))

We acknowledge that the student Dr B Bulajic will also be involved in this study.

**Please quote the HREC REF in all your correspondence.**

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

**PROFESSOR M BLOCKMAN**  
**CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE**

Federal Wide Assurance Number: FWA00001637.

Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical

Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki guidelines.

The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.



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REFERENCE: WC\_2015RP5\_34

ENQUIRIES: Ms Charlene Roderick

**University of Cape Town**

**Anzio Road**

**Observatory**

**7935**

For attention: **Dr Bojana Bulajic**

**Re: CLINICAL PRESENTATION AND DIAGNOSTIC WORK UP OF SUSPECTED PULMONARY EMBOLISM IN A DISTRICT HOSPITAL EMERGENCY CENTRE SERVING A HIGH HIV/TB BURDEN POPULATION.**

Thank you for submitting your proposal to undertake the above-mentioned study. We are pleased to inform you that the department has granted you approval for your research.

Please contact the following people to assist you with any further enquiries in accessing the following sites:

**Mitchells Plain Hospital**

**H J Human**

**Contact No: 021-3774305**

Kindly ensure that the following are adhered to:

1. Arrangements can be made with managers, providing that normal activities at requested facilities are not interrupted.
2. Researchers, in accessing provincial health facilities, are expressing consent to provide the department with an electronic copy of the final feedback (**annexure 9**) within six months of completion of research. This can be submitted to the provincial Research Co-ordinator ([Health.Research@westerncape.gov.za](mailto:Health.Research@westerncape.gov.za)).
3. In the event where the research project goes beyond the *estimated completion date* which was submitted, researchers are expected to complete and submit a progress report (**Annexure 8**) to the provincial Research Co-ordinator ([Health.Research@westerncape.gov.za](mailto:Health.Research@westerncape.gov.za)).
4. The reference number above should be quoted in all future correspondence.

Yours sincerely

*AJ Hawkrige*

**DR A HAWKRIDGE**

**DIRECTOR: HEALTH IMPACT ASSESSMENT**

**DATE:** 12/4/2016

**CC:**

**Appendix 5:**

INSTITUTION AUTHORIZATION

**TITLE OF THE RESEARCH PROJECT:** Clinical presentation and diagnostic work up of suspected Pulmonary Embolism in a district level hospital emergency centre in a high HIV/TB burden population

**REFERENCE NUMBER:** HREC 762/2015

**PRINCIPAL INVESTIGATOR:** Dr Bojana Bulajic

**ADDRESS:** **Division of Emergency Medicine**  
**Department of Surgery**  
**University of Cape Town**  
**Rm J46.56, J-Floor, OMB, GSH**

**CONTACT NUMBER:** 0827762399

To whom it may concern,

I DR J MARSZALEK representing the Western Cape Government Department of Health under his/her capacity as **CEO: Mitchell's Plain Hospital** - herewith authorize the above-titled study at this institution. The principal investigator will be Dr Bojana Bulajic, Emergency Medicine Registrar at UCT, student number BLJBOJ001.

It is accepted by the principal researcher that all legal and ethical aspects of this study will be considered and mitigated as outlined in the presented study proposal and adhered to at all times. The study will not commence before achieving ethical clearance from the human research ethics committee at UCT, as well as institutional approval.

Signed at (place) Mitchells Plain On (7) December 2015.

Signature J Marszalek

Department of Health  
Mitchells Plain Hospital  
Dr J Marszalek  
Manager Medical Services  
Print Name in full  
07 DEC 2015  
Sign: J Marszalek

DR J MARSZALEK

ORIGINALITY REPORT

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# Research Proposal

Clinical presentation and diagnostic work up of suspected Pulmonary Embolism in a District Hospital Emergency Centre serving a high HIV/TB burden population

Submitted in partial fulfilment of the requirements for the MMed (Emergency Medicine)

Student: Dr Bojana Bulajic  
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# Clinical presentation and diagnostic work up of suspected Pulmonary Embolism in a high HIV/TB burden population

## 1. Introduction:

### Purpose of the study

To describe the presentation of patients with suspected Pulmonary Embolism (PE) and subsequent diagnostic workup, including bedside and laboratory tests as well as CT Pulmonary Angiography at a District Hospital in Cape Town. The study will initially identify all CTPAs, performed at Mitchell's Plain Hospital, on the Picture Archiving and Communication System (PACS) and then include those patients who underwent CTPA imaging for suspected PE. Data collected from patient notes and the NHLS database will be used to describe the clinical presentation of patients who were confirmed positive and negative for PE. The study will also check whether clinical decision rules (CDRs) are used to make an assessment of pre-test probability of a PE, and if they were not, a retrospective CDR (revised Geneva score) will be worked out for each patient. Furthermore, an assessment will be made whether the CDR or clinical gestalt parallel the results of the CTPA. An estimate of the prevalence of HIV and TB in this sample population will be made. As both HIV and TB induce a hypercoagulable state, the researcher supposes that a higher prevalence of HIV and TB among those patients with confirmed Pulmonary Embolism would signify a need for prospective evaluation of a clinical decision rule that includes these as criteria.

## 2. Background and Literature Review:

### Incidence

The true incidence of Pulmonary Embolism (PE) is unknown in the general population. In the United States (USA) annual incidence is estimated at 0.5 – 1 per 1000. (1) For South Africa, no incidence rate for PE could be found in the literature. Also no local data is available on the prevalence of HIV and TB in patients with PE. Mortality rates attributed to diseases of the pulmonary circulation would greatly underestimate the burden of disease. In the developed world, it is one of the leading causes of death in hospitalized patients and otherwise adds significant morbidity to patients due to chronic sequelae. (2)

The diagnosis of PE is thought to be potentially missed more than 400 000 times per year in the USA. (2) Autopsy studies have shown gross emboli in 1.5 to 30% of routine autopsies, and 60-80% of fatal PE cases are clinically unsuspected and undiagnosed. (3)

### Clinical decision rules

The concern for morbidity and mortality being directly caused by failing to diagnose PE has led to an increase in the use of D-dimer testing and CT pulmonary angiography (CTPA). In order to increase the net efficiency of the diagnostic work-up for PE and minimize exposure to ionizing radiation, pre-test probability prediction rules have been designed and validated in clinical practice. (4) Examples of prediction rules or CDRs (clinical decision rules) are the Wells (5) and revised Geneva scores(6).

For practical purposes, both rules have been simplified by assigning only one point to each item. (7) (See Appendix 1) The Prometheus study group compared 4 CDRs (the Wells, revised Geneva score, simplified Wells and simplified revised Geneva score) together with D-dimer testing and found that any one of them can be used in clinical practice with equal safety and clinical utility.(8) They also prospectively validated the use of the simplified CDRs in an outpatient and inpatient setting in academic and non-academic hospitals.(8) Hence the choice of rule used depends on the local preference.

The clinical evaluation and diagnosis of PE is challenging and determination of pre-test probability can help the clinician to:

- 1) determine whether to initiate investigation for PE
- 2) determine the investigation needed (by following a diagnostic algorithm ), and

- determine the patients who would benefit from treatment with anticoagulation prior to the completion of investigations.

### Diagnostic algorithms

A simple diagnostic algorithm, as first proposed by the Christopher Study Investigation, uses a clinical decision rule to work out pre-test probability and risk stratifies patients into “PE likely” and “PE unlikely” categories (dichotomized rule).(9) The algorithm is then followed to determine if the patient needs D-dimer testing or CTPA (9)

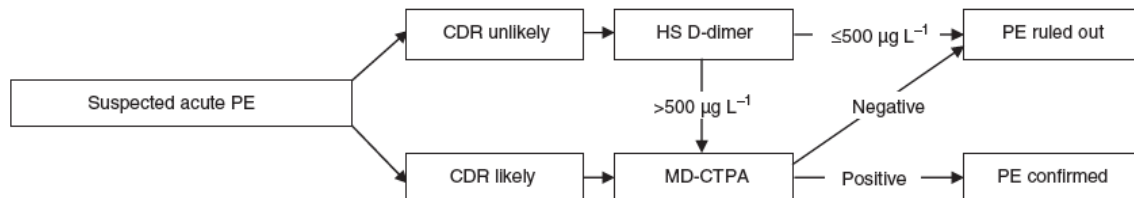


Figure 1: Diagnostic Algorithm for clinically suspected Pulmonary Embolism (7)

The PERC criteria were developed to rule out PE in a subset of patients with suspected PE but deemed to be very low risk.(10) (See Appendix 2) A multicenter prospective study in patients presenting to emergency departments found that the combination of pre-test probability of less than 15% as assessed by clinician gestalt and PERC negative criteria reduced the probability of venous thromboembolism (VTE) to less than 2%.(11) However, new data suggests that the PERC criteria alone cannot safely rule out PE in a population with a low pre-test probability and a relatively high prevalence of PE (Specificity 33.2% and NPV 93.6% for the PERC rule). (12)

All of the above can be combined in a diagnostic algorithm. See Appendix 3 for one method conceptualised by Ouellette and Patocka which uses the PERC criteria and Wells score.(2)

The use of such validated diagnostic algorithms has been found to be associated with lower healthcare costs and a decreased complication risk. However despite overwhelming evidence to support the latter, adherence to these algorithms in clinical practice is poor. (7)

### D-dimer test

A D-dimer test combined with a pre-test probability (CDR) can safely rule out PE.(7) The sensitivity of an elevated D-dimer concentration for venous thromboembolism (VTE) is very high.(13) In contrast, the specificity is very low as D-dimer levels can be elevated in other clinical conditions that are associated with enhanced fibrin (e.g. malignancy, trauma, increased age, disseminated intravascular coagulation, inflammation, infection, sepsis, postoperative states and pre-eclampsia).(13) Therefore D-dimer tests are useful in ruling out DVT or PE. A large variety of assays are available for D-Dimer testing and even though some are superior to others, no one has a 100% sensitivity.(7) Therefore the use of D-dimer testing should be restricted to patients with low pre-test probabilities. The normal threshold for a highly sensitive D-Dimer test is  $500\mu\text{g L}^{-1}$ . (7) (See Figure 1)

### CT Pulmonary Angiography

CT Pulmonary Angiography (CTPA) is currently the dominant imaging modality in the investigation of PE and most centres use MDCT (Multi row detector CT) as their sole diagnostic test. (2) The CT positivity rate for pulmonary embolism, requested from Emergency Departments in the United States is around 10%. (14)

MDCT has a two-dimensional array of detector elements (i.e. multiple, parallel row of detectors) compared to the single row of detector elements used in single detector scanners.(15) This allows the acquisition of multiple slices simultaneously and increases the speed of CT imaging. MDCT refers to CT scanners able to acquire 2 or more slices and this has expanded to 4-, 8-, 16-, and 64-slices.(15) MDCT scanners with 16 or more slices have reduced scan time, decreased movement artefacts and increased spatial resolution.(16) This newer CT technology has a sensitivity ranging between 83% and 100% and a specificity of greater than 95%.(2)

Therefore the use of CT scanners with less than 16 detector rows cannot be advocated anymore for obtaining CTPA.(16)

### **Subsegmental pulmonary embolism**

The high sensitivity of MDCT has led to an increase in the detection of small pulmonary emboli in the subsegmental arteries (9.4% vs 4.7% for single row detector CT). (17) However mortality or case fatality rates did not increase and therefore a hypothesis was derived that subsegmental pulmonary embolism (SSPE) could be clinically irrelevant.

Den Exter and colleagues have challenged this hypothesis with their findings that symptomatic SSPE mimics more proximal PE with regards to risk profile and short-term clinical course.(17) Also compared to patients without PE, SSPE is associated with a higher incidence of recurrent VTE and mortality. (17) With regards to the controversy of anticoagulation of SSPE, a Cochrane review in 2014 found no randomized controlled trials to provide evidence for the effectiveness and safety of anticoagulation versus no therapy. (18)

The jury is still out and eagerly awaiting the findings of an ongoing prospective management study on the safety of withholding anticoagulation in SSPE.(19)

Therefore CTPA results confirming SSPE will still be included in this study.

### **HIV and TB**

According to the World Health Organization (WHO), South Africa is a high-HIV, high-TB burden country.(20) The South African National HIV Survey estimated the prevalence rate of HIV in adults aged 15-49 at 18.8% in 2012.(21) The UNAIDS estimate for 2013 for the same age group is 19.1%.(22) The WHO Global TB Control Report 2014 estimated the South African TB prevalence rate at 715/100 000 and an incidence rate of 860/100 000.(20) The prevalence of HIV infection in TB patients is 62%.(20)

The importance of these figures relate to the relationship between HIV, TB and the risk of venous thromboembolism (VTE).

HIV infection has been recognized as a pro-thrombotic condition and this association has been proven by a large number of studies, mostly done in the pre-HAART era. These studies estimated an overall increase in the risk of VTE in HIV-infected patients to be 2-10 fold higher than expected in the general population.(23) A more recent US study evaluated the risk of DVT/PE in HIV infected patients by calculating Odds Ratios (OR) while adjusting for age and found a 43% increase in the OR for developing PE, 10% increase for developing DVT and 40% increase for developing a PE or DVT over the 9 year period of the study.(24) For African populations, a Kenyan study reported a 10.9% prevalence rate of HIV in a group of PE patients.(25) In South Africa, HIV-infected individuals were reported to have abnormal markers of coagulation. The markers improved after the initiation of HAART, but were still significantly different than that of non HIV-infected controls. This showed evidence of a persistent haemostatic disturbance.(26)

Tuberculosis induces a hypercoaguable state by various mechanisms.(27) Adults with active tuberculosis have a greater risk of VTE than those without and mortality is greater in those with active TB and VTE.(28) One retrospective review found that more than half of TB patients diagnosed with VTE had no apparent risk factor except for the TB.(29)

A recent South African study reviewing the risk factors for DVT found that 64.4% were HIV-infected, 56.5% had TB and 43.3% were co-infected. (30)

### **Background: Mitchell's Plain Hospital**

Currently, patients with suspected PE at Mitchell's Plain Hospital are sent for CTPA when the clinical suspicion of PE is high. This decision is mostly made implicitly i.e. based on the clinician's own knowledge and experience. Studies elsewhere have also shown that even those clinicians familiar with CDRs for determining pre-test probability for PE, only use them in 50% of applicable cases. Although evidence demonstrates that 'physician gestalt' and the 2 validated clinical decision rules (Wells and Geneva) have similar accuracy, the use

of CDRs by less experienced clinicians may increase accuracy of assessing clinical probability(2), thereby optimising the use of a scarce and expensive resource.

At Mitchell's Plain Hospital EC, multiple factors such as long waiting times, overcrowding, language barriers, laboratory delays and partial availability of CTPA may contribute to a delay in diagnosis and treatment of patients presenting with PE.

In our setting, the high prevalence of tuberculosis, chronic obstructive airways disease, congestive heart failure and acute coronary syndrome present a diagnostic dilemma as these conditions often present with similar clinical features to PE. Chest pain and shortness of breath are the two most common symptoms associated with PE.(2) And these are also known to be the two most common symptoms presenting to emergency centres.(31) In addition, PE spans the spectrum of medical presentations from asymptomatic to cardiovascular collapse and death.(2) This leaves the junior or less experienced clinician with a long list of differential diagnoses. Clinical symptoms, signs and abnormalities of blood gases, chest radiograph, and electrocardiogram have a low predictive value for suspected DVT or PE when considered singly.(32)

By using a CDR to assess pre-test probability as part of a simplified algorithm (See Figure 1), it should guide the clinician to determining whether a PE is likely or unlikely (9). The use of a CDR could therefore lead to a shorter time to imaging and diagnosis.

With regards to choice of CDR, one possible limitation of the Wells' score is that it includes the clinician's judgement of whether an alternative diagnosis is more likely than that of PE.(32) This is a subjective criteria, which carries a major weight in the score. To obviate the standardization problems, the Revised Geneva score was validated on patients admitted to emergency wards for clinically suspected PE. The rule is entirely based on clinical variables and is independent of a physician's implicit judgement.(6) Therefore we could apply this score retrospectively in our sample population to work out the pre-test probability and determine if it differs from clinical gestalt or the CTPA result.

Literature from the developed world reports that both HIV and TB induce a hypercoagulable state. South Africa has a high prevalence of HIV and TB, yet no local studies explore whether this increases the risk of PE. The researcher supposes that the high prevalence of HIV and TB, confers an increased risk for PE in our population, which is not identified by a current CDR and therefore it might not be applicable in our setting.

By describing the clinical presentation, risk factors, bedside testing, HIV and TB status in our high probability sample for PE, we can compare the characteristics of those who were found CTPA positive and negative. This can set the background for future studies to derive a CDR for our population.

A future prospective study is needed to determine how HIV and TB could be included in a locally tailored predictive score and validated.

### **3. Research question:**

'What is the clinical presentation and diagnostic work up of patients with suspected Pulmonary Embolism in a high HIV/TB burden population who underwent CTPA at Mitchell's Plain Hospital?'

### **4. Aim and objectives:**

#### **4.1 Aim:**

- To determine the clinical presentation and diagnostic work up in patients with suspected Pulmonary Embolism, who underwent CTPA, in a population with a high prevalence of HIV and TB.

#### **4.2 Objectives:**

- To describe the clinical presentation of patients having received a CTPA for suspected PE, including history and physical examination
- To determine which investigations (e.g. ECG, D-Dimer, CXR) were done, including their interpretation
- To determine whether any pre-test probability was documented

- Reapply a CDR retrospectively (the revised Geneva score) and determine pre-test probability and categorise into PE likely and PE unlikely.
- To determine if pre-test probability (CDR) parallels clinical gestalt and CTPA results in this sample
- To determine the prevalence of HIV and TB in the sample population with confirmed PE

## 5. Study methodology:

### 5.1 Study design:

Retrospective chart review

### 5.2 Study setting and population:

The study will be done at the emergency centre of Mitchell's Plain Hospital in Cape Town, South Africa. Mitchell's Plain Hospital is a district level hospital with 230 beds. The 24-hour emergency centre (EC) sees 3500 patients per month.

The decision to send patients for CTPA is made by the Emergency Medicine (EM) consultant on duty, on patients who are implicitly deemed to be high risk for PE. Practically, this means that on morning ward rounds; patients with suspected PE, are presented to the EM consultant who decides (presumably) on clinical grounds or internal heuristic, which patients need to be send for CTPA imaging. It is unknown if CDRs are used or documented.

A 16 slice MDCT is used for CTPA and is reported on by the in-house radiologist.

CTPA scans are only available on site from 8am to 4pm, Mondays to Fridays. After-hours or on weekends, patients with high clinical probabilities are anti-coagulated while awaiting CTPA. If unstable, patients are anti-coagulated and sent to the tertiary hospital for CTPA.

#### Inclusion criteria:

All adult patients over the age of 18 (male and female), who had CTPA performed at Mitchell's Plain Hospital for suspected PE.

#### Exclusion criteria:

- patients with CTPAs performed for other indications, e.g. thoracic trauma, investigation of lung mass
- patients referred after hours for CTPAs to tertiary hospital
- repeat CTPAs on the same patient during same or subsequent presentation (if PE diagnosed on initial CTPA)
- patients with a chronic PE and/or chronic thromboembolic pulmonary hypertension (CTEPH)
- patients' notes that could not be traced on ECM and their physical folders not found within 1 week of being requested

Chronic pulmonary thromboembolism is mainly a consequence of incomplete resolution of pulmonary thromboembolism and may lead to the development of CTEPH. Therefore it will not be included in the study.

Patients referred for CTPA after hours to the tertiary hospital are usually unstable patients in whom the diagnosis of PE is highly likely. These numbers will be very few and it is not possible in this study to trace the notes of referred patients and therefore they are not included.

The study population will include all patients who had CTPAs done for suspected PE at Mitchell's Plain Hospital over a period of 24 months (October 2013 up to October 2015) as identified on the Picture Archiving and Communication System (PACS). The Mitchell's Plain Hospital Emergency Centre opened in October 2013 and therefore data for patients can only be obtained from this date. The hospital uses PACS to store radiological imaging such as CTPAs. The images and reports are identified on the system by the patients' hospital admission number. The 24 month period is therefore chosen from the opening of the emergency centre and inception of CTPA scanning at the hospital.

The estimated sample size is 150 CTPAs.

### 5.3 Data collection:

At Mitchell's Plain Hospital, a few electronic databases are available for accessing of patient information:

- The Picture Archiving and Communication System (PACS) is used for the acquisition of digital images from X-rays and CT scans, as well as storage on an archive that can be accessed from software loaded onto hospital computers. DICOM (version 3, 2007) is currently in use. The images are available on the system almost immediately after the being taken and reports on CTPAs are available within an hour.
- Enterprise Content Management (ECM) is an electronic medical record that stores scanned copies of patients' emergency centre and inpatient notes. There is often a delay in the uploading of notes onto the system (2weeks). Also physical folders that have been lost therefore will not be available on ECM.
- The National Health Laboratory Service (NHLS) offers 2 platforms: DISA and Trackcare for accessing patients' laboratory results. This service often experiences unexpected downtime. However it is beneficial for finding results requested from primary health care clinics and other hospitals.

All patients who had CTPAs done during the study period will be identified on PACS. Those patients identified on PACS will have their emergency centre and inpatient notes traced on ECM. From the notes it will be deemed whether the patient meets the inclusion and exclusion criteria for the study. Data collection, for the study sample obtained as above, will be done from the electronic medical record (ECM) and entered onto a predesigned excel spreadsheet (see appendix 4) on a personal laptop computer.

If patient notes cannot be found on ECM, the clerk responsible for ECM will be contacted to find the physical folder and upload the notes (usually takes 1-2 days). This request will be reviewed in 2 days and if not uploaded, the physical folder will be requested (takes 1-2 days). The latter request will be repeated once 1 week later and if the folder cannot be found then, it will be excluded from the study.

The National Health Laboratory Service (NHLS) will be accessed to obtain laboratory parameters i.e. d-dimer result, HIV result and CD4 count.

Data to be collected includes:

- patient demographics (age, sex)
- triage time, time seen by clinician, time of decision to CTPA, time of CTPA, time of first anticoagulation
- risk factors and previous medical history
- signs and symptoms, vitals, physical examination, and
- results of basic investigations i.e. ECG, d-dimer, blood gas, CXR
- CTPA result

For full list of parameters see Appendix 4: Data collection sheet

Data will also be collected on whether pre-test probability was documented and then a CDR (revised Geneva score) retrospectively worked out from data collected.

Therefore patient notes that do not contain parameters for all 8 criteria in the revised Geneva Score (See Appendix 1) will be excluded. If other parameters (i.e. other than the 8 criteria above) are not found in patient notes, the case will still be used; however the statistics will be adjusted accordingly. I.e. the denominator is changed according to the number of cases per variable. For example if only 95 of 100 patients had ECGs done and 70 of those have sinus tachycardia then 70/95 (73,7%) would have been found to have sinus tachycardia.

### 5.4 Data safety and monitoring:

Data will be reviewed from the electronic medical records (PACS, ECM, NHLS) and entered directly onto an electronic data collection spreadsheet (Microsoft Excel for Mac 2011, version 14.5.1) to minimize paper records and transcribing errors.

Individual patient data will be coded with a study number on a decoding sheet and patient identifiers will not be entered onto the data collection spreadsheet. This separate decoding sheet (Excel spreadsheet) will be password encrypted. All electronic data will be stored separately on a personal computer that is password protected. This database will be kept for 5 years and a back-up stored on 2 external hard drives that are property of the researcher and also password protected. Back-ups of data will be done weekly on both hard drives.

Once data collection is complete, the researcher will recheck 10% of the cases by reviewing random study numbers to ensure correct data entry onto the data collection spreadsheet.

The researcher has access to the PACS, NHLS and ECM databases via pre-approved login details. These databases (except PACS) can be accessed from the researcher’s personal computer via a safe internet connection. PACS will be accessed from the computers at the Mitchell’s Plain Hospital’s EC.

### 5.5 Data analysis:

Simple descriptive statistics (means, medians and interquartile ranges) will be used to describe all data. These will be summarised in tables and charts.

Excel macro’s will be used to extract data needed to work out the revised Geneva Score and document pre-test probability as PE likely or PE unlikely. The association between the retrospective pre-test probability and the CTPA result will be analysed using the Chi-squared test.

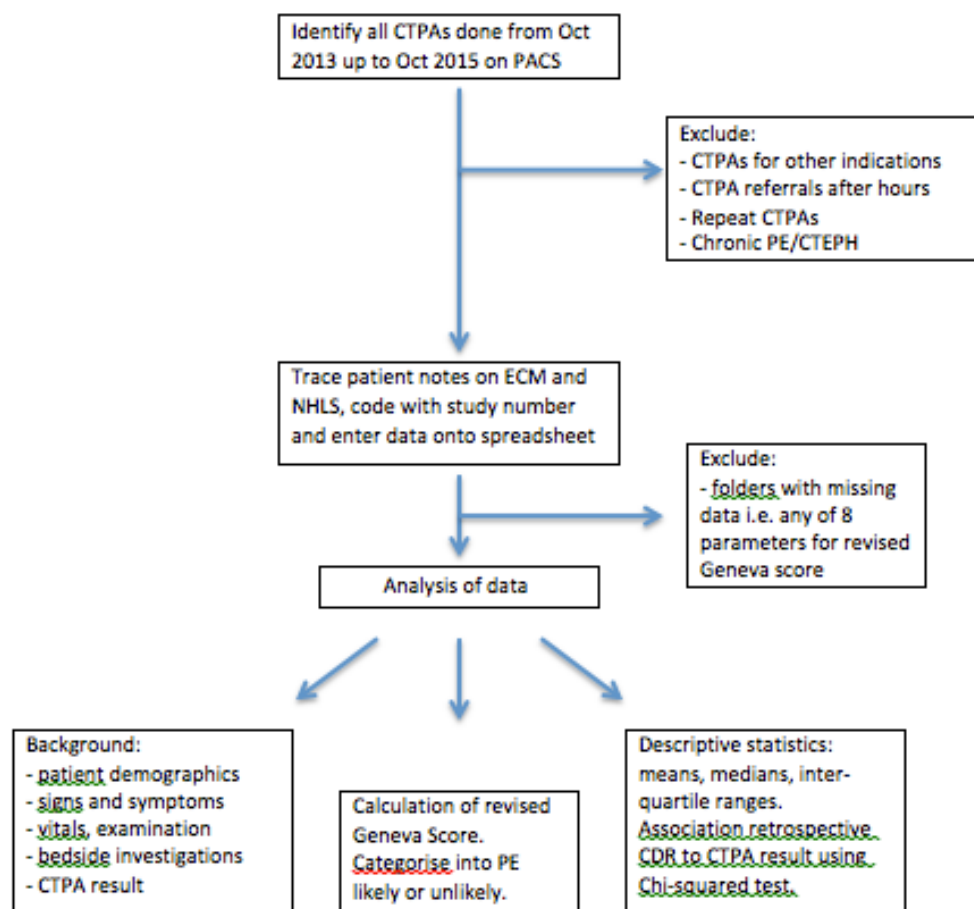


Figure 2: Study methodology flowchart

### 6. Ethical Considerations:

As stated, individual patient data will be coded with a study number and stored separately on a decoding sheet that will be password encrypted. The latter as well as the data collection spreadsheet will be stored on a personal computer that is password protected. Only the researcher will have access to the patient data obtained from the PACS, ECM and NHLS databases; and only while reviewing the data from a personal computer via a secure internet connection. As no patient identifiers will be used on the data collection sheet, confidentiality of HIV test results and CD4 counts will be ensured.

The study will be compliant with the ethical principles as outlined by the Declaration of Helsinki, 2013.

The level of risk in this study is considered to be minimal as there is no direct patient contact and no intervention or additional testing needed of patients. As this is a chart review, patients' exposure to harm is no more than that experienced in daily life and provision is made for confidentiality of recorded patient data. Therefore the ethics committee will be asked to grant a waiver of individual informed consent.

After ethical approval is obtained, approval will be asked from the Provincial Department of Health. Subsequently, permission from the Head of Unit (EC Manager) and Hospital Clinical Manager will be requested. (See Appendix 5). Approval from the data collection databases (PACS, ECM, NHLS) will also be obtained.

## **7. Limitations:**

Data collection could be limited due to lost files, or the paucity of recorded data on patient notes. It is expected that many variables will not be available. Here, selection bias could be introduced as exclusion variables could alter the study findings. Therefore cross-referencing data from multiple sources i.e. PACS, ECM and NHLS will be done.

Also, patients referred for CTPA after hours to the tertiary hospital are excluded, as it is impossible to trace these patients. However they are few.

Due to the study design, the chart review can only describe data and not make inferences with regards to the incidence of PE or the extra risk conferred by HIV or TB on the incidence of PE.

As the study population only includes those patients clinically suspected of PE who were investigated with CTPA (i.e. implicitly believed to be high-risk), the study cannot determine local incidence rates, as it only includes those who underwent CTPA and not very-low risk patients. The study also cannot measure 'missed PE' or the prevalence of the PE in our setting.

The decision to send patients for CTPA is made by a number of EM consultants on a clinical basis, therefore bias is introduced as it is their opinion of which patients are considered high risk. However, the study looks at and describes the actual practice in this EC. The correlation, if any, between the retrospectively worked out CDR and CTPA results can be used to describe the need for a prospective study to develop a new CDR for this environment.

Also the study population may be small and not a representative sample of the source population.

## **8. Data Dissemination Plan:**

Findings from the data will be organised into tables and charts and together with the discussion of the findings will be presented in a journal article format. This will be sent for review for publication.

A poster presentation will be submitted for the International Conference on Emergency Medicine (ICEM) 2016. Feedback will also be given to the Emergency Medicine Department at Mitchell's Plain Hospital.

## 9. Timeline:

	Feb 2015	July	Sept	Oct	Nov-Jan 2016	Feb- Mar	Apr	May
<b>Summary Submission to EM-DRC</b>	X							
<b>Protocol submission to EM-DRC</b>		X						
<b>UCT Ethics Provincial Approval</b>			X					
<b>Data Collection</b>				X				
<b>Data Analysis</b>						X		
<b>Compilation of Final Report</b>							X	
<b>Poster presentation at ICEM</b>							X	
<b>Submission</b>								X

## 10. Budget:

The costs below will be covered by the researcher.

<b>Budget</b>				
<b>July 2014 – May 2015</b>				
<b>Item</b>	<b>Description</b>	<b>Unit cost</b>	<b>Nº of Units</b>	<b>Total cost</b>
<b>Consumables</b>				
1. Stationery costs	Pens, paper, printing of report, printing of poster			R400
2. Internet costs	Internet search for Literature review	R305,25 /month	X2	R610,50
<b>Research travel</b>				
1. Travel to site		R2,20/km	48km/ day X12	R1267,20
<b>Minor research equipment</b>				
1. Laptop for data collection	Own laptop			R0
<b>Personnel</b>				
1. Statistician	2 hours covered by UCT	R480/hr	x 2hrs	R0
<b>Total</b>				<b>R2277,70</b>

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## 12. Appendices

### Appendix 1

Wells rule			Revised Geneva score		
Items	Original	Simplified	Items	Original	Simplified
Previous PE or DVT	1.5	1	Previous DVT or PE	3	1
Heart rate > 100/min	1.5	1	Heart rate 75-94/min	3	1
			Heart rate ≥ 95/min	5	2
Surgery or immobilization < 4 weeks	1.5	1	Surgery or fracture within 1 month	2	1
Hemoptysis	1	1	Hemoptysis	2	1
Active malignancy	1	1	Active malignancy	2	1
Clinical signs of DVT	3	1	Unilateral lower limb pain	3	1
Alternative diagnosis less likely than PE	3	1	Pain on lower limb deep vein palpation and unilateral edema	4	1
			Age > 65 years	1	1
Clinical probability			Clinical probability		
Low	< 2		Low	0-3	
Intermediate	2-6		Intermediate	4-10	
High	> 6		High	≥ 11	
PE unlikely	≤ 4	≤ 1	PE unlikely	≤ 5	≤ 2
PE likely	> 4	> 1	PE likely	> 5	> 2

Taken directly from: Huisman MV, Klok FA. Diagnostic management of acute deep vein thrombosis and pulmonary embolism. *J Thromb Haemst* 2013; 11:412-22.

### Appendix 2:

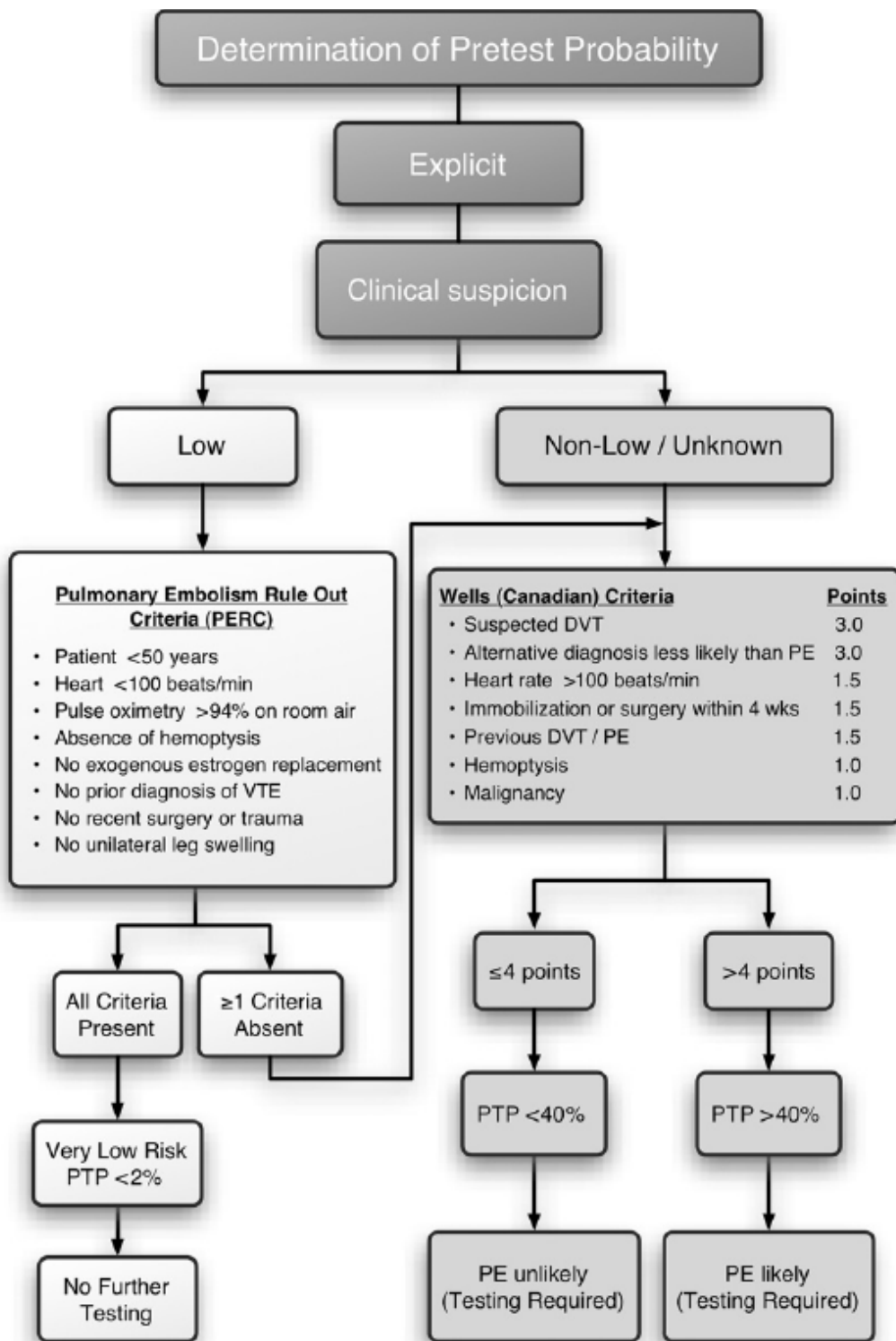
#### (A) The Pulmonary Embolism Rule-out Criteria (PERC) rule

Age < 50 years  
Pulse < 100 bpm  
Pulse oxymetry > 94%  
No unilateral leg swelling  
No hemoptysis  
No surgery or trauma within 4 weeks  
No prior deep vein thrombosis or pulmonary embolism  
No oral hormone use

Patients must meet all eight criteria to be identified as PERC negative.

Taken directly from: Hugli O, Righini M, Le Gal G, Roy PM, Sanchez O, Verschuren F, et al. The pulmonary embolism rule-out criteria (PERC) rule does not safely exclude pulmonary embolism. *Journal of thrombosis and haemostasis* : JTH. 2011;9(2):300-4.

Appendix 3:



Taken directly from: Ouellette DW, Patocka C. Pulmonary embolism. Emergency medicine clinics of North America. 2012;30(2):329-75.