

ORIGINAL 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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ABSTRACT

Introduction: The diagnosis of pulmonary embolism (PE) is challenging to make and is often missed in the emergency centre. 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. CDRs have not been validated in the South African environment where HIV and tuberculosis (TB) are highly prevalent. Both conditions are known to induce a hyper-coagulable state. The objective of this study was to describe the clinical presentation and diagnostic workup of suspected PE in our setting and to determine the prevalence of HIV and TB in our sample of patients with confirmed PE.

Methods: This study was a retrospective chart review of patients with suspected PE who had CTPAs performed between October 2013 and October 2015 at a district hospital in Cape Town, South Africa. Data were collected on demographics, presenting signs and symptoms, vitals, bedside investigations, HIV and TB status. A Revised Geneva score (RGS) 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%). Deep venous thrombosis (DVT) was present in 29%. No sign or symptom was observed to be markedly different in patients with confirmed PE vs no PE. Among patients with confirmed PE, 37% were HIV positive and 52% had current TB. RGS compared poorly with CTPA results.

Conclusions: PE remains a diagnostic challenge. 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 develop a predictive CDR for the local environment.

African relevance

- Many African countries have a high burden of HIV and TB - both conditions increase pro-thrombotic risk.
- Pulmonary embolism has a high rate of mortality and morbidity.
- Early diagnosis and treatment could decrease the strain on resource-limited settings.
- Clinical decision rules like the Wells and Revised Geneva scores were not derived from populations with high rates of TB and HIV.
- CT pulmonary angiography is a scarce resource that should be used effectively for clinical decision making.

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- and middle-income (LMIC) countries such as South Africa, no reliable data are 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].

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The use of Clinical Decision Rules (CDRs) and increased availability of CT pulmonary angiography (CTPA) have improved the diagnostic workup of PE. However, the currently used CDRs have never been validated in the South African environment, in which both HIV and tuberculosis (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 workup of patients who presented to a district hospital's emergency centre in South Africa with 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 (RGS) were calculated retrospectively and compared to the CTPA results. The study also sought to determine the prevalence of HIV and TB in the sample population with confirmed PE.

Methods

This study was done at the emergency centre (EC) of Mitchell's Plain Hospital in Cape Town, South Africa, a district level hospital with 230 beds. The 24-hour EC sees 3500 patients per month. The decision to send a patient for CTPA is made after discussions with the Emergency Medicine consultant, for patients who are deemed to be at high risk of having a PE. 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.

A retrospective chart review was done. 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 folders could not be found. 160 patients met the inclusion and exclusion criteria; due to missing patient notes the final sample size was 127. An *a priori* sample size was not calculated.

Data collection was performed using three databases: radiological imaging (CTPAs) 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 were collected and entered onto a pre-designed Excel spreadsheet (Microsoft Excel, USA).

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 (Appendix A). The simplified dichotomised version of the RGS, with pre-specified cut offs [(PE likely (score > 2) or PE unlikely (score ≤ 2)] was compared to the reference standard (evidence of PE on CTPA).

All the data collected were entered onto a pre-designed Excel

Table 1
Patient demographics.

Demographic	PE suspected (whole sample) n = 127	PE confirmed (CTPA positive) n = 41
Mean age, years (sd)	43 (15.3)	45 (13.5)
Age > 65 years, % (n)	10 (13)	10 (4)
Female sex, % (n)	72 (92)	68 (28)

PE, pulmonary embolism; sd, standard deviation; CTPA, CT pulmonary angiography.

spreadsheet (Microsoft Excel, USA). Statistical analyses were performed in Stata (StataCorp, USA). Descriptive statistics were used and categorical data (from clinical and bedside investigations) were presented in frequency tables with means, standard deviations and confidence intervals where appropriate. Chi-squared and Fisher exact tests were used (at a confidence level of 95%) to compare data between groups (confirmed PE vs no PE). Data were checked for normality using histograms. For the retrospectively applied Revised Geneva score, sensitivity, specificity, positive and negative predictive values as well as likelihood ratios were calculated for our study population.

This study was approved by the University of Cape Town, Human Research Ethics Committee (Ref 762/2015) and the Western Cape Provincial Government (WC_2015RP5_34).

Results

Patient demographics are outlined in Table 1.

Except for recent hospitalisation (36%), age >65 years (10%), being post-partum (10%), having a previous VTE (6%), and immobilisation (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 comorbidities, 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 chronic obstructive pulmonary

Table 2
Vital signs and clinical features on presentation.

Features	Confirmed PE (n = 41)	No PE (n = 86)
Vitals in EC		
Tachycardia (> 94 bpm), % (n)	80 (33)	76 (65)
Heart rate, mean [\pm 95%CI] (SD)	114 [\pm 6] (19)	109 [\pm 5] (23)
Tachypnoea (RR > 20), % (n)	71 (29)	58 (50)
Hypoxaemia (Sats < 95%), % (n)	46 (19)	44 (38)
Saturation (%), mean [\pm 95% CI] (SD)	90 [\pm 4] (12)	93 [\pm 2] (7)
Hypotension (SBP < 90mmHg), % (n)	5 (2)	8 (7)
Symptoms		
Cough, % (n)	51 (21)	53 (46)
Dyspnoea, % (n)	83 (34)	83 (71)
Chest pain, % (n)	41 (17)	60 (52)
Chest pain (pleuritic), % (n)	37 (15)	49 (42)
Sudden onset of symptoms, % (n)	39 (16)	35 (30)
Signs		
Chest: crackles, % (n)	53 (21)	50 (43)
Chest: wheezes, % (n)	25 (10)	14 (12)
Chest: clear, % (n)	33 (13)	37 (32)
Pulmonary hypertension, % (n)	25 (10)	26 (22)
Leg pain and/or swelling suggesting DVT, % (n)	37 (15)	15 (13)

PE, pulmonary embolism; EC, emergency centre; sd, standard deviation; bpm, beats per minute; RR, respiratory rate; Sats, saturation; SBP, systolic blood pressure; DVT, deep venous thrombosis.

disease.

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

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 confirmed PE patients, 29% presented with clinical signs of DVT.

Table 2 compares vital signs and clinical features between patients with confirmed PE and those with no PE. No sign or symptom was observed to be statistically significant at the 95% level between patients with confirmed PE and those without PE.

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%).

With regards to arterial blood gas measurements, there were very small differences in PaO₂, PaCO₂, and oxygen saturation between patients with confirmed PE and no PE.

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.

The Revised Geneva score contains only objective variables compared to the Wells score that includes a heavily weighted subjective criterion. The simplified dichotomised Revised Geneva score categorises patients into ‘PE likely’ (score > 2) or ‘PE unlikely’ groups (score ≤ 2). This was calculated retrospectively on the collected data and the categories compared poorly with the CTPA result (Fig. 1).

In our study population, the RGS had a sensitivity of 29%, 95% CI [16.1–45.5], specificity of 83% [72.9–89.9], positive predictive value (PPV) of 44% [29.2–60.8] and a negative predictive value (NPV) of 71% [66.3–75.3]. The positive likelihood ratio was 1.68 [0.87–3.25] and negative likelihood ratio was 0.86 [0.69–1.07].

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

The CTPA yield for PE in our study population was 32% [24.2–40.4] (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 three patients (7.3%) had purely sub-segmental emboli.

D-Dimer testing was performed in 21 patients (17%). The level was

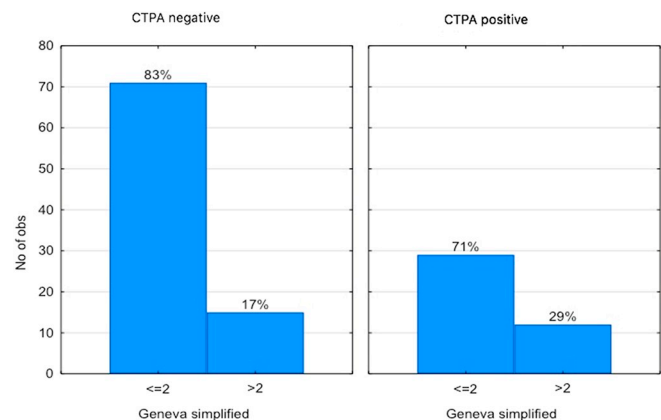


Fig. 1. Comparison: Revised Geneva Score vs CTPA. Note: CTPA, CT pulmonary angiography.

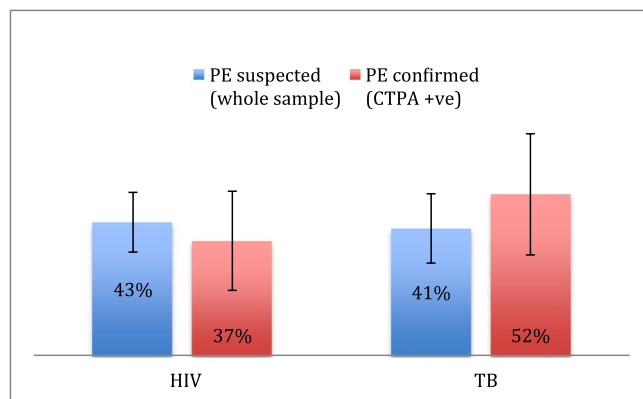


Fig. 2. Prevalence of HIV and TB in suspected PE vs confirmed PE. Note: PE, pulmonary embolism; CTPA, CT pulmonary angiography; HIV, human immunodeficiency virus; TB, tuberculosis.

above the cut-off value (> 500 µg/ml) in 76%. Ordering of D-dimer tests did not correlate with documented CDR score (Wells) or retrospective CDR score (Revised Geneva).

In our study population of patients with suspected PE, the prevalence of HIV was 43% and that of TB was 41% (Fig. 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 (Fig. 2).

Of the 52% (n = 13) with current TB and PE, twelve patients also had previous TB and eight 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.

In HIV positive patients with suspected PE, the CTPA was positive in 30% (compared to 38% 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. Still, PE is a condition that often 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.

In our study population, the mean age at diagnosis of PE was 45 years and only 10% of patients were 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].

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 markedly different between patients with confirmed PE and those without. A systematic review and meta-analysis by West, et al. concluded that no feature in isolation 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 United States (US) study, no differences in vital signs were

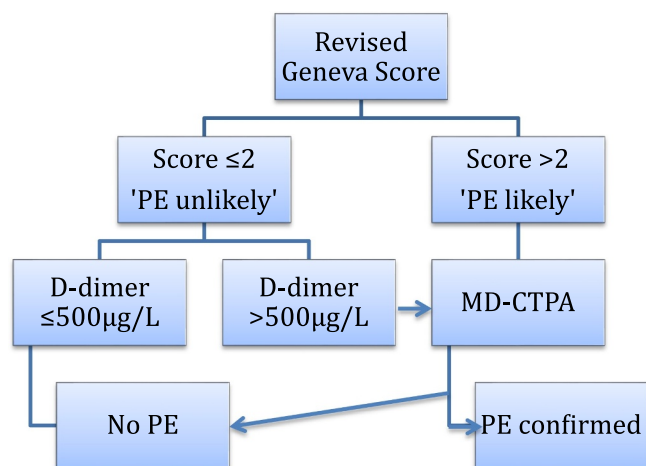


Fig. 3. Diagnostic algorithm for pulmonary embolism. Note: PE, pulmonary embolism; MD-CTPA, Multi-detector; CT Pulmonary Angiography.

detected between the PE positive and PE negative groups [11]. A possible explanation is that patients presenting with a significant cardiorespiratory 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 (e.g., 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 US, found dyspnoea, chest pain and extremity swelling suggesting DVT to be the most common presentations [11].

We found a DVT by compression ultrasonography in 15 of 28 patients with suggestive leg pain/swelling. Of the 15 patients diagnosed with a DVT, twelve also had PE confirmed on CTPA. This means that in our sample of confirmed 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.

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 [12]. These have been combined into a diagnostic algorithm, using the Revised Geneva Score in this example (Fig. 3).

The use of a validated diagnostic algorithm has been found to lower healthcare costs and also decrease complication risk [13]. However, despite the overwhelming evidence to support the use of diagnostic algorithms, adherence in clinical practice even in HICs is poor [14]. 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 (the Wells score was used by our clinicians). 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. The Revised Geneva score was applied retrospectively to see how it would perform in our study population. We chose the

Revised Geneva score because it only includes objective criteria [15] (Appendix A), versus the Wells score, which includes a highly subjective criterion (i.e. "no alternative diagnosis better explains the illness").

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 dichotomised Revised Geneva score in this example [16]. The categories correlate with the patient's estimated risk of PE and guide the next step in the diagnostic algorithm [17]. (Fig. 3)

In our study population, the RGS had a sensitivity of 29% and specificity of 83%. The sensitivity compares poorly, but the specificity is improved when compared to the values described by Lucassen et al. in a meta-analysis (91% and 37%, respectively) [18]. The latter study also noticed an increase in sensitivity and a decrease in specificity when prevalence was increased, which is in contrast to our findings. A higher prevalence, as found in our sample population, is known to increase the positive predictive value of a test, PPV 44% vs 32%.

In our study, 71% of patients with confirmed PE (CTPA positive) would have been incorrectly categorised as 'PE unlikely' using the RGS. Therefore, if the decision to perform CTPAs in our population was based on the RGS, CTPA would have not been performed and 71% of PEs would have been missed (Fig. 1).

The diagnostic yield of the 'PE unlikely' group could have been improved by the addition of a D-dimer test (Fig. 3), however it was only performed in 21 patients (17%). The low use of D-dimer testing is a reflection of the low use of CDRs by clinicians (13%) in our study. This shows not only the need for a predictive CDR for our environment but also an improved adherence to using a diagnostic algorithm combining CDR, D-dimer and CTPA (as shown in Fig. 3).

Multi-Detector Computed Tomography Pulmonary Angiography (MD-CTPA) 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) [19]. 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 [20].

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 utilisation 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% [21]. Only three of those studies had rates above 20%, however these followed an ideal workup of patients instead of actual clinical practice [21]. A recent study concluded that adhering to a diagnostic protocol increased the yield of CTPA and reported a yield of 29.6% [22].

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.

According to the World Health Organization (WHO), South Africa is a high-HIV, high-TB burden country [23]. The 2015 mid-year statistics estimate for the prevalence of HIV in adults aged 15-49 was 16.6% [8]. 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% [23]. The importance of these figures relate to the relationship between HIV, TB and the risk of 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 recognised 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 two- to ten-fold higher than in the general population [5].

Although prolonged hospitalisation 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/mm³), or a diagnosis of AIDS [24].

A Kenyan study reported a 10.9% prevalence rate of HIV in a group of PE patients [25]. 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 [26]. The above compares to our study of patients with confirmed PE where 37% were 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 TB [27]. 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.

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 centre 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.

Appendix A. Simplified Revised Geneva score.

Adapted from Klok FA, Mos IC, Nijkeuter M, Righini M, Perrier A, Le Gal G, et al. Simplification of the Revised Geneva score for assessing clinical probability of pulmonary embolism. *Archives of internal medicine*. 2008; 168(19): 2131-2136.

	Points
Variable	
Age > 65	1
Previous DVT or PE	1
Surgery or fracture within 1 month	1
Active malignancy	1
Unilateral lower limb pain	1
Haemoptysis	1
Heart rate 75–94 bpm > 95 bpm	1
Pain on lower limb deep venous palpation and unilateral oedema	2
Clinical probability	
PE unlikely	≤ 2
PE likely	> 2

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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 CDR. In our study population, the retrospectively calculated CDR was not predictive of 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 and should consider PE as part of the differential diagnosis. However, further studies are needed to develop a predictive CDR for the local environment.

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgements

We thank the staff from Mitchell's Plain Hospital Radiology Department for their assistance in obtaining the CTPA reports.

Dissemination of results

The results of the study were shared with the Emergency Centre staff of Mitchell's Plain Hospital during a morning teaching session. The results were also presented at the University of Cape Town/Stellenbosch University's Emergency Medicine Registrar's weekly teaching session.

Authors' contribution

Authors contributed as follows to the conception or design of the work; the acquisition, analysis, or interpretation of data for the work; and drafting the work or revising it critically for important intellectual content: BB 55%, TW 35% and KV 10%. All authors approved the version to be published and agreed to be accountable for all aspects of the work.

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