ADMISSIONS FOR PULMONARY EMBOLISM AT A TERTIARY SOUTH AFRICAN HOSPITAL

By

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As the candidate's supervisor/co-supervisor I have approved this thesis for submission.

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DEDICATION

For: My dear wife Natasha Naidoo and grandfather Ramsamy Moodley. Thank you for your unceasing encouragement and support.

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Firstly, I would like to thank God for providing me with the opportunities to serve mankind as a medical doctor and the strength and guidance to complete the thesis.

I sincerely thank my supervisor Dr Yoshan Moodley and co supervisor Dr Susan. L. Brown for their dedication and hard work. Without their help and guidance this thesis would not have been possible.

I would like to take this opportunity to thank the department of internal Medicine and the post graduate research department of UKZN for their effort and guidance.

Finally, I would like to take the opportunity to thank the patients whose data formed the core of this research project and hopefully the results would have a beneficial bearing in the lives of future patients.

LIST OF ABBREVIATIONS

Overview

SA	South Africa
PE	Pulmonary embolism

Part 1: Literature review

DVT	Deep vein thrombosis
PE	Pulmonary embolism
VTE	Venous thromboembolism
UK	United Kingdom
US	United States
CTPA	Computed tomography pulmonary angiography
AT3	Antithrombin III

Part 2: Submission-ready manuscript

PE	Pulmonary embolism
SA	South Africa
DVT	Deep vein thrombosis
VTE	Venous thromboembolism
SP	Study population
IALCH	Inkosi Albert Luthuli Central Hospital
ICD-10	International Classification of Diseases 10th Revision
CI	Confidence interval
NYHA	New York Heart Association
N/A	Not applicable
ED	Emergency department
CCU	Critical care unit
URL	Upper reference limit

LIST OF FIGURES

Overview

No figures.

Part 1: Literature review

Part 2: Submission-ready manuscript

LIST OF TABLES

OVERVIEW

Noncommunicable diseases are becoming increasing important in South Africa (SA). In particular, diseases of the circulatory system (including pulmonary embolism – PE) were responsible for over 2500 deaths in the country during 2007. Although reports of PE from SA are rare, there are SA studies of deep vein thrombosis (of which PE is a complication) which suggest setting-specific risk factors for thromboembolic disease as well as certain risk factors reported in the overseas literature. This might also hold true for PE. Furthermore, there might be setting-specific risk factors for mortality in SA patients with PE. A better description of PE in a SA setting would be useful in efforts to improve patient management and subsequent patient outcomes in this setting.

The aim of this study was to improve the current understanding of PE in a SA setting. The objectives of this study were to: 1) Describe the presentation of PE in patients who were admitted to a tertiary SA hospital with the condition; 2) Determine the incidence of inpatient mortality in these patients; and 3) Determine which presenting characteristics are associated with inpatient mortality in SA patients with PE.

This study was an analysis of data for 61 adult patients admitted to a tertiary SA hospital over a five-year period with a primary diagnosis of PE. Data related to patient demographics, PE presentation, risk factors, treatment, and inpatient mortality were collected and analysed using appropriate statistical tests. Overall, this study reports differences and similarities in certain aspects of the presentation and outcomes associated with PE between SA and overseas settings. It is hoped that this research will lead to the generation of hypotheses which will improve PE management and subsequent patient outcomes in SA settings.

TABLE OF CONTENTS

Part 1: Literature review

1.1 Definition of pulmonary embolism:

Venous thromboembolism (VTE) includes deep vein thrombosis (DVT) and pulmonary embolism (PE).[1] Pulmonary embolism is an uncommon but catastrophic complication of DVT during which a thrombus in the lower extremities fragments, forming emboli. These emboli migrate to the lung.[1-3] where they adversely affect pulmonary and cardiac function through disruption of the pulmonary circulation by occlusion.[3] Where there is haemodynamic instability which can only be attributed to a PE, then a PE may be classified as massive.[4] Submassive PE occurs when there is haemodynamic stability, but evidence of right ventricular dysfunction or myocardial necrosis.[4] As with other conditions of the vascular system such as stroke and myocardial infarction, pulmonary embolism can be acute or chronic.[2]

1.2 Pathophysiology of pulmonary embolism:

The pathophysiology of PE begins with Virchow's triad for VTE, namely: endothelial dysfunction/damage, hypercoagulability, and stasis (Figure 1).[3] These are the mechanisms through which DVT arises.[3] As PE is a complication of DVT, Virchow's triad also holds true for PE.

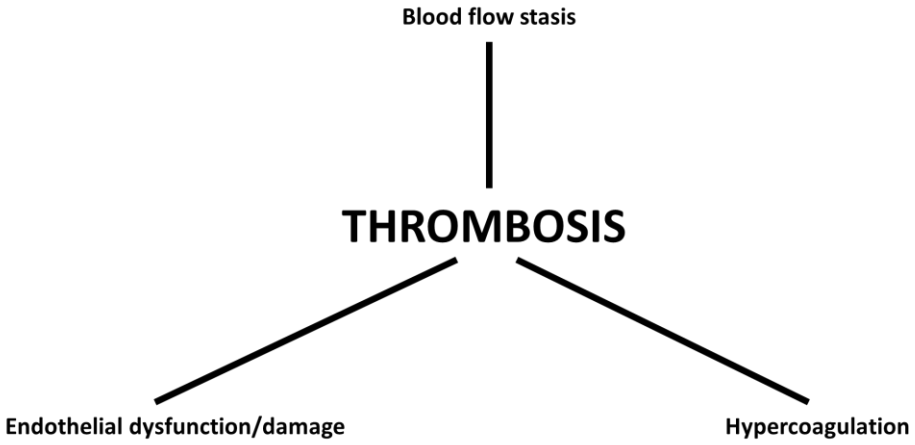

Figure 1. Virchow's triad

The migrating embolus can anatomically occlude the pulmonary circulation.[5] This has three physiological consequences. Firstly, there might be an increase in "dead space" (areas of lung where there is ventilation but no perfusion).[6,7] The ratio of ventilation to perfusion is usually close to 1.0 (or balanced between ventilation and perfusion).[8] An imbalance in this ratio is commonly referred to as a mismatch between the ventilation:perfusion ratio, or a V:Q mismatch.[8] A V:Q mismatch is associated with arterial hypoxaemia.[9] A PE might also cause vascular compromise, atelectasis, and subsequent V:Q mismatch.[9] Lastly, there might be haemodynamic consequences resulting in potentially fatal heart failure, tachycardia, or hypotension.[7] Chemical messengers such as serotonin are released into the circulation in response to an embolus. Serotonin can cause vasoconstriction, increased pulmonary resistance, and subsequent V:Q mismatch.[7] Increased pulmonary resistance can also result in cardiovascular dysfunction (potentially fatal heart failure, tachycardia, or hypotension). Histamine

released in response to a PE can induce bronchoconstriction, which leads to alveolar hypoxia and V:Q mismatch.[7] An increase in respiratory rate is a compensatory response for hypoxaemia arising from the aforementioned V:Q mismatch.[9] This manifests as the most common signs and symptoms of PE.[10]

1.3 Incidence of pulmonary embolism:

The incidence of VTE in various regions of the world has been summarized in a review document compiled by the 15th Steering Committee for World Thrombosis Day.[11] The findings for PE have been extracted from the aforementioned review and are presented in Table 1, as incidence per 1000 people per year. Data from Western Europe suggests that the incidence of PE in this region ranges between 0.15 and 0.95.[11] The upper and lower range values for the incidence of PE in North America are much higher than those reported in the published literature for Western Europe. The incidence of PE in the North American regions ranged from 0.45 (Canada) to 1.15 (United States). There were only two published studies describing the incidence of PE in the Australasian region at the time, with both these studies emanating from Australia (incidence range: 0.31-0.53).[11] The incidence of PE in Asia (from two published studies) ranged between 0.039 and 0.070. There was only one published study from South America (Argentina) at the time the review was compiled, with the estimated incidence of PE falling within the ranges reported for Western Europe and North America. There were no published studies identified as part of the review which specifically reported the incidence of PE in African countries.[11]

Table I. Incidence of pulmonary embolism around the world*

Study	**Setting**	**VTE incidence#**	**PE incidence#**
Morreti et al.	Italy	Not reported	0.189
Severinsen et al.	Denmark	1.15	0.51
Cohen et al.	France, Germany, Italy, Spain, Sweden, UK	Not reported	0.95
Heurta et al.	UK	0.745	0.342
Naess et al.	Norway	1.43	0.50
Guijjaro et al.	Spain	0.036	0.15
Oger et al.	France	1.83	0.60
Tagalakis et al.	Canada	1.22	0.45
Yusuf et al.	US	2.39	1.15
Weiner et al.	US	Not reported	1.12
Cushman et al.	US	1.61	0.45
Stein et al.	US	1.30	0.36
Janke et al.	US	Not reported	0.60-0.90
Silverstein et al.	US	1.17	0.69
Anderson et al.	US	1.07	0.23
Shiraev et al.	Australia	Not reported	0.53
Ho et al.	Australia	0.83	0.31
Vazquez et al.	Argentina	1.65	0.64
Jang et al.	Korea	0.138	0.070
Cheuk et al.	Hong Kong (China)	Not reported	0.039

*Extracted from a published review[11].
#Incidence per 1000 people per year.
VTE: Venous thromboembolism; PE: Pulmonary embolism, UK: United Kingdom, US: United States.

1.4 Risk factors for pulmonary embolism:

In 2003, The British Thoracic Society published a guideline document for the management of PE which also provided an overview of risk factors associated with the condition.[12] Risk factors for PE where classified as minor risk factors (risk factors with a relative risk of between 2.0 and 4.0) or major risk factors (risk factors with a relative risk of between 5.0 and 20.0).[12] Minor risk factors were broadly categorized as cardiovascular (congenital heart disease, heart failure, hypertension, superficial venous thrombosis, indwelling central vein catheter), oestrogen use (oral contraceptives or hormone replacement therapy), and miscellaneous risk factors (chronic obstructive pulmonary disease, neurological disability, occult malignancy, thrombotic disorders, long distance travel, and obesity).[12] Major risk factors identified in the guideline document included: Surgery (open abdominal/pelvic, hip/knee arthroplasty, postoperative critical care admission), obstetric factors (late pregnancy, caesarean section, puerperium), lower limb conditions (fracture, varicose veins), malignancy (abdominal/pelvic, advanced/metastatic disease), immobilization (due to hospitalization, institutional care), and previous VTE (DVT/PE).[12]

A review by Kranidis et al., categorized risk factors for VTE as primary risk factors and secondary risk factors.[10] Primary risk factors included: Factor V Leiden, antithrombin deficiency, resistance to activated protein C, hyperhomocysteinemia, prothrombin 20210 mutation, antiphospholipid antibodies, protein C deficiency, and protein S deficiency.[10] Most of the secondary risk factors were also cited in the British Thoracic Society guidelines,[12] with the exception of advanced age, diabetes, and smoking.[10] There is also evidence of HIV and tuberculosis infection as potential risk factor for PE in regions of the world where these infectious diseases are endemic.[13] The importance of these risk factors cannot be ignored and some of these are components of risk stratification methods for PE.

1.5 Mortality associated with pulmonary embolism:

Mortality is the most severe outcome of PE. There are a few studies which report 90 day mortality rates in outpatients with PE, or mortality rates for patient admitted to hospital with a primary diagnosis of PE.[2] The International Cooperative Pulmonary Embolism Registry (N=2454) reported the 90 day all-cause mortality rate in registry patients to be 17%.[2,14] An American study conducted in Massachusetts reported the 90 day all-cause mortality rate in outpatients with PE to be 11%.[2,15] Analysis of the Registry of Patients with Venous Thromboembolism (N=6264) reported a lower 90 day all-cause mortality rate of 8.6%.[2,16] In fact, PE might account for up to 10% of all inpatient deaths.[5]

Most estimates of mortality in patients admitted to hospital with PE come from sub-analyses of large, administrative datasets. A sub-analysis of 34108 PE admissions from the 2012 American Healthcare Cost and Utilization Project National Inpatient Sample, found the overall inpatient mortality rate to be 3.4%.[17] An analysis of another American hospital administrative database, the Nationwide Inpatient Sample, reported mortality rates of between 3.2% and 7.1 % in patients admitted with PE over a 10-year

period.[18] A study of Portuguese hospital admissions with PE between 2003 and 2013 (N=35200) reported in-hospital mortality rates of between 11.2% and 25%.[19] The mortality rates of patients with untreated PE have been described as much higher than those reported for patients where PE has been treated.[10] However, appropriate treatment can only be initiated once a diagnosis of PE is made. This highlights the importance of effective diagnostic management in patients where PE is suspected.

1.6 Signs and symptoms of pulmonary embolism:

The signs and symptoms of PE vary considerably. In their published review, Kranidis et al., listed some of the common signs and symptoms associated with PE.[10] Tachypnea, or an increased respiratory rate (>20 breaths per minute), is the most common sign and is reported in up to 70% of patients with PE.[10] Tachycardia (a heart rate >100 beats/minute) is reported in 26% of patients with PE. Signs of DVT, such as lower limb pain or swelling, is reported in 15% or patients. Cyanosis (discolouration of the skin, nails, and mucosa) is observed in 11% of patients with PE. Pyrexia (temperature of >38^{o}C) might be present in 7% of patients.[10]

Dyspnoea (shortness of breath) is the most common symptom reported in patients with PE (up to 80% of patients with PE).[10] Chest pain is another common symptom. There are two types of chest pain reported in patients with PE, namely pleuritic chest pain (in up to 52% of patients) and substernal chest pain (in up to 12% of patients). Up to 20% of patients with PE might present with cough.[10] Haemoptysis (expectoration of blood originating from the tracheobronchial tree or pulmonary parenchyma) is reported in 11% of patients. Approximately 19% of patients with PE reported a history of recent syncope (abrupt loss of consciousness with a concomitant loss of postural tone) or its prodrome (presyncope).[10] Cardiac enzyme measurements, such as troponins, might also be elevated in patients with PE and have been associated with increased mortality.[20] This is likely the result of cardiac dysfunction modulated by PE.[7]

1.7 Diagnostic and therapeutic management of pulmonary embolism:

The varying clinical presentation of PE and the overlap of some signs and symptoms with that of cardiac disease pose a considerable diagnostic challenge.[10] Therefore a diagnosis of PE is unlikely to be made based solely on clinical presentation. Goolam-Mahomed has provided a diagnostic algorithm for PE in South African settings (Figure 2).[21] The first step of the algorithm involves assessing the probability of PE. This is commonly done using tools such as the Well's Score (Table 2),[22] although there are other scoring systems which can also be used (the Geneva Score or the Pisa Score).[23,24] These scoring systems are based on the presence of certain clinical signs, symptoms, and risk factors which are each allocated a weighted point score. Total point scores can then be used to stratify if a patient has a low, intermediate, or high probability of PE.[22-24]

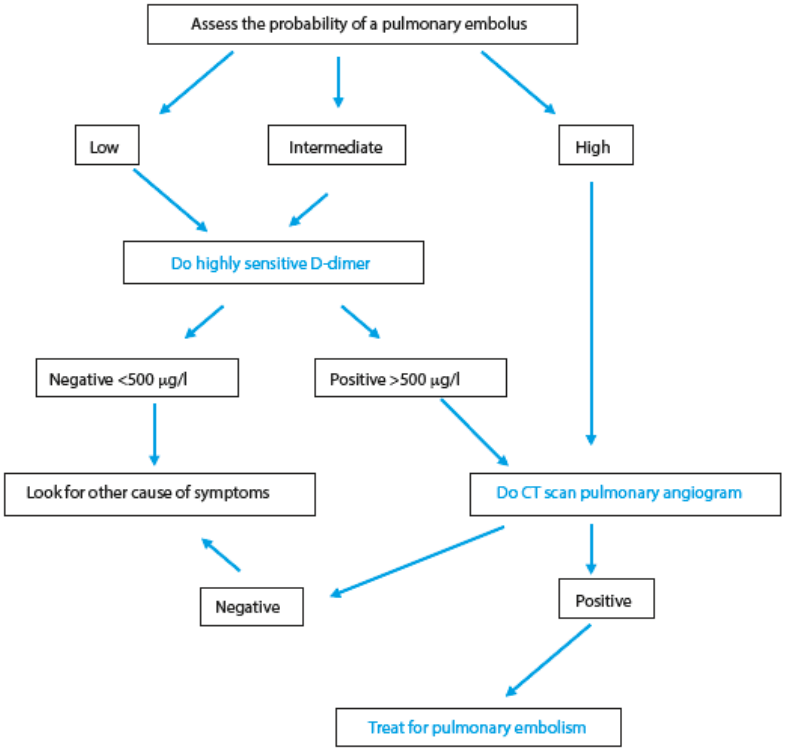

Figure 2. Algorithm for the diagnosis of pulmonary embolism*
*From: Goolam-Mahomed (2013)[21]

Table II. The Well's Score*

Clinical feature	**Points**
Clinical signs and symptoms of DVT	3
An alternative diagnosis is less likely than PE	3
Heart rate > 100 beats per minute	1.5
Immobilisation for more than 3 days or surgery in the previous 4 weeks	1.5
Previous DVT/PE	1.5
Haemoptysis	1
Malignancy (on treatment, treated in the last 6 months, or palliative)	1

*From: Wells et al. (1998)[22]

Patients with a high probability of PE are required to undergo computed tomography pulmonary angiography (CTPA).[21] This imaging modality involves the use of computed tomography to visualize the pulmonary arteries and any filling defects. The

sensitivity and specificity of CTPA for PE is impressive (sensitivity of 83-100% and specificity of 89-96%).[25] Patients with a low or intermediate probability of PE are required to undergo d-dimer measurements.[21] D-dimers are cross-linked fibrin degradation products following fibrinolysis of a thromboembolism.[26] Any d-dimer measurement of 500µg/L or higher is considered potentially indicative of PE and requires further investigation with CTPA.[21] Causes of symptoms, other than PE, should be investigated in patients with d-dimer measurements of <500µg/L. This step is also applicable in patients with no findings suggestive of PE on CTPA. Patients with findings suggestive of PE on CTPA should be offered treatment for PE.[21]

Treatment options for PE include: Anticoagulation, thrombolysis, and embolectomy.[27-29] Anticoagulation is the primary choice of therapy for PE.[2] Anticoagulation agents can be intravenous (such as unfractionated heparin, or low weight molecular heparin agents such as enoxaparin) or oral anticoagulation agents (the most widely used being warfarin).[27] Antithrombin III (AT3) inhibits several activated clotting factors. Therefore, drugs which augment the function of AT3 serve as anticoagulants.[27] Heparin is known to increase the activity of AT3. Warfarin inhibits the activities of the enzyme vitamin K-epoxide reductase, which produces the active form of the vitamin K-dependent clotting factors.[27] A randomized controlled study by Barritt et al., provided the first evidence suggesting that there was reduced mortality associated with anticoagulation therapy in patients with PE.[30] Several studies since then have confirmed the benefits of anticoagulation therapy in patients with PE.[31-33] However, haemorrhage is a possible adverse event associated with anticoagulation therapy.[27]

Thrombolytic agents are based on fibrinolytic substances produced by streptococci bacteria.[34] The most well-known of these agents is streptokinase, which is also used in the treatment of acute myocardial infarction.[28,34] Thrombolysis is indicated in situations of massive PE with hypotension or systemic hypoperfusion, right ventricular dysfunction, pulmonary hypertension, extensive DVT, and prevention of recurrent PE.[35] Important drawbacks of thrombolytic agents include allergic reactions, hypotension, reperfusion arrhythmias, and haemorrhage.[35] As such, thrombolysis is contraindicated in patients with a high risk of haemorrhage, recent major surgery/trauma, gastrointestinal bleeding, central nervous system neoplasm or known bleeding diathesis.[35] A Cochrane Systematic Review reported that there was low quality evidence supporting a reduction in mortality in patients with acute PE receiving thrombolytic therapy when compared with heparin.[36] Furthermore, the same systematic review reported that while thrombolytic therapy might be helpful in reducing recurrent PE, it may cause more haemorrhagic events and stroke.[36] Therefore, thrombolysis should be used only when clinically indicated.

Pulmonary embolectomy, through which a PE is removed through an open thoracic surgery procedure, is performed in patients where thrombolysis is contraindicated or unsuccessful.[29,35] It is therefore an important management option in patients with advanced PE.[29,35] Although the procedure was initially associated with high levels of mortality,[29] a collective review of cases suggests that there has been a decreasing trend in mortality associated with pulmonary embolectomy (32% before 1985 versus 20% in the period between 1985 and 2005).[37] Nevertheless, the mortality associated with this procedure still remains high and there should be careful consideration on the part of

physicians and surgeons when deciding to perform the procedure.

1.8 Gap in the literature:

Published descriptions of PE in African settings are rare.[11] Many African countries (including South Africa) are undergoing an "epidemiological transition",[38-40] whereby the burden of noncommunicable disease, including VTE (DVT and PE) and some of its risk factors, are approaching levels similar to that of communicable disease which has traditionally accounted for most of the morbidity and mortality on the continent. A better understanding of PE in an African setting would contribute towards improving patient care for PE in this setting.

1.9 Problem statement:

South Africa is currently experiencing an epidemiological transition, whereby the national noncommunicable disease burden is approaching that of communicable disease.[38-41] Non-communicable diseases comprised 60% of the ten leading underlying natural causes of death in South Africa for 2015.[42] While no specific data is available for PE, a 2007 report found 2566 deaths in the country could be attributed to diseases of the circulatory system, a composite measure which includes PE, stroke, and myocardial infarction.[21] Interestingly, embolic pathophysiology also appears to play some role in stroke and myocardial infarction.[43,44]

However, descriptions of PE in South African settings are rare. Recent evidence from a study of DVT in a South African setting suggest that there are some setting-specific risk factors for VTE, most notably HIV infection and tuberculosis.[13] It is also possible that there might be some discordancy between other clinical/laboratory presentation and risk factors for PE between South African settings and European/American settings, however this is yet to be demonstrated. It might also be possible that there are differences in mortality between South African and overseas patients with PE. A better description of PE in a South African setting would be useful in efforts to improve patient management and subsequent patient outcomes in this setting.

1.10 Aim:

The aim of this study was to improve the current understanding of PE in a South African setting.

1.11 Objectives:

The objectives of this study were to
1. Describe the presentation of PE in patients who were admitted to a tertiary South African hospital with the condition (the study population)
2. Determine the incidence of mortality in the study population

3. Determine which presenting characteristics are associated with inpatient mortality in the study population

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Part 2: Submission-ready manuscript

(Prepared for submission to the “SA Heart Journal”)

Title: Admissions for pulmonary embolism at a tertiary South African hospital

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Running Title: Pulmonary embolism

Conflict of Interest: None

ABSTRACT

Background: Published descriptions of pulmonary embolism (PE) from South African (SA) settings are rare. We sought to address this gap in the literature.
Methods: This was a case series involving 61 adult patients admitted to a tertiary SA hospital over a five-year period with a primary diagnosis of PE. Data related to patient demographics, PE presentation, risk factors, treatment, and inpatient mortality were collected and analysed using appropriate statistical tests.
Results: Most of our study population were younger (86.9%), female (67.2%), and of black African ethnicity (73.8%). Dyspnoea and chest pain were the most common symptoms (prevalence of 86.9% and 41.0%). Prevalent clinical signs included tachypnea (47.5%) and tachycardia (42.6%). The most prevalent established risk factors were cardiac failure (49.2%) and a history of deep vein thrombosis (up to 19.7%). Massive PE was diagnosed in 8.2% of study patients. Most patients received anticoagulation therapy (95.1%), with thrombolysis and embolectomy performed only in smaller proportions (24.6% and 11.5%) of patients. The incidence of inpatient mortality was 23.0%. Characteristics associated with mortality included: admission route ($p=0.008$), dyspnoea ($p=0.002$), tachycardia ($p<0.001$), and embolectomy ($p=0.042$).
Conclusion: Our study findings have important implications related to the management of PE in SA.

Keywords: Pulmonary embolism; South Africa; Clinical presentation; Risk factors; Mortality.

INTRODUCTION

Pulmonary embolism (PE) is an important complication of deep vein thrombosis (DVT).[1] Both PE and DVT are manifestations of venous thromboembolism (VTE). An incidence rate of nearly 1.0 case per 1000 people has been reported for PE in North American/European settings.[2] Mortality is much higher in patients with undiagnosed, untreated PE. Therefore, a better understanding of the presentation of PE is required such that patients can be diagnosed timeously and treatment can be initiated.[3] However, the presentation of PE itself is highly variable and can pose diagnostic challenges.[2-4] While there are no specific data available for PE in a South African (SA) setting, a 2007 report found 2566 deaths in the country could be attributed to diseases of the circulatory system, a composite measure which includes PE, stroke, and myocardial infarction.[5] Interestingly, embolic pathophysiology also appears to play some role in stroke and myocardial infarction.[6,7] While descriptions of PE in SA settings are rare, recent evidence from a study of DVT in a SA setting suggest that there might be some setting-specific differences in the characteristics and risk factors for VTE between SA and overseas settings.[8] It is possible that there might be some discordancy between the characteristics, risk factors, and mortality associated with PE between SA settings and overseas settings. However, this is yet to be demonstrated. A better description of PE in a SA setting would be useful in efforts to improve patient management and subsequent patient outcomes in this setting. Therefore, the aim of this study was to improve the current understanding of PE in a SA setting. The objectives of this study were to 1) Describe the presentation/characteristics of PE in patients who were admitted to a tertiary SA hospital with the condition (the study population - SP); 2) Determine the incidence of mortality in the SP; 3) Determine which characteristics are associated with inpatient mortality in the SP; and 4) Discuss similarities and differences related to PE between SA and overseas settings.

MATERIALS AND METHODS

Study design, study setting, and study population:

This was a retrospective case series of 61 adult patients who were admitted with a primary diagnosis of PE to the tertiary-level Inkosi Albert Luthuli Central Hospital (IALCH) in Durban, South Africa over a five-year period (01 January 2011 to 31 December 2015). These patients were identified using the hospital admissions database and the International Classification of Diseases 10th Revision (ICD-10) code I26 (includes I26.0, I26.9, and sub-categories thereof). Furthermore, PE was confirmed through review of patient computed tomography reports. Patients aged <18 years old, repeat admissions for PE, and patients admitted outside the specified study period were excluded from this study.

Data collection:

The medical records of all patients included in this study were reviewed and information related to patient demographics, clinical presentation, potential risk factors, classification and treatment of PE, and inpatient mortality were collected using a paper-

based data collection tool. The data were then transferred to an electronic spreadsheet in preparation for statistical analyses.

Statistical analysis:

We initially analysed our data using descriptive statistical methods. Results for the descriptive statistical analysis are presented as frequencies and percentages. We calculated the incidence of inpatient mortality in our SP using conventional epidemiological methods, and present this as a percentage with a 95% confidence interval (95% CI). We also tested for the presence of crude statistical associations between various characteristics and inpatient mortality using chi-squared or Fisher's tests. Results for this component of the statistical analysis are presented as frequencies and percentages, with a corresponding p-value. A p-value <0.050 was considered a statistically significant result. All statistical analyses were performed using the Statistical Package for the Social Sciences version 24.0 (IBM Corp, USA).

Study ethical approval:

This study received ethical approval from the University of KwaZulu-Natal Biomedical Research Ethics Committee (BE589/17).

RESULTS

Description of the SP:

Demographic profile of the SP:
The demographic profile of the SP is presented in Table I. Most patients in our SP were <65 years old (n/N=53/61, 86.9%). Just over two-thirds of the SP were female (n/N=41/61, 67.2%). Approximately three-quarters of the SP were of black African ethnicity (n/N=45/61, 73.8%). Almost one-third of the SP was admitted through the emergency department/critical care unit (n/N=20/61, 32.8%).

Distribution of PE clinical symptoms and signs in the SP:
A description of PE clinical symptoms and signs in the SP is shown in Table I. A large proportion of the SP did not report any chest pain on admission to hospital (n/N=36/61, 59.0%), while pleuritic chest pain and substernal chest pain were reported in 24.6% (n/N=15/61) and 16.4% (n/N=10/61) of the SP. Dyspnoea on admission was common (86.9% of the SP, n/N=53/61), with 24.6% (n/N=15/61) of study patients reporting dyspnoea of ≥NYHA grade III, 6.6% (n/N=4/61) of study patients reporting dyspnoea of <NYHA grade III, and 55.7% (n/N=34/61) of study patients experiencing dyspnoea of unreported grade. Just over one-third of the SP presented with cough (n/N=23/61, 37.7%). Haemoptysis was reported in a total of 16.4% (n/N=10/61) of the SP. Haemoptysis was reported as major in 3.3% (n/N=2/61) of the SP and minor in 4.9% (n/N=3/61) of the SP. The severity of haemoptysis could not be established from the medical records of five study patients (8.2% of the SP) who presented with haemoptysis. Approximately 15.0% of the SP experienced syncopal events prior to hospital admission (4.9% with syncope and 9.8% with presyncope). Just under half the

SP presented to hospital with tachypnea (n/N=29/61, 47.5%). Similarly, just under half the SP presented to hospital with tachycardia (n/N=26/61, 42.6%). Cyanosis and pyrexia were reported in 4.9% (n/N=3/61) and 3.3% (n/N=2/61) of the SP. Just over a third of the SP presented to hospital with lower limb swelling or pain (n/N=23/61, 37.7%). One in every four patients presented with abnormal O_2 saturation measurements (n/N=17/61, 27.9%). One-third of the SP presented with abnormal pO_2 measurements (n=21/61, 34.4%), 4.9% (n/N=3/61) presented with normal pO_2 measurements, and pO_2 measurements could not be established for the remainder of the SP (n/N=37, 60.7%). Half the SP received supplemental oxygen on admission (n/N=31/61, 50.8%). Five study patients (8.2% of the SP) required mechanical ventilation. Most of the SP was normotensive (n/N=45/51, 73.8%), while hypotension and hypertension was reported in 8.2% (n/N=5/61) and 18.0% (n/N=11/61) of the SP. Half of the patients in the SP (n/N= 31/61, 50.8%) had elevated D-dimer measurements, 4.9% (n/N=3/61) had normal D-dimer measurements, while the results of D-dimer tests were not reported for 37 patients (44.3% of the SP). Approximately one-quarter of the SP had elevated cardiac enzyme measurements on admission to hospital (n/N=14/61, 23.0%). Cardiac enzyme measurements were normal or not reported in 39.3% (n/N=24/61) and 37.7% (n/N=23/61) of the SP, respectively.

Prevalence of PE risk factors in the SP:
The distribution of PE risk factors in the SP is shown in Table I. Half of the SP presented to hospital with cardiac failure (n/N=30/61, 49.2%). Only two patients (3.3%) had a history of stroke. Eight patients (13.1%) reported recent immobilization. Two patients (3.3%) reported recent long-distance travel. Around one in every six patients in the SP (16.4%) had recently undergone surgical procedures. Malignancy was present in 3.3% of the SP (n/N=2/61, one patient with lymphoma and one patient with solid tumour). One in every ten study patients reported tobacco use (n/N=6/61, 9.8%). A prior history of PE was reported in 8.2% of the SP (n/N=5/61). A prior history of DVT was reported in 11.5% of patients (n/N=7/61). One in five study patients presented with concurrent DVT (n/N=12/61, 19.7%). No patients in the SP were pregnant. One patient (1.6% of the SP) was on hormonal therapy/contraception. Obesity was noted in 17 patients (27.9% of the SP), while 14 patients (23.0% of the SP) were not obese. Body mass index could not be calculated for 49.1% of the SP (n/N=30/61). Seventeen patients had HIV infection (27.9% of the SP). Eight patients (13.1 of the SP) reported a prior history of tuberculosis. Three patients (4.9% of the SP) had current tuberculosis infection.

Classification of and treatment of PE in the SP:
Five patients (8.2% of the SP) presented with a massive PE (Table I). Almost two-thirds of the SP (62.3% of patients) presented with submassive PE, while 8.2% of the SP (n/N=5/61) presented with minor PE. We were unable to classify PE in the remaining 21.3% of the SP (n/N=13/61) as the relevant information (either cardiac enzyme measurements or cardiac function investigations) was not reported in the patient medical records. Data related to the treatment of PE in our SP is also presented in Table I. Almost all patients in the SP received anticoagulation therapy (n/N=58/61, 95.1%). Embolectomy was performed in 11.5% of the SP (n/N=7/61). Thrombolysis was performed in a quarter of the SP (n/N=15/61, 24.6%).

Table I. Description of the SP (N=61)

Characteristic	**Sub-category**	**n (% of N)**
Elderly age (Age ≥65 years old)	Yes	8 (13.1)
	No	53 (86.9)
Gender	Male	20 (32.8)
	Female	41 (67.2)
African ethnicity	Yes	45 (73.8)
	No	16 (26.2)
Admitted via ED/CCU	Yes	20 (32.8)
	No	41 (67.2)
Chest pain	Yes, pleuritic	15 (24.6)
	Yes, substernal	10 (16.4)
	No	36 (59.0)
Dyspnoea	Yes, ≥ NYHA grade III	15 (24.6)
	Yes, < NYHA grade III	4 (6.6)
	Yes, grade not reported	34 (55.7)
	No	8 (13.1)
Cough	Yes	23 (37.7)
	No	38 (62.3)
Haemoptysis	Yes, major	2 (3.3)
	Yes, minor	3 (4.9)
	Yes, not reported	5 (8.2)
	No	51 (83.6)
Syncopal events	Yes, syncope	3 (4.9)
	Yes, presyncope	6 (9.8)
	No	52 (85.3)
Tachypnea (Respiratory rate >20 breaths/min)	Yes	29 (47.5)
	No	32 (52.5)
Tachycardia (Heart rate >100 beats/min)	Yes	26 (42.6)
	No	35 (57.4)
Cyanosis	Yes	3 (4.9)
	No	58 (95.1)
Pyrexia (Temperature >38.5ºC)	Yes	2 (3.3)
	No	59 (96.7)
Lower limb swelling/pain	Yes	23 (37.7)
	No	38 (62.3)
O_2 saturation (as per pulse oximetry)	≤95%	17 (27.9)
	>95%	44 (72.1)
Abnormal pO_2 (pO_2 outside 80-100 mmHg)	Yes	21 (34.4)
	No	3 (4.9)
	Not reported	37 (60.7)
Supplemental O_2	Yes	31 (50.8)
	No	30 (49.2)
Mechanical ventilation	Yes	5 (8.2)
	No	56 (91.8)
Systolic blood pressure on admission	Hypotensive (≤90 mmHg)	5 (8.2)
	Normotensive (91-139 mmHg)	45 (73.8)
	Hypertensive (≥140 mmHg)	11 (18.0)
D-dimer	>99th percentile URL	31 (50.8)
	≤99th percentile URL	3 (4.9)
	Not reported	37 (44.3)

Troponin	>99th percentile URL	14 (23.0)
	≤99th percentile URL	24 (39.3)
	Not reported	23 (37.7)
Cardiac failure	Yes	30 (49.2)
	No	31 (50.8)
Stroke	Yes	2 (3.3)
	No	59 (96.7)
Recent immobilization*	Yes	8 (13.1)
	No	53 (86.9)
Recent long-distance travel**	Yes	2 (3.3)
	No	59 (96.7)
Recent surgery*	Yes	10 (16.4)
	No	51 (83.6)
Recent trauma*	Yes	2 (3.3)
	No	59 (96.7)
Malignancy (Solid tumour or Haematological)	Yes	2 (3.3)
	No	59 (96.7)
Tobacco use	Yes	6 (9.8)
	No	55 (90.2)
Prior PE	Yes	5 (8.2)
	No	56 (91.8)
Prior DVT	Yes	7 (11.5)
	No	54 (88.5)
Current DVT	Yes	12 (19.7)
	No	49 (80.3)
Pregnancy	Yes	0 (0.0)
	No	61 (100.0)
Hormonal therapy/contraception	Yes	1 (1.6)
	No	60 (98.4)
Obesity (Body mass index >30 kg/m^2)	Yes	17 (27.9)
	No	14 (23.0)
	Not reported	30 (49.1)
HIV	Yes	17 (27.9)
	No	44 (72.1)
Prior tuberculosis	Yes	8 (13.1)
	No	53 (86.9)
Current tuberculosis	Yes	3 (4.9)
	No	58 (95.1)
PE classification$^{\#}$	Massive	5 (8.2)
	Submassive	38 (62.3)
	Minor	5 (8.2)
	Not reported	13 (21.3)
Embolectomy	Yes	7 (11.5)
	No	54 (88.5)
Thrombolysis	Yes	15 (24.6)
	No	46 (75.4)
Anticoagulation	Yes	58 (95.1)
	No	3 (4.9)

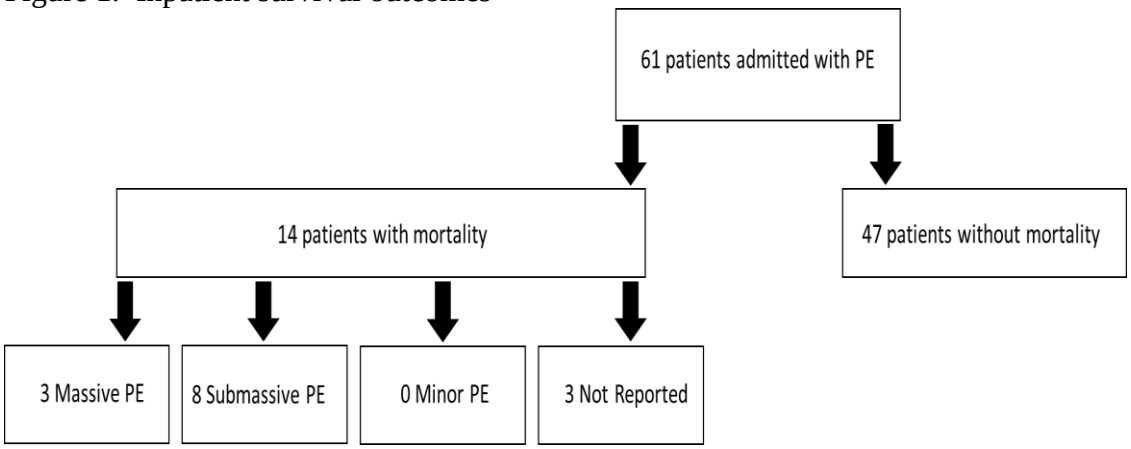
SP: Study population; N/A: Not applicable; ED: Emergency department; CCU: Critical care unit; NYHA: New York Heart Association; URL: Upper reference limit; PE: Pulmonary embolism; DVT: Deep vein thrombosis.

*Within the last 4 weeks; **Duration >4 hours within the last 4 weeks; $^{\#}$As per reference 26.

Mortality in the SP:

Incidence of mortality in the SP:
Figure 1 shows the inpatient survival outcomes of the SP. Of the 61 patients in the SP, 14 suffered inpatient mortality (Incidence of 23.0%, 95% CI: 13.2-35.5%). Of the 14 patients who suffered inpatient mortality, the distribution of the classes of PE is as illustrated in Figure 1.

Figure 1. Inpatient survival outcomes



PE: Pulmonary embolism

Statistical comparisons between various characteristics and inpatient mortality in the SP:
Statistical comparisons between various characteristics and inpatient mortality in our SP are shown in Table II. Statistically significant crude associations ($p<0.050$) were noted between several characteristics/variables investigated in this study and inpatient mortality. A higher proportion of patients admitted through the emergency department/critical care unit suffered inpatient mortality when compared to patients who were admitted via alternative departments (64.3% versus 23.4%, $p=0.008$). Dyspnoea was also found to be statistically associated with inpatient mortality ($p=0.002$). Of note, the proportion of patients with dyspnoea of NYHA grade III or more was higher in patients who died versus patients who did not die (42.9% versus 19.1%). The proportion of patients with tachycardia was higher in the mortality group when compared to the no-mortality group (85.7% versus 29.8%, $p<0.001$). Lastly, the proportion of patients who underwent embolectomy was higher in the mortality group when compared to the no-mortality group (28.6% versus 6.4%, $p=0.042$). We did not find statistically significant associations between the remaining characteristics investigated in this study and inpatient mortality.

Table II. Statistical comparisons between characteristics in the SP and inpatient mortality

Characteristic	**Sub-category**	**No mortality (n=47)**	**Mortality (n=14)**	**p-value**
Elderly age (Age ≥65 years old)				0.999
	Yes	6 (12.8)	2 (14.3)	
	No	41 (87.2)	12 (85.7)	
Gender				0.116
	Male	18 (38.3)	2 (14.3)	
	Female	29 (61.7)	12 (85.7)	
African ethnicity				0.490
	Yes	36 (76.6)	9 (64.3)	
	No	11 (23.4)	5 (35.7)	
Admitted via ED/CCU				0.008
	Yes	11 (23.4)	9 (64.3)	
	No	36 (76.6)	5 (35.7)	
Chest pain				0.914
	Yes, pleuritic	11 (23.4)	4 (28.6)	
	Yes, substernal	8 (17.0)	2 (14.3)	
	No	28 (59.6)	8 (57.1)	
Dyspnoea				0.002
	Yes, ≥ NYHA grade III	9 (19.1)	6 (42.9)	
	Yes, < NYHA grade III	4 (8.5)	0 (0.0)	
	Yes, grade not reported	31 (66.0)	3 (21.4)	
	No	3 (6.4)	5 (35.7)	
Cough				0.999
	Yes	18 (38.3)	5 (35.7)	
	No	29 (61.7)	9 (64.3)	
Haemoptysis				0.647
	Yes, major	1 (2.1)	1 (7.1)	
	Yes, minor	2 (4.3)	1 (7.1)	
	Yes, not reported	4 (8.5)	1 (7.1)	
	No	40 (85.1)	11 (78.7)	
Syncopal events				0.666
	Yes, syncope	3 (6.4)	0 (0.0)	
	Yes, presyncope	4 (8.5)	2 (14.3)	
	No	40 (85.1)	12 (85.7)	
Tachypnea (Respiratory rate >20 breaths/min)				0.153
	Yes	20 (42.6)	9 (64.3)	
	No	27 (57.4)	5 (35.7)	
Tachycardia (Heart rate >100 beats/min)				<0.001
	Yes	14 (29.8)	12 (85.7)	
	No	33 (70.2)	2 (14.3)	
Cyanosis				0.999
	Yes	3 (6.4)	0 (0.0)	
	No	44 (93.6)	14 (100.0)	
Pyrexia (Temperature >38.5ºC)				0.409
	Yes	1 (2.1)	1 (7.1)	
	No	46 (97.9)	13 (92.9)	

Lower limb swelling/pain				0.999
	Yes	18 (38.3)	5 (35.7)	
	No	29 (61.7)	9 (64.3)	
O_2 saturation (as per pulse oximetry)				0.506
	≤95%	12 (25.5)	5 (35.7)	
	>95%	35 (74.5)	9 (64.3)	
Abnormal pO_2 (pO2 outside 80-100 mmHg)				0.498
	Yes	15 (31.9)	6 (42.9)	
	No	2 (4.3)	1 (7.1)	
	Not reported	30 (63.8)	7 (50.0)	
Supplemental O_2				0.079
	Yes	21 (44.7)	10 (71.4)	
	No	26 (55.3)	4 (28.6)	
Mechanical ventilation				0.074
	Yes	2 (4.3)	3 (21.4)	
	No	45 (95.7)	11 (78.6)	
Systolic blood pressure on admission				0.151
	Hypotensive (≤90 mmHg)	2 (4.3)	3 (21.4)	
	Normotensive (91-139 mmHg)	36 (76.6)	9 (64.3)	
	Hypertensive (≥140 mmHg)	9 (19.1)	2 (14.3)	
D-dimer				0.999
	>99th percentile URL	24 (51.1)	7 (50.0)	
	≤99th percentile URL	2 (4.3)	1 (7.1)	
	Not reported	21 (44.7)	6 (42.9)	
Troponin				0.857
	>99th percentile URL	10 (21.3)	4 (28.6)	
	≤99th percentile URL	19 (40.4)	5 (35.7)	
	Not reported	18 (38.3)	5 (35.7)	
Cardiac failure				0.999
	Yes	23 (48.9)	7 (50.0)	
	No	24 (51.1)	7 (50.0)	
Stroke				0.999
	Yes	2 (4.3)	0 (0.0)	
	No	45 (95.7)	14 (100.0)	
Recent immobilization*				0.668
	Yes	7 (14.9)	1 (7.1)	
	No	40 (85.1)	13 (92.9)	
Recent long-distance travel**				0.999
	Yes	2 (4.3)	0 (0.0)	
	No	45 (95.7)	14 (100.0)	
Recent surgery*				0.999
	Yes	8 (17.0)	2 (14.3)	
	No	39 (83.0)	12 (85.7)	
Recent trauma*				0.999
	Yes	2 (4.3)	0 (0.0)	
	No	45 (95.7)	14 (100.0)	
Malignancy (Solid tumour or Haematological)				0.050
	Yes	0 (0.0)	2 (14.3)	
	No	47 (100.0)	12 (96.7)	

Tobacco use				0.321
	Yes	6 (12.8)	0 (0.0)	
	No	41 (87.2)	14 (100.0)	
Prior PE				0.999
	Yes	4 (8.5)	1 (7.1)	
	No	43 (91.5)	13 (92.9)	
Prior DVT				0.999
	Yes	6 (12.8)	1 (7.1)	
	No	41 (87.2)	13 (92.9)	
Current DVT				0.999
	Yes	9 (19.1)	3 (21.4)	
	No	38 (80.9)	11 (78.6)	
Pregnancy				UC
	Yes	0 (0.0)	0 (0.0)	
	No	47 (100.0)	14 (100.0)	
Hormonal therapy/contraception				0.999
	Yes	1 (2.1)	0 (0.0)	
	No	46 (97.9)	14 (100.0)	
Obesity (Body mass index >30 kg/m^2)				0.674
	Yes	13 (27.7)	4 (28.6)	
	No	12 (25.5)	2 (14.3)	
	Not reported	22 (46.8)	8 (57.1)	
HIV				0.311
	Yes	15 (31.9)	2 (14.3)	
	No	32 (68.1)	12 (85.7)	
Prior tuberculosis				0.180
	Yes	8 (17.0)	0 (0.0)	
	No	39 (83.0)	14 (0.0)	
Current tuberculosis				0.549
	Yes	2 (4.3)	1 (7.1)	
	No	45 (95.7)	13 (92.9)	
PE classification[#]				0.167
	Massive	2 (4.3)	3 (21.4)	
	Submassive	30 (63.8)	8 (57.1)	
	Minor	5 (10.6)	0 (0.0)	
	Not reported	10 (21.3)	3 (21.4)	
Embolectomy				0.042
	Yes	3 (6.4)	4 (28.6)	
	No	44 (93.6)	10 (71.4)	
Thrombolysis				0.483
	Yes	13 (27.7)	2 (14.3)	
	No	34 (72.3)	12 (85.7)	
Anticoagulation				0.129
	Yes	46 (97.9)	12 (85.7)	
	No	1 (2.1)	2 (14.3)	

N/A: Not applicable; ED: Emergency department; CCU: Critical care unit; NYHA: New York Heart Association; URL: Upper reference limit; PE: Pulmonary embolism; DVT: Deep vein thrombosis. *Within the last 4 weeks; **Duration >4 hours within the last 4 weeks; [#]As per reference 26.

DISCUSSION

Importance of our study:

We provide a report of patients admitted to a tertiary SA hospital with a primary diagnosis of PE. Our study is important as it is, to the best of our knowledge, the first study from a SA setting wherein a thorough description of characteristics in patients admitted to a tertiary-level healthcare facility with PE is given. We also report several differences and similarities related to PE between SA and overseas populations.

Demographic profile of the SP:

Only a small proportion of patients in our SP were elderly. Evidence from overseas settings suggests that the risk of VTE (including PE) increases with age. An incidence of 2.0 per every 1000 persons per year was reported for patients up to 64 years old in the European study by Naess et al.[9] The same study reported that the incidence of VTE increased to almost 8.0 per every 1000 persons per year in patients 65 years old or older.[9] It therefore appears that our study finding for age contradicts the findings from studies of overseas populations. It is possible that the interaction of various risk factors in the younger and older SA population might possibly explain this difference. This would require further research to confirm. Almost one in every three patients in our study population was female. This finding is in agreement with much of the published literature from overseas settings which suggests a higher incidence of PE in females versus males.[10] *In vivo* and *ex vivo* studies have shown a difference in platelet reactivity between males and females, specifically the formation of larger platelet aggregates in females, which offers a potential explanation for the gender disparity in PE.[10] We found that the majority of patients with PE in our SP were of African ethnicity. There might be two explanations for this finding. Firstly, this finding might reflect the demographic profile of the South African population and the population served by our healthcare facility.[11,12] Secondly, studies of American and European populations have also found persons of African ethnicity to be at a higher risk for VTE when compared to Caucasians (up to 40.0% higher risk).[13] This appears to be linked to genetic polymorphism, as well as the burden of some VTE risk factors in the African ethnic group.[13] A British study by Aylin et al., reported that only 2.1% of patients admitted to hospital for PE were elective admissions, with the remaining 97.9% of patients being non-elective/emergency admissions.[14] In contrast to the study of Aylin and colleagues,[14] we report a much higher proportion of elective admissions (ie. Admissions route not the emergency department/critical care unit) versus non-elective/emergency admissions (ie. Admissions route not the emergency department/critical care unit) for PE. This seems to suggest much lower levels of critical illness/higher levels of chronic illness related to PE admissions in our setting when compared with overseas settings.

Symptoms and signs of PE in the SP:

As with descriptions of PE in overseas settings, we report the presentation of PE to be highly variable in our setting. There were several similarities and differences in the distribution of PE symptoms in our SP versus that described for overseas populations

with PE. Chest pain and dyspnoea were the most common presenting symptoms in our SP, which is in agreement with the overseas literature.[3] Both symptoms are reflective of the pathophysiological impact of PE on the cardiopulmonary system.[15] However, we report a lower prevalence of pleuritic chest pain and a higher prevalence of substernal chest pain in our SP when compared to these descriptions of chest pain reported for overseas populations (24.6% versus 52.0% and 16.4% versus 12.0%, respectively).[3] There was a slightly higher prevalence of dyspnoea in our study population when compared with that reported for overseas settings (86.9% versus 80.0%).[3] With regard to other presenting symptoms, there was also a higher prevalence of cough and haemoptysis in our SP when compared with evidence from overseas settings. Lastly, the prevalence of syncopal events in our SP was lower than that reported for overseas populations with PE (14.7% versus 19.0%).[3] Tachypnea and tachycardia were the most frequently encountered presenting signs in our SP. This overall finding is once again in agreement with the overseas literature. However, there were differences in the distribution of tachypnea and tachycardia between our SP and overseas populations. When compared with the overseas literature, our study reports a lower frequency of tachypnea (47.5% versus 70.0%) and a higher frequency of tachycardia (42.6% versus 26.0%) in patients with PE.[3] There was also a lower prevalence of cyanosis and pyrexia in our SP when compared with overseas populations (4.9% versus 11.0% and 3.3% versus 7.0%, respectively).[3] However, we do report a higher prevalence of lower limb swelling/pain in our SP when compared with the overseas literature (37.7% versus 15.0%).[3] The differences in the distribution of various symptoms and signs between our SP and overseas populations highlights the challenges that clinicians in different settings might face during initial attempts at diagnosing PE through clinical examination and patient medical histories. Considering that there was a lower prevalence of many of the symptoms and signs described for PE in overseas settings in our SP, the suspicion of PE might be underestimated in SA settings if overseas characteristics are applied. It is therefore important that further studies of PE are performed in order to identify associated symptoms and signs which are more relevant in SA settings.

Other important aspects of clinical presentation:

While abnormal pulse oximetry or arterial blood gas (pO_2), and the requirement for supplemental oxygen or mechanical ventilation are not considered specific symptoms/signs of PE, their presence in patients with this condition is indicative of hypoxia.[16-18] Our findings therefore suggest that hypoxia is frequent in SA patients with PE. This would be in keeping with the proposed pathophysiological effects of PE.[15] The majority of patients in our SP were normotensive. This finding suggests that cardiac output was not significantly affected by PE in most of our SP, as haemodynamic instability in PE is usually a consequence of ventricular dysfunction and reduced cardiac output.[15] As expected, the majority of patients with recorded d-dimer tests in our SP had elevated measurements of this analyte reported. D-dimers are cross-linked fibrin degradation products following fibrinolysis of a thromboembolism.[19] A number of patients in our SP also had elevated cardiac troponin measurements. As cardiac troponin is released into the circulation following myocardial injury,[20] we can deduce that myocardial necrosis/myocardial ischaemia also accompanied PE in some of

our patients. This would also be in accordance with the proposed pathophysiological effects of PE on the pulmonary and systemic circulation.[15]

Prevalence of PE risk factors in the SP:

Many of the established risk factors for VTE cause the condition through one of the pathological pathways comprising Virchow's triad, which includes blood flow stasis, endothelial dysfunction/damage, and hypercoagulation.[21] As with the clinical symptoms and signs, we observed similarities and discrepancies in the distribution of established risk factors for PE between our SP and overseas populations. The prevalence of cardiac failure and stroke in our SP was much higher than that reported for overseas populations (49.2% versus 8.2% and 3.3% versus 1.8%, respectively).[22] The proportion of patients with recent immobilization was similar in our SP and overseas populations with PE (13.1% versus 12.0%).[22] The proportion of patients in our SP with recent long distance travel was also similar to that reported for overseas populations with thromboembolic disease (3.3% in our setting versus up to 3.9% in overseas settings).[23] A higher proportion of our SP had undergone recent surgery when compared with overseas PE populations (16.4 versus 11.2%).[22] The prevalence of recent trauma was similar between our SP and overseas PE populations (3.3% versus up to 3.7%), while the prevalence of malignancy in our SP was almost seven times lower than that reported for overseas populations with PE (3.3% versus 22.3%).[22] Smoking was less prevalent in our SP when compared with overseas settings (9.8% versus 30.5%).[24] A history (current or prior) of venous thromboembolism was 8.2-19.7% in our SP when compared with a reported 26.0% in overseas settings.[22] Data from overseas settings show that there is a low prevalence of pregnancy in populations with PE (estimated prevalence of 1.1%).[22] Our study reports no cases with pregnancy, which appears to be in accordance with the reported low prevalence in overseas settings. The prevalence of hormonal therapy/oestrogen use appears similar between SA and overseas settings (1.6% and 2.0%, respectively).[22] Obesity is more prevalent in overseas populations with PE versus SA populations with this condition (37.8% versus 27.9%).[22] While HIV and tuberculosis have not been identified as potential comorbidities of interest in populations with PE in overseas settings,[3,22] recent evidence from SA has suggested that HIV and tuberculosis are amongst the most prevalent comorbidities in patients with DVT.[8] Interestingly, we report a much lower prevalence of HIV and tuberculosis in SA patients with PE when compared with DVT patients from a similar setting (27.9% and 4.9-13.1% versus 51.9% and 35.8%, respectively).[8] Our findings of discrepancies in the prevalence of PE risk factors between SA and overseas populations might have important implications for the initial diagnosis of PE in SA settings, as overseas management guidelines (which describe overseas risk factors) are often used in our setting. Differences in the prevalence of PE risk factors between SA and overseas populations also important implications related to risk reduction initiatives for PE in SA settings. Therefore, appropriate setting-specific studies of PE risk factors in SA patients are required.

Classification and treatment of PE in the SP:

The PE population in overseas settings is comprised of patients with massive PE, submassive PE, and minor PE in the following proportions: 5.0%, 40.0% and 55.0%,

respectively.[25] Our findings suggest a slightly higher prevalence of massive PE, a much higher prevalence of submassive PE, and a much lower prevalence of minor PE in our SP when compared with overseas populations. However, we report an overall finding of a lower prevalence of massive versus non-massive (submassive and minor) PE which is in keeping with the overseas literature.[25] Almost two-thirds of our SP were classified as having submassive PE, with less than one in every ten patients classified as having massive PE according to currently accepted definitions, which are based on the presence/absence of haemodynamic instability and cardiac dysfunction/injury.[26] The presence of haemodynamic instability is often a proxy for the degree of occlusion caused by a PE in the pulmonary circulation.[26] We can therefore conclude that most patients with PE in our SA setting did not have more severe manifestations of PE with associated haemodynamic instability. As in overseas settings,[26] anticoagulation therapy formed the backbone of PE treatment in SA patients. Also in keeping with overseas management practices, intervention by thrombolysis or embolectomy was carefully considered in our setting and was only performed when there was a relevant indication to perform either of these interventions.[26,27] It therefore appears that the management of PE in our SA setting is in accordance with overseas guidelines/recommendations.

Mortality and associated characteristics in the SP:

The incidence of inpatient mortality in our SP was within the range reported for overseas populations with PE (<1.0% to 60.0%).[28-31] The majority of deaths in our SP were in patients who had submassive PE. This suggests that in addition to PE with haemodynamic instability (ie. massive PE) which has traditionally been considered to account for most inpatient deaths in overseas settings,[25] PE in haemodynamically stable patients might be of concern in SA settings. We found crude statistical associations between five of the patient/clinical characteristics investigated in our study and inpatient mortality, which included: admission through the emergency department/critical care unit, dyspnoea, tachycardia, and embolectomy. As patients with acute PE are more likely to be admitted as non-elective/emergency cases,[31] our findings for hospital admission route suggest that acute PE is associated with increased mortality in SA patients. The overseas literature also reports a high mortality rate (of up to 50.0%) in patients with acute PE.[32] While there is no specific evidence from overseas settings reporting the association of dyspnoea grading on outcomes in patients with PE, our finding for dyspnoea is in agreement with prior reports of dyspnoea from general medical populations in overseas settings which show an almost three-fold increased risk of cardiovascular or all-cause mortality when compared with dyspnoea-free populations.[33] Similarly, there is no specific literature reporting the impact of tachycardia on mortality in patients with PE. However, data from general populations in overseas settings have shown this clinical sign to be associated with a higher risk of morbidity and mortality,[34] which our findings appear to mirror. Pulmonary embolectomy has traditionally been associated with high mortality rates of up to 32.0% in overseas settings.[35] It is therefore no surprise that we observed increased mortality in patients who underwent pulmonary embolectomy versus patients who did not undergo this high-risk surgical procedure.

We did not observe statistically relevant associations between the other characteristics investigated in our study and inpatient mortality. There are two possible explanations for this. Firstly, it might be that these characteristics are genuinely not associated with mortality in SA patients with PE. Secondly, it could be that our modest sample size did not allow for weaker statistical associations between these characteristics and inpatient mortality to be detected. Nevertheless, we report on the characteristics which had the strongest statistical associations with inpatient mortality in our study.

Strengths and limitations of our study:

A strength of our study is that we provide an in-depth description of the presentation, risk factor prevalence, treatment, and outcome in patients with PE from a SA setting. As previously mentioned, reports of PE from African settings are rare. A limitation of our study is that our modest sample size prevented us from performing further statistical investigations of characteristics associated with inpatient mortality in our SP. Another limitation of our study is that our study population was from a single, tertiary-level healthcare facility. Therefore, our study findings might not be applicable to SA patients with PE attending lower-level healthcare facilities. Data was missing for some characteristics, however we did not exclude patients with missing data from our analysis and accounted for missing data with the "not reported" category. Finally, we only report on inpatient outcomes and we do not report patient outcomes following discharge from hospital. Large, multicentre, prospective studies are required to address these study limitations.

Conclusion:

We provide a report of the presentation, risk factor prevalence, treatment, and outcomes of PE in SA patients. There were several differences and similarities between the presentation and prevalence of risk factors associated with PE in SA and overseas settings. This has potentially important implications with regard to the initial diagnosis of PE in SA patients, as well as potentially important implications related to risk stratification in SA patients with PE. Treatment of SA patients with PE is in line with that recommended in overseas management guidelines. Inpatient mortality in SA patients with PE was in the range reported for overseas populations with PE. Further research is required to confirm our findings, as well as to address the limitations of our study.

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Appendix 1: Study protocol

Admissions for pulmonary embolism at a tertiary South African hospital

Master of Medicine (MMed) Research Proposal

Short title: Pulmonary embolism at a tertiary hospital

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BACKGROUND

Pulmonary embolism (PE) is amongst the most important complications of deep vein thrombosis (DVT).[1] Specifically, pulmonary embolism results from the migration of a thrombus in the lower limbs to the lung.[2,3] The thrombus may then cause occlusion of the pulmonary circulation which has adverse consequences on pulmonary and cardiac function.[3] Both DVT and PE are manifestations of thromboembolic disease.[1] The incidence of PE in overseas settings is estimated at 1.0 case per 1000 people.[4] Early mortality rates in patients with PE are high. It is reported to account for 5-10% of all inpatient deaths.[5] The presentation of PE is varied and can pose diagnostic challenges.[2,4,5] The mortality rate is much higher in patients with undiagnosed, untreated PE and this highlights the importance of understanding the clinical and biochemical presentation of PE such that patients can be diagnosed timeously and treatment can be initiated.[5]

South Africa is currently experiencing an epidemiological transition, whereby the national noncommunicable disease burden is approaching that of communicable disease.[6] Non-communicable diseases comprised 60% of the ten leading underlying natural causes of death in South Africa for 2015.[7] While no specific data is available for PE, a 2007 report found 2566 deaths in the country could be attributed to diseases of the circulatory system, a composite measure which includes PE, stroke, and myocardial infarction.[8] Interestingly, embolic pathophysiology also appears to play some role in stroke and myocardial infarction.[9,10] However, descriptions of PE in South African settings are rare. Recent evidence from a study of DVT in a South African setting suggest that there are some setting-specific risk factors for thromboembolic disease, most notably HIV infection and tuberculosis.[11] It is also possible that there might be some discordancy between clinical/biochemical presentation and risk factors for PE between South African settings and European/American settings, however this is yet to be demonstrated. It might also be possible that there are differences in mortality between South African and overseas patients with PE. A better description of PE in a South African setting would be useful in efforts to improve patient management and subsequent patient outcomes in this setting.

AIM

The aim of this study will be to improve the current understanding of PE in a South African setting.

OBJECTIVES

The objectives of this study will be

1. Describe the presentation of PE in patients who were admitted to a tertiary South African hospital with the condition (the study population)
2. Determine the incidence of mortality in the study population
3. Determine which presenting characteristics are associated with inpatient mortality in the study population

METHODS

Study design, study setting, and study population:

This will be a retrospective case series of adult (≥18 years old) patients who were admitted to the tertiary-level Inkosi Albert Luthuli Central Hospital (IALCH) in Durban, South Africa between over a 5-year period (2011-2015) with a primary diagnosis of PE. Briefly, the hospital admissions database will be screened for all patients with a primary diagnosis of International Classification of Diseases 10th Revision (ICD-10) code I26 (includes I26.0 and sub-categories and I26.9 and sub-categories). Specific inclusion and exclusion criteria for this study are provided in Table 1.

Table 1. Inclusion and exclusion criteria for the proposed study

Inclusion Criteria	*Exclusion Criteria*
Patients aged 18 years or older	Patients younger than 18 years old
Patients who were admitted for PE at IALCH between 01 January 2011 and 31 December 2015	Patients who were not admitted for PE at IALCH between 01 January 2011 and 31 December 2015
Patient not previously included in study	Patient previously included in study

Sample size:

As descriptive statistics for a case series do not involve direct statistical comparisons between groups (ie. There is no comparator group – all patients have PE),[12] our minimum sample size will be based on the planned mortality analysis (study objective 3) where there will be comparisons made between two groups (patients who died and patients who did not die). This will involve a chi-squared statistical test. The rule of thumb minimum sample size for a chi-squared test is 20 patients.[13] As PE is rarely encountered, we estimate that there will be between 60 and 100 patients who were admitted to the hospital with PE as a primary diagnosis over the five year study period (out of all patients admitted to hospital during the study period). All these patients will be included in our study. Therefore our projected sample size exceeds the rule of thumb sample size for a chi-squared test, and will be sufficient for our case series study design.

Data collection:

The electronic medical records of all eligible patients will be reviewed and data related to various patient characteristics/other comorbidity, clinical and laboratory presentation at admission, treatment, and inpatient mortality will be collected using a data collection form (Appendix 1). These variables have been identified in the published literature as potentially important with regard to PE.[2,4,14] In addition, we will collect data related to HIV infection and tuberculosis as these have been shown to be associated with deep vein thrombosis (an established risk factor for PE) in a South African setting.[11] All data will then be transferred from the data collection forms to a de-identified, password protected database compatible with a statistical software package.

Statistical analysis:

We will conduct a descriptive analysis of data for variables collected in Appendix 1. Some variables may be dichotomized or categorized in order to facilitate our planned statistical analyses. These categories will be based on meaningful definitions obtained from the published literature. Results for the descriptive analysis will be presented as frequencies and percentages. The incidence of inpatient mortality will be determined using standard epidemiological methods.[15]

In addition, crude associations between various aspects of PE clinical/laboratory presentation and inpatient mortality will be investigated using a chi-squared test. Results from this crude statistical analysis will be presented as frequencies (with percentages) in each group, and a corresponding p-value. A p-value <0.050 will be considered statistically significant. All statistical analyses will be performed using the Statistical Package for the Social Sciences version 24.0 (IBM Corp, USA).

Ethical approval:

This is a sub-analysis of data being collected as part of a larger study of hospital admissions, inpatient outcomes, and quality improvement at IALCH which has already received approval from the University of KwaZulu-Natal Biomedical Research Ethics Committee (BE595/16). Approval/a waiver from the University of KwaZulu-Natal Biomedical Research Ethics Committee will still be sought prior to commencing this specific sub-analysis.

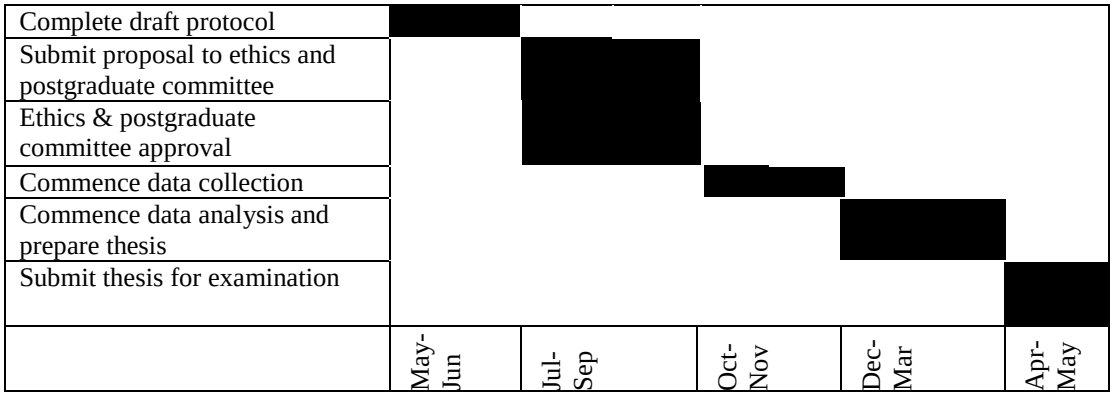
POTENTIAL IMPACT OF RESEARCH

This study will provide important information which will allow for improved management of South African patients with PE. We believe that the South African setting is unique in regards to patients who may suffer pulmonary embolism. Patient demographics, medical comorbidities and heightened risk factors are all variables which contribute to a differing subset of patients previously described in western literature or in developed-world settings. As such, we believe, this study can contribute to determining the additional factors to be considered in suspecting, diagnosing and ultimately treating patients with pulmonary embolism in our setting.

DISSEMINATION OF STUDY RESULTS

The results of this research will be made available to the scientific community through publication in an accredited, peer-reviewed medical journal. The results of the research will also be reported to the KwaZulu-Natal Department of Health. A lay summary of the results will also be made available on selected print and electronic media.

PROPOSED WORK PLAN (WITH REFERENCE MAY 2017- MAY 2018)



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APPENDIX 1: PULMONARY EMBOLISM STUDY (Data collection form)

Participant Study Number (For office use only): _____

PATIENT DEMOGRAPHICS & ADMISSION ROUTE

1. Age in years:_____
2. Gender (Male/Female): _____
3. Ethnicity: _____
4. Admitted through emergency department/critical care unit (Y/N): _____

SYMPTOMS AT TIME OF ADMISSION

1. Dyspnoea – If "Y", NYHA grade or grade not reported (Y/N): _____
2. Chest pain – if "Y", pleuritic/substernal/nature not reported (Y/N):_____
4. Cough (Y/N): _____
5. Haemoptysis – if "Y", specify minor/major/nature not reported (Y/N):_____
6. Syncopal event – if "Y" specify syncope/presyncope (Y/N): _____
7. Massive PE – Acute PE and secondary hypotension with no other cause of hypotension other than PE (Y/N): _____

SIGNS AT TIME OF ADMISSION

1. Tachypnoea >20 breaths per min (Y/N): _____
2. Tachycardia >100 beats per min (Y/N): _____
3. Cyanosis (Y/N): _____
4. Temperature >38.5^{o}C (Y/N): _____
5. Lower limb swelling/pain (Y/N): _____

OTHER IMPORTANT SIGNS/VITALS AT TIME OF ADMISSION

1. O_2 saturation (%): _____
2. pO_2 from arterial blood gas test (mmHg): _____
3. Supplemental O_2 (Y/N): _____
4. Mechanical ventilation (Y/N): _____
5. Systolic blood pressure (mmHg): _____
6. Diastolic blood pressure (mmHg): _____

PRE-ADMISSION RISK FACTORS

1. Systemic Hypertension (Y/N): _____
2. Immobilization of three days or more within last 4 weeks (Y/N): _____
3. Long distance travel (more than four hours) within last 4 weeks (Y/N): _____
4. Surgery within last four weeks – list procedure if Yes (Y/N): _____
5. Trauma within last four weeks (Y/N): _____
6. Malignancy – haematologic or solid if Yes (Y/N): _____
7. Tobacco use(Y/N): _____
8. Cerebrovascular disease – stroke or TIA (Y/N): _____
9. History of previous PE or DVT (Y/N): _____
10. Heart failure (Y/N): _____
11. HIV infection (Y/N): _____
12. Current pregnant state (Y/N): _____
13. Hormone replacement therapy/hormonal contraception (Y/N): _____

14. Current tuberculosis infection (Y/N): _____
15. Obesity – Body mass index>30 kg/m^2 (Y/N): _____

LABORATORY FINDINGS ON ADMISSION

1. Quantitative D-dimer (μg/L): _____
2. Cardiac enzymes (Specify Troponin or CKMB and respective units):_____

TREATMENT WHILE ADMITTED

1. Anticoagulation eg. Heparin, enoxaparin, warfarin (Y/N): _____
2. Thrombolysis (Y/N): _____
3. Pulmonary embolectomy (Y/N): _____

INPATIENT OUTCOME

1. Mortality (Y/N): _____

Appendix 2: Journal guidelines

SA HEART IS AN OFFICIAL JOURNAL OF THE SOUTH AFRICAN HEART ASSOCIATION AND APPEARS ON A QUARTERLY BASIS

Instructions for authors

SA Heart publishes peer reviewed articles dealing with cardiovascular disease, including original research, topical reviews, state-of-the-art papers and viewpoints. Regular features include an ECG quiz, image in cardiology and local guidelines. Case reports are considered for publication only if the case or cases are truly unique, incorporates a relevant review of the literature and makes a contribution to improved future patient management.

Publication policy

Articles must be the original, unpublished work of the stated authors. Written permission from the author or copyright holder must be submitted with previously published material including text, figures or tables. Articles under consideration elsewhere or previously published (except as abstracts not exceeding 400 words) may not be submitted for publication in SA Heart. On acceptance transfer of copyright to the South African Heart Association will be required. No material published in SA Heart may be reproduced without written permission. Permission may be sought from the Editor (Email: afd@sun.ac.za).

Disclosures

Authors must declare all financial disclosures and conflicts of interest in the cover letter and on the title page of the manuscript.

Ethics

All studies must be in compliance with institutional and international regulations for human and animal studies such as the Helsinki declaration (2008) (http://www.wma.net/en/30publications/10policies/b3/17c.pdf) and the South African MRC ethics guidelines (http://www.sahealthinfo.org/ethics/index.htm). Human studies require ethics committee approval and informed consent which must be documented in your manuscript. Animal studies require ethics committee approval and must conform to international guidelines for animal research. Compliance with these requirements must be documented in your manuscript.

Content

1. Title page: It should contain the title of the manuscript, the names of all authors in the correct sequence, their academic status and affiliations. If there are more than 4 authors, the contribution of each must be substantiated in the cover sheet. The main author should include his/her name, address, phone, fax and email address.
2. Authors are solely responsible for the factual accuracy of their work.
3. Articles should be between 3 000 and 5 000 words in length.
4. A 200-word abstract should state the main conclusions and clinical relevance of the article.
5. All articles are to be in English.
6. Abbreviations and acronyms should be defined on first use and kept to a minimum.
7. Tables should carry Roman numeral, I, II etc., and figures Arabic numbers 1, 2 etc.
8. References should be numbered consecutively in the order that they are first mentioned in the text and listed at the end in numerical order of appearance. Identify references in the text by Arabic numerals in superscript after punctuation, e.g. …trial.[13]

The following format should be used for references:

Articles

Kaplan FS, August CS, Dalinka MK. Bone densitometry observation of osteoporosis in response to bone marrow transplantation. Clin Orthop 1993;294:73-8. (If there are more than six authors, list only the first three followed by et al.)

Chapter in a book

Young W. Neurophysiology of spinal cord injury. In: Errico TJ, Bauer RD, Waugh T (eds). Spinal Trauma. Philadelphia: JB Lippincott; 1991:377-94.

Online media

Norback JS, Lwellyn DC and Hardin JR (2001). Shoptalk 101. Integrating workplace communication into undergraduate engineering curricula [online]. Retrieved February 15, 2012: http://www.lionhrtpub.com/orms/orms-8-01/norback.html.

9. Articles are to be submitted by email. The text should be in MS Word. Pages should be numbered consecutively in the following order wherever possible: Title page, abstract, introduction, materials and methods, results, discussion, acknowledgements, tables and illustrations, references.
10. Where possible all figures, tables and photographs must also be submitted electronically. The illustrations, tables and graphs should not be imbedded in the text file, but should be provided as separate individual graphic files, and clearly identified. The figures should be saved as a 300 dpi jpeg file. Tables should be saved in a MS Word or PowerPoint document. If photographs are submitted, two sets of unmounted high quality black and white glossy prints should accompany the paper. Figures and photographs should be of high quality with all symbols, letters or numbers clear enough and large enough to remain legible after reduction to fit in a text column. Each figure and table must have a separate self-explanatory legend.
11. Remove all markings such as patient identification from images and radiographs before photographing.

Submission of manuscripts

Please submit the manuscript to the Editor (afd@sun.ac.za) and copy it to the Guest Editor (if applicable) and the secretary of the South African Heart Association (erika@saheart.org).

Appendix 3: Study approvals

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

24 October 2017

Dr SR Kistensamy (204501801)
School of Clinical Medicine
College of Health Sciences
drrickist@yahoo.com

PROTOCOL: Admissions for pulmonary embolism at a tertiary South African Hospital.
Degree: MMed
BREC Ref No: BE589/17

EXPEDITED APPROVAL

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 26 September 2017.

The study was provisionally approved pending appropriate responses to queries raised. Your response received on 17 October 2017 to BREC correspondence dated 13 October 2017 have been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given **full ethics approval** and may begin as from 24 October 2017.

This approval is valid for one year from 24 **October 2017**. To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **RATIFIED** by a full Committee at its next meeting taking place on **14 November 2017**.

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

Professor J Tsoka-Gwegweni
Chair: Biomedical Research Ethics Committee

cc postgraduate administrator: konar@ukzn.ac.za
cc supervisor: moodleyyo@ukzn.ac.za
cc co supervispr: s.l.brown.mail@gmail.com