An Audit of the Utility of the D-Dimer Test in the Diagnosis of Pulmonary Embolism in a Private Emergency Unit in Johannesburg

By

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfillment of requirements for the degree of Master of Science in Medicine in Emergency Medicine.

Johannesburg, 2013
DECLARATION

I, Dr Amanda J Schur, student number 8402598, hereby declare that this research project is my own unaided work. It is being submitted for the degree of Masters of Science (Medicine) in Emergency Medicine, in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

- I am aware that plagiarism (the use of someone else’s work without their permission and/or without acknowledging the original source) is wrong.

- I have followed the required conventions in referencing the thoughts and ideas of others.

- I understand that the University of the Witwatersrand, Johannesburg, may take disciplinary action against me if there is a belief that this is not my own work or if I have failed to acknowledge the source of the ideas or words in my writing.

Signed:

On this 24th day of July 2011.
DEDICATION

This research project is dedicated to my husband Sean and my daughter Tamara and my parents Michael and Joan Schur, for their support, patience and understanding during the time spent researching and compiling this project.
PRESENTATIONS ARISING FROM THIS STUDY


ABSTRACT

Background: The D-Dimer test has a high negative predictive value used primarily to exclude clinically suspected possible thrombo-embolic disease. In Emergency Unit (EU) practice, this test is often done not only for suspected Pulmonary Emboli (PE) but also to rule out atypical PE. In South Africa, diagnostic usefulness of this test has not been evaluated in a private hospital EU. The health profile of patients presenting in public and private EUs is different and therefore, it was hypothesized that the usefulness of the D-Dimer test in these two settings may be different. Results of this study may inform private hospital EU best practice in the optimal utilization of this test.

Objective: To evaluate the usefulness of the D-Dimer test in the diagnosis of PE at the Morningside MediClinic (MMC) private hospital EU in Johannesburg, South Africa.

Patients and Methods: After approval by the University of the Witwatersrand Human Research Ethics Committee, audit of clinical records was done at the MMC EU from 1 March to 1 June 2009. Informed consent was not required from study subjects as the study was done retrospectively with data extracted from clinical records in an anonymous and delinked fashion. The study population included all patients who had a D-Dimer test done in the MMC EU as part of their diagnostic workup. Extracted data included demographic information, diagnoses and confirmatory tests done. Continuous and categorical variables of data collected were summarized using Stastistica version 9.0 statistical package. A Wells Score was calculated according to the Wells Criteria.

Results: In the study period, 189 of 2948 (5%) patients seen at MMC EU had D-Dimers measured. Their population mean age was 57 years (range 38 – 84 years) and 51% were males. Positive D-Dimers were present in 40 (21%) of the total patient population sample group (189 patients). Within the diagnostic categories, the following percentages were the
results found per category of the positive D-Dimers within each category: PE (5)(100%), Chest Infection (5)(56%), AMI (2)(33%), Arrhythmia (2)(33%), Hypertension (2)(25%), Chest Pain (6)(14%), Anxiety (3)(23%), Headache (1)(14%), Syncope (1)(14%) and Others (13)(32%). The mean Wells Score in PE was 3.6 (3.0-4.5.) indicating medium probability of PE. All other diagnostic groups had low probability Wells Scores. It was impossible to comment on findings in public hospitals, as there is no known literature found to date on an audit performed concerning the usefulness of the D-Dimer test in a public hospital or any of the public sector, in Johannesburg or elsewhere in South Africa, regarding the diagnosis of PE. However, data has been published by other countries regarding the D-Dimer in various hospital and EU settings (public and private).

**Conclusion:** In the cohort, the D-Dimer was done in only a fifth of patients seen at the private MMC EU and it was positive in less than half of cases. The test yield was highest in PE and had high negative predictive value in more than half of non-PE diagnoses. Therefore, the results suggested that a positive D-Dimer is highly predictive of a diagnosis of PE in this private EU. A negative D-Dimer result appears to be largely associated with any of the non PE wide differential of diagnoses.
ACKNOWLEDGEMENTS

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The Morningside Radiology Department, Dr Bloch and Partners, for allowing me to use Chest CT Scans.
# LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 The pathophysiology of pulmonary embolism</td>
<td>6</td>
</tr>
<tr>
<td>1.2 Chest CT Scan images demonstrating a massive PE</td>
<td>20</td>
</tr>
<tr>
<td>1.3 Chest CT Scan images demonstrating normal chest pathology</td>
<td>31</td>
</tr>
<tr>
<td>2.1 Principles of D-Dimer testing</td>
<td>36</td>
</tr>
</tbody>
</table>
# LIST OF TABLES

<table>
<thead>
<tr>
<th>Tables</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Wells prediction rule for diagnosing pulmonary embolism</td>
<td>22</td>
</tr>
<tr>
<td>1.2 The Revised Geneva Score</td>
<td>23</td>
</tr>
<tr>
<td>5.1 Basic characteristics of study population</td>
<td>53</td>
</tr>
<tr>
<td>5.2 D-Dimer and Wells results</td>
<td>54</td>
</tr>
<tr>
<td>5.3 Positive for D-Dimer</td>
<td>54</td>
</tr>
<tr>
<td>5.4 Performance of D-Dimer in relation to confirmatory tests diagnoses</td>
<td>55</td>
</tr>
<tr>
<td>5.5 D-Dimer vs PE</td>
<td>56</td>
</tr>
<tr>
<td>5.6 D-Dimer vs Wells Score</td>
<td>56</td>
</tr>
<tr>
<td>5.7 D-Dimer vs CT Chest</td>
<td>57</td>
</tr>
</tbody>
</table>
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>DECLARATION</td>
<td>ii</td>
</tr>
<tr>
<td>DEDICATION</td>
<td>iii</td>
</tr>
<tr>
<td>PRESENTATIONS ARISING FROM THIS STUDY</td>
<td>iv</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>v</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>vi</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>viii</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>ix</td>
</tr>
<tr>
<td>TABLE OF CONTENTS</td>
<td>x</td>
</tr>
<tr>
<td>LIST OF ABBREVIATIONS</td>
<td>xi</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>1.0 PULMONARY EMBOLI</td>
<td>1</td>
</tr>
<tr>
<td>1.1 Pulmonary Emboli epidemiology</td>
<td>1</td>
</tr>
<tr>
<td>1.2 Pathogenesis of PE</td>
<td>2</td>
</tr>
<tr>
<td>1.3 Risk Factors for PE</td>
<td>7</td>
</tr>
<tr>
<td>1.3.1 Acquired risk factors</td>
<td>7</td>
</tr>
<tr>
<td>1.3.2 Inherited risk factors</td>
<td>12</td>
</tr>
<tr>
<td>1.4 Clinical presentation</td>
<td>16</td>
</tr>
<tr>
<td>1.5 Diagnostic options leading to confirmation of diagnosis</td>
<td>24</td>
</tr>
<tr>
<td>1.6 Diagnosis of PE in private and state facilities</td>
<td>32</td>
</tr>
<tr>
<td>1.7 Review of literature on audits done in private and public EUs</td>
<td>33</td>
</tr>
<tr>
<td>2.0 THE D-DIMER TEST</td>
<td>33</td>
</tr>
<tr>
<td>2.1 What is the D-Dimer and how is it generated?</td>
<td>33</td>
</tr>
<tr>
<td>2.2 The principles of D-Dimer test</td>
<td>36</td>
</tr>
<tr>
<td>2.3 D-Dimer tests and different methodologies available</td>
<td>37</td>
</tr>
<tr>
<td>2.4 Causes of raised D-Dimer</td>
<td>42</td>
</tr>
<tr>
<td>2.5 Interpretation and performance characteristics of D-Dimer test</td>
<td>44</td>
</tr>
<tr>
<td>2.6 Limitations of the D-Dimer test</td>
<td>45</td>
</tr>
<tr>
<td>3.0 STUDY OBJECTIVES</td>
<td>46</td>
</tr>
<tr>
<td>4.0 MATERIALS AND METHODS</td>
<td>47</td>
</tr>
<tr>
<td>4.1 Ethics approval</td>
<td>47</td>
</tr>
<tr>
<td>4.2 Study Population</td>
<td>48</td>
</tr>
<tr>
<td>4.3 Study design</td>
<td>48</td>
</tr>
<tr>
<td>4.4 Review of records</td>
<td>48</td>
</tr>
<tr>
<td>4.5 Collation of other tests done</td>
<td>49</td>
</tr>
<tr>
<td>4.6 Analysis of data</td>
<td>49</td>
</tr>
<tr>
<td>4.7 Calculation of Wells Score</td>
<td>49</td>
</tr>
<tr>
<td>4.8 Analysis of results by statistical tools</td>
<td>49</td>
</tr>
<tr>
<td>5.0 RESULTS</td>
<td>50</td>
</tr>
<tr>
<td>5.1 Data Analysis</td>
<td>50</td>
</tr>
<tr>
<td>6.0 DISCUSSION</td>
<td>57</td>
</tr>
<tr>
<td>7.0 CONCLUSION</td>
<td>76</td>
</tr>
<tr>
<td>APPENDIX A: D-Dimer study data collection sheet</td>
<td>79</td>
</tr>
<tr>
<td>APPENDIX B: Wits Human Research Ethics Clearance Certificate</td>
<td>80</td>
</tr>
<tr>
<td>APPENDIX C: Letter of approval of change of title</td>
<td>81</td>
</tr>
<tr>
<td>APPENDIX D: Letters of permission</td>
<td>82</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>86</td>
</tr>
</tbody>
</table>
LIST OF ABBREVIATIONS

AAA Abdominal Aortic Aneurysm
AAD Acute Aortic Dissection
ABG Arterial Blood Gas
ACLS Advanced Cardiovascular Life Support
ACS Acute Coronary Syndrome
AMI Acute Myocardial Infarction
APC Activated Protein C
APLA Antiphospholipid Antibodies
APS Antiphospholipid Syndrome
ATIII Antithrombin III
ATLS Advanced Trauma Life Support
BNP Brain-type Natriuretic Peptide
BP Blood Pressure
BTS British Thoracic Society
CAP Community Acquired Pneumonia
CCF Congestive Cardiac Failure
CHD Congenital Heart Disease
CMV Cytomegalovirus
COPD Chronic Obstructive Pulmonary Disease
CRF Chronic Renal Failure
CRP C-Reactive Protein
CT Spiral Computed Tomography Scan
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>cTnI</td>
<td>cardiac Troponin I</td>
</tr>
<tr>
<td>CTPA</td>
<td>CT Pulmonary Angiography</td>
</tr>
<tr>
<td>CVA</td>
<td>Cerebrovascular Accident</td>
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<td>CVP</td>
<td>Central Venous Pressure</td>
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<td>CXR</td>
<td>Chest X-ray</td>
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<td>DIC</td>
<td>Disseminated Intravascular Coagulation</td>
</tr>
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<td>DVT</td>
<td>Deep Vein Thrombosis</td>
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<td>ECG</td>
<td>Electrocardiogram</td>
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<td>ECHO</td>
<td>Echocardiography</td>
</tr>
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<td>EDTA</td>
<td>Ethylene-diamine-tetra-acetic Acid</td>
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<td>ELFA</td>
<td>ELISA and Fluorescence Assay</td>
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<td>ELISA</td>
<td>Enzyme-linked Immunosorbent Assay</td>
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<td>EU</td>
<td>Emergency Unit</td>
</tr>
<tr>
<td>EUs</td>
<td>Emergency Units</td>
</tr>
<tr>
<td>GORD</td>
<td>Gastro-oesophageal Reflux Disease</td>
</tr>
<tr>
<td>HCP</td>
<td>Health Care Provider</td>
</tr>
<tr>
<td>HR</td>
<td>Heart Rate</td>
</tr>
<tr>
<td>IBS</td>
<td>Inflammatory Bowel Syndrome</td>
</tr>
<tr>
<td>IL-6</td>
<td>Interleukin 6</td>
</tr>
<tr>
<td>IMA</td>
<td>Ischemia-Modified Albumin</td>
</tr>
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<td>MMC</td>
<td>Morningside MediClinic</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Angiography</td>
</tr>
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<td>O₂/CO₂</td>
<td>Oxygen/Carbon dioxide</td>
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<tr>
<td>PaCO₂</td>
<td>Partial arterial carbon dioxide pressure</td>
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<tr>
<td>PaO₂</td>
<td>Partial arterial oxygen pressure</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
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<td>-------------------------------------------------------</td>
</tr>
<tr>
<td>PALS</td>
<td>Paediatric Advanced Life Support</td>
</tr>
<tr>
<td>PE</td>
<td>Pulmonary Embolism</td>
</tr>
<tr>
<td>PEs</td>
<td>Pulmonary Emboli</td>
</tr>
<tr>
<td>PERC</td>
<td>The Pulmonary Embolism Rule-out Criteria</td>
</tr>
<tr>
<td>PESI</td>
<td>PE Severity Index</td>
</tr>
<tr>
<td>PID</td>
<td>Pelvic Inflammatory Disease</td>
</tr>
<tr>
<td>RR</td>
<td>Respiratory Rate</td>
</tr>
<tr>
<td>SLE</td>
<td>Systemic Lupus Erythematosus</td>
</tr>
<tr>
<td>SOB</td>
<td>Shortness of Breath</td>
</tr>
<tr>
<td>SPECT</td>
<td>Single Photon Emission CT</td>
</tr>
<tr>
<td>SVC</td>
<td>Superior Vena Cava</td>
</tr>
<tr>
<td>UTI</td>
<td>Urinary Tract Infection</td>
</tr>
<tr>
<td>VQ</td>
<td>Ventilation Perfusion</td>
</tr>
<tr>
<td>β-TI</td>
<td>β-Thalassaemia Intermedia</td>
</tr>
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<td>β-TM</td>
<td>β-Thalassaemia Major</td>
</tr>
</tbody>
</table>
INTRODUCTION

1.0 PULMONARY EMBOLI

1.1 Pulmonary Emboli epidemiology

Pulmonary Emboli (PEs) are common and have been increasing in incidence in the adult age group,\textsuperscript{1,2} with just over half a million patients being diagnosed per annum in the USA.\textsuperscript{3-5} They are however uncommon in the paediatric population,\textsuperscript{3} whilst they occur in all ages and sexes, there is an association between increasing age and PEs in both sexes. The latter observation may in part be due to the presence of more risk factors with increasing age.\textsuperscript{6,7} Elderly patients that have been hospitalised have been found to commonly suffer from fatal PEs, often only diagnosed at post-mortem examination.\textsuperscript{6,7}

Evidence also shows that females are less likely to have a second episode of Pulmonary Embolism (PE), however the risk is increased during pregnancy and postpartum.\textsuperscript{8} Studies have documented a higher mortality (20-30%), among male patients with a PE, compared to females.\textsuperscript{8} In terms of ethnicity, Africans have a 50% higher probability of thrombotic illness and 50% increase risk of death, compared to Caucasians. Caucasians have a 50% higher probability of PE as well as risk of death compared to other races like, American Indians and Asians, however, this observation may partly be due to reporting bias as very few studies have been done in Africa and Asia.\textsuperscript{6-8}
There are many other factors such as immobilisation, previous major surgery, malignancy, pregnancy and protein C or S deficiency, that increase the risk of an individual’s susceptibility to a PE. PEs are associated with high mortality, which may reach 50 - 200 000 a year.

In Emergency Units (EUs), the frequency of PE has increased with atypical presentations more frequent with consequent greater morbidity and mortality due to missed diagnoses. Diagnosis of PE is often complex, requiring an array of diagnostic modalities including clinical, radiological and blood investigations.

1.2 Pathogenesis of PE

- **Virchow’s Triad** - Virchows’ triangle is the term that refers to the triad of immobility/venous stasis, vascular injury/inflammation and propensity for clotting (Hypercoagulability), which encompasses both hereditary and acquired factors.

Immobility/venous stasis, refers to disruptions in the normal circulation which can occur as a result of turbulent blood flow, varicosities as well as cardiac conditions like mitral stenosis, pregnancy and vessel valve compromise, to name a few predisposing conditions. The lower limb venous system is a low pressure system, composed of superficial and deep vasculature and interconnecting veins. The latter blood flow depends on the lower limb muscle activity, which is affected by an individual’s activity or the lack of it, especially when for example, bedridden post-surgery.
Vascular injury/inflammation refers to any form of damage to the vessel endothelium such as injury from traumatic shearing and surgical procedures (angiogram, Central Venous Percutaneous catheterisation (CVP)), high blood pressure, any foreign matter including infective and/or medical equipment (pace maker), or any other condition that causes stress or irritation of the vasculature.\textsuperscript{16,17}

Any changes in the composition of the blood, affecting the hypercoagulability, can be caused by numerous factors including pregnancy, age, smoking, clotting factor abnormalities, non-O blood types, burns, renal pathologies, malignancies, and oestrogen based medicines, among many other conditions.\textsuperscript{16,17}

- **Promoting and risk factors** - Age (especially >40 years),\textsuperscript{4,10,14} sex and ethnicity have importance when considering risk factors involved in PE and Deep Vein Thrombosis (DVT) occurrence.\textsuperscript{2,8,18}

Other factors placing an individual at risk include air or road travel (more commonly with air travel), involving four or more hours in the month prior to the patient’s initial symptoms, can also result in a DVT/PE due to venous stasis as a result of immobility.\textsuperscript{4,5}

Various conditions such as polycythaemia, dehydration, smoking, a tumour compressing venous circulation externally, any form of cancer, previous PE,\textsuperscript{4,10,14} and extended periods of sitting in front of a computer, cause a build-
up of clotting factors and fibrin which increases the formation of thrombin often with a resultant clot.\textsuperscript{4,19}

The incidence of PE is much higher in the African as opposed to the Caucasians, with an increased risk of death of 50% compared to a similar Caucasians with PE.\textsuperscript{8,18} However, the Caucasians have a higher risk of PE as well as 50% likelihood of death compared to other races such as Asians and Native Americans.\textsuperscript{8,18} There is conflicting information regarding males being at higher risk for PE although mortality has been found higher among men than in women (20-30%).\textsuperscript{8,18}

In a recent study, female patients younger than 65 years, with idiopathic venous thrombo-embolic disease with a normal range D-Dimer result, four weeks after stopping their anti-coagulation therapy, were at very low risk of recurrence of the thrombotic episode.\textsuperscript{7,20}

- **VQ mismatch** – It has recently been proposed that approximately 50% of patients suffering from thrombotic pathology may have a ventilation/perfusion abnormality. There is a debate whether the fatality from PE is related to haemodynamic abnormalities, Oxygen/Carbon dioxide ($O_2/CO_2$) gaseous exchange or other endocrine factors.\textsuperscript{21} Several important reasons for compromised circulation include an anatomical cause of obstruction followed by other vasoactive substances which can affect the interpretation of Ventilation Perfusion (VQ) ratio such as serotonin.\textsuperscript{4,6,10} Around 50% of the blood flow through the lungs would need to be compromised by a PE before
this would result in significant pulmonary vascular obstruction since a healthy individual is able to double their cardiac output without major local effect on arterial pressures in response to such a mechanical threat. Thrombotic lung disease alters lung tissue by changing the usual functioning components into areas of anatomical “dead space”. The latter results in blood gas arterial abnormalities due to the changes in partial arterial oxygen pressure (PaO\(_2\)) and partial arterial carbon dioxide pressure (PaCO\(_2\)) (VQ mismatch), which will be evident in the patient’s clinical presentation.

- **Local effect of an embolus on pulmonary circulation** - A PE is a clot that is formed somewhere in the body and moves to the lungs, which can obstruct the flow of blood in the cardiopulmonary circulation. This is commonly the result of migration of a blood clot originating in the deep vessels of the lower limbs or pelvis.

The most common origin of a PE is in the lower limb calf veins near valves where there is less dynamic flow. Other less common sites of origin of a PE include haemorrhoidal vasculature and the Superior Vena Cava (SVC), or may arise in the lungs, or travel from the right side of the heart to reach the lungs.
Figure 1.1 The pathophysiology of pulmonary embolism. Although pulmonary embolism can arise from anywhere in the body, most commonly it arises from the calf veins. The venous thrombi predominately originate in venous valve pockets (inset) and at other sites of presumed venous stasis. To reach the lungs, thrombo-emboli travel through the right side of the heart. RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle. Sutherland SF. Pulmonary Embolism. (Image reprinted with permission from eMedicine.com, 2010.)
1.3 Risk Factors for PE

These can be acquired or hereditary and can help in guiding the Health Care Provider (HCP) in their choice of further investigations and prophylactic measures.3,4,14,18

1.3.1 Acquired risk factors

- **Trauma** - Especially recent trauma (last three months), where venous injury may have occurred, increases clotting factors as well as may confine a patient to bed rest thereby increasing their risk of forming a DVT/PE.18,22,23

  In the literature, major trauma has been associated with 58% risk of DVT in the lower limbs, and an 18% risk of the latter being found in the proximal circulation.22

- **Limbs** - Fractures of the femur and tibia, pelvis, vertebrae, as well as amputations involving limbs, have been documented to have a higher risk of associated PE, as well as total hip and knee replacements and spinal cord injuries can predispose to PE and DVT.4,18

- **Burns** - Major burns increase the risk of hypercoagulable state and therefore PE and DVT.18 This has been supported by various studies
where burns of the peripheries (limbs), appeared to be a risk factor for the formation of DVT. In a particular study, there was a 2.4% incidence (8 patients with DVT and 2 with PE out of 327 adult burn patients). These appeared to occur in veins draining from the area of burnt tissue in these peripheral areas.

- **Other** - Other concerns are in patients suffering from cancers of pancreatic, lung, urological, gastric and breast origin, in descending order of occurrence (increased risk by 17%), as well as patients with decreased mobility (for example bed rest as a result of injury or a limb cast placed peripherally), as well as those suffering from acute medical illness such as, increased venous pressure as in Congestive Cardiac Failure (CCF), hypotension and paralysis. Obesity also alters the fine equilibrium of coagulation.

Recent central venous catheterisation (last three months), Cerebrovascular Accidents (CVA), previous PE or Chronic Obstructive Pulmonary Disease (COPD), varicose veins and Inflammatory Bowel Syndrome (IBS), are some of the medical and surgical risk factors. Current or past thrombophlebitis, within the last three months is another risk factor. This is due to an enhanced inflammation and activation of blood coagulation factors.

*Antiphospholipid Antibodies (APLA)* – This syndrome implies the presence of a hypercoagulable state which is linked with the presence of APLA causing Antiphospholipid Syndrome (APS). The latter has
been linked with autoimmune pathologies but has also commonly been linked to various viral infections such as Human Parvovirus B19 which can imitate autoimmune diseases resulting in DVT/PE. Cytomegalovirus (CMV) has also been linked with APLA/APS.²⁶ Both viral infections are hypothesised to have been responsible for thrombotic events through several mechanisms involving molecular mimicry.²⁶

**Stem cell transplant** – This is associated with an increased clotting risk in the post-transplantation state. This thrombotic risk may change according to the pre-transplant cell preparatory regimens used, the type of transplant, any underlying chronic disorder and possible medication post-transplantation.¹⁴,²⁷ The increased use of haematopoietic growth factors used to treat cytopaenias in order to mobilise stem cells, is for example, thought to be one of the causes of the latter thrombotic events.¹⁴

- **Surgery** – Surgery affects the clotting factors.¹⁸,²²,²³ There have been reports of up to 15% increased risk post-operatively of PE.¹⁸,¹⁹ Post-operative (hip and knee replacements/abdominal procedures) or immobile patients also show a high propensity of clotting abnormalities such as DVT and PE.³,¹³

- **Pregnancy** – This is one of the hypercoagulable states which, interferes with the very fine equilibrium between coagulation and anticoagulation.
There is an increased risk of thrombosis in pregnancy in the antepartum stage where sudden miscarriage has been linked with APLA (see below), which are associated with clotting, as well as during the postpartum state, due to factors which cause hypercoagulability among which is an increase in platelet count.\textsuperscript{4,18} The prevalence has been documented to range from 1 in 200 deliveries to 1 in 1400 with fatality documented as 1 - 2 cases per 100 000 pregnancies.\textsuperscript{18}

- **Sepsis** – Sepsis alone as well as its serious complication – DIC, resembles other inflammatory disorders in which an on-going stimulus is responsible for constant activation of blood coagulation, resulting in on-going thrombin and therefore fibrin production which depletes the normal clotting factors including inhibitors.\textsuperscript{2}

- **Drugs** – Oral contraceptives, especially when combined with smoking,\textsuperscript{4,5} and hormone replacements (oestrogen) in healthy females, triple the risk (20 - 30 cases per 100 000 per year).\textsuperscript{18,19} Chemotherapy and immunotherapy have been associated with increase clotting. There have been studies done involving the relationship of thrombosis with thalidomide treatment in multiple myeloma. Also other cytotoxic and immuno-therapies can increase thrombotic tendency in malignancy.\textsuperscript{28,29} Heparin preparations have also been noted to be linked with an increased risk of thrombosis.\textsuperscript{4}

- **Disseminated Intravascular Coagulation (DIC)** – This is a serious and fairly common complication of a number of disorders, mainly septicaemia, cancer, obstetric pathologies as well as other inflammatory
pathologies, which cause continuous activation of the blood coagulation pathways. This, results in on-going intravascular thrombin and fibrin production, which eventually results in consumption of all clotting factors and their inhibitors, resulting in a clotting and/or haemorrhagic event. It is therefore essential to diagnose DIC as early as possible, so as to be able to begin appropriate treatment, mainly related to the elimination of the causative agent or pathology for improved prognosis.14

- **Congenital Heart Disease (CHD)** – Haematological problems are common in cyanotic CHD and can affect the outcome of these patients. Erythrocyte numbers are regulated by factors that affect tissue oxygenation, that involve erythropoietin produced in the kidneys.30 The resultant activation of erythropoietin produces an increase in red blood cell mass, thereby increasing blood viscosity. Iron deficiency can also affect blood viscosity. This increase in blood viscosity increases the risk of DVT, PE and resultant CVA have been recorded.30 There are also documented cases where circulatory shunts in patients with cyanotic CHD involving venous blood bypassing the normal filtration action of the pulmonary system, have resulted in PEs which originally arose in the venous circulation, passing directly to the systemic vessels. These patients often have underlying polycythaemia and cyanosis.31

- **Lupus antibodies** – Systemic Lupus Erythematosus (SLE) is a disease thought to be linked with immunological mechanisms of tissue injury with various clinical presentations and outcomes. It is typically found to have a number of antibodies to cellular nuclear components among
A sub-set of patients with Lupus are at increased risk for thrombosis or may develop a second antibody to prothrombin that could result in hypoprothrombinaemia resulting in haemorrhagic episodes.\textsuperscript{32}

### 1.3.2 Inherited risk factors

- **Sickle cell disease** – This occurs in African, Indian, Caribbean, Mediterranean populations among others, which is characteristically represented by a genetic mutation of one of the haemoglobin molecules. Heterozygotes (sickle cell traits), 8 to 13\% of African Americans are not anaemic, but have one abnormal gene (HbAS), whereas in homozygotes (sickle cell anaemia), approximately 0.3\% of African Americans, both genes are abnormal (SS).\textsuperscript{32,33} Distorted and inflexible red blood cells obstruct the microvasculature which results ultimately in thrombosis and or infraction. This disease can produce a hypercoagulable state as part of the “sickle cell crises”, most likely as a result of abnormal platelet function, thrombin production, regulation and fibrinolysis.\textsuperscript{33} An increase has been found, in levels of markers of endothelial tissue activation including E-selectin, von Willebrand factor, and Interleukin 6 (IL-6), among others, which encourages thrombin production. Carriers of the sickle cell trait may also be predisposed to thrombosis.\textsuperscript{2,34} The percentage risk has not been documented thus far according to my literature research.
- **Thalassaemia** – Clotting is a well-known complication of Thalassaemia. This is a group of familial microcytic anaemias with typically impaired haemoglobin synthesis with resultant decreased haemoglobin. This disorder is particularly common in populations of Mediterranean, African as well as South East Asian origin and is one of the most commonly found genetic haematological disorders. Unbalanced haemoglobin synthesis is a result of impaired productions rates of one or more of the globin polypeptide chains ($\alpha$, $\beta$, $\gamma$, $\delta$). In particular, significant haemostatic changes have been found in patients with $\beta$-Thalassaemia Major ($\beta$-TM) and $\beta$-Thalassaemia Intermedia ($\beta$-TI), as well as in $\alpha$-Thalassaemia (Haemoglobin H Disease). Increased thrombotic events have been especially linked with $\beta$-TI from infancy, which is now acknowledged as a chronic thrombotic state linked to abnormalities in coagulation factor and inhibitor levels, as well as various alterations in fibrinolytic system factors.

There is chronic platelet activation in Thalassaemia which has been found after measuring the breakdown products of thromboxane $A_2$ and prostacyclin ($PGI_2$), in the urine. Increased levels of endothelial cell adhesion proteins found in the blood of Thalassaemic patients, has also been thought to be linked to the thrombotic complications of Thalassaemia, due to endothelial cell stimulation or injury. Monocyte and granulocyte cell activation, are also thought to be factors contributing to endothelial damage and thereby the thrombotic state found in Thalassaemia. Decreased levels of coagulation factor
inhibitors such as protein C and protein S, have also been found in patients with β-Thalassaemia.\textsuperscript{35}

Decreased levels of heparin co-factor II are known to be another cause of the hypercoagulable state linked to Thalassaemia.\textsuperscript{35} There are also higher levels of thrombin-ATIII found in many patients (young and old), with β-TM.\textsuperscript{35} It has been suggested that the red blood cells in patients suffering from β-TM and β-TI have negatively charged phospholipids, which may contribute to a greater production of thrombin and thereby greater activation of platelets, which in turn would all increase the thrombotic state linked to Thalassaemia.\textsuperscript{35} Therefore, the continuous thrombin production and increased fibrinolysis are thought to be the main two mechanisms contributing to the hypercoagulable state of the Thalassaemic disorder.\textsuperscript{35}

- **Activated Protein C Resistance (APC)** – This has been linked with 20-40\% cases of DVT/PE.\textsuperscript{36} APC forms part of the anticoagulation system which operates by disabling through cleavage, factors V and VIII of the clotting cascade. When there is poor anticoagulant reaction to APC, this is called APC resistance and is attributed mostly to Factor V Leiden mutation (>95\%).\textsuperscript{36} The latter ultimately by means of several mechanisms involving amino acid replacement, decreases Factor V destruction by APC.\textsuperscript{36}
- **Protein C deficiency** – Is a Vitamin K dependant protein which has been associated with abnormal clotting. APC which results from thrombin binding to a receptor on the endothelial cells (thrombomodulin), has protease enzymatic catalytic activity, which ultimately affects the clotting cascade. Therefore the finding of this deficiency increases the risk of general thrombosis by up to 10%. It has been found to be associated with 2-5% with patients of DVT. This has been linked with thrombotic incidences in patients as young as newborns.

- **Protein S deficiency** – This protein acts as a co-factor of Protein C. It is a Vitamin K dependant protein which has been associated with abnormal clotting (see details above). This deficiency has been linked with an increased clotting risk of up to 10%. It has been found to be linked with 5-6% of patients with DVT/PE.

- **Antithrombin III (ATIII) deficiency** – ATIII is the primary inhibitor of key clotting cascade enzymes: thrombin, factor Xa, and factor IXa. This deficiency (heterozygotes only have been identified), can increase the risk of clotting in the younger population by 10%. This has been found to be linked with 2-4% of patients with DVT/PE.

- **Factor V Leiden mutation** – This is a very common congenital cause of PE as a result of altered response to APC producing impairment of the natural anticoagulation system. This is found in 5% of the average population and is a very common cause of PE and DVT. The presence of this factor increases the risk of venous thrombotic events 7 fold in
heterozygotes and 80 fold in homozygotes. The risk of thrombotic incidences is further increased in pregnancy (60% DVT/PE during pregnancy, especially second trimester or post-delivery), diabetes mellitus, any form of hormone therapy (oral contraception as well as long immobilisation due to various causes). Studies have documented up to 33% of families demonstrating inherited clotting disorders, having two genetic impairments, one of which being Factor V Leiden mutation. Many of these families have been found to have deficiencies of mainly Protein C, Protein S and or Antithrombin III (ATIII). (See Protein C, Protein S and ATIII above).

Other factor deficiencies – Other factors include, Dysfibrinogenaemia, Plasminogen deficiency, possibly others such as raised lipoprotein levels, elevated homocysteine, factors VIII, IX and XI, thrombin-activated fibrinolysis inhibitor.

1.4 Clinical presentation

The clinical presentation of a PE is seldom the “typical” symptomatology of acute shortness of breath (SOB) with haemoptysis, pleuritic chest pain and tachycardia. Also a PE does not always present with a DVT. In fact, the majority of PEs present with atypical symptoms or as silent pathologies.

A PE may occur alone, or in combination with DVT in an estimated 70-80% of patients. In approximately 50% of the latter patients, there is a proximal DVT.
About a 33% of the patients with PE may have an associated DVT that may have embolised at the time of diagnosis. Approximately 66% of PEs are only diagnosed post mortem, or about 40% may have no specific symptoms, but upon vague clinical presentation, a PE may be confirmed by an imaging technique.

The distribution of DVT has been found to be below the knee in 48% of cases, between the knee and inguinal ligament in 36% and above the inguinal ligament in 15%. Portal venous thrombosis associated with liver cirrhotic disease (6 – 11%), is another form of venous thrombosis but is very uncommon.

A PE can present in the following manner:

- **Classic** - As previously noted, the classic symptoms of a PE are acute SOB, haemoptysis, pleuritic chest pain with and without SOB. Also tachycardia and/or increased respiratory rate (RR) may be clinically noted. Classically a DVT has embolised and caused a PE, however, this is in fewer than 20% of patients.

- **Atypical** - Vague scenarios such as nausea, vomiting or syncope, as well as abdominal pain, fever (<39°C, especially with pulmonary infarction), convulsions, persisted cough, wheezing, new onset of atrial fibrillation, confusion and other, are some of the atypical clinical presentations of PE forming a group of about 25% to 35% of patients whose final diagnosis is PE.
In the latter group, the following risk factors may be of benefit in diagnosing a PE, travelling four hours or more in the last month, smoking, central venous procedures within the last three months, heart failure, chronic obstructive airway disease, Irritable Bowel Syndrome (IBS) and varicose veins.\textsuperscript{18,23}

- **Silent** – Approximately 60\% to 70\% of patients with a final diagnosis of PE may be discovered accidentally when a patient presents with no significant symptoms or a vague symptom such as slow progressive SOB, followed by a sudden fatal collapse.\textsuperscript{18,40} The latter could be the result of an underlying massive PE, where the patient may be extremely haemodynamically unstable or even present in full cardiorespiratory arrest.\textsuperscript{4,5}

The presentation of patients with PE can be divided into four groups according to the amount and seriousness of the arterial occlusion. These are massive PE, acute pulmonary infarction, acute PE without infarction, and multiple PEs.\textsuperscript{18} The physical manifestation of the four groups is as follows:\textsuperscript{6,10}

- **Massive PE** – these patients are usually shocked with increased Heart Rate (HR) and RR, low Blood Pressure (BP), poor peripheral perfusion and findings of pulmonary hypotension (see figure 1.2).\textsuperscript{6,10}

- **Acute pulmonary infarction** – this group may have palpable tenderness, a possible pleural rub and/or a decreased chest expansion and possibly signs of a pleural effusion.\textsuperscript{6,10}
• **Acute PE without infarction** – this group may have increased HR and RR, pleuritic pain and/or crackles/wheeze may be found on occasion. There can be other physical signs and there is often a co-morbid disease happening.\(^6,10\)

• **Multiple PEs** – these patients may have pulmonary hypotension, signs of right sided heart failure, however, mostly non-specific signs that should alert the HCP to exclude a PE.\(^6,10\)
The following four Chest Computer Tomographic Scan (CT Scan) images demonstrate a massive PE in a 37 year old female presenting with acute onset of dyspnoea:

Figure 1.2 A series of four Chest CT Scan images demonstrating a massive PE in a 37 year old female presenting with acute onset of dyspnoea. Permission granted from Drs Bloch and Partners Morningside MediClinic Radiology Department.
Due to the aforementioned variable presentations of a PE which makes the diagnosis of PE at times very difficult, a consensus came about, to use a standard set of clinical criteria in order to assist in diagnosing PE. It has been suggested that the use of the Wells Criteria in combination with the D-Dimer as a negative predictive tool, as well as the use of special investigations, also called confirmatory tests, is the best way of diagnosing or excluding a PE.\textsuperscript{11,41,42}

Two main clinical prediction rules have been used to assess the likelihood of the presence of a PE in various population groups, these being the Wells Score and the Geneva Score.\textsuperscript{42} These scores have been found to confirm PE in around 10\% of the low probability category, 30\% in the moderate group and in 70\% of the high probability group.\textsuperscript{42} In our study, all our positive PEs had a moderate probability Wells Score.

In a review, Segal and colleagues, assessed fifteen studies in terms of the Wells Prediction Criteria.\textsuperscript{41} The highest pre-test probability group, was found to have DVT ranging from 17\% to 85\%, the intermediate Wells Score probability group had a finding of 0\% to 38\% and those with the lowest probability score were found to have between 0\% to 13\% positive findings of DVT.\textsuperscript{41} Similar pre-test probability scores were done in another large group of patients (4693), the average age was 51 to 64 years with males being the majority.\textsuperscript{41} The positive PEs were found in 38\% to 78\% of patients with a high probability score in the intermediate probability score group, PEs were positive between 16\% to 28\% whereas in the low probability score group, PEs were positive only in 1\% to 3\% in this group.\textsuperscript{41} Therefore this review supports the use of a clinical prediction rule system in order to predict the likelihood of thrombotic disease in patients who are clinically suspected to have this.\textsuperscript{41}
Siner and Foley also agreed that a low probability Wells Score with a negative D-Dimer result is both accurate and highly sensitive in the exclusion of patients suspected of having a PE, they also emphasised that clinical findings and judgement should be part of this workup for exclusion of PE.¹⁰

Hugli and colleagues, looked at another set of criteria – The Pulmonary Embolism Rule-out Criteria (PERC), to see the diagnostic efficiency and accuracy of it, as being able to either alone, or in combination with the revised Geneva score, exclude safely a PE in a patient.⁴³ This study was a retrospective study like ours but, involved six EUs, and a very large study population (1675), compared to ours (189). The end results recommended that the PERC criteria, whether alone or used together with the revised Geneva Score, cannot safely exclude PE even in those patients who have a low risk probability score, especially in high risk populations.⁴³

### Table 1.1 Wells Prediction Rule for Diagnosing Pulmonary Embolism

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous pulmonary embolism or deep vein thrombosis</td>
<td>+ 1.5</td>
</tr>
<tr>
<td>Heart rate &gt;100 beats per minute</td>
<td>+ 1.5</td>
</tr>
<tr>
<td>Recent surgery or immobilization (within the last 30 d)</td>
<td>+ 1.5</td>
</tr>
<tr>
<td>Clinical signs of deep vein thrombosis</td>
<td>+ 3</td>
</tr>
<tr>
<td>Alternative diagnosis less likely than pulmonary embolism</td>
<td>+ 3</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>+ 1</td>
</tr>
<tr>
<td>Cancer (treated within the last 6 mo)</td>
<td>+ 1</td>
</tr>
</tbody>
</table>

Wells Prediction Rule for Diagnosing Pulmonary Embolism: Clinical Evaluation Table for Predicting Pre-test Probability of Pulmonary Embolism
Note: Clinical probability of pulmonary embolism: low 0–1; intermediate 2–6; high ≥7


**Table 1.2 The Revised Geneva Score**

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age older than 65 y</td>
<td>1</td>
</tr>
<tr>
<td>Previous DVT or PE</td>
<td>3</td>
</tr>
<tr>
<td>Surgery (under general anesthesia) or fracture (of the lower limbs) within 1 month</td>
<td>2</td>
</tr>
<tr>
<td>Active malignant condition (solid or hematologic, currently active or considered cured &lt;1 y)</td>
<td>2</td>
</tr>
</tbody>
</table>

**Symptoms**

| Unilateral lower limb pain | 3 |
| Hemoptysis | 2 |

**Clinical Signs**

| Heart rate 75–94 beats/min | 3 |
| Heart rate ≥95 beats/min | 5 |
| Pain on lower limb deep venous palpation and unilateral edema | 4 |

**Clinical Probability**

| Low | 0–3 total |
| Intermediate | 4–10 total |
| High | ≥11 total |

The Revised Geneva Score*

*Adapted from Prediction of pulmonary embolism in the emergency department: the revised Geneva score. Le Gal G, Righini M, Roy PM, Sanchez O, Aujesky D,
1.5 Diagnostic options leading to confirmation of diagnosis

Since the 1990’s many imaging and laboratory tests have been assessed for their possible accuracy in confirming a PE/DVT, but the scientific evidence has been poor as to their reliability since no single confirmatory test or clinical discovery, has been found to be sensitive or adequately specific enough.\textsuperscript{4,9,10}

The HCP must start with a patient’s medical history, including noting any risk factors for PE, followed by a clinical examination of the patient suspected of having a PE as long as the patient is haemodynamically stable.\textsuperscript{10,44,45}

Diagnostic modalities may also assist in exclusion of other pathologies which are part of the large differential of PE.\textsuperscript{18} After the clinical examination, the following diagnostic modalities have been used alone or in conjunction with the clinical assessment:\textsuperscript{3,44,45}

- **Chest X-ray (CXR)** - These are often non-specific and limited in value unless an infrequent finding such as oligaemia or Hampton’s Hump is found on the CXR.\textsuperscript{18,40} The CXR findings are often normal or in the case of extensive PEs, can comprise of the following: a Westermark sign, pleural effusion, raised
hemidiaphragm and atelectasis. Alternate diagnoses such as pneumonia and CCF may be confirmed with a CXR, and may also be present together with a PE.40

- **Electrocardiogram (ECG)/Echocardiography (ECHO)** – These both have a limited role in the assessment of PE and are used primarily to confirm other diagnoses such as pericarditis or AMI. The classic “text book” finding on ECG of S1Q3T3 is rarely found and can be found in the presence of many other conditions.3,6 More commonly a finding of tachycardia with or without inverted T-waves in the precordial leads is present.40 Other ECG signs observed in the presence of especially larger PEs include right heart strain, acute cor-pulmonale, right bundle branch block and right axis deviation.3,6 The latter ECG findings are only found in approximately a fifth of patients with documented PEs.3,6

- **Arterial Blood Gas (ABG)** – This is an invasive and painful test for the patient. It has low sensitivity and specificity and therefore, also has a limited role in diagnosing PE, but rather assists in confirming the severity of other alternative diagnoses.40

- **D-Dimer** – This is a non-invasive and fairly easy method used to exclude thrombotic disease. It is a fairly nonspecific test due to “false positives” that can result from other causes such as infection, in postoperative patients, injuries and other.40 Other studies have shown that the D-Dimer value is directly related to the size of a PE and has a fairly accurate prognostic
value.\textsuperscript{3,5,45} The D-Dimer assay is thought to have a fairly reliable negative predictive value and therefore, when it has a negative value, can almost always be used to exclude the diagnosis of PE.\textsuperscript{40} This test detects the fibrin end product after fibrinogen is degraded.\textsuperscript{11,14,46} The latter is quantified by several assays available, measuring this fibrinolytic activity of plasmin in the circulation.\textsuperscript{44}

- **Pulmonary Angiography** – This diagnostic modality has been thought to be the “gold standard” for diagnosing PE. However, it is invasive, costly, uses intravenous contrast that may cause renal toxicity, allergic reactions and other complications, is a lengthy procedure and not available at all medical facilities.\textsuperscript{40}

- **VQ Scan** – This is done in two stages, one stage involving ventilation and the other perfusion. Radioactively labelled agents are injected intravenously as well as inhaled in order to demarcate the areas of the lungs that are being perfused as well as ventilated. Here an abnormality such as compromised areas of ventilation or areas without sufficient circulation will alert the investigator to the probability of a PE. The shortcomings of this modality involve patients with possible pre-existing pulmonary pathology that will give rise to abnormal VQ Scans with or without current acute mismatch. There is also the need to consider pre-test probability scores in these patients that can also help increase the diagnostic accuracy of this scan.\textsuperscript{40}
• **CT Chest** - The Spiral CT is frequently used as it is less complicated, less “operator dependant”, non-invasive, more rapid and more available than pulmonary angiography.\(^{40}\) It is also less expensive and fairly accurate diagnostically, compared to the VQ Scan, Magnetic Resonance Angiography (MRI) Scan and pulmonary angiography, whilst confirming other pathologies that may be present, such as infection or tumours. Unfortunately the Spiral CT also uses contrast that can affect kidney function or cause other complications.\(^{40}\) It is 85% reliable and if positive, there is no need for further confirmatory investigations.\(^{14,47,48}\)

• **Other** – Other modalities such as the MRI, cardiac biomarkers, such as cardiac Troponin levels, can be markedly raised especially with the larger PEs.\(^{18}\)

Alveolar dead space evaluations may become a future diagnostic measure to be implemented with other modalities to exclude PE. Alveolar dead space is an abnormal finding, occurring when the alveoli are ventilated but are not receiving circulation due to obstruction caused by the PE.\(^{40}\)

In pregnant patients, the role of D-Dimer assays in diagnosing thrombotic disease is still being debated. A recent review article by Durán-Mendicuti and Sodickson, points out that a different approach is therefore warranted in this population group, based on clinical suspicion and history, involving the use of CXR and doppler/Ultrasound of extremities.\(^{49}\) The CT Pulmonary Angiography (CTPA), although being highly sensitive and specific, also involves contrast media and is higher in radiation than a VQ Scan. This is an
acceptable alternative radiological confirmatory investigation especially if there is
contraindication to the CTPA.\textsuperscript{49} The decision will depend on local protocols, resources and
availability of the various imaging modalities as well as specialist cover and specific
medical history of the patient, for example, allergies to contrast media.\textsuperscript{49}

A study done by \textit{Kline} and colleagues in an EU, looked at the use of exhaled CO\textsubscript{2} in
detecting a segmental/subsegmental PE in moderate risk patients, based on the assumption
that a PE decreases the ratio of exhaled End-Tidal CO\textsubscript{2}/O\textsubscript{2}.\textsuperscript{50} The study was conducted on
495 patients. The D-Dimer measurement was taken into account and the conclusion was
that in moderate risk stratified patients, who had a positive D-Dimer and an End-Tidal
CO\textsubscript{2}/O\textsubscript{2} ratio <0.28, the presence of a segmental or subsegmental PE was strongly
suggested, while an End-Tidal CO\textsubscript{2}/O\textsubscript{2} ratio >0.45 inferred the absence of such a PE as
would be confirmed on CT angiography.\textsuperscript{50}

There has also been a suggestion to combine spiral CT (angiography) with CT venography
in order to increase the sensitivity of the spiral CT outcome to 90\%.\textsuperscript{18}

Over the last twenty years, a spiral CT of the chest has become the procedure of
radiological investigative choice for the diagnosis of PE.\textsuperscript{42,51} CT Scan results need to be
used with the pre-test probability in mind.\textsuperscript{52}

A Spiral CT cannot be used in patients with pre-existing renal pathology as it can cause
nephropathy. In the latter case, a VQ Scan can be used instead of a Spiral CT.\textsuperscript{5} A VQ Scan
used to be the main radiological study, prior to the Spiral CT and were also useful when
CT Scans were not available or contraindicated, for example if a patient is allergic to the
intravenous contrast.\textsuperscript{11,52} If the VQ Scan cannot be clearly interpreted, a CT angiogram should be performed.\textsuperscript{11} The CT Scan of the chest should be used together with clinical probability D-Dimer blood assay with or without lower limb dopplers, in order to confirm or exclude thrombotic disease, instead of using one of these tests on its own, which is not thought to be accurate in confirming DVT/PE.\textsuperscript{5,19}

In a study performed by Pesavento and colleagues, the value of a 64-detector row CT in confirming a PE in suspected patients, was assessed in a recently conducted study (2011).\textsuperscript{53} They concluded that the 64-detector row CT is a very efficient radiological investigation which can potentially rule out with no hesitation, the presence of a PE in suspected patient populations.\textsuperscript{53}

In a study performed by Kluge and colleagues, involving 221 patients suspected of having an acute PE, a multi-technique thoracic MRI Scan of the lungs was used in combination with MRI venography. The two latter investigations together confirmed a final diagnosis of PE in this group of patients.\textsuperscript{3,54}

Certain biomarkers such as blood Troponin levels, have been found to help in the exclusion of PE. This biomarker is not sensitive when used alone but, can be used as part of risk assessment in patients with a known PE.\textsuperscript{3} Blood Troponin levels have been found to be raised in as many as 50% of patients with moderate to large PEs and this is thought to be due to sudden right ventricular muscle stretch.\textsuperscript{55} There is also an associated mortality predictive value, where studies have documented an association with worse outcome when raised Troponin levels are found in the presence of a PE, but more research is necessary.\textsuperscript{56}
Another biomarker is the Brain-type Natriuretic Peptide (BNP) which increases in CCF and other conditions that cause pulmonary hypotension, due to the ventricle enlarging.$^{3,57}$

A study performed by Fedullo and Tapson, highlights the ECHO and biochemistry such as Troponin levels and/or BNP levels as helpful in evaluating the right ventricle function.$^5$ They are not diagnostic of a PE but, can help with assessment of prognostic outcome as one of the fatal complications of PE involves systemic hypotension as a result of right ventricular impairment. It was suggested in this article that repeating blood tests which are similar to the latter blood tests, could be done after therapeutic intervention, but this is not yet a definite practise protocol.$^5$

There has been an on-going debate regarding the best approach that should be used to diagnose and manage a patient with an acute PE, two articles in 2011 dealt with this.$^{58,59}$ The one written up by Stein and colleagues was a survey of various “investigators” who looked at the current approach to the diagnosis of an acute PE and noted that VQ Scans or Perfusion Scans on their own, as well as Single Photon Emission CT (SPECT) VQ Scan, are among the common radiological investigations of choice due to the on-going awareness of the hazards of radiation.$^{60}$ However, the patient’s sex, age and plain CXR had a bearing on these decisions.$^{58}$ Sheares in her article discussed the importance of specific hospitals having individualised strategies for assessment of patients with suspected PE.$^{59}$ This would involve early risk assessment as well as a specific D-Dimer assay and a scoring system for pre-test probability assessment, which in combination would help select those requiring further radiological investigations.$^{59}$ These models according to the author, should take into account the local specialist availability and resources among other variables.$^{59}$
The use of the CT Chest is highlighted in Figure 1.3, by the two normal Chest CT Scan images of an 82 year old male. The CT Chest was one of the investigations of choice to exclude a PE in this elderly patient.

Figure 1.3 Chest CT Scan images demonstrating a normal chest pathology in an 82 year old male. Permission granted from Drs Bloch and Partners Morningside MediClinic Radiology Department.
In our private EU, *best practise* depends on the resources of the patient (medical aid or private paying patients). Generally our practise involves diagnosis or exclusion of PE based on clinical examination, ECG, Wells Criteria, D-Dimer, Spiral CT of the chest, or a VQ Scan in the case of a pregnant patient.

1.6 *Diagnosis of PE in private and state facilities*

The incidence of PE has been increasing in the EU with atypical clinical presentations becoming more frequent and therefore a greater resultant morbidity and mortality due to the subtlety of many of these presentations.\(^3,6^1\) Therefore, an HCP cannot rely on the clinical examination and history to accurately diagnose or exclude a PE. In fact, the PE has been referred to as the “*great trickster*” for this reason.\(^3\) The size of the PE may affect the way in which a patient presents to the EU.\(^5,5,4^5\)

The confirmation of a PE once a D-Dimer is positive should follow with a Spiral CT of the chest or a VQ Scan if the former is not available.\(^1^5,4^7,6^2\) Pulmonary angiography used to be the gold standard for diagnosis of a PE.\(^1^1,4^6\) It requires expertise and is an invasive procedure with possible complications such as respiratory and renal failure. Therefore this conventional diagnostic method is not commonly used these days, if the former modalities are available.\(^1^4,6^3,6^4\)
1.7 Review of literature on audits done in private and public EUs

Diagnostic usefulness of this test has been evaluated in various hospital and EU settings (public and private) in other countries but not in South Africa or in our private hospital EU. Results of this study will inform private hospital EU “best practice”.

There is very little literature pertaining to the usefulness of the D-Dimer test within private EU worldwide. In South Africa, there are no other studies that have been written up documenting an audit of the usefulness of the D-Dimer test in the diagnosis of PE in a private EU. There is also no literature to date of the latter pertaining to the public sector in Johannesburg, South Africa.

2.0 THE D-DIMER TEST

2.1 What is the D-Dimer and how is it generated?

The D-Dimer is commonly used in our EU, as in other EUs in other countries, to exclude a number of sinister medical conditions, the leader being the PE, in suspected patients.

The D-Dimer is a measure of the breakdown product of cross-linked fibrin, which is found in the blood and used to detect and/or quantify the degree of fibrin formed, in order to monitor the change or development of various clinical
pathologies. This fibrin formation can also be used to ascertain the effectiveness of a therapeutic course being given to a patient to treat a thrombotic disorder.\textsuperscript{4,5,45} This test should always be interpreted with the patient’s history and clinical findings in mind and never viewed in isolation.\textsuperscript{48}

An HCP would use D-Dimer levels as a screening test commonly in certain scenarios. These would include where the patients present with possible thrombotic disease or if thrombo-embolic disease is clinically suspected.\textsuperscript{48,63,68} Other scenarios include the diagnosis and monitoring of the coagulation activity in DIC, detection of recurrent thrombo-embolic disease or the risk stratification of the latter patients.\textsuperscript{45,68} It has also been suggested that the D-Dimer may be a possible future biomarker that could play a very important role in diagnosis and prognostic outcome of AAA, as well as in severely atherosclerotic patients and patients with clinically localised prostatic cancer.\textsuperscript{69-71} There have been other recent studies showing the possible significance of the D-Dimer assay in the detection of “silent” phlebothrombosis.\textsuperscript{72}

The D-Dimer can also be used as a predictor of mortality in patients with PE, since raised D-Dimer levels have been associated with death.\textsuperscript{42} There has been a direct correlation between the level of the D-Dimer and the severity of illness, radiological degree of the illness as well as the mortality outcome (in hospital).\textsuperscript{73} Also in the literature, there is much emphasis on how the knowledge of the D-Dimer results affects the clinical probability score for PE. Hence, the clinical assessment of the patient is very important prior to obtaining the D-Dimer assay result.\textsuperscript{68}
A negative D-Dimer is thought to rule out a PE and DVT with low clinical probability, with relatively greater certainty.\textsuperscript{11,41,74} There is a debate whether D-Dimer testing alone, is accurate enough to confirm or exclude a PE.\textsuperscript{11,15}

It has been suggested that patients whose D-Dimer falls between 200 and 500ng/ml have very low risk stratification and thereby may not need any other radiological or other investigations.\textsuperscript{75}

Another study supported that the accuracy and specificity of the D-Dimer test decreases as time increases from the time of onset of initial symptoms in a patient with suspected PE/DVT, especially after three days from the time of onset of symptoms in elderly patients. No actual age range for these patients is documented in this review.\textsuperscript{41,76}

The use of the quantitative ELISA D-Dimer assay has been looked at in literature as the assay of choice for patients suspected clinically to have a PE, however, it has been suggested that it be made less expensive and be designed to be faster in its turnaround time so that this test can be used efficiently to screen these patients.\textsuperscript{64}

The D-Dimer is commonly used in our EU at the Morningside Private MediClinic to exclude conditions, especially PE.
2.2 The principles of D-Dimer test

The different principles of assays available for D-Dimer testing are:\(^{67}\)

- Whole blood/Latex agglutination
- Enzyme-linked immunosorbent/Monoclonal antibodies
- Turbidimetric
- Immunofiltration

![Diagram of D-Dimer testing](http://en.wikipedia.org/wiki/D-Dimer)

Figure 2.1 Principles of D-Dimer testing

2.3 D-Dimer tests and different methodologies available

- Whole blood/Latex agglutination (for example, commercially available
  Semi-quantitative Latex Agglutination and manual Whole-blood
  Agglutination)\textsuperscript{11,14}

These tests do not require complicated advanced equipment, and allow fast clinical decision making. They are less sensitive methods and therefore cannot detect low levels of D-Dimer antigen but, are specific enough for the exclusion of PE and DVT.\textsuperscript{14}

This is a qualitative red cell agglutination (whole blood) technique, with a sensitivity of 84.8% and a specificity of 68.4% as found in a patient trial,\textsuperscript{77} and is therefore commonly used for the diagnosis and exclusion of PE. It is a fast technique that has been noted by the British Thoracic Society (BTS) among others, to be used safely in conjunction with Wells Criteria showing a low pre-test probability score in exclusion of a PE in low risk patients.\textsuperscript{78}

This assay depends on visually detecting the flocculation of latex particles, and therefore there is a strong component of operator subjectivity. The latter may be one of the reasons for this qualitative latex fixation D-Dimer assay being noted to be less sensitive for PE detection in published studies.\textsuperscript{79}

The principle of this assay involves using two monoclonal antibodies against fibrin breakdown products, which contain the D-Dimer structure element.\textsuperscript{12}
One of the antibodies is gold labelled, and the other antibody is bound to biotin. These two antibodies bind to the D-Dimer and form a sandwich like entity. Once the red blood cells have been removed from the blood sample collected, the plasma passes through the detection area where the gold labelled D-Dimer entities bind, showing up as a red ("signal") line. Unbound gold tagged antibodies will attach to the control "line", validating the specific assay. The colour of the signal line will intensify in direct proportion with the amount of the D-Dimer concentration found in the plasma and will be shown as a quantitative result.

Computerised methods that quantitate latex agglutination rates, have also been found to have excellent sensitivity and correlate well with Enzyme-linked Immunosorbent Assay (ELISA). ELISA and latex quantifying assays, have both been approved by the American Food and Drug Administration, for the exclusion of PE and DVT and are being used internationally.

When comparing the tests, the ELISA, ELISA and Fluorescence Assay (ELFA), the micro-plate ELISA and the automotive quantitative measuring assays are much more sensitive than the whole blood agglutination assay, but have lower specificity. Therefore, further diagnostic imaging would be necessary to confirm the diagnosis of a PE and/or DVT when ELISA based methods are used. The whole blood agglutination assays have a higher negative predictive value, in populations with lower risk factors.
Latex agglutination assays depend on the availability of a sufficient amount of D-Dimer antigen that would be present on fibrin degradation products. This would determine whether agglutination will be initiated. This assay, is run in plasma and detects D-Dimer antigen once fibrin has cross-linked with the assistance of factor XIIIa.\textsuperscript{14}

The latter assay has shown poor correlation with the diagnosis of PE, therefore is notoriously unreliable but, often used in diagnosing haematological conditions such as DIC.\textsuperscript{6} Sensitivity has been found to be between 50-70% and specificity slightly higher at 76%, which is thus a limitation as far as its use in diagnosing PE.\textsuperscript{6,11}

- **Enzyme-linked immunosorbent/Monoclonal antibodies (for example, Microplate ELISA and ELFA)**\textsuperscript{11,14}

  The ELISA methods were initially developed for the purpose of research, before latex agglutination assays, and they relied on antibody binding to the D-Dimer antigen, after the marking of the antigen with an antibody detection system. The latter assay was extremely sensitive, especially when compared to the latex agglutination test,\textsuperscript{6} but was more time consuming and technically not easily performed.\textsuperscript{14}

  The ELISA based assays have a high sensitivity of 97%, but specificity can be as low as 8%.\textsuperscript{6,81,82} They can detect elevated D-Dimer antigen associated with various pathologies, making this a nonspecific marker, as a positive result may also be present in sepsis, neoplasm, trauma and other injury states.\textsuperscript{6,14,83} These
assays can take several hours to run. A negative result can assist in excluding a PE in low and moderate probability Wells scoring groups.

Computerised latex agglutination assays, record the rate that different antibody coated particles combine with available D-Dimer antigen. These assays require specialised, computerised machines. The specificity of these antibodies, are not the same and they may react differently with high and low molecular weight fibrin breakdown products. Each assay is known to have a specific sensitivity to different size breakdown products.

- **Turbidimetric (for example, Second-generation latex agglutination - immunoturbidimetric)**
  These assays use spectrophotometry to detect the rate of precipitation of latex particles which are coated with antibody to the D-Dimer peptide. This method involves a plasma sample which when placed in a cuvette containing latex particles, the particles will start to adhere to each other. As they combine, this will affect the amount of light detected across the cuvette which is directly proportional to the amount of D-Dimer present in the blood plasma.

  The immunoturbidimetric assays have shown a sensitivity of greater than 95%, but nonspecific for detecting PE in the EU and take long to run. They have been likened in their methodology to the ELISA method.

- **Immunofiltration (for example, Immunofiltration and sandwich-type assays)**
These are assays involving fluorescent end point detection. They use light microscopy with a fluorescence microscope. The method engages specific antibodies to targeted antigens aimed at fluorescent dyes binding to specific cellular molecules, which will ultimately allow the visualisation by the fluorescent microscope. These cellular structures which have been tagged with the fluorescent dye, will be seen lit up as opposed to a black background. This technique maybe problematic due to “photobleaching” which can cause less activity, hence falsifying the ultimate D-Dimer result.

They are equally as sensitive as they are specific. They are faster with a wider linear range that could detect D-Dimer levels between 0 and 1000µg/ml, making them new and promising in efficacy, with shortened lab turnaround times and excellent sensitivity of 97-99% and 97-99% specificity. These assays also have exceptional negative and positive predictive values as opposed with the gold standard ELISA.

A newer D-Dimer assay by the name of “Tina-quant”, has been evaluated in a study performed by Sanchez and his colleagues published in 2011. The authors looked at this assay’s diagnostic accuracy as compared to the VIDAS D-Dimer assay (an automated system that uses the enzyme-linked fluorescent assay method). This was a retrospective study conducted on patients who had D-Dimer assays done at an EU over six months before and after the change to the new “Tina-quant” assay. The authors concluded that the new D-Dimer assay was more effective in terms of reducing a patient’s transit time.
through the EU as well as reducing the number of unnecessary radiological investigations.\textsuperscript{88}

2.4 Causes of raised D-Dimer

A positive or high D-Dimer suggests increased clotting and fibrinolysis, prompting further investigations to reach a definitive diagnosis.\textsuperscript{3,41} It is not conclusive in diagnosing a PE and maybe non-specific and positive in different situations, requiring a Spiral Computed Tomography Scan (CT) of the chest or a VQ Scan for final confirmation.\textsuperscript{3,45,46}

The D-Dimer can be fairly non-specific and may be positive in a number of different situations besides PE and DVT, including Acute Coronary Syndromes (ACS), pregnancy, Chronic Renal Failure (CRF),\textsuperscript{73,90} sepsis, malignancy, various anaemia’s including sickle cell disease, leukaemia, pregnancy, and other inflammatory/pyrexial disorders, as well as post operatively.\textsuperscript{11,19,44} The elderly and hospitalised patients may also have increased D-Dimers.\textsuperscript{41} D-Dimers can also be raised for a time period as long as six months post therapeutic course for a previous DVT.\textsuperscript{6,45,62} There have also been suggestions in the literature that repeated D-Dimer assays, post-anticoagulation therapy, can help plan the length of management of the specific patient being treated for a thrombotic episode, when this is their first episode.\textsuperscript{32}

With ACS, the D-Dimer value is used in combination with cardiac Troponin I (cTnI) to assess risk of the patient immediately and six hours post-admission, and
believed to be fairly accurate in early exclusion, rather than early recognition of those patients with possible cardiac pathology presenting with atypical chest pain.90

Pneumonia (especially Community Acquired Pneumonia (CAP)), is thought to be one of those disorders that increase D-Dimer levels, due to activation of the fibrinolytic system (clotting cascades) within the alveoli, by means of endotoxins released by Gram-negative micro-organisms that are responsible for the pneumonia.73 In other words, a direct relationship (the D-Dimer increases with the severity of the disease) has been suggested between the raised D-Dimer found in various disorders and coagulation within or outside vessels during acute and chronic injury to the lungs.73

Pelvic Inflammatory Disease (PID) is another example of a condition where the D-Dimer plays a very important role in indicating the severity of this disease.91 This may have major implications pertaining to therapeutic options and success, as well as effects on the fertility of the concerned patient, but needs further investigation.91 The latter study which looked at PID, also was a retrospective analysis. The data obtained definitely showed an increase of D-Dimer in PID and is being suggested as being more sensitive than a C-Reactive Protein (CRP) blood test in terms of assessing severity of PID, although this article suggests that more studies are necessary to confirm this fact.91

African American males with hypertension have been found in clinical studies to have raised D-Dimer levels compared to non-hypertensive African Americans.92
The same study also found high D-Dimer levels with increase in age. D-Dimer levels have been found to be raised with cardiovascular pathology as well as higher than in the non-Hispanic Caucasians. This was age independent.  

Recent studies are looking at the D-Dimer as a potentially, very significant biomarker used for prognostic and diagnostic purposes, in patients with Abdominal Aortic Aneurysm (AAA).  

Literature notes that the sensitivity of D-Dimer is very high, however, the specificity is much lower. The D-Dimer concentrations are known to rise with a patients’ age, with the specificity of the latter test declining with increasing age. This appears to make this test less effective with excluding a PE in these older patients. A suggestion has been made to increase the D-Dimer test range results, thereby improving the test specificity. This age corrected D-Dimer range, together with a clinical risk assessment, should aide the usefulness of the D-Dimer test with excluding PEs amidst older patients. The exact range requires further clinical studies.  

2.5 Interpretation and performance characteristics of D-Dimer test  

There are different assays being performed which are of different sensitivity and specificity ranging from 80-100%.  


The D-Dimer test has a high negative predictive value used primarily to confirm or exclude possible thrombo-embolic disease.\textsuperscript{11,13,96} In EU practice, this test is often done not only for suspected PE, but also to rule out atypical PE.\textsuperscript{2,66,96}

An untreated or undetected PE may be associated with high morbidity and mortality, which can be minimised by a high index of suspicion on part of the HCP.\textsuperscript{10,64,94} This should prompt the HCP to investigate further by means of the D-Dimer testing with or without the follow up appropriate imaging, depending on the patient’s risk factors and clinical findings.\textsuperscript{2,4,5}

### 2.6 Limitations of the D-Dimer test

Limitations of the D-Dimer test, include it being a nonspecific test which may be imprecise and inaccurate despite strict operational and technical attempts at quality control.\textsuperscript{55,74,97} This can arise from many factors including various drugs that have been possibly taken by the patient even though in therapeutic doses. The presence of rheumatoid factors can also affect the validity of the D-Dimer test.\textsuperscript{4,5,41}

Recent research suggests that the timing of the D-Dimer assay, relative to the onset of symptoms might have an impact on the final diagnosis, especially if the assay is done a week later, this could decrease the value of the D-Dimer in risk stratification of the patient suspected of DVT or PE.\textsuperscript{76} Most modalities are less reliable than the D-Dimer test, according to the literature.\textsuperscript{11,14,37}
The D-Dimer can be an expense to the patient which is another reason for its role to be justified or negated.\cite{11,45,62} However, it is still cheaper and more rapid than other confirmatory investigations, such as the CT, and can be used as a screening test in the EU.\cite{65,74,97}

Other factors such as raised D-Dimer levels (>50µg/ml), high concentrations of the D-Dimer fragments that occur as a result of thrombolysis and the presence of lipoic acid, may result in incorrect lower values of the D-Dimer test.\cite{3,14,74}

The D-Dimer assays may be limited in both specificity and sensitivity,\cite{41,44,45} where in some literature, sensitivity of the D-Dimer test has been documented to be mostly very high, and the specificity has been noted to be much lower.\cite{14,64,74}

The experience of the lab technician reading the results, is of the utmost importance in order to identify a weak positive result.\cite{62}

3.0 STUDY OBJECTIVES

This study was a clinical audit which aimed to establish the usefulness of the D-Dimer test in the diagnosis of PE in an EU of the Morningside Private MediClinic (MMC) in Johannesburg.

The specific objectives were to:

- Get results of all D-Dimer tests performed (the D-Dimer test and other tests are part of routine diagnosis of PE in our EU setting).
• Establish the proportion of those who had a D-Dimer test as part of their diagnostic test for PE
• Identify patients presenting with non-specific clinical features of PE in the EU
• Establish PE confirmatory tests performed on the identified patients
• Correlate the D-Dimer test results with clinical features and confirmatory tests
• Summarise the usefulness of the D-Dimer test in this study population.

The idea of this research project is to find out statistically how valuable the D-Dimer investigation is in confirming the presence of a PE, and therefore the following was tabulated:

  o D-Dimer vs PE, positive and negative predictive value, sensitivity and specificity of the D-Dimer in diagnosing PE
  o D-Dimer vs Wells Criteria, positive and negative predictive value, sensitivity and specificity of the D-Dimer in diagnosing PE
  o D-Dimer vs CT Chest, positive and negative predictive value, sensitivity and specificity of the D-Dimer in diagnosing PE.

4.0 MATERIALS AND METHODS

4.1 Ethics approval

This study was approved by the University of the Witwatersrand Human Research Ethics Committee, Clearance Certificate number: M090659. (See Appendix A).
4.2 Study Population

**Inclusion Criteria**
- Patients at the MMC EU with D-Dimer test done.
- Adults over 18 years of age or older
- Both male and female

**Exclusion Criteria**
- Patients <18 years old
- Patients with trauma
- Patients with other causes of raised D-Dimers such as a) ACS b) pregnancy c) sepsis d) malignancy e) anaemias f) pyrexial disorders g) post-operative patients h) elderly i) hospitalised patients j) patients less than or equal to six months post therapy for previous DVT/post thrombolytic therapy k) renal dysfunction as measured by raised plasma creatinine above the upper limit of normal.

4.3 Study design

This was a retrospective, cross-sectional uncontrolled study.

4.4 Review of records

After approval by the University of the Witwatersrand Human Research Ethics Committee and the management of the Morningside Private MediClinic EU, a
clinical audit of records was done at the Morningside Private MediClinic EU from 1\textsuperscript{st} March to 1\textsuperscript{st} June, 2009.

4.5 Collation of other tests done

The confirmatory tests were tabulated according to whether they were “done” or “not done”, as well as if done, whether they were negative (neg) or positive (pos). (Table 5.4).

4.6 Analysis of data

A data collection sheet was used (see Appendix A).

4.7 Calculation of Wells Score

The Wells Score was calculated according to the Wells Criteria. (Table 1.1).

4.8 Analysis of results by statistical tools

Extracted data included demographics, diagnoses and confirmatory tests done. Continuous and categorical variables of data collected were summarized using the Statistitca 9.0 package.
5.0 RESULTS

5.1 Data Analysis

The results are presented in Tables 5.1 – 5.7. A data base of 189 (= N) of 3948 patients (5%) seen at MMC EU had D-Dimers measured, over the data collection period (1st March to 1st June, 2009).

Table 5.1 depicts the demographics of the study population used. Out of the 189 patients 93 were females and 96 were males. There were various categories of diagnoses, of the total 189 (N) patients 6(3%) had AMI, 13(7%) Anxiety, 6(3%) Arrhythmia, 5(3%) CVA, 9(5%) Chest Infection, 42(22%) Chest Pain, 19(10%) GORD, 7(4%) Headache, 8(4%) Hypertension, 55(29%) Other, 5(3%) PE and 14(7%) Syncope. The next demographic was age. In the various categories of diagnoses of the total 189 (N) patients, the following were the ages in years with the ranges being in brackets: 59(37-73) AMI, 31(19-45) Anxiety, 68(24-89) Arrhythmia, 59(39-75) CVA, 54(23-86) Chest Infection, 44(21-86) Chest Pain, 41(22-77) GORD, 42(23-67) Headache, 58(42-87) Hypertension, 46(18-88) Other, 57(38-84) PE and 42(22-87) Syncope. (Table 5.1)

Gender wise, a greater percentage of females predominated in the following categories: Arrhythmia (67%), Syncope (71%), PE (60%), GORD (63%), Headache (57%), Anxiety (54%), Chest Infection (56%), the latter is supported by literature. A minor percentage of females presented with AMI (33%), CVA (20%), Chest Pain (43%), Hypertension (50%), and Other (42%). (Table 5.1).
Out of 189 D-Dimers taken, there were 40 (21.16%) which were positive for a number of conditions including PE (Table 5.3). The highest positive D-Dimers within the specific categories, were recorded for PE, 5 positive D-Dimers out of 5 patients within this category equalled 100%, Chest Infections which were 5 out of 9 patients equalled 56%, Acute Myocardial Infarction (AMI) which is 2 out of 6 patients equalled 33%, Arrhythmia which is 2 out of 6 patients equalled 33%, Hypertension which is 2 out of 8 patients equalled 25%, Chest Pain which is 6 out of 42 patients equalled 14%, Anxiety which is 3 out of 13 patients equalled 23%, Headache which is 1 out of 7 patients equalled 14%, Syncope which is 1 out of 14 patients equalled 7% and Other which is 13 out of 55 patients equalled 24% (Table 5.1 and 5.3). We note here, that the group of Other, constitutes 32.5% of those positive for D-Dimer, whereas, AMI forms 5% of this total group, Anxiety 7.5%, Arrhythmia 5%, Chest Infection 12.5%, Chest Pain 15%, Headache 2.5%, Hypertension 5%, PE 12.5% and Syncope 2.5% of the positive D-Dimer group. Patients with the diagnosis of CVA and Gastro-oesophageal Reflux Disease (GORD) had no positive D-Dimer results, hence were not listed in Table 5.3. The group of Other, appears to be the largest group of positive D-Dimers, within the positive D-Dimer group (32.5%). This group includes patients with diagnosis such as Oesophageal Spasm, Muscle Strain Back, Unknown diagnosis, TB, Upper Respiratory Tract Infections, Hypoglycaemia, Gastritis, Hepatitis, Chicken Pox, DVT, Urinary Tract Infection (UTI), Costochondritis, Anaemia, Palpitations, Pharyngitis, Cellulitis, Abdominal Mass, Left Ventricular Failure, Dizziness for investigation, Parenchymal Mass, Renal Failure, Soft Tissue injury of the thigh, CCF and Seizure. As noted, there is a wide range of “non-specific” diagnoses that
have resulted in a documented positive D-Dimer under the umbrella of the group of Other.

The average ages for positive D-Dimers was higher for arrhythmia, chest infection, chest pain, hypertension and syncope with lower age groups recorded for patients diagnosed with AMI, PE and other, and the youngest were those recorded with anxiety and headache. The mean total age was 57 years (38.0 – 84.0), 51% of which were males. (Table 5.1 and 5.3).

Average D-Dimers were recorded for Syncope, Hypertension and Arrhythmias. (Table 5.2 and 5.3). Lower positive D-Dimers were recorded for AMI and Headache. (Table 5.3).

For the group diagnosed with PE, sample size was small (N=5), with 100% of D-Dimers being positive (1.92 ± 0.70 (1.20 – 2.80)). The age group was in the lower age group (57.0 ± 18.4 (38.0 – 84.0)). The mean Wells Score in PE was 3.6 (3.0 - 4.5) indicating medium probability of PE. All other diagnostic groups had low probability Wells Score. (Table 5.2 and 5.3). The only high score resulting from the calculation of the Wells Criteria was found under the group of Other diagnoses. (Table 5.3). Most patients had a low (<2) or moderate score (2-6) in terms of PE risk assessment, with few having a high score (>6), this was used as the pre-test probability used to assess the risk of PE.

Moderate probability was found in the category of PE, Syncope, Other, GORD, Chest Pain, Chest Infection, Arrhythmia and Anxiety. Borderline Wells total
score was found in the category of AMI. (Table 5.2). There were positive D-Dimers that had a medium probability score of significance in the Chest Pain category. The rest mostly had low probability scores with only the group of Other having a high score. (Table 5.3). No correlation was found between D-Dimers and Wells Score, in fact little correlation was found between the probability score and diagnosis. (Table 5.2).

Looking at the confirmatory tests for the positive D-Dimers, (Table 5.4), the category of PE has 5 patients with positive D-Dimers, all with positive CT Chest and CXRs. Two out of the 3 ECGs for this group were positive, and no ECHOs were done. Other categories were Anxiety, (1 positive ECG, 1 positive ECHO), Arrhythmia (1 positive ECG), Chest Infection (1 positive ECG, 1 positive CXR), Chest Pain (2 positive ECGs, 2 positive CXRs), Other (1 positive CT Chest, 4 positive CXR). The other categories being AMI, CVA, GORD, Headache, Hypertension and Syncope had no confirmatory positive tests for the positive D-Dimer patients within these categories. (Table 5.4).

Table 5.1 Basic characteristics of study population (N=189)

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>N (%)</th>
<th>AGE</th>
<th>FEMALE GENDER (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMI</td>
<td>6 (3)</td>
<td>59 (37 - 73)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>ANXIETY</td>
<td>13 (7)</td>
<td>31 (19 - 45)</td>
<td>7 (54)</td>
</tr>
<tr>
<td>ARRHYTHMIA</td>
<td>6 (3)</td>
<td>68 (24 - 89)</td>
<td>4 (67)</td>
</tr>
<tr>
<td>CVA</td>
<td>5 (3)</td>
<td>59 (39 - 75)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>CHEST INFECTION</td>
<td>9 (5)</td>
<td>54 (23 - 86)</td>
<td>5 (56)</td>
</tr>
<tr>
<td>CHEST PAIN</td>
<td>42 (22)</td>
<td>44 (21 - 86)</td>
<td>18 (43)</td>
</tr>
<tr>
<td>GORD</td>
<td>19 (10)</td>
<td>41 (22 - 77)</td>
<td>12 (63)</td>
</tr>
<tr>
<td>HEADACHE</td>
<td>7 (4)</td>
<td>42 (23 - 67)</td>
<td>4 (57)</td>
</tr>
<tr>
<td>HYPERTENSION</td>
<td>8 (4)</td>
<td>58 (42 - 87)</td>
<td>4 (50)</td>
</tr>
<tr>
<td>OTHER</td>
<td>55 (29)</td>
<td>46 (18 - 88)</td>
<td>23 (42)</td>
</tr>
<tr>
<td>PE</td>
<td>5 (3)</td>
<td>57 (38 - 84)</td>
<td>3 (60)</td>
</tr>
<tr>
<td>SYNCOPE</td>
<td>14 (7)</td>
<td>42 (22 - 87)</td>
<td>10 (71)</td>
</tr>
</tbody>
</table>
Table 5.2 D-Dimer and Wells results

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>N</th>
<th>D-DIMER (Mean ± SD)(Range)</th>
<th>WELLS SCORE TOTAL</th>
<th>Wells Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMI</td>
<td>6</td>
<td>0.29 ± 0.25 (0.00 - 0.64)</td>
<td>2.0 ± 1.2</td>
<td></td>
</tr>
<tr>
<td>ANXIETY</td>
<td>13</td>
<td>0.38 ± 0.60 (0.10 - 2.20)</td>
<td>2.1 ± 1.8</td>
<td></td>
</tr>
<tr>
<td>ARRHYTHMIA</td>
<td>6</td>
<td>0.46 ± 0.34 (0.11 - 1.10)</td>
<td>2.9 ± 1.2</td>
<td></td>
</tr>
<tr>
<td>CVA</td>
<td>5</td>
<td>0.27 ± 0.12 (0.12 - 0.46)</td>
<td>1.7 ± 1.3</td>
<td></td>
</tr>
<tr>
<td>CHEST INFECTION</td>
<td>9</td>
<td>1.38 ± 1.39 (0.10 - 3.70)</td>
<td>2.3 ± 2.1</td>
<td></td>
</tr>
<tr>
<td>CHEST PAIN</td>
<td>42</td>
<td>0.35 ± 0.66 (0.10 - 3.40)</td>
<td>2.9 ± 1.1</td>
<td></td>
</tr>
<tr>
<td>GORD</td>
<td>19</td>
<td>0.17 ± 0.10 (0.10 - 0.48)</td>
<td>2.4 ± 1.6</td>
<td></td>
</tr>
<tr>
<td>HEADACHE</td>
<td>7</td>
<td>0.26 ± 0.19 (0.10 - 0.54)</td>
<td>0.9 ± 1.5</td>
<td></td>
</tr>
<tr>
<td>HYPERTENSION</td>
<td>8</td>
<td>0.36 ± 0.33 (0.10 - 0.96)</td>
<td>1.8 ± 2.2</td>
<td></td>
</tr>
<tr>
<td>OTHER</td>
<td>55</td>
<td>0.52 ± 0.82 (0.10 - 4.00)</td>
<td>2.4 ± 1.9</td>
<td></td>
</tr>
<tr>
<td>PE</td>
<td>5</td>
<td>1.92 ± 0.70 (1.20 - 2.80)</td>
<td>3.6 ± 0.8</td>
<td></td>
</tr>
<tr>
<td>SYNCOPE</td>
<td>14</td>
<td>0.21 ± 0.21 (0.10 - 0.87)</td>
<td>2.8 ± 1.5</td>
<td></td>
</tr>
</tbody>
</table>

Table 5.3 Positive for D-Dimer (N=40)

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>N</th>
<th>D-DIMER (Mean ± SD)(Range)</th>
<th>WELLS TOTAL (Mean ± SD)(Range)</th>
<th>LOW</th>
<th>MEDIUM</th>
<th>HIGH</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMI</td>
<td>2</td>
<td>0.59 ± 0.08 (0.53 - 0.64)</td>
<td>1.5 ± 2.1 (0 - 3.0)</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>ANXIETY</td>
<td>3</td>
<td>1.24 ± 0.84 (0.68 - 2.20)</td>
<td>3.0 ± 2.6 (0 - 4.5)</td>
<td>5</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>ARRHYTHMIA</td>
<td>2</td>
<td>0.81 ± 0.42 (0.51 - 1.10)</td>
<td>3.5 ± 0.7 (3.0 - 4.0)</td>
<td>2</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>CHEST INFECTION</td>
<td>5</td>
<td>2.38 ± 1.05 (1.00 - 3.70)</td>
<td>2.7 ± 2.0 (0 - 4.5)</td>
<td>4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>CHEST PAIN</td>
<td>6</td>
<td>1.56 ± 1.22 (0.50 - 3.40)</td>
<td>2.9 ± 1.6 (0 - 4.5)</td>
<td>4</td>
<td>38</td>
<td>0</td>
</tr>
<tr>
<td>HEADACHE</td>
<td>1</td>
<td>0.54 (0.54 - 0.54)</td>
<td>0 (0 - 0)</td>
<td>5</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>HYPERTENSION</td>
<td>2</td>
<td>0.87 ± 0.13 (0.78 - 0.96)</td>
<td>2.3 ± 3.2 (0 - 4.5)</td>
<td>5</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>OTHER</td>
<td>13</td>
<td>1.53 ± 1.23 (0.52 - 4.00)</td>
<td>2.9 ± 1.8 (0 - 6.0)</td>
<td>20</td>
<td>33</td>
<td>2</td>
</tr>
<tr>
<td>PE</td>
<td>5</td>
<td>1.92 ± 0.70 (1.20 - 2.80)</td>
<td>3.6 ± 0.8 (3.0 - 4.5)</td>
<td>0</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>SYNCOPE</td>
<td>1</td>
<td>0.87 (0.87 - 0.87)</td>
<td>4.5 (4.5 - 4.5)</td>
<td>3</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 5.4 Performance of D-Dimer in relation to confirmatory tests and diagnoses

<table>
<thead>
<tr>
<th>RESULTS</th>
<th>AMI</th>
<th>ANXIETY</th>
<th>ARRHYTHMIA</th>
<th>CVA</th>
<th>CHEST INFECTION</th>
<th>CHEST PAIN</th>
<th>GORD</th>
<th>HEADACHE</th>
<th>HYPERTENSION</th>
<th>OTHER</th>
<th>PE</th>
<th>SYMPTOME</th>
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</thead>
<tbody>
<tr>
<td>N</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>12</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>CT CHEST</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CT CHEST</td>
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<td>0</td>
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<td>0</td>
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<td>ECG</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>ECG</td>
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<td>0</td>
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<td>0</td>
<td>0</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
</tr>
<tr>
<td>ECHO</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
<td>0</td>
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</tr>
<tr>
<td>CXR</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>CXR</td>
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<td>0</td>
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<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
</tr>
</tbody>
</table>

The negative predictive value of the D-Dimer test has been found to be high in our study when used to predict a PE, whereas the positive predictive value was very low regarding the finding of a PE. The same was evident when looking at the D-Dimer versus the Wells Score, and when comparing the D-Dimer versus the CT Chest findings, whereby, in all three tables the D-Dimer was 100% but the positive predictive value was less than 50% (see Table 5.5, 5.6 and 5.7).

The sensitivity in all the above tables of the D-Dimer versus PE, D-Dimer versus Wells Score and D-Dimer versus CT-Chest, in predicting a PE, was very low compared to the specificity which was by far higher (see Table 5.5, 5.6 and 5.7). Our study had a very low sample number hence the validity of these results would need confirmation with a much larger sample size.
A number of patient categories exhibited false positive results, with the highest number found in the category of Other, followed by the categories of Chest Pain and Chest Infection. Other categories of Anxiety, AMI, Arrhythmia, Hypertension, Headache and Syncope, also showed false positive results.

There were no false negatives for D-Dimer, D-Dimer versus Wells and D-Dimer versus CT Scan. All five patients who had a documented PE had raised D-Dimers with a positive CT Chest and a moderate Wells Score. There were no negative D-Dimers with a CT Scan finding of a PE, nor were there low Wells Scores with a positive finding of PE. There were also no positive CT Scans that had a negative D-Dimer or a low Wells Score (see Table 5.5, 5.6 and 5.7).

<table>
<thead>
<tr>
<th>Table 5.5 D-DIMER vs PE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PE</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>D-Dimer</td>
</tr>
<tr>
<td>Positive</td>
</tr>
<tr>
<td>Negative</td>
</tr>
<tr>
<td>Sensitivity</td>
</tr>
<tr>
<td>Specificity</td>
</tr>
<tr>
<td>Predictive value of positive D-Dimer</td>
</tr>
<tr>
<td>Predictive value of negative D-Dimer</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 5.6 D-DIMER vs WELLS SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WEllS SCORE</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>D-Dimer</td>
</tr>
<tr>
<td>Positive</td>
</tr>
<tr>
<td>Negative</td>
</tr>
<tr>
<td>Sensitivity</td>
</tr>
<tr>
<td>Specificity</td>
</tr>
<tr>
<td>Predictive value of positive D-Dimer</td>
</tr>
<tr>
<td>Predictive value of negative D-Dimer</td>
</tr>
</tbody>
</table>
### Table 5.7 D-DIMER vs CT CHEST

<table>
<thead>
<tr>
<th></th>
<th>CT CHEST</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
<td>Total</td>
</tr>
<tr>
<td>D-Dimer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>6</td>
<td>11</td>
<td>17</td>
</tr>
<tr>
<td>Negative</td>
<td>0</td>
<td>172</td>
<td>172</td>
</tr>
<tr>
<td>Sensitivity</td>
<td></td>
<td>3.17%</td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td></td>
<td>91%</td>
<td></td>
</tr>
<tr>
<td>Predictive value of positive D-Dimer</td>
<td></td>
<td>35.29%</td>
<td></td>
</tr>
<tr>
<td>Predictive value of negative D-Dimer</td>
<td></td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

#### 6.0 DISCUSSION

The D-Dimer is known to be a non-specific parameter, which can be positive for a wide differential of diagnoses.\(^{61,66,96}\) A highly sensitive D-Dimer assay will be well above the normal range in most patients with a PE.\(^{52,98}\) In our study we only looked at whether the D-Dimer was negative or positive, but not at the specific level of the positive D-Dimer.

The specific D-Dimer assay performed at our hospital by AMPATH laboratories was the *Roche Cardiac D-Dimer Cardiac Reader*, which is a quantitative immunological assay for the detection of D-Dimer in freshly collected heparinised venous blood.\(^{74}\) (Blood sample collection tubes which contain substances such as Ethylene-diamine-tetra-acetic Acid (EDTA), citrate, sodium fluoride, should not be used).\(^{74}\)

The former test principles include the use of two monoclonal antibodies to act against the fibrin breakdown products which contain the D-Dimer product. The one antibody is gold labelled. The antibodies adhere to the D-Dimer product, forming a compound
which will remain and be detected in the blood plasma, after red blood cells from the sample are removed. A positive test is displayed as a red line. The more intense the line, the greater the accumulation of the gold labelled antibodies, the more positive the D-Dimer test will be. This is picked up by the cardiac reader instrument and is interpreted as a quantitative result.

Our research did not address time periods in which the D-Dimer was performed. This was looked at in two other different studies. The first being a study by Goldin and colleagues, who looked at the time period from the time symptoms presented, until a D-Dimer test was performed. The D-Dimer concentrations appeared to increase immediately after a thrombotic event had occurred, but then the value would start to decrease. It was concluded that the timing of the D-Dimer test has diagnostic bearings, and a health professional who suspected a DVT or PE in their patient, should bear in mind the time period from the onset of the patient’s symptoms, especially if a patient presents a few days or even a week later. The authors therefore suggested that the healthcare professional does not exclude a PE/DVT if the D-Dimer is negative, if found several days post onset of symptoms. They concluded that the time period had significant impact on the validity and relevance of the quantitative D-Dimer, which appears to be one week from the onset of the specific symptoms. A negative D-Dimer after one week from onset of the symptoms, cannot exclude a thrombotic episode in such a case.

Our research showed positive D-Dimers to be higher in males with a mean age group of 57 years (range 38 – 84 years), and was completed over three months. A
retrospective study by Fumeaux and Cornuz, similar to ours except over a longer period (six months), at a regional hospital in Switzerland, dealt with patients who were found to have a clinical high probability of thrombotic disease but a negative D-Dimer result. The authors emphasised that such a patient should undergo further investigations before the diagnosis of PE/DVT is excluded and looked at the negative predictive value of D-Dimer which, was very different to our study objective. It also showed no significant differences in age or gender in the negative D-Dimer group.

There were 22% of patients that had a positive diagnosis of thrombotic disease. These latter patients were mainly young women with a moderate to high pre-test probability score of PE.

Our results emphasise that a D-Dimer is non-specific, however, it is positive mostly in patients with PE, even in our small sample size. The remaining positive D-Dimers showed a significant association to chest infection that should be explored further. What has been documented concerning the latter, is that after 24 to 72 hours, loss of pulmonary surfactant as a result of a significant PE, may cause atelectasis and alveolar infiltrates, which are impossible to differentiate from pneumonia, where similar can be found by means of clinical examination and CXR. In such a case, the raised D-Dimer is thought to be a result of catabolic breakdown processes involving fibrin degradation within the alveoli which directly influence the D-Dimer levels.

Our study, found more males with positive D-Dimers for PE/DVT and a mean age of 57 years (range 38 – 84 years), as compared to the average age of patients documented to be suffering from CAP (62 ± 12 years), with females dominating the group, in an article published.
Our results reflected a wide range of conditions (the group of Other) for which the D-Dimer was positive, which is supported in the literature, where pathologies such as malignancies, severe inflammatory disorders and sepsis (for example DIC), trauma, postoperative patients, stroke (acute phase), anaemia (sickle-cell), CCF, juvenile idiopathic arthritis, rheumatoid arthritis and ulcerative colitis are also clinical conditions that result in positive D-Dimer levels.\textsuperscript{73,79,91} We also found that the wide differential for a positive D-Dimer emphasises how non-specific D-Dimers are, thus having a low positive but high negative predictive value and therefore cannot be used in isolation to confirm a PE (see Table 5.5, 5.6 and 5.7).\textsuperscript{42,52}

As noted above, the D-Dimer may be raised in many other conditions including CVA,\textsuperscript{15} however, in our study we had negative D-Dimer results found for the CVA and GORD patients. There has been no documentation in literature read thus far about the association between GORD and the D-Dimer.\textsuperscript{76}

As previously noted, the average age of patients in our study was 57 years (range 38 – 84 years), and we used the normal standard range of D-Dimer (0.1 – 0.5), in our single-centre study. Research shows two different retrospective, multicentre studies were conducted, looking at D-Dimer ranges. The first was by Douma and colleagues in older patients, looked at the changing D-Dimer range in this population group (50+ and especially in 70+ years), in other words an age adjustment, which together with the clinical probability increases the safety margin of exclusion of PE in this sector of the population.\textsuperscript{55} Douma and colleagues concluded that the D-Dimer is not as useful for diagnosing PE, due to its reduced specificity in these older patients.\textsuperscript{55} The authors
hence suggested a new range for D-Dimer values in the older patient, which would be adjusted to age, especially when used together with the clinical pre-test probability score. They suggested that the latter could be a useful tool for excluding a PE in an older patient with a greater safety margin. The second retrospective PROLONG study was done in 2008, by Legnani and colleagues. Here a group of patients was analysed by means of four different quantitative D-Dimer assays, in order to try and predict the risk of recurrence of thrombotic disease. The range of the D-Dimer values was looked at, as an additional tool to be used to identify patients with high as opposed to a lower probability of recurrence. The authors suggest, based on the data they found, that a slightly raised cut-off level of D-Dimer could be more useful in predicting the risk of recurrence of thrombotic illness. The other conclusion made by these authors was that an abnormal D-Dimer value, is a stronger positive predictor of PE/DVT recurrence compared to a normal D-Dimer value being a negative predictor. This study supports higher cut-off D-Dimer values in order to safely predict the risk of recurrence of PE/DVT in the elderly patient group (70+ years).

More positive D-Dimers irrespective of recurrences were found in our study, in males with a mean age of 57 years (range 38 – 84 years), than in females. In a PROLONG study, which was an extended follow-up performed by Cosmi and colleagues in 2010, the question was raised whether sex and age together with a normal D-Dimer are risk factors for the recurrence of thrombotic disease. The conclusion (once patients that were on anticoagulant medications were excluded), was that recurrent thrombotic disease was higher in males and in patients older than 65 years. Patients with a normal D-Dimer who were younger than 65 years had recurrences more in males than in
females and both genders older than 65 years had more recurrences than females younger than 65 years.\textsuperscript{7}

In our study, regarding the Wells criteria, the patients with PE had a medium overall score (2 – 6), which supports and confirms the usefulness for this set of criteria in the risk prediction of those patients with possible PE. In other words, a medium Wells Score has a very high probability of a PE outcome in the final diagnosis (see Table 5.2). \textit{Grüning} and colleagues concluded similarly, that a D-Dimer assay can more accurately be interpreted when used in combination with a clinical pre-test probability score.\textsuperscript{15}

We found that the patients with a confirmed PE had an intermediate Wells probability score, and these positive PEs were found in males with a mean age of 57 years (range 38 – 84 years). This was supported by \textit{Fedullo} and \textit{Tapson}, who noted that about 25\% to 65\% of patients with suspected PE had an intermediate Wells probability score, of which 25\% to 45\% of these ultimately had a confirmed PE.\textsuperscript{5} A VQ Scan confirmed this in 88\% to 93\% in this group of patients.\textsuperscript{5}

In our study, our patients with a confirmed PE, had an intermediate probability Wells Score as mentioned previously. In comparison, a study done in 2007 by \textit{Froehling} and colleagues, to determine the sensitivity and specificity of a quantitative D-Dimer test, to confirm an acute PE, 15\% of the CT Scans interpreted were positive for acute PE and D-Dimer levels were moderately raised for those with PE.\textsuperscript{100} The authors of the article concluded that a negative quantitative D-Dimer assay with a low pre-test probability score is enough for the exclusion of an acute PE.\textsuperscript{100} Our study is supported
by a study performed by Taira and colleagues, where three out of four patients were documented to have an intermediate clinical Wells probability score and were positive for PE on CT angiography.\textsuperscript{75} The conclusion of the latter study was that patients with low risk probability score and D-Dimer levels less than 500ng/ml are at low risk for PE/DVT, and may not need further assessment.\textsuperscript{75}

Our study was a retrospective study, whilst a prospective study performed by Gopinath and Gildes, showed that there was definite correlation between the clinical findings of an experienced medical doctor which included the patient’s symptoms, signs, laboratory blood results and radiological investigations, and a positive result of a PE, which highlighted the usefulness of the Wells probability scores (“low” “intermediate” and “high”).\textsuperscript{51,52} This article also looked at the usefulness of a spiral CT Scan as an investigation that can be used as a high-negative predictive agent. No conclusion was reached aside from that the scoring prediction rules (such as the Wells) together with laboratory results and radiology should be used as a combination approach with the greatest reliability in terms of diagnosing PE.\textsuperscript{51,52}

In our study, specificity of the D-Dimer test was found to be high but sensitivity low (see Table 5.5), yet Brown and his colleagues, found that the specificity of the D-Dimer assays, is generally low and hence cannot be used as the sole diagnostic test for exclusion of PE/DVT.\textsuperscript{79} They also emphasised that patients should have a confirmatory imaging test like a CT Chest if they present with a high pre-test probability score and/or the D-Dimer test is positive, due to the very high morbidity and mortality of missed diagnoses of PE/DVT.\textsuperscript{79} Agterof and colleagues looked at a model that would help predict possible complications in the first ten days following
the diagnosis of an acute PE.\textsuperscript{101} This model was thought to be useful in predicting which patients were likely to develop morbidity/mortality complications. This would assist in the planning of management of such a patient early on, in other words, which should be treated in hospital and which one as an outpatient.\textsuperscript{101}

Not all patients in our study with the final diagnosis of PE had all or even most of the Wells Criteria for PE (Table 5.2). Some literature notes that the Wells screening score is better used and more accurate in outcome in younger patients that do not have other co-morbid conditions or a history of previous thrombotic or thrombo-embolic disease.\textsuperscript{23} There is another score, called the revised Geneva Score, which has been compared in its accuracy to the Wells Score.\textsuperscript{94}

Our study as previously mentioned, was a retrospective study of 189 EU patients, and we only used the Wells Score for pre-test probability risk assessment. A study by Penaloza and colleagues in Belgium in 2011 also in an EU, compared the Wells Score and the Revised Geneva Score in terms of their accuracy in assessing their pre-test probability in predicting PE.\textsuperscript{102} Two prospective studies were used which had data from 339 patients, suspected to have PE.\textsuperscript{102} A prospective assessment using the Wells Score, was used for the pre-test probability of a PE in these patients, with the Geneva Score calculated retrospectively. They concluded that the Wells Score appeared to be more accurate in patients suspected to be suffering from a PE.\textsuperscript{102}

Our study used the Wells Score only, as part of our pre-test risk stratification. We found that the Wells Score had a low sensitivity and but high specificity in diagnosing PE (see Table 5.6). A study by Wong and colleagues, performed in Australia in 2011,
compared the accuracy of the Wells Score and Revised Geneva Score, in diagnosing PE. The authors felt that the Wells Score is commonly a subjective score, while the Revised Geneva Score, a more recent score was more objective. This study used a smaller population group (98), compared to ours (189), and was also performed in an EU. Similarly to our study, they found the Wells Score to have a lower sensitivity, however, a higher specificity than the Revised Geneva Score, although the accuracy of both appeared to be almost the same. The authors concluded that a larger prospective study is needed to confirm that a Wells Score with higher specificity could safely select the patients requiring CT Scans of the chest.

We assessed a fairly small population group (189), using the Wells probability score. Patients with confirmed PE were found to have a moderate Wells Score. Those with a low Wells Score did not have a positive diagnosis of PE. A study by Bertolotti and his colleagues in 2011, looked at the prognostic value of the Revised Geneva Score in a population group where PE has been excluded. This was a retrospective study of data gathered prospectively between six teaching medical centres involving Switzerland, Belgium and France. This study involved a larger population group (1334) compared to ours. The authors concluded that the initial probability assessment score, using the Revised Geneva Score, can correlate with the patient’s probable outcome. Especially patients with a low probability score appeared to have a better prognosis.

Our study was a retrospective study of only 189 patients, and we used the Wells Score to predict clinical probability of PE in our population group. A study by Hogg and colleagues performed in the UK in 2011, compared the BTS Score to the Wells Score
in its accuracy in diagnosing PE.\textsuperscript{105} This was a prospective study of 779 patients. The Wells Score appeared to be the more accurate score for diagnosing PE.\textsuperscript{105}

Our study, did not look at any specific vitals, unlike a study performed by \textit{Singanayagam} and colleagues, which had a different objective to ours, as it looked at whether adding biomarkers, specifically a Troponin I, to the PE Severity Index (PESI), which is a thirty day mortality predictive scoring system, would improve the accuracy of the PESI.\textsuperscript{106} This was a retrospective study, similar to ours, however it specifically looked at normotensive patients who were diagnosed with acute PE.\textsuperscript{106} The outcome showed that this combination definitely improved the predictive value of the mortality scoring system, which could then be helpful when planning the initial management of a patient with acute PE who has a normal BP.\textsuperscript{106}

Our study, compared to \textit{Hariharan} and colleagues study, was also a retrospective study, however the authors looked at the PESI. They performed a retrospective study of EU patients with PE presenting between May 2006 and April 2008, in order to see if the PESI could predict which patients would be free of clinical complications during hospitalisation, these complications included different forms of morbidity or mortality.\textsuperscript{107} The study included 245 patients diagnosed with PE, of which 47\% were male with an average age of 57 $\pm$ 17 years,\textsuperscript{107} compared to our population group of 189 (only 5 diagnosed with PE), with an average age of 57 years (range 38 -84 years), and in our PE category of patients, the dominant gender being female (60\%). \textit{Hariharan} and colleagues concluded that the PESI was not a comprehensively safe predictive index scoring system in terms of prognostic outcome, hence improvements are necessary in this scoring system.\textsuperscript{107}
In a study very different to ours, with a very different objective, which was a prospective multicentre study, a very large sample size of patients (7940) was used.\textsuperscript{108} Courtney and colleagues, used the clinical examination and history in order to predict whether a PE is present in EU symptomatic patients.\textsuperscript{108} Thirteen variables were assessed in terms of their predictive value regarding the presence of a PE. The authors validated that variables such as family history of thrombotic disease, thrombosis in the absence of malignancy, pleuritic chest pain, recent surgery, use of hormone replacement therapy (especially oestrogen), which are part of accepted pre-test risk stratification scoring systems, increase the likelihood of the presence of a thrombotic disorder such as PE or DVT.\textsuperscript{108} This study was unique as it has been the only study to date that compared and quantified the predictive value of the aforementioned variables as regarding the presence or absence of a PE in symptomatic EU patients.\textsuperscript{108}

As regarding the confirmatory tests used in our study, we observed that in the confirmed PE category of patients, all five CT Chest and CXRs were positive, which confirmed these studies to be important in the final diagnosis of PE. (Table 5.4). This has been supported by studies that documented that Spiral CTs can pick up a PE with a sensitivity of more than 90\% (53\% and 100\%), which may be as small as 2mm, with a specificity of around 95\% (80\% to 100\%).\textsuperscript{41,42,51} Other literature has noted that CT scanning can pick up alternate diagnosis in up to 57\% of patients.\textsuperscript{4,10,47} The one limitation of significance associated with Spiral CT scanning, is the possibility of missing small sub-segmental PEs (false-negative) or falsely detected PEs (false-positive).\textsuperscript{18,52} The Single Detector Helical scanner may miss a sub-segmental PE
hence its sensitivity is found to be variable across a variety of studies. The proximal thrombi are usually detected easily by a CT Scan.

In our study, we used the Wells Score clinical probability, together with the D-Dimer and confirmatory tests to diagnose or exclude PE. Of the five patients who were diagnosed with a PE, a CT Spiral Scan of the chest was one of the confirmatory tests. Only the Spiral CT was used in our study unless a DVT was strongly suspected, in which case, a Doppler Ultrasound Scan of the limb involved was also ordered. All patients had ECGs and CXRs preceding the scan as part of their set of confirmatory tests.

We found that the negative predictive value of a negative D-Dimer and a low pre-test probability Wells Score, has a high negative predictive value for PE (see Table 5.6 above). Similarly in a review published by Segal and colleagues, it was strongly recommended to use the clinical prediction scoring systems to assess pre-test probability of the recurrence of DVT/PE, before using extra confirmatory tests. It was also suggested that if the D-Dimer assay is normal and a low clinical pre-test probability score is found, this resulting negative predictive value may preclude the need to use other confirmatory tests especially the more expensive radiological tests such as the spiral CT.

The CT Chest can now be available as either a Single Detector Helical Scan or Multi Detector Scan, however, the latter scans are very new in terms of their sensitivity and specificity in detecting unusually located PEs. In our study, our positive PE findings were documented and confirmed by means of clinical judgement and findings as well
as the Wells probability score, D-Dimer testing and finally confirmatory tests, mainly the spiral Chest CT Scan.

Regarding the ECG, most common and non-specific ECG findings occurring in the presence of a PE, are an increased HR and non-specific ST-T abnormalities,\textsuperscript{3,6} which was supported in our study. We found tachycardia in most of our positive PE patients. We also agreed that the CXR is far from diagnostic and showed very little. It helped however, to exclude other clear diagnoses such as pneumonia and haemo/pneumothorax.\textsuperscript{3}

Our study was mostly different to Sakamoto and colleagues study, excepting that both were retrospective studies performed in an EU, as well as all our patients with positive D-Dimers also had a spiral CT Chest for confirmation of diagnosis. They looked at the usefulness of the D-Dimer test in differentiating Acute Aortic Dissection (AAD) and acute PE from AMI.\textsuperscript{109} These are all conditions that present with acute chest pain, affect the coagulation pathway and often present with similar signs and symptoms. This study showed that AAD and PE patients had D-Dimer values that were considerably raised compared to those of patients suffering from an AMI. The D-Dimer cut off value of 5.0g/ml was used in distinguishing the latter conditions with a specificity of 90% and sensitivity of 68%.\textsuperscript{109} The authors concluded that the D-Dimer assay can be used as a screening tool to differentiate AAD and PE from AMI. A CT Chest would be the radiological investigation of choice, with any D-Dimer level \(>5.0\text{g/ml}\) prioritised over the coronary angiography in the latter case.\textsuperscript{109}
Our study showed a high specificity as well as a high negative predictive value of the D-Dimer, in diagnosing PE (see Table 5.5). Guttte and colleagues and Türedi and colleagues, look at a marker (BNP) and its prognostic value in predicting which PE’s will complicate post admission to hospital, in two separate studies. These complications may include among others, right ventricular dysfunction in an acute phase of a PE. There is also mention of the Ischemia-Modified Albumin (IMA), which is suggested in literature to be 93% sensitive and 75% specific for PE. This is thought to be even more accurate in terms of prognosis when combined with the Wells and Geneva screening scores. However, other sources of literature believe the D-Dimer is a much more reliable marker for the prognosis of a PE as compared to the new marker – the IMA.

Our study did not find the ECHO to be a useful diagnostic tool but, due to our low sample number, this would have to be verified. In the literature, ECHO results have been found to help guide treatment as well as detect large PEs. Clots moving through the heart to the lungs can be confirmed via ECHO. There is also intravascular ultrasound that can be used by the bedside to see large clots. The ECHO clinical findings may include a hypokinetic or enlarged right ventricle wall. The ECHO can also pick up pulmonary hypotension signs. A second article does not believe that the cardiology ECHO can be used as a diagnostic tool for PE, instead it noted the trans-oesophageal ECHO to have a sensitivity of 60% to 80% and a specificity of 95% to 100% in detection of a PE. In our study, an insignificant number of ECHOs were done as part of the diagnosis of the positive PEs, however, a recommendation has been made to use an ECHO in combination with the spiral CT or VQ Scan, which in combination may help in diagnosing massive PEs.
We looked at all patients that came through the EU within a three month period who had a D-Dimer test done, however, an EU based retrospective study performed by *Taira* and colleagues, specifically assessed those with venous thrombo-embolism. The study used a computerised data base in order to determine the rate of thrombotic disease in the patients with suspected PE/DVT, and looked at the D-Dimer level as a tool for risk stratification. The patient mean age was 48 ± 19 years with 63% being females. Low risk patients with a moderate D-Dimer value (200 to 500ng/ml) were investigated.

We conducted a similar study to *Kline* and colleagues, however, they included a very large number of patients 2303, compared to our smaller sample of 189 patients. The former study used patients of all ages unlike ours that only involved adults (>18 years). Both studies enrolled patients with specific symptoms including SOB, chest pain, syncope and vitals such as tachycardia.

Our study found 21.16% of patients had a positive D-Dimer for a number of conditions, of which the highest positive D-Dimers were recorded for PE and concluded that the D-Dimer was done in only a fifth of patients seen in our private EU and positive in less than 50% of cases, the D-Dimer test yield was highest in patients with PE as their final diagnosis. The D-Dimer test we used (Roche Cardiac Quantitative Immunological Assay), had high negative predictive value in more than half of the non-PE diagnoses. We used the Wells Score for pre-test probability values and found that the patients who had a positive diagnosis of PE had mostly a moderate Wells Score. In comparison, the previously noted study performed by *Kline* and
colleagues which involved EU patients, looked at a different D-Dimer assay to ours – the “Point of Care” D-Dimer testing, as a rapid tool for exclusion of PE in the EU situation. The sensitivity of this assay was found to be 80.6% and the specificity 72.5%. They found a 4.7% of patients positive for the diagnosis of PE. They also found that patients with low risk predictive score prior to the D-Dimer testing and subsequently negative D-Dimer results had an almost 0% outcome of diagnosis of PE. They concluded that the simple D-Dimer assay (the point-of-care assay) had moderate sensitivity as well as relatively high specificity in the diagnosis of PE in a low risk group of emergency department patients. They used the Canadian Score and the Charlotte Criteria.

There are similarities and differences when comparing our study to that performed by Stein and colleagues in 2011. Theirs differed to ours as it was a study on hospitalised patients with different objectives. The authors looked at the prognostic value of the D-Dimer assay when taken from a stable patient diagnosed with a PE. This showed mixed results where there was no direct correlation between very high D-Dimer levels and mortality from PE in in-hospital stable patients. The similarities were that the population group was also small (292), and it was a retrospective study using documentation from patient charts.

Our study used the Wells Criteria together with the D-Dimer value in order to risk stratify patients suspected to have PE. No computerised algorithm was used as part of our decision making and final results, as far as confirmation of the diagnosis of PE in this group of patients. Those patients that were found to have a positive diagnosis of PE, had mostly a moderate Wells Score, positive D-Dimer, as well as positive findings.
on CT Chest. In comparison, Drescher and colleagues, tried to include modified Wells Criteria into a computerised programme in order to assist the emergency physician with their evaluation of a suspected PE.\textsuperscript{112} This kind of algorithm was looked at to assist in reducing the number of requested CT Chest investigations ordered by emergency physicians in EUs. Unlike our study, it was a prospective interventional study that used a retrospective pre-interventional group of patients for comparative purposes.\textsuperscript{112} The authors found that this computerised algorithm definitely was associated with an improved selection of patients for CT Chest with overall more positive results. However, it was time consuming, hence not used consistently by the emergency physicians.\textsuperscript{112}

A study in 2011, performed by Lee and colleagues, looked at the cost of diagnostic investigations in patients with high, moderate or low clinical pre-test probability of PE.\textsuperscript{113} The authors suggested that a diagnostic strategy of performing a D-Dimer test followed by a CT Chest was most cost effective.\textsuperscript{113} This, as opposed to the traditional VQ Scan that was usually followed by pulmonary angiography and CT.\textsuperscript{113} This was very different to our study objective, although we did use the same diagnostic strategy of a CT Chest rather than a VQ Scan, following a positive D-Dimer result in a patient.

We looked at the usefulness of the D-Dimer assay in the diagnosis of PE, using patient data that was collected over three months, irrespective of the day of the week. A study by Gallerani and his colleagues, looked at the difference in mortality between patients hospitalised for an acute PE during the weekend as opposed to during the week.\textsuperscript{114} The aim was to focus on the possible part-time availability of medical expertise, specific management, as well as specific radiological investigations in some hospitals in
The conclusion of this study was that weekend admissions for PE do have an association with worse prognostic outcome and higher mortality compared to those admitted during the week. As noted, the two studies have completely different objectives.

The group of Other which comprised a wide range of different diagnoses, as recorded in the Results section of this report was another major limitation of our study. Each one of these different diagnoses was limited to very few patients and therefore, was grouped under Other. Due to this fact, the high percentage of positive D-Dimers (24%), recorded for this category, was not a true representation, as the individual groups of diagnoses were extremely small within this big group.

A large diversity of patients presents to our private EU which is an EU with differing clinical severity levels of disease, and different financial predicaments, some patients being on a medical aid or insurance and others private paying patients. They may also be clinically stable or may require medical intervention to be stabilised, may present with minor SOB which has lasted for days or severely incapacitated by acute symptomatology. The medical doctors treating these patients are updated in all three emergency courses (Advanced Trauma Life Support (ATLS), Advanced Cardiac Life Support (ACLS), Paediatric Advanced Life Support (PALS)), and many are specialising and are also working at the provincial hospitals.

The patients who have no financial resources, will not be able to afford the D-Dimer and Spiral CT of the chest. These will then have to be referred to the provincial hospitals where there will be time delays in obtaining the latter tests which may
amount to several days, rather than the one to two hours spent waiting for these tests to be done in our private EU. This can compromise the patient’s health further and may have a fatal outcome as many may look well despite an underlying major PE.

We used a small patient population (189), our average age was 57 years (38.0 – 84.0), 49% of which were female patients. Our patient population was from a single EU and we used the Wells predictive variables in conjunction with a D-Dimer and further confirmatory tests, that were done on some of the patients. Courtney and colleagues looked at the predictive value of thirteen “new” parameters, as compared to the previously used prediction criteria. They used a prospective multi-centre study from many emergency departments. A D-Dimer CT angiography, or VQ Scan was performed. Thirteen new parameters added to twelve pre-existing variables. A very large sample size (7940) was used, with an average age of 49± 17 years, 67% of which were female. There were several parameters of the “new” listed ones that showed a strong positive predictive value of PE/DVT and they included pleuritic chest pain and family history of thrombotic disease, as well as an individual’s history of thrombophilia. This study also reaffirmed previous known positive predictive variables such as one month post-operative period, previous history of thrombosis, history of cancer among other.115

In our retrospective study performed in a private EU at a secondary facility, we used a different D-Dimer test, the Quantitative Roche Assay. Our sample size was small (189) and it was performed over three months. Our sample included all patients who had a D-Dimer test done, some had confirmatory tests done depending on the doctor’s working diagnosis at the time of patient assessment. A study by Lucassen and
colleagues was performed in a primary care facility in the Netherlands, where the Wells Criteria were used in combination with the D-Dimer test (Point-of-Care), whereby a PE was excluded with a moderate degree of certainty. This prospective study included a very large sample size of 3306 patients over almost a two year period. The patients who had a normal D-Dimer were not considered to have a PE but, all others had a spiral CT and a three months follow up for recurrence of thrombosis was done. It was concluded that the use of this D-Dimer test, with the Wells predictive criteria, excluded a PE safely with only a reasonable degree of effectiveness.¹¹⁶

7.0 CONCLUSION

Our results have shown that a PE is easily confused with multiple other conditions. We have also observed from our results, that the Wells Criteria seem to be a sound screening test for the diagnosis of a PE, and that the D-Dimer test is useful for its positive and negative predictive values, and is extremely reliable as a negative predictive marker.

Our study confirmed that the clinical presentations of patients with PE is non-specific, however the best known screening test for PE – the D-Dimer, which may be positive in a wide variety of diagnoses, is useful in establishing the diagnosis of PE, when it is found to be positive.

The documented Wells Score Criteria together with a CT Chest, may help further in excluding the wide differential available for a positive D-Dimer. Although we only
used the Wells Score, there are other scores such as the Revised Geneva Score that have proved to be effective in other studies.\textsuperscript{42} Our study also found the negative predictive value of the D-Dimer to be high, but the positive predictive value to be low. The specificity of the D-Dimer was high yet we found the sensitivity to be low as regards the diagnosis of PE in our group of patients. Therefore this study confirmed that the predictive value of a D-Dimer together with the Wells Criteria is improved with the use of a Spiral CT of the Chest.

This study presented with many challenges including a small sample size, missing data, the need to rely on a laboratory technician to perform the D-Dimer assay and periods of equipment malfunctions. There were often periods of equipment failure whereby the D-Dimer test and/or CT Chest would take longer to obtain during the allocated study period in which the data was collected, and a large group of Other that included a diversity of diagnoses. The D-Dimer was done in only a fifth of patients seen at the MMC private hospital EU and was positive in less than half of these cases. This test appears to be grossly underutilised in the private EU even though it has the highest yield in the diagnosis of PE and a high negative predictive value in non-PE diagnoses.

Our study has highlighted the need in the future, to do more studies with larger sample groups, as there was an inadequate sample group to base firm conclusions upon.

This study has never been undertaken in South Africa before in a private emergency setting, although it proved to be inadequate, due to the very small sample size of patients with PE. There is a need to do a larger study, possibly over a longer time
period, to ascertain the true usefulness of the D-Dimer test in our EU population, in order to confirm whether this is an adequate tool for PE screening.
APPENDIX A: D-Dimer study data collection sheet

1. DEMOGRAPHIC INFORMATION

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<thead>
<tr>
<th>DATE</th>
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<tbody>
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2. PRESENTING SYMPTOMS

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<tr>
<td>SHORTNESS OF BREATH</td>
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<tr>
<td>PALPITATIONS</td>
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<tr>
<td>NAUSEA/VOMITING</td>
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<tr>
<td>OTHER SYMPTOMS</td>
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</table>

3. WELLS CRITERIA FOR PULMONARY EMBOLISM

<table>
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<tr>
<td>CLINICAL SIGNS OF DVT</td>
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<td>ALTERNATIVE DIAGNOSIS LESS PROBABLE THAN PE</td>
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<tr>
<td>HEART RATE &gt; 100 BPM</td>
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<tr>
<td>IMMOBILIZATION OR SURGERY &lt; 4 WEEKS AGO</td>
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<tr>
<td>PREVIOUS DVT OR PE</td>
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<td>HAEMOPTYSIS</td>
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<tr>
<td>Moderate (score 2 – 6)</td>
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<tr>
<td>High (score &gt;6)</td>
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4. D-DIMER TEST RESULTS

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<td>V/Q SCAN</td>
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<td>ECHO</td>
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<tr>
<td>PULMONARY ANGIO</td>
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<td>OTHERS</td>
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5. CONFIRMATORY DIAGNOSTIC TESTS

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<td>V/Q SCAN</td>
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APPENDIX B: Wits Human Research Ethics Clearance Certificate

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

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Amanda J Schur

CLEARANCE CERTIFICATE M90659
PROJECT Utility of the D-Dimers Test in the diagnosis of Pulmonary Embolism in an Emergency Unit

INVESTIGATORS Dr Amanda J Schur.
DEPARTMENT Molecular Medicine & Haematology
DATE CONSIDERED 09.06.26
DECISION OF THE COMMITTEE* Approved unconditionally

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

DATE 09.07.25
CHAIRPERSON (Professor PE Cleaton-Jones)

*Guidelines for written ‘informed consent’ attached where applicable
cc: Supervisor: Prof J Mahlangu

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

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...
APPENDIX C: Letter of approval of change of title

Faculty of Health Sciences
Medical School, 7 York Road, Parktown, 2193
Fax: (011) 717-2119
Tel: (011) 717-2745

Reference: Ms Tania Van Leeve
E-mail: tania.vanleeve@wits.ac.za
27 July 2009
Person No: 8402598
PAG

Dr AJ Schur
P.O. Box 1274
HIGHLANDS NORTH
2037
South Africa

Dear Dr Schur

Master of Science in Medicine (Emergency Medicine): Approval of Title

We have pleasure in advising that your proposal entitled "An audit of the utility of the D-Dimer test in the diagnosis of pulmonary embolism (PE) in a private hospital emergency unit in Johannesburg" has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

[Signature]

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences
APPENDIX D: Letters of permission

-----Original Message-----
From: Zika, Daniel [mailto:DZika@webmd.net]
Sent: 08 September 2010 22:11
To: Mandy Behr
Subject: RE: PERMISSION TO USE COPY-WRITTEN MATERIAL

Dear Dr Schur,

Thank you for your query and interest in eMedicine. In response to your email below, eMedicine grants you permission to reprint image #1 from the eMedicine article Pulmonary Embolism. There is no fee associated with this permission.

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Please feel free to contact me at any time if you have further questions or requests.

Dan Zika
Associate Editor/Permission Coordinator
dzika@webmd.net

Phone & Fax: 646-674-6905

From: Mandy Behr [mailto:mandy@behr.co.za]
Sent: Sunday, September 05, 2010 10:47 AM
To: Editor2
Cc: Johnny Mahlangu
Subject: PERMISSION TO USE COPY-WRITTEN MATERIAL

Dear Sir/Madam
I am currently doing my Masters in Emergency Medicine at the University of Witwatersrand, South Africa. I would like to ask you for permission to use some of your copy-written material in my assignment. The material I am referring to is the illustration: “The pathophysiology of pulmonary embolism”. Sutherland SF. Pulmonary Embolism. emedicine updated May 8, 2009, page 2 of 21.

Awaiting your response.

Sincerely
Dr Mandy Schur

-----Original Message-----
From: Zika, Daniel [mailto:DZika@webmd.net]
Sent: 08 September 2010 23:09
To: Mandy Behr
Subject: RE: PERMISSION TO USE COPY-WRITTEN MATERIAL

Dr Schur,

As you have noted, the images are courtesy of Justin Wong, MD. I cannot grant permission for those images that we do not have copyright of and I have no contact information for Dr Wong. eMedicine can grant permission to use the 2 tables listed below. The same terms of the other images apply. If you have any questions, please let me know.

Dan Zika
Associate Editor/Permission Coordinator
dzika@webmd.net
Phone & Fax:646-674-6905

From: Mandy Behr [mailto:mandy@behr.co.za]
Sent: Sunday, September 05, 2010 11:04 AM
To: Editor2
Cc: Johnny Mahlangu
Subject: PERMISSION TO USE COPY-WRITTEN MATERIAL

Dear Sir/Madam

With regards to my last email, I would also like to request permission to use the following illustrations from emedicine, Pulmonary Embolism, “A chest radiograph with normal findings in a 64-year-old woman who presented with worsening breathlessness”. Kamangar N, McDonneli MS, Sharma S. Pulmonary Embolism. (Page 11 of 47) and “A posteroanterior chest radiograph showing a peripheral wedge-shaped infiltrate caused by pulmonary infarction secondary to pulmonary embolism. Hampton hump is a rare and nonspecific finding”. Courtesy of Justin Wong, MD. Kamangar N, McDonneli MS, Sharma S. Pulmonary Embolism.” (Page 11 of 47) Also Tables 1 and 2 on pages 8/9 of 47.

Thanks again.

Sincerely
Dr Mandy Schur
17th June 2009

TO WHOM IT MAY CONCERN

Ampath Laboratory Morningside, has granted Dr A J Schur of the Emergency Unit at Morningside Medi-Clinic permission to use the casualty patients’ D-dimer data in her study titled ‘An Audit of the Utility of the D-Dimer test in the Diagnosis of Pulmonary Embolism in a Private Hospital Emergency Unit in Johannesburg’.

Yours faithfully

MS MA GREENWOOD
OPERATIONS MANAGER
AMPATH LABORATORY
MORNINGSIDE

DR F KRAMER
PATHOLOGIST IN CHARGE
AMPATH LABORATORY
MORNINGSIDE
Dear Dr Schur,

We, Drs Bloch and Partners at the Morningside MediClinic Radiology department, hereby grant you permission to use a series of four Chest CT scan images demonstrating a massive PE in a 37 year old female presenting with acute onset of dyspnoea.

We also grant you permission to use the Chest CT scan images demonstrating a normal chest pathology in an 82 year old male.

Sincerely,

Dr Bloch and Partners.
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Accessed 03/06, 2011.

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Dimer testing in severe pelvic inflammatory disease: A new usable marker to assess the 


