The prognostic value of electrocardiography to predict inpatient mortality in patients with acute pulmonary embolism: a retrospective cohort analysis.

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List of Abbreviations

AF	Atrial fibrillation
AHA	American Heart Association
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
CT-PA	Computed tomography pulmonary angiogram
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ECHO	Echocardiogram
GP	General practitioner
HIC	High-income country
LMIC	Low- and middle-income country
LR	Likelihood ratio
NPV	Negative predictive value
OR	Odds ratio
PE	Pulmonary embolism
PERC	Pulmonary embolus rule-out criteria
POCUS	Point-of-care ultrasound
PPV	Positive predictive value
RAD	Right axis deviation
RBBB	Right bundle branch block
RVD	Right ventricular dysfunction
TWI	T-wave inversion
V/Q	Ventilation/perfusion
WRCR	Western Cape Rehabilitation Centre

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Abstract

Introduction

Pulmonary embolism represents the third leading cause of mortality globally after myocardial infarction with an overall mortality of 30%. ECG findings may play a valuable role in the prognostication of patients with PE, with various ECG abnormalities proving to be reasonable predictors of haemodynamic decompensation, cardiogenic shock, and even mortality. This study aims to assess the prognostic value of electrocardiography in predicting inpatient mortality in patients with acute pulmonary embolism, as diagnosed with computed tomography pulmonary angiogram.

Method

This was a retrospective cohort design study based at Tygerberg Hospital, Cape Town, South Africa. Eligible patients were identified from all CT-PA performed between 1 January 2017 and 31 December 2019. The ECGs were independently screened by two blinded emergency medicine physicians for predetermined signs that are associated with right heart strain and higher pulmonary artery pressures, and these findings were analysed to in-hospital mortality.

Results

Of the included 81 patients, 61 (75%) were female. Of the 41 (51%) patients with submassive PE and 8 (10%) with massive PE, 7 (17%) and 3 (38%) suffered inpatient mortality (p=0.023) respectively. Univariate ECG analysis revealed that complete right bundle branch block (OR, 8.6; 95% CI, 1.1 to 69.9; p=0.044) and right axis deviation (OR, 5.6; 95% CI, 1.4 to 22.4; p=0.015) were significant predictors of inpatient mortality.

Conclusion

Early identification of patients with pulmonary embolism at higher risk of clinical deterioration and in-patient mortality remains a challenge. Even though no clinical finding or prediction tool in isolation can reliably predict outcomes in patients with pulmonary embolism, this study demonstrated two ECG findings at presentation that were associated with a higher likelihood of inpatient mortality. This single-centre observational study with a small sample precludes concrete conclusions and a large follow-up multi-centre study is advised.

Keywords:

Pulmonary embolism

ECG/Electrocardiography

Mortality

Emergency Centre

LMIC

Introduction

Pulmonary embolism (PE) is the third leading cause of mortality globally after myocardial infarction and stroke.(1, 2) It is estimated to have accounted for 1 in 4 deaths worldwide in 2010 - an increase from 1 in 5 deaths in 1990.(3) The estimated burden of disability-adjusted life years from thromboembolism is 7.6 per 100 000 population in high-income countries (HICs), but estimated to be 2.4 times greater in low- and middle-income countries (LMICs).(3) In Tunisia for example, Bahloul et al. (2013) found that PE was present in 17.5% of patients presenting with an acute exacerbation of chronic obstructive pulmonary disease (COPD),(4) while Amar et al. (2015) found that 61.5% of patients with tuberculosis (TB) had concurrent PE.(5) The pro-thrombotic state produced by both HIV and TB, leads to the formation of venous thromboembolism, and contributes to the higher incidence of PE in LMICs.(6-8) The long-term effects of PE, characterised by the risk of recurrent PE or post-thrombotic syndrome with pulmonary hypertension, results in significant morbidity and burden on the healthcare system.(9, 10)

The American Heart Association (AHA) categorised PE into massive, submassive, and low risk based on the presence or absence of hypoperfusion/shock and right ventricular dysfunction (RVD).(11) This classification tailors medical and interventional therapies for patients with an acute PE.(11, 12) Clinical characteristics on initial presentation may, however, change during the hospital stay. It is not uncommon for patients to become progressively unstable with overt right ventricular failure, leading to rapid clinical deterioration and death.(13, 14) This is particularly true for patients with submassive PE, which contributes to 40% of all acute PE with a mortality rate ranging from 3% to 15%.(15) Current evidence-based guidelines to manage patients with massive PE are fairly well-defined, but identifying the cohort of patients with submassive PE that may clinically deteriorate after admission remains a challenge.(11) Clot burden on computed tomography (CT) scan poorly predicts adverse outcomes, but rather the physiological changes to the right ventricle as seen on CT scan or ultrasound.(11) In resource constrained settings, however, these are not readily available.(16) Routine thrombolysis for all patients with submassive PE increases the risk of bleeding and does not outweigh the risks, as demonstrated in the MOPPET and PEITHO trials.(13, 17)

Electrocardiogram (ECG) findings may play a valuable role in the prognostication of patients with PE, with various ECG abnormalities proving to be reasonable predictors of haemodynamic decompensation, cardiogenic shock, and even mortality.(2, 18-22) The ECG features seen in PE are often paroxysmal and transient,(23) and revert to normal within a week of anticoagulant therapy.(2) Choi & Park (2012), reported that patients with an acute PE complicated by RVD, was associated with precordial T-wave inversion (TWI) on ECG, and with improvement of the right ventricular function after treatment, there was normalisation of the T-wave.(20) It is also hypothesised that a Qr in V1 (pseudo infarct pattern) was the strongest predictor of RVD and it was highly associated with troponin leakage and myocardial damage, and in the presence of TWI in V2 or V3, predicted a more complicated hospital stay.(24) These findings were associated with a poor prognosis and an increased mortality rate.(20, 25) ECG scoring systems such as the Daniel score (19) and TwiST (26) were developed to assist in the prognostication of PE, but have yet to be validated in LMICs.

If clinical deterioration or mortality can be reliably predicted, patients who require more rigorous monitoring can be identified and the benefits of thrombolysis or thrombectomies may outweigh the risks, even in the submassive category. The aim of this study is to evaluate the prognostic value of electrocardiography in predicting inpatient mortality in patients with acute pulmonary embolism.

Methods

Study design

A retrospective cohort design was used and data was collected from existing databases and folder reviews.

Study setting

This study was conducted at Tygerberg Hospital, a tertiary level hospital in Cape Town, South Africa. It is the largest hospital in the Western Cape and the second largest in South Africa. It serves a population of over 3.4 million people and is also one of the two major referral facilities for surrounding district and regional hospitals. Patients with suspected PE are risk stratified according to their pre-test probabilities, such as Wells score.(27) Patients with a high pre-test probability receives a computed tomography pulmonary angiogram (CT-PA) or ventilation/perfusion (V/Q) scan depending on specific characteristics, and those with an intermediary pre-test probability -determined by a raised D-dimer- receives a CT-PA or V/Q scan. The Pulmonary Embolus Rule Out Criteria (PERC) is applied to those with a low pre-test probability,(28) and any positive criteria gets upscale to intermediary. The Wells score and the PERC rule, however, are not validated in a population with a high HIV and TB burden - both of which are notable risk factors for the development of thrombosis. Patients with a confirmed PE are classified into massive and submassive, depending on their clinical characteristics.(11) Patients with submassive PE receive oral anticoagulation therapy, while those with massive PE receive intravenous thrombolysis in the emergency centre, or get referred to the vascular surgery department for intravascular intervention or surgery.

Study Population and Sampling

All adult patients (≥12 years old) with a confirmed PE as diagnosed by a radiologist reported CT scan during the study period of 3 years (1st of January 2017 - 31st of December 2019) were eligible for inclusion. Patients with missing or incomplete data, as well as those with repeat CT-PA, were excluded.

Data Collection and Management

Data were collected in three phases. First, eligible cases were collated from the Picture Archiving and Communication System (PACS) database by exporting all CT-PA studies performed and reported on by a radiologist during the study period. CT outcome was then dichotomised as either positive or negative for pulmonary embolism. Phase 2 entailed the extraction of all clinical information, including all ECGs done at the time of diagnosis, and the demographic details of the patient from the Enterprise Content Manager (ECM) database. The two emergency medicine physicians involved in this study were blinded to the clinical history,

PE classification, and patient outcomes; independently analysed all ECGs in phase 3. ECGs were assessed for the presence or absence of pre-determined characteristics as guided by evidence.(8, 14, 20, 24, 29-31) The definitions and measurements of ECG characteristics were standardised by the researchers prior to the initiation of phase 3 to minimise information bias.(Supplementary Table 1) The predictive values of existing scoring systems will be validated on this cohort by calculating diagnostic accuracy for both the Daniel and TwiST tools.

Data Analysis

Categorical data were presented as frequencies and proportions (%) and continuous variables as median and inter- quantile ranges. Categorical data were assessed for non-random associations with the use of the Fisher's exact test or the Chi^2 test, depending on the characteristics of the variables. Continuous variables were assessed for significant differences with the Mann-Whitney U test. The prognostic value of electrocardiography to predict inpatient mortality was assessed univariately by calculating diagnostic odds ratios and p-values. Prognostic accuracy of existing clinical decision rules was assessed by calculating sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV), as well as positive and negative likelihood ratios (LR). Two-sided p-values were calculated and statistical significance was defined as $p<0.05$. Data were analysed with the help of IBM SPSS Statistics version 27.

Ethical Considerations

This study received ethical approval from the University of Cape Town Human Research Ethics Committee (HREC Ref: 722/2020).

Results

During the 36 month study period, 301 patients received a CT-PA for a suspected PE, of which 99 (33%) were positive. Eighty-one (82%) patients were included in the final sample. Figure 1 details the exclusions.

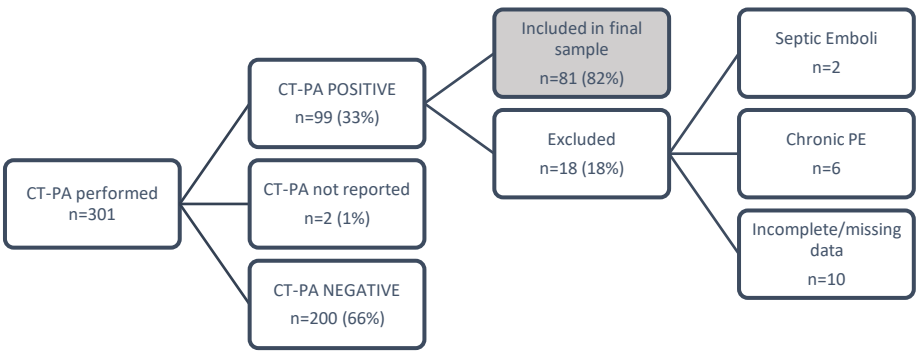

Figure 1: Flow of participants

Table 1 describes and compares the demographic details and relevant clinical findings between patients who suffered inpatient mortality and those who survived to hospital discharge. The median age of the sample was 43 years, with a female preponderance (n=61, 75%). Ten (12%) patients suffered inpatient mortality, of which nine (90%) were females. The most prevalent co-morbidities included hypertension (n=33, 41%), HIV/AIDS (n=24, 30%), and cardiac failure (n=10, 12%). Hypertension was significantly more prevalent in patients who survived to hospital discharge (n=32, 45% vs. n=1, 10%; p=0.035). Risk factors for the development of a PE were similarly distributed between the two groups, with the most prevalent being cigarette smoking (n=25, 31%), obesity (n=23, 28%) and recent immobilisation (n=12, 15%). Patients reported dyspnoea (n=74, 91%) to be the most common presenting complaint, followed by chest pain (n=55, 68%) and coughing (n=53, 65%), while tachycardia (n=61, 75%) and tachypnoea (n=57, 70%) were the most prevalent abnormal clinical signs. Regarding symptoms and clinical signs at presentation, there were no significant differences between those who suffered inpatient mortality and those who survived to hospital discharge.

There were no significant differences between the vital signs on presentation between the two groups: median systolic BP 116 vs 120 mmHg, p=0.636; median diastolic BP 72 vs. 77 mmHg, p=0.351; median HR 108 vs 110 bpm, p=0.874 and SpO_2 94% vs 95%, p=0.203. Only 37 patients received a Troponin T test on initial presentation, of which 12 (32%) were positive (≥50 ng/ml). One (8%) patient with a positive troponin and three (13%) patients with a negative troponin level demised during their admission. Only 38 patients received a serum D-dimer essay - 36 (95%) were raised, of which four (11%) patients demised during in-hospital stay. Of the 31 patients who had point-of-care ultrasound to detect right heart strain, 21 (68%) were positive.

Of the 41 (51%) patients with submassive PE and eight (10%) with massive PE, seven (17%) and three (38%) suffered inpatient mortality (p=0.023) respectively. Two out of the seven (9%) patients who received thrombolysis died and of the three patients who had embolectomies, all survived to hospital discharge. The cause of death was attributed to the PE in all non-survivors and no complications of thrombolysis were described.

Table 1: Patient demographics and clinical characteristics for each patient outcome (n=81)

		Total	In-hospital death 10 (12%)	Survived to hospital discharge 71 (88%)	P
Gender (n, column%)					
	Male	20 (25%)	1 (10%)	19 (27%)	.250
	Female	61 (75%)	9 (90%)	52 (73%)	
Age categories (n, column%)					
	12-17	2 (2%)	1 (10%)	1 (1%%)	
	18-25	7 (9%)	0 (0%)	7 (10%)	
	26-35	17 (21%)	1 (10%)	16 (23%)	
	36-45	20 (25%)	1 (10%)	19 (27%)	.252
	46-55	18 (22%)	3 (30%)	15 (21%)	
	56-65	7 (9%)	2 (20%)	5 (7%)	
	>65	10 (12%)	2 (20%)	8 (11%)	

Referral from (n, column%)				
Community health centre	14 (17%)	0 (0%)	14 (20%)	
District hospital	42 (52%)	6 (60%)	36 (51%)	
*GP	4 (5%)	2 (20%)	2 (3%)	.052
Home	16 (20%)	1 (10%)	15 (21%)	
Inter-department	2 (2%)	1 (10%)	1 (1%)	
*WCRC	3 (4%)	0 (0%)	3 (4%)	
Co-morbidities (n, proportion)				
HIV/AIDS	24 (30%)	2 (20%)	22 (31%)	.476
TB	8 (10%)	0 (0%)	8 (11%)	.264
Hypertension	33 (41%)	1 (10%)	32 (45%)	.035
Cardiac Failure	10 (12%)	3 (30%)	7 (10%)	.070
Stroke	7 (9%)	1 (10%)	6 (9%)	.870
COPD	4 (5%)	0 (0%)	4 (6%)	.441
Risk Factors (n, proportion)				
Recent immobilisation	12 (15%)	0 (0%)	12 (17%)	.159
Recent long haul travel	7 (9%)	1 (10%)	6 (9%)	.870
Recent surgery	8 (10%)	0 (0%)	8 (11%)	.264
Recent trauma	7 (9%)	0 (0%)	7 (10%)	.299
Malignancy	2 (3%)	0 (0%)	2 (3%)	.591
*DVT	10 (12%)	1 (10%)	9 (13%)	.810
Other	24 (30%)	2 (20%)	22 (31%)	.476
Tobacco use	25 (31%)	4 (40%)	21 (31%)	.564
Obesity	23 (28%)	2 (20%)	21 (31%)	.594
Prior PE	2 (3%)	0 (0%)	2 (3%)	.583
Prior DVT	5 (6%)	2 (20%)	3 (4%)	.060
Prior TB	10 (12%)	3 (30%)	7 (10%)	.082
Hormonal/contraceptive Rx	4 (5%)	0 (0%)	4 (6%)	.435
Presenting Symptoms (n, proportion)				
Chest pain	55 (68%)	5 (50%)	50 (70%)	.195
Dyspnoea	74 (91%)	10 (100%)	60 (90%)	.299
Cough	53 (65%)	7 (70%)	46 (65%)	.746
Haemoptysis	9 (11%)	1 (10%)	8 (11%)	.905
Syncope	6 (7%)	1 (10%)	5 (7%)	.738
Clinical Signs (n, proportion)				
Tachypnoea	57 (70%)	8 (80%)	49 (70%)	.427
Tachycardia	61 (75%)	8 (80%)	53 (75%)	.713
Cyanosis	0	0	0	
Pyrexia	0	0	0	
Lower limb swelling/pain	27 (33%)	4 (40%)	23 (32%)	.633
Special Investigations (n, proportion)				
Raised Troponin T (n=37)	12 (32%)	1 (10%)	11 (33%)	.737
Raised D-dimer (n=38)	36 (95%)	4 (40%)	32 (94%)	.618
Right ventricular strain on *POCUS (n=31)	21 (68%)	2 (20%)	19 (68%)	.967
Classification of PE (n, column%)				
Massive	8 (10%)	3 (30%)	5 (7%)	.023
Submassive	41 (51%)	7 (70%)	34 (48%)	.190
Low-Risk	32 (39%)	0	32 (45%)	.006
Treatment Received (n, proportion)				
Mechanical ventilation	6 (7%)	3 (30%)	3 (4%)	.004
Thrombolysis	7 (9%)	2 (20%)	5 (7%)	.172
Embolectomy	3 (4%)	0	3 (4%)	.508

**GP, general practitioner; WCRC, Western Cape Rehabilitation Centre; COPD, DVT, deep vein thrombosis; POCUS, point-of-care ultrasonography. Statistically significant different variables are highlighted; Percentages may not add to 100% because of rounding.*

Two emergency physicians individually assessed all ECGs (n=81). Tachycardia (HR ≥100/minute) was the most common ECG feature (n=59, 73%) and the most sensitive (90%) predictor of in-hospital mortality. Complete right bundle branch block (RBBB) and incomplete RBBB were the most specific predictors of in-hospital death, with a specificity of 97% and 92% respectively. TWI in leads V1-V4 (82%), TWI in II (86%), Q-wave in AvF (89%) were reasonably specific changes that predicted in-hospital mortality. Unadjusted

diagnostic odds ratios (OR) of ECG characteristics to predict in-hospital mortality (Table 2) found a complete RBBB (OR, 8.6; 95% CI, 1.1 to 69.9; p=0.044) and right axis deviation (RAD) (OR, 5.6; 95% CI, 1.4 to 22.4; p=0.015) to be significant predictors of in-hospital mortality.

Table 2: Univariate analysis of ECG characteristics to predict in-hospital mortality

N (%)	Total N=81	In-hospital death N=10	OR (95% CI)	P	Sensitivity	Specificity
Tachycardia ≥100 *bpm	59 (73%)	9 (90%)	1.358 (0.264-6.997)	.714	90%	30%
Atrial fibrillation	1 (1%)	0				
TWI in leads V1-V2	24 (30%)	3 (30%)	1.020 (0.240-4.330)	.978	30%	70%
TWI in leads V1-V3	20 (25%)	3 (30%)	1.361 (0.317-5.851)	.678	30%	76%
TWI in leads V1-V4	14 (17%)	1 (10%)	0.496 (0.058-4.263)	.523	10%	82%
S wave in lead I	35 (43%)	6 (60%)	2.171 (0.563-8.386)	.260	60%	59%
TWI in lead AvF	25 (31%)	2 (20%)	0.522 (0.103-2.656)	.433	20%	68%
TWI in lead II	12 (15%)	2 (20%)	1.525 (0.282-8.245)	.624	20%	86%
TWI in lead III	38 (47%)	3 (30%)	0.441 (0.105-1.843)	.262	30%	51%
$S_IQ_{III}T_{III}$ pattern	16 (20%)	0				
Incomplete RBBB	7 (9%)	1 (10%)	1.204 (0.130-11.181)	.870	10%	92%
Complete RBBB	4 (5%)	2 (20%)	8.625 (1.064-69.886)	.044	20%	97%
Q wave in lead III	25 (31%)	1 (10%)	0.218 (0.026-1.820)	.159	10%	66%
Q wave in lead AvF	9 (11%)	1 (10%)	0.875 (0.098-7.842)	.905	10%	89%
Right axis deviation	21 (26%)	6 (60%)	5.600 (1.398-22.428)	.015	60%	79%
Left axis deviation	3 (4%)	0				
Low voltage	3 (4%)	0				
Qr in V1	11 (14%)	2 (20%)	1.722 (0.315-9.427)	.531	20%	87%

**bpm, beats per minute.*

Table 3 depicts the application of the TwiST and Daniel scores to the study sample with various clinically relevant cut-offs.(19, 26) A TwiST score of ≥5 was 70% sensitive with a 93% NPV. A Daniel score of ≥10 had the highest specificity of 80%. No patients had TwiST scores of ≤2.

Table 3: Application of the Daniel score and Twist score on the included sample

	OR (95% CI)	P	Sensitivity	Specificity	PPV	NPV	LR+	LR-
Entire sample N=81; prevalence=12%								
Daniel score ≥7	1.093 (0.257-4.650)	.904	30%	72%	13%	88%	1.07	0.97
Daniel score ≥10	0.452 (0.053-3.872)	.469	10%	80%	7%	86%	0.51	1.12
Twist score ≥5	2.539 (0.607-10.615)	.202	70%	52%	17%	93%	1.46	0.58
Submassive PE N=41; prevalence=17%								
Daniel score ≥7	0.571 (0.097-3.376)	.537	29%	59%	13%	80%	0.69	1.21
Daniel score ≥10	0.400 (0.043-3.764)	.423	14%	71%	9%	80%	0.49	1.21
Twist score ≥5	0.556 (0.105-2.948)	.490	57%	29%	14%	77%	0.81	1.46

Discussion

The risk of rapid clinical deterioration and death in patients with PE remains difficult to predict, despite the high mortality and prevalence in LMICs. Resources to diagnose and monitor RVD are not always available and clinical decision and prediction rules are not validated in high HIV/TB settings. Despite the small study sample, this study identified two ECG characteristics that were associated with a higher likelihood of inpatient mortality. The Daniel and TwiST scores did not perform well in this cohort to predict mortality, despite its validity in HICs to predict right sided heart strain secondary to a massive PE,(19, 26) further reinforcing the need for the development of LMIC-specific clinical decision rules and predictors.

The demographical characteristics of the sample were different from global trends: 75% (n=61) of the sample were female, including nine out of the 10 who suffered inpatient deaths. The sample was younger, with 88% (n=71) of the patients been less than 65 years of age, including eight out of 10 inpatient deaths. This was most likely due to the high prevalence of HIV/AIDS (n=24, 30%) and TB (n=8, 10%). Data shows that the risk of PE in patients living with HIV have a two-to ten-fold increase as compared to healthy population of similar age.(6)

This study demonstrated two ECG characteristics that were associated with an increased inpatient mortality: the odds of patients who suffered inpatient mortality to have a RAD or a complete RBBB, was 5.6 and 1.2 times as high respectively, as in those who survived to hospital discharge. However, the confidence intervals

were very wide because of the small sample size and low number of non-survivors. Various ECG patterns have shown to predict the degree of pulmonary hypertension, right ventricular dysfunction and the clinical outcome of PE.(2, 19) Geibel et al., found that an ECG with at least one abnormality known to be associated with PE to have an OR of 2.56 for predicting 30-day mortality.(29) Tayama et al. also reported that there were more than two abnormal ECG findings observed in 71.4% of patients with an acute massive and submassive PE.(32) In a systemic review and meta-analysis conducted by Qaddoura et al., it was found that features most predictive of in-hospital death included S1Q3T3, complete RBBB, TWI, ST-depression in V4 through V6, ST-elevation in V1 and lead III, Qr in V1, RAD, AF, and RV transmural ischaemic pattern.(31) Sinus tachycardia was the most common and most sensitive ECG feature associated with fatality, while complete and incomplete RBBB were the most specific. Of note, TWI in V1-V4, TWI in lead II, and Q wave in AvF were reasonably specific in predicting in-hospital death, even though not statistically significance. These ECG changes reflect RVD in patients with large clot load and have been shown to predict a poorer outcome when present.(20, 21, 24) Therefore, patients presenting with a suspected PE with any of these signs, may warrant a more intensive monitoring and management approach.

The TwiST and Daniel score did not demonstrate any value in this cohort. The Daniel scoring system that was developed in 2001, assigned points (0-21) to ECG components that predicted increased pulmonary arterial hypertension and a score of >8 predicted a worsened clinical outcome, including death, shock, or respiratory failure.(19) Hariharan et al. also hypothesised that right heart strain, secondary to a pulmonary embolus, was independently associated with T-wave inversion in lead V1-V3, S wave in lead I, right axis deviation, and a sinus tachycardia. This lead to the development of the TwiST score which stated that a score of ≤2 points can exclude right sided heart strain with an 85% sensitivity, and a score of ≥5 points was 93% specific for right sided heart strain in patients with PE.(26) The outcome of the TwiST score when applied to the entire sample of this study found that a score of ≥5 to be 70% sensitive, 52% specific, with a 93% NPV, +LR of 1.46, and a -LR of 0.58. There was no significant value of the TwiST score when applied to the submassive group alone. Because of the small sample size and the lack of power, this score cannot be adapted into standard practices, but there is room for further research with a larger cohort; and with addition to current evidence, we can validate that ECG features can play a greater role as a prognostic adjunct in the management of patients with a PE.

The pulmonary embolism short-term clinical outcomes risk estimation (PE-SCORE) was most recently developed and validated in the United States of America.(33) This was a prospective, observational, multi-centre study where data was used to develop a 9-point PE-SCORE to identify PE patients at low- and high-risk for clinical deterioration. The score was based on the theory of PE-induced RVD leading to right ventricular failure that is commonly assessed by blood biomarkers such as the cardiac troponin levels and right ventricular dilatation, showing RVD on cardiac echocardiogram (ECHO). Hence, a new prognostic tool using readily available findings from CT/ECHO, vital signs, and clinical parameters was created, with no recognition been made on the prognostic value of an ECG, which is an easy-to-use, widely available, non-

invasive procedure. Using the PE-SCORE in LMICs like South Africa will not be ideal as CT facilities are not always available or only functional during office hours on a Monday to Friday in certain health care facilities. Furthermore, the low competency level of clinicians conducting an emergency point-of-care ultrasound, and the underutilisation and misguidance of blood biomarkers as seen in this study can lead to the misdiagnosis of an acute PE.

Limitations and Strengths

This study was the first of its kind in a LMIC with a high HIV/TB prevalence. There were, however, a few limitations. The relatively small sample size with only 10 deaths significantly affected the power of the study and prevented multivariate regression analysis or adjusted odds ratios from providing reliable information. The small sample size also decreased the probability of identifying significant findings in other variables. The sampling strategy of including only adult patients who received a confirmatory CT-PA excluded younger patients, and those who had confirmatory lung scintigraphy. This likely resulted in selection bias, as younger patients and those who received lung scintigraphy could have been physiologically different. Using all-cause mortality as the outcome measure requires an in-depth analysis of the effect of possible confounders. Patient characteristics were similar between the two groups and clinical treatment was standardised. Confounders during hospital admission were however not analysed and may have influenced outcomes. Future research should aim to collect prospective data from multiple facilities, as well as investigate the clinical outcomes when clinical deterioration or death can be reliably predicted.

Conclusion

Early identification of patients with pulmonary embolism at higher risk of clinical deterioration and in-patient mortality remains a challenge. Even though the sample size is considerably small, this study found that RBBB and RAD may be useful predictors of mortality in patients with pulmonary embolism. No clinical finding or prediction tool in isolation can reliably predict outcomes in patients with pulmonary embolism, but ECG findings show promise. This single-centre observational study with a small sample precludes concrete conclusions and a large follow-up multi-centre study is advised.

Competing Interests and Funding

The authors declare no competing interest and the study was self-funded.

Author Contributions

Authors contributed as follows to the conception or design of the work (NR,SL,CH); the acquisition (NR), analysis (CH), or interpretation of data for the work (NR,CH) ; and drafting the work (NR) or revising it critically for important intellectual content (NR,SL,CH): NR contributed 50%, CH contributed 40%, SL contributed 10%. All authors approved the version to be published and agreed to be accountable for all aspects of work.

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Supplementary Table 1: ECG Analysis Sheath

Study Number (n)	1	2	3	4	5	6
Sinus Tachycardia (*HR >100)						
S1Q3T3						
*TWI V1						
TWI V2						
TWI V3						
TWI V4						
TWI II						
TWI III						
TWI AvF						
Complete *RBBB						
Incomplete RBBB						
Right Axis Deviation						
Left Axis Deviation						
ST-Elevation V1 (>1mm)						
ST-Elevation V2 (>1mm)						
ST-Elevation V3 (>1mm)						
ST-Elevation V4 (>1mm)						
ST-Depression V1						
ST-Depression V2						
ST-Depression V3						
ST-Depression V4						
ST-Elevation AvR						
Q-Wave Lead III						
Q-Wave AvF						
Low Voltage Complexes (V1-V6, Amplitude <5 mm)						
Tall R wave in V1 (Amplitude ≥ 7 mm)						
Qr in V1						
P Pulmonale (Amplitude >2.5 mm)						
Atrial Flutter/Fibrillation						
Sinus Rhythm						

**HR, Heart rate; TWI, T-wave inversion; RBBB, right bundle branch block.*

Part B: Addenda

Addenda 1: Author Guidelines: British Medical Journal

Author guidelines are available at:

https://www.bmj.com/about-bmj/resources-authors/article-types

Addenda 2: Research Proposal

Dissertation Proposal

The prognostic value of electrocardiography to predict inpatient mortality in patients with acute pulmonary embolism

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This proposal is submitted in partial fulfilment of the requirements for the degree Masters of Medicine (Emergency Medicine) at the University of Cape Town

August 2020

Declaration

I, Nishen Raghubeer, hereby declare that the work on which this thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university. I authorise the University to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever. I further declare the following:

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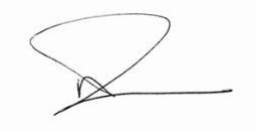

28/08/2020

Signature: ……. **Date: ……**

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List of Abbreviations

AHA	American Heart Association
BNP	Brain natriuretic peptide
CT-PA	Computed tomography pulmonary angiography
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ECHO	Echocardiogram
ECM	Enterprise Content Management
HIV	Human Immuno-deficiency Virus
HREC	Human Research Ethics Committee
LV	Left Ventricular
MI	Myocardial Infarction
PACS	Picture Archiving and Communication System
PE	Pulmonary Embolism
PIOPED II	Prospective Investigation of Pulmonary Embolism Diagnosis II
RBBB	Right bundle branch block
RV	Right Ventricular
SBP	Systolic Blood Pressure
TB	Tuberculosis
TBH	Tygerberg Hospital
UCT	University of Cape Town

Abstract

Introduction

Pulmonary embolism (PE) is one of the most common cause of preventable deaths in hospitalised patients. Because of the increasing burden of HIV and TB in South Africa, both of which produce a hypercoagulable state, the incidence of patients presenting with clinical features of a suspected PE is increasing. The current prescribed risk stratification into massive- or submassive pulmonary embolism lacks the ability to predict poor outcomes or mortality, especially in the submassive group. Evidence suggest that ECG abnormalities with right heart strain and increased pulmonary pressures have prognostic value. This study, therefore aims to assess the prognostic value of electrocardiography in predicting inpatient mortality in patients with acute pulmonary embolism.

Methodology

A retrospective cohort design will assess the ECG changes associated with massive PE. This study will be based at Tygerberg Hospital, Western Cape. Eligible patients will be identified from all CT-Pulmonary Angiogram performed from 1 January 2017 until 31 December 2019. Patient demographics, vital signs and ECG's performed on presentation will be collated. ECG's will be screened for predetermined signs that is associated with right heart strain and higher pulmonary artery pressure. These findings will be compared with inhospital mortality. Descriptive and predictive analyses will be performed, including sensitivity, specificity, predictive values and likelihood ratios.

Ethical Considerations

Due to this being a retrospective study dating back to 2017, informed consent would be impossible and a waiver for informed consent will thus be requested. No identifying variables will be collected, excluding the folder number that will link the radiology database and ECM. Thereafter the folder number will also be removed and saved in a separate file. The ethical risk is very low and meets the criteria to apply for a consent waiver. The data will be saved in a password-protected personal computer, and it will only be made available to the study team involved. Institutional approval will be obtained after HREC approval.

Conclusion

This is a study of interest. Early identification of high risk patients with acute pulmonary embolism remains a challenge in clinical practice. It has been argued that the development of right ventricular dysfunction as a

result of acute pulmonary hypertension is a crucial pathophysiological event which may initiate a vicious cycle of progressive haemodynamic instability. ECG changes seen in patients with right ventricular dysfunction have shown to be associated with fatal outcomes in patients with acute PE. Therefore, this study will assess the value of ECG's in prognosticating inpatient mortality in patients with acute pulmonary embolism.

Introduction

Background

Pulmonary embolism (PE) is one of the most common causes of preventable deaths in hospitalised patients.[1] It is the third leading cause of vascular death after myocardial infarction and stroke.[2] It is estimated that 600 000 episodes occur each year in the United States resulting in 100 000-200 000 deaths.[3] Data on the prevalence and clinical burden of PE in South Africa could not be found.[1, 4] The prevalence of DVT in Africa varies between 2.4% and 9.6% in patients after surgery, and between 380-448 per 100 000 births per year in pregnant and postpartum women whereas the prevalence of PE varied between 0.14% and 61.5% with a mortality rate between 40% and 69.5%.[5] However, in 2014, there were 2525 deaths in SA, attributable to diseases of the circulatory system which was a composite measure that included PE, stroke and myocardial infarction (MI).[4] Because of the increasing burden of HIV and TB in South Africa, both of which produce a hypercoagulable state, the incidence of patients presenting with clinical features of a suspected PE is increasing.[1]

PE usually occurs when a portion of a venous clot breaks off, travels through the venous system, into the right side of the heart, and subsequently enters a pulmonary artery. This causes an occlusion of the blood supply to a portion of the lung and thus prevents oxygenated blood from reaching the brain and supplying other vital organs. Hence, acute PE interferes with both, circulation and gas exchange process in the body. Right ventricular (RV) failure due to pressure overload from the occluded pulmonary vasculature is considered the primary cause of death in massive PE [6]. Clinical features of PE are highly variable and ranges from sudden death to incidental diagnosis in asymptomatic patients. PE can be considered when a patient presents with acute shortness of breath, pleuritic chest pain, unexplained tachycardia, hypoxaemia, syncope or shock, especially in the absence of any findings suggestive of an alternative diagnosis.

Massive PE is a medical emergency that frequently results in RV failure and death [7]. The American Heart Association (AHA) guidelines classify PE into massive, submassive and low-risk PE [8].

a) Massive PE: defined as acute PE with sustained hypotension (SBP < 90mmHg for at least 15 minutes or requiring inotropic support, not due to a cause other than PE, such as arrhythmias, hypovolemia, sepsis, or left ventricular dysfunction), pulselessness, or persistent profound bradycardia (HR < 40 bpm) with signs or symptoms of shock.

b) Submassive PE: defined as acute PE without systemic hypotension (SBP ≥ 90 mmHg) but with either RV dysfunction or myocardial necrosis.
   RV dysfunction is defined the presence of at least one of the following:

1. RV dilatation (apical 4 chamber RV diameter divided by LV diameter >0.9) or RV systolic dysfunction on ECHO.
2. RV dilatation on CT-PA
3. Elevated BNP (>90 pg/ml)
4. Elevation of N-terminal pro-BNP (>500 pg/ml)
5. ECG changes (new complete or incomplete RBBB, anteroseptal ST-elevation or depression, or anteroseptal T wave inversion)

Myocardial necrosis is defined as either one of the following:

1. Elevation of Trop I (>0.4 ng/ml)
2. Elevation of Trop T (>0.1 ng/ml)

c) Low-risk PE: acute PE and the absence of the clinical markers of adverse prognosis that defined massive or submassive PE.

The above classification does not take into consideration the size/site of the embolus or the degree of pulmonary artery obstruction, but rather the clinical and physiological changes that occur secondary to a pulmonary embolus. PE can be treated by anticoagulation with heparin which prevents clot extension or by thrombolysis or surgical intervention. Thrombolysis results in the dissolving of the clot by using thrombolytic agents such as alteplase. Patients with a massive PE that is haemodynamically unstable is treated by thrombolysis, whereas the treatment of submassive PE with RV dysfunction with thrombolytics is controversial even though patients with a submassive PE with RV dysfunction have a potential risk of becoming haemodynamically unstable with overt right ventricular failure, and if not managed aggressively on initial presentation could lead to rapid clinical deterioration and/or death.[9] Therefore, it is in this cohort of patients that we postulate that the ECG will assist with predicting poor outcome, thus helping clinicians to decide which patients with submassive PE require a higher level of intervention and closer follow up.

The current treatment guideline recommends the risk-stratification of patients to assess the severity of PE.[10] With this approach, those who are at high risk of clinical deterioration or death can be considered for treatment beyond anticoagulation.[10] The risk-stratification approach includes haemodynamic status, clinical scores, blood biomarkers, CT-PA and/or ECHO findings.[10] CT-PA is the procedure of choice for diagnosing PE. It is the gold standard in the diagnosis of acute PE with high accuracy and rapid turnaround time.[11] Lung scintigraphy (V/Q scans) was the diagnostic study of choice prior to CT-PA. It is used to determine the presence of a pulmonary embolus.[11] Ventilation (V) and perfusion (Q) scans has a lower radiational dose to the breast which makes it useful for young women in their reproductive age group.[12] V/Q scans are still in use for the evaluation of PE in patients that are pregnant and in those that have a

contraindication to iodinated contrast medium such as severe contrast allergy and compromised renal function (GFR <30).[12] According to the PIOPED II trial, CT-PA showed a sensitivity of 83% and specificity of 96%, while V/Q scans had a sensitivity of 85% and specificity of 93%.[11]

There is a wide range of ECG features associated with PE with the commonest presentation been a sinus tachycardia.[7] The 12-lead ECG also provides information about the severity of PE. ECG findings in massive PE will represent a greater potential threat to mortality versus ECG changes in submassive PE, and failure of this pattern to resolve over the next several days suggest that a high physiologically important degree of pulmonary artery obstruction.[13] Other features that are significantly more frequent with fatal outcomes include atrial arrhythmias (mostly atrial fibrillation or flutter), complete right bundle branch block (RBBB), low voltage QRS complex in lead V1-V6, pseudo infarct pattern (Q waves) in lead III and AvF, and ST segment changes (elevation or depression) over the left precordial leads.[14] T-wave inversion (TWI) also occurs, usually on the precordial chest leads and it has been proven to appear more frequently in patients with RV dysfunction [15]. There have been a few ECG scoring systems developed in the past to help predict adverse clinical outcomes such as Daniel score.[16] The Daniel scoring system was developed in 2001 that assigns points (0-21) to ECG components that predicted increased pulmonary arterial hypertension, this score was found to correspond to the degree of perfusion defects on ventilation and perfusion lung scanning, and a score >8 predicted worsened clinical outcome, including death, shock, or respiratory failure.[16] However, this score has not been validated in South Africa.

Motivation

Pulmonary embolism is a potentially fatal disease that is most often difficult to diagnose. Acute PE is a medical emergency that results in RV dysfunction and failure secondary to pulmonary artery obstruction. This requires prompt management to reduce potentially preventable deaths. RV dysfunction is associated with a poor prognosis and high mortality rate in patients with acute PE.[15] There are several ECG abnormalities that are present in patients with PE, with evidence suggesting that these abnormalities may have predictive value regarding the prognosis and outcomes. The AHA classification that is widely utilised suggests that massive PE requires thrombolysis, intravascular interventions or surgery, as the benefits outweigh the risks. Submassive PE, however, is managed conservatively and patients are anticoagulated and observed. It is in this group where prognostication will aid clinicians the most as a certain subset of patients deteriorate clinically and die. A score that can predict clinical deterioration or mortality may suggest that the benefits of lysis/surgery outweigh the risks, even in the submassive category. Therefore, this study will provide us with information regarding the prognostic value of electrocardiography to predict mortality in patients with acute PE.

Aim

To assess the prognostic value of electrocardiography in predicting inpatient mortality in patients with acute pulmonary embolism.

Objectives

1. To describe the demographics of all patients who received computed tomography pulmonary angiogram during the study period.
2. To describe the ECG findings of all patients that received a computed tomography pulmonary angiogram.
3. To describe their relevant clinical findings and subsequent categorisation into massive, submassive or low-risk PE.
4. To describe the outcomes of all patients with regards to mortality and interventions performed (thrombolysis, intravascular procedures or surgery).
5. To assess the prognostic value of ECG findings in predicting mortality.

Methodology

Study design

A retrospective cohort design will be used and data will be collected from existing databases and folder reviews.

Study setting

The research study will be based at Tygerberg Hospital (TBH), a tertiary level hospital based in Parow, Cape Town. It is the largest hospital in the Western Cape and the second largest in South Africa. TBH services a population of over 3.4 million people including the Northern sub-district, Khayelitsha, Eastern Tygerberg, West Coast, Cape Winelands and Overberg rural. TBH is also a referral institute whereby patients are transferred from surrounding district hospitals for definitive management. The radiology department operates 24/7 and is staffed by specialist radiologists that are on call and available 24/7. TBH radiology department is also a training site for radiology registrars and is academically linked to Stellenbosch University.

Medical emergencies are triaged and managed at TBH C1D west (emergency centre). Patients suspected of having PE are stratified into different categories, depending on their pre-test probabilities, with the help of Wells Score.[3] Patients with a high pre-test probability will receive a CT-PA or V/Q scan depending on patient characteristics. Those with an intermediary pre-test probability will receive a CT-PA or V/Q scan if their D-dimer is raised. The Pulmonary Embolus Rule Out Criteria (PERC) is a clinical decision tool that is applied to those with a low pre-test probability.[17] Hence, patients with any positive criteria will be upscaled to an intermediary pre-test probability. See addendum 1. Although the Wells score and the PERC rule assist in

the pre-test probability in the diagnosis of PE, they however do not take into consideration the high prevalence of patients with HIV and TB in our setting, both of which produce a hyper-coagulable state leading to venous thromboembolism. Therefore, these clinical decision tools are not validated in our setting with a high HIV and TB prevalence. The decision to use either a CT-PA and a V/Q scan depends on the patient characteristics, including the presence of contra-indication for intravenous contrast, etc.

Patients with a confirmed PE are classified into massive and submassive, depending on their clinical characteristics. Submassive PE are anticoagulated and admitted to the medical department while massive PE receive IV thrombolysis in the emergency centre or referred for intravascular interventions or surgery via the vascular surgical department.

Study Population and Sampling

Inclusion Criteria

All adult patients (≥ 18 years old) who received a CT-PA for a suspected PE and reported on by a radiologist during the study period will be eligible for inclusion. Data will be collected for a period of 2 years between the 1st of January 2018 and the 31st of December 2019. The sample includes referrals from any department and won't take into consideration the initial criteria and diagnostic threshold used to determine the need for CT-PA.

Exclusion Criteria

All patients <18 years of age will be excluded. Patients with missing clinical data such as ECG's on first presentation/suspicion of PE will also be excluded from the study. CT-PA's performed for other indications (e.g. Thoracic trauma) and repeat CT-PA's (in patients already diagnosed with PE on initial CT-PA) will be excluded.

Data Collection and Management

Data will be collected in three phases.

Phase 1: Identifying study sample from the Picture Archiving and Communication (PACS) database.

The study sample will be identified using PACS. All CT-PA's done for a suspected PE and reported on by the radiologist between 1 January 2018 and 31 December 2019 (study period) will be selected. The patient's folder number will be the only identifying detail captured and this is necessary to link with the other phases. CT-PA reports will be dichotomised (stratified into no PE and PE diagnosed).

Phase 2: Collating clinical and demographic details.

Clinical details and demographics from patients identified in phase 1 will be sourced from the Enterprise Content Manager (ECM) database. Based on the American Heart Association (AHA) definition of PE, the clinical details will be used to categorise PE into massive, submassive and low-risk. The American Heart Association (AHA) definition of PE is as follows [8]:

Massive PE: Acute PE with sustained hypotension, pulselessness, or persistent profound bradycardia with signs or symptoms of shock.

Submassive PE: Acute PE without systemic hypotension but with either RV dysfunction or myocardial necrosis.

Low-risk PE: Acute PE and the absence of the clinical markers of adverse prognosis that defined massive or submassive PE.

The above definition does not take into consideration the size/site of the clot as evidence shows that the clot burden measured on angiography does not predict adverse outcome, rather than the physiological changes to the right ventricle leading to right ventricular dysfunction which is a poor prognostic predictor.[8]

Phase 3: Analysis of ECG's

All ECG's from all patients identified in phase 2 will be analysed independently by all investigators: 1 emergency medicine registrar and 2 emergency medicine physicians, and inter-rater agreements will be calculated. The 2 emergency medicine physicians will be blinded to the clinical history, diagnosis and outcome of all patients to minimise bias. ECG's will be assessed for pre-determined signs as identified from literature reviews of studies investigating the value of electrocardiography in PE.[1, 9, 10, 14, 15, 18, 19] A list of ECG definitions will be discussed prior to the phase 3 to assure that all investigators are using the same methods and criteria to diagnose ECG changes.

Although ECG changes alone are not reliable in making a diagnosis of PE, and it's main value in this setting is its ability to identify other potentially life-threatening diagnosis such as myocardial ischaemia/infarction or pericarditis, there are however some dynamic changes found in the acute phase of pulmonary embolism that assist in the prognostication of PE.[20]

Patients with submassive PE have an elevated risk of haemodynamic collapse.[9] ECG changes seen in acute PE are usually transient and resolves after prompt treatment. Atrial fibrillation/flutter, complete RBBB, peripheral low voltage pseudo infarct pattern (Q waves) in lead III and AvF, and ST-segment elevation/depression over left precordial leads were all significantly more frequent in patients with poor outcome.[14] Heart rate >100, S1Q3T3, T wave inversion in V1-V4 and ST elevation in AvR is also associated with circulatory shock and death.[9] It has also been hypothesised that patients with precordial T-wave inversion (V1-V4) in patients with acute PE to have been closely related to right ventricular dysfunction, and the normalization of this pattern as the right ventricular function improves over the next few days after prompt treatment.[15] Other features that are associated with PE are Qr pattern in V1, right axis

deviation, incomplete right bundle branch block, and P-pulmonale.[21] Variables that will be analysed on the ECG is depicted on Addendum 2: ECG Analysis Sheath.

Missing Data or Incomplete Records

Cases will be excluded if patients clinical details that are required is missing or inaccessible. A tally of such cases will be kept, along with all available data and compared with the definitive cases that is included.

Variables and Data Source

A list of all variables can be found in Addendum 3: Data analysis plan.

Data will be collected from the following systems:

PACS – Picture archiving and communication system

ECM – Enterprise content manager

Data Safety and Monitoring

Care will be taken to protect the identity of patients. Patient folder numbers will be collected from the radiology database which will be required to access patient demographics and clinical data from ECM. All data will then be de-identified and a study number will be allocated to each case and saved in a password-protected folder. Patients folder numbers will then be put into a separate sheet corresponding to their allocated study number and saved into another password-protected folder. It will only be accessed in case of a query. All data will be saved in a password-protected folder in a university computer at UCT, which will also be password-protected. All information obtained will be backed up in a cloud server which will be password-protected. Information on the study will only be accessed by myself and supervisors.

Data Analysis

A sample size of 250-300 cases is estimated, based on a 1-month audit. A sample size calculation suggested a minimum size of size of 182 participants. The following variables were used: Two independent groups with a dichotomous outcome (mortality) – 5% and 20% incidence in each group respectively, as well as an enrolment ratio of 1:3, an alpha error of 0.05 and a power of 80%. Categorical data will be as frequency and proportions (%) and continuous variables as mean and standard deviation or median and quantiles if not normally distributed. Summary statistics will be used to represent frequency (frequency tables). Categorical data will be compared with the use of the Fisher's exact test or the Chi^2 test, depending on the characteristics of the variables. Continuous variables will be compared with Student's t-test or a non-parametric equivalent.

The prognostic value of electrocardiography to predict inpatient mortality will be analysed univariately using the Fisher's exact test. Prognostic accuracy will be assessed by calculating sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV). Univariate Odds Ratios will be calculated for ECG features with 95% confidence intervals (CI). Statistical significance will be defined as $p < 0.05$ and calculated two-sided. Data will be analysed with the help of IBM SPSS Statistics version 26.

Ethical Considerations

Risk to the Patient

No identifying variables will be collected, excluding the folder number that will link the radiology database and ECM. Thereafter, the folder number will also be removed and saved in a separate file. Due to this being a retrospective study dating back to 2017, obtaining informed consent would be impossible and with the ethical risk being very low, a waiver for informed consent will thus be requested. Patient care will not be affected.

Risk to the Community

The study will not pose any risk to the community. It will assist in the reduction of mortality and morbidity with the early identification of patients, especially with a submassive PE, which will be flagged for earlier invasive investigation and treatment.

Risk to the Institution

There is no potential risk to the institution foreseeable. Intuitional approval will be obtained after the study has been approved by Human Research Ethics Committee (HREC) of the University of Cape Town.

COVID-19 Era and Staff Safety

Due to unfortunate circumstances, staff and public safety is of importance. This is a retrospective study in which the data required will be reviewed from archived notes made available from the electronic database manager, ECM. The list of all patients that received a CT-PA during the study period will be requested from the radiology database manager which will be saved in a password-protected spreadsheet. Neither the database manager nor the investigators will be required to be on-site (in the facility) as access to the registry will occur securely via an off-site VPN (virtual private network).

There will be no reimbursement for participation in this study.

Limitation and Strengths

Limitation

Selection Bias:

All adult patients that received a CT-PA for the diagnosis of PE during the study period are included. Patients that received lung scintigraphy (V/Q Scan) for the diagnosis of PE are excluded. Therefore, this may influence the results and not show the accurate reflection of all patients diagnosed with PE during the study period. This could lead to an under- or over estimate of the study effect.

Because of the retrospective nature of this study, missing or incomplete data will be inevitable. All such data will be excluded from the study population and will be saved in a separate sheath in which it will be presented in as much detail as possible for comparison with the study population. This will potentially reduce the sample size leading to a reduction in the power of the study. The research team will try as much as possible to prevent this as far as possible.

ECG finding interpretation could potentially be a source of bias and could result in misclassification. This will be minimised by blinding the investigators to all clinical details, as well as calculating a post-hoc interrater agreement. Criteria and definitions of ECG findings will also be standardised pre-hoc.

Strengths

This study is the first of its kind in South Africa. With the foundation of this study, it could be translated into larger studies such as the external validation of clinical scoring systems in a South African setting or possibly creating a different ECG scoring system according to local evidence. Driven by evidence-based medicine, a clinician will become more aware and confident when treating a patient with a suspected PE.

Data Dissemination Plan

This study will be in partial fulfilment of an MMED thesis. A publication in a peer review journal is anticipated. The findings of this study will be presented to the division of Emergency Medicine Cape Town.

Projected Timeline

Table 4: Project Timeline

2020	***Jan***	***Feb***	***Mar***	***Apr***	***May***	***Jun***	***July***	***Aug***	***Sep***	***Oct***	***Nov***	***Dec***
EMDRC								X	X			
Ethics										X	X	
Hospital Permission												X
2021	***Jan***	***Feb***	***Mar***	***Apr***	***May***	***Jun***	***July***	***Aug***	***Sep***	***Oct***	***Nov***	***Dec***
Data Collection	X	X										
Data Analysis		X	X									
Writeup			X	X	X	X						
Submission						X						

Resources and Budget

Required Resources

Table 5: Resources and Budget

June 2020 – May2021				
Item	**Description**	**Unit cost**	**Nº of Units**	**Total cost**
Consumables				
1. materials and supplies				
2. materials and supplies				
3. specialised services				
4. office supplies, printing & reproduction for data collection				
5. office supplies, printing & reproduction for reports	Printing-data collection, reports, paper			R100
Research travel				
1. travel to sites	Travel to TBH: x10 trips = 340km @R1.43/km (SARS rates)			R487
Minor research equipment				
1. internet access				R500
2.				
3.				
Sub-Total				
Total				**R1087**

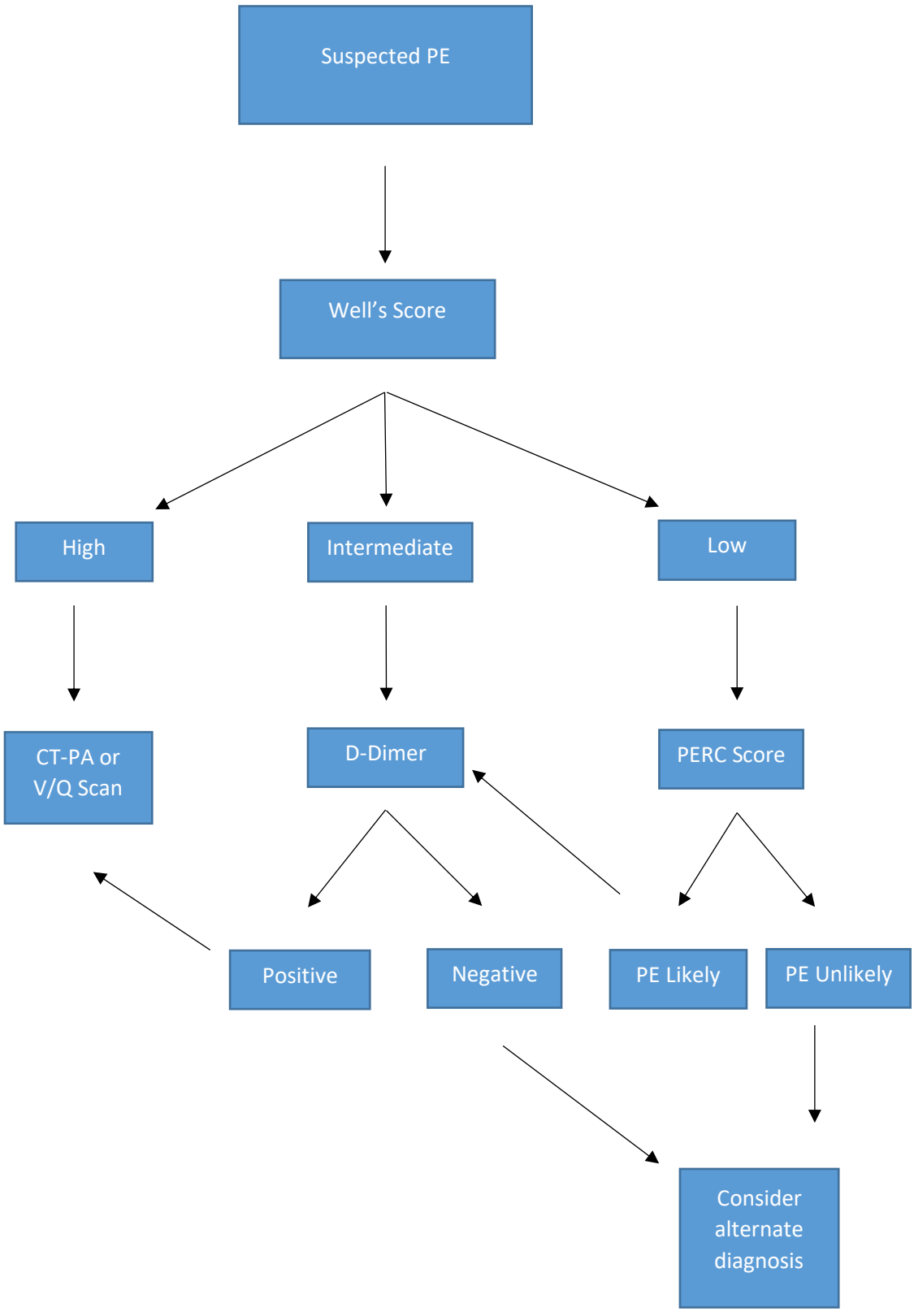
Existing Resources

Hardware: Laptop, external hard drive.

Software: Microsoft office, Reference manager, Data management software and Statistical analysis software – institutional subscription.

Addendum

Addendum 1: Diagnostic approach to patient with a suspected pulmonary embolism



Addendum 2: ECG analysis sheath

n	1	2	3	4	5
Sinus Tachycardia (HR >100)					
S1Q3T3					
T-Wave Inversion:					
V1					
V2					
V3					
V4					
Complete RBBB					
Incomplete RBBB					
RAD					
LAD					
ST-Elevation (left precordial leads)					
ST-Depression (left precordial leads)					
ST-Elevation in AvR					
Q Waves:					
Lead III					
AvF					
Low Voltage Complex (V1-V6)					
Qr in V1					
P Pulmonale					
Atrial Fib/Flutter					
Sinus Rhythm					

Addendum 3: Data analysis plan

Objective	Variable	Type	Source	Analysis
1. To describe the demographics	• Age • Gender	• Numerical, discreet • Categorical. dichotomous (nominal)	• ECM	• Frequencies and proportions (%) • Normality tests • Median and quartiles/range for skewed and mean and standard deviation if normally distributed
2. To describe the ECG findings	• List of pre-defined ECG features (See Addenda X)	• Categorical, nominal (dichotomous) (yes/no)	• ECM	• Fisher's exact test
3. To describe their relevant clinical findings and subsequent categorisation into massive, submassive or low-risk PE.	• Category of PE	• Categorical, ordinal	• ECM	• Frequencies and proportions (%) • Fisher's exact test
4. To describe the outcomes with regards to mortality and interventions performed	• Mortality • Interventions	• Categorical, nominal (dichotomous) • Categorical, nominal	• ECM	• Frequencies and proportions (%) • Fisher's exact test
5. To assess the prognostic value of ECG findings in predicting mortality.	• List of pre-defined ECG features (see addenda X)	• Categorical, nominal (dichotomous) (yes/no)	• ECM	• Sensitivity • Specificity • Positive predictive value • Negative predictive value • Univariate Odds Ratios

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Addenda 3: Ethical Approval Letter

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

Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

30 November 2020

HREC REF: 722/2020

Dr C Hendricks
Division of Emergency Medicine
F-51, OMB
Email: - clint.hendricks@uct.ac.za
Student: nishen7@live.co.za

Dear Dr Hendricks

PROJECT TITLE: THE PROGNOSTIC VALUE OF ELECTROCARDIOGRAPHY TO PREDICT INPATIENT MORTALITY IN PATIENTS WITH ACUTE PULMONARY EMBOLISM (MASTERS CANDIDATE: DR N RAGHUBEER)

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

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned stud, subject to Stellenbosch approval.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020 & 06 July 2020.

Approval is granted for one year until the 30 November 2021.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: - Dr Nishen Raghubeer will also be involved in this study.

Please quote the HREC REF in all your correspondence.

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

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Addenda 4: HREC Approval Letter

Western Cape Government
Health

TYGERBERG HOSPITAL
REFERENCE:
Research Projects
ENQUIRIES: **Dr GG Marinus**
TELEPHONE:**021 938 5752**

Ethics Reference: HREC REF: 722/2020

TITLE: **THE PROGNOSTIC VALUE OF ELECTROCARDIOGRAPHY TO PREDICT INPATIENT MORTALITY IN PATIENTS WITH ACUTE PULMONARY EMBOLISM (MASTERS CANDIDATE: DR N RAGHUBEER)**

Dear Dr Hendricks

PERMISSION TO CONDUCT YOUR RESEARCH AT TYGERBERG HOSPITAL.

1. In accordance with the Tygerberg Hospital Health Research Policy and Protocol of **April 2018**, permission is hereby granted for you to conduct the above-mentioned research here at Tygerberg Hospital.

2. Researchers, in accessing Provincial health facilities, are expressing consent to provide the Department with an electronic copy of the final feedback within six months of completion of research. This can be submitted to the Provincial Research Co-Ordinator (Health.Research@westerncape.gov.za).

DR GG MARINUS
MANAGER: MEDICAL SERVICES

Date: 13/May

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