Prognostic Utility of Tricuspid Annular Plane Systolic Excursion in Pulmonary Embolism

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PROGNOSTIC UTILITY OF TRICUSPID ANNULAR PLANE SYSTOLIC EXCURSION IN PULMONARY EMBOLISM

A Thesis Presented to
The Faculty of the School of Medicine
Yale University

In Candidacy for the degree of
Master of Medical Science

May 2018

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Class of 2018
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<tbody>
<tr>
<td>APE</td>
<td>Acute Pulmonary Embolism</td>
</tr>
<tr>
<td>CHF</td>
<td>Congestive heart Failure</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
</tr>
<tr>
<td>CTPA</td>
<td>Computed Tomography Pulmonary Angiogram</td>
</tr>
<tr>
<td>ED</td>
<td>Emergency Department</td>
</tr>
<tr>
<td>Echo</td>
<td>Echocardiogram</td>
</tr>
<tr>
<td>FOCUS</td>
<td>Point-of-care Focused Cardiac Ultrasound</td>
</tr>
<tr>
<td>DVT</td>
<td>Deep Vein Thrombosis</td>
</tr>
<tr>
<td>HIPPA</td>
<td>Health Insurance Portability and Accountability Act of 1996</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard Ratio</td>
</tr>
<tr>
<td>ICC</td>
<td>Intraclass Correlation Coefficient</td>
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<tr>
<td>ICOPER</td>
<td>International Cooperative Pulmonary Embolism Registry</td>
</tr>
<tr>
<td>PE</td>
<td>Pulmonary Embolism</td>
</tr>
<tr>
<td>PESI</td>
<td>Pulmonary Embolism Severity Index</td>
</tr>
<tr>
<td>PVR</td>
<td>Pulmonary Vascular Resistance</td>
</tr>
<tr>
<td>RV</td>
<td>Right Ventricle</td>
</tr>
<tr>
<td>RVD</td>
<td>Right Ventricular Dysfunction</td>
</tr>
<tr>
<td>RV/LV Ratio</td>
<td>Right Ventricular to Left Ventricular End Diastolic Ratio</td>
</tr>
<tr>
<td>or RVED/LVED</td>
<td></td>
</tr>
<tr>
<td>RVEF</td>
<td>Right Ventricular Ejection Fraction</td>
</tr>
<tr>
<td>TAPSE</td>
<td>Tricuspid Annular Plane Systolic Excursion</td>
</tr>
<tr>
<td>VTE</td>
<td>Venous Thromboembolism</td>
</tr>
<tr>
<td>VQ Scan</td>
<td>Ventilation and Perfusion Scan</td>
</tr>
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Abstract
Inpatient mortality for hemodynamically stable patients with pulmonary embolism (PE) averages 5-10%. Tricuspid annular plane systolic excursion (TAPSE), a reliable and reproducible measure of right ventricular (RV) dysfunction has been shown to identify patients with worse prognosis in the cardiology literature, but prognostic utility of TAPSE using point-of-care echocardiogram (FOCUS) in the emergency department (ED) population is sparse. We propose that in a prospective cohort of patients with confirmed PE, those with TAPSE less than 15mm on FOCUS will have greater overall mortality and need for escalation of care than those with TAPSE greater than 17mm. We will enroll and follow patients diagnosed with acute PE, performing FOCUS with measurement of TAPSE within 6 hours of anticoagulation at academic emergency departments. We hypothesize TAPSE will independently predict outcomes in PE. Quantifiable and reliable measures that improve prognosis of ED patients may allow earlier identification of patients requiring escalation of care.
CHAPTER ONE: INTRODUCTION

1.1 Background

1.1.1 Epidemiology

Pulmonary embolism (PE) is the third leading cause of death from cardiovascular disease in the United States accounting for approximately 100,000 deaths per year\(^1\). The incidence rate for venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE) in the United States is 1 to 2 per 1000\(^2,3\). Though malignancy, surgery, and heart failure are all risk factors for VTE, the majority are idiopathic. Hospitalization is a significant risk factor for VTE, as approximately 25% are hospital acquired. However, 75% of VTE are community acquired making early diagnosis and prognostication in the emergency setting fundamental to effective treatment\(^4\).

There currently exists no registry for officially tracking the incidence of PE, but there have been several studies, which have demonstrated the burden this disease presents. In 1998 Silverstein et al.\(^3\) performed a 25 year population based study in Olmsted County, Minnesota and revealed an incidence of VTE to be 1.17 per 1,000 with a .69 per 1,000 incidence of PE. This trend has continued as Cushman et al.\(^5\) demonstrated an incidence rate for first time VTE of 1.92 per 1,000 in a 2004 retrospective cohort study. The study also noted a 28-day case-fatality rate of 11%. The 1999 International Cooperative Pulmonary Embolism Registry examined 2454 patients with acute PE presenting at 52 hospitals in 7 countries revealing an overall all cause mortality rate of 17.4%, from which 45.1% were from PE\(^6\). Pulmonary embolism remains disease with high incidence and high mortality.
The high incidence of first time VTE and its idiopathic etiology make emergency department diagnosis and assessment of prognosis very important to treatment. A 10-year cross-sectional study found an increase of PE diagnosis in the emergency department from 2001-2010. 86% of all PE patients were admitted with 75.1% of these patients were hemodynamically stable. A retrospective cohort study of 61,249 PE admissions by Admon et al. identified a variation in ICU admission rates for PE from 2.9% to 79.9%. This evidence suggests inconsistent criteria for ICU admission in patients with PE. This also demonstrates not only an increasing incidence of PE diagnosed in the ED but also highlights the importance of the ED in managing and directing care of these patients. As the emergency department is where care is initiated, the importance of reliable risk stratification is essential to guide appropriate care.

1.1.2 Pathophysiology

Pulmonary emboli are most commonly the result of deep vein thrombosis, when parts of the clot break off the thrombus, travel through the venous system, and become lodged in the pulmonary arteries. Here the clot grows, which ultimately obstructs blood flow to the pulmonary arteries of the lungs. The clot continues to grow and obstruct the pulmonary vasculature, leading to an increase in pulmonary vascular resistance (PVR). Significant rises in PVR leads to pulmonary hypertension, which increases right ventricular (RV) afterload. This increased RV afterload increases the tension within the ventricle, and severely increased tension leads to RV dilation, as well as increased end diastolic pressure in the right ventricle, RV compliance, and tricuspid regurgitation. Reduced efficacy of RV systolic function reduces LV filling, eventually reducing stroke
volume. As stroke volume is reduced significantly, cardiac output is reduced, leading to hypotension, systemic hypoperfusion and ultimately, hemodynamic collapse\textsuperscript{9,10}.

Pulmonary emboli are categorized as small, submassive, or massive based upon clinical presentation. Massive PE as characterized by hemodynamic instability commonly defined as a systolic arterial blood pressure of $< 90$ mm Hg or a drop of at least 40 mm Hg for at least 15 min or shock\textsuperscript{11,12}. Submassive PE patients are hemodynamically stable but exhibit right ventricular dysfunction (RVD) most commonly defined as RV hypokinesia, RV dilation, new onset pulmonary hypertension or paradoxical septal wall motion\textsuperscript{12}. Small PE are pulmonary emboli with hemodynamic stability and no RV dysfunction\textsuperscript{10}. At time of presentation up to 20\% of patients with PE have abnormal blood pressure. 27-55\% normotensive patients have evidence of RV dysfunction, suggesting submassive PE can as such be ascribed to 21-44\% of PE cases\textsuperscript{13-15}. Identifying the severity of PE is important, as it influences treatment.

1.1.3 Diagnosis

Acute pulmonary embolism (APE) can present in a variety of ways ranging from asymptomatic to shock and sudden death. Dyspnea, pleuritic chest pain, and cough are the most commonly associated symptoms\textsuperscript{16,17}. Because of these nondescript symptoms other clinical tools are utilized to assess the likelihood of PE, which are collected in Appendix A for reference. Tests validated to assess the likelihood of PE include the wells score, modified wells score, modified Geneva score, and PE rule out criteria (PERC) scores in combination with a D-dimer\textsuperscript{18-23}. The gold standard of diagnosis of Pulmonary embolism is the CT pulmonary angiogram (CTPA)\textsuperscript{24-26}. In this specialized CT scan
intravenous contrast is injected to visualize the pulmonary arteries, which are then assessed for evidence of occlusion. When CTPA is unavailable or contraindicated, ventilation and perfusion (VQ) scans are sensitive and specific enough to diagnose PE. Though often called a "great masquerader" due to its nonspecific symptoms, specific and sensitive pretest likelihood scores, and diagnostic tests such as CTPA and VQ scans make it possible to reliably diagnose the presence of PE.

1.1.4 Treatment

Treatment of pulmonary embolism patients is currently based largely on their hemodynamic status upon diagnosis. Appendix B contains a sample treatment flow chart by Jaff et al\textsuperscript{12} consistent with the current literature on care of PE patients. Treatment for all noncontraindicated patients centers on anticoagulation, however further treatment depends on symptoms present.

Patients, who are hemodynamically unstable, require invasive therapy secondary to initiation of hemodynamic rescue with fluid resuscitation and intravenous vasopressors, as well as empiric anticoagulation\textsuperscript{28}. Treatment with thrombolytic therapy has been established as a mainstay therapy for unstable patients with PE, with a large body of evidence advocating its efficacy\textsuperscript{29}. Thrombolytic therapy carries a significant risk of intracranial hemorrhage and major bleed. Contraindications for thrombolysis include prior intracranial hemorrhage, recent stork, active bleeding, closed head trauma, suspected aortic dissection and known structural cerebral vascular lesion. In patients that thrombolytic therapy is contraindicated or failed, surgical embolectomy is indicated\textsuperscript{30}. 

\textsuperscript{}
Patients who are hemodynamically stable with a small PE are often treated by anticoagulation alone. Though PE are often admitted for initiation of treatment, low risk patients with small pulmonary emboli can be managed as outpatients. The typical length of anticoagulation is 3 months for an unprovoked VTE or 6-12 months if risk factors present.

In patients with submassive PE the treatment plan becomes less clear. When treated with heparin alone, submassive PE can carry an in hospital mortality rate of up to 12%. The current standard of care for patients remains anticoagulation. Typical anticoagulation regimens begin with unfractionated heparin therapy upon diagnosis, until patients are bridged to low molecular weight heparin, warfarin or direct oral anticoagulation. Given the associated mortality with submassive PE, patients are often risk stratified using a Pulmonary Embolism Severity Index (PESI) score. The PESI score uses history of cancer, heart failure, chronic lung disease, heart rate, systolic blood pressure, respiratory rate, temperature, mental status and O2 saturation to risk stratify patients into levels 1-5 based on disease severity. The PESI and simplified PESI have been validated as accurate predictors of adverse outcomes in PE patients. This can be used to inform treatment options for patients, however many other patient specific prognostic factors also influence this decision.

Thrombolytic therapy is sometimes indicated in patients with submassive PE but it is currently utilized on a case-by-case basis. The literature regarding the use of thrombolysis in normotensive patients is contentious but tends to advocate against the use of thrombolysis in submassive PE. Though not always statistically significant, studies such as the one performed by Meyer et al. show clinically significant benefit to
treated submassive PE, patients with tenectepase over anticoagulation alone, with a statistically significant reduction in hemodynamic decompensation. This was however coupled with a 2.0% increase in hemorrhagic stroke and 6.3% increase in major extra cranial hemorrhage. This study highlights the current paradox in management of submassive PE. Thrombolytic management of the patient's risk of death and hemodynamic decompensation puts the patient at increased risk for bleed\(^42\). One observational study noted an improvement of RV function in patients with reduced TAPSE, who received thrombolytic therapy, however it was not powered to assess mortality benefit\(^43\). A more refined quantifiable assessment of hemodynamic risk, such as TAPSE, would allow a clinician to better navigate the risk of bleed and hemodynamic decompensation when managing normotensive PE patients.

1.1.5 Prognosis

Though CTPA and VQ scans provide clear diagnosis for PE, predicting the clinical course of patients with pulmonary emboli is far more nuanced. Evidence of hemodynamic instability and shock have been clearly associated with increased mortality, which demonstrates a need for consideration invasive treatment and escalation of care\(^11,35\). In normotensive patients with PE, there remains a risk of hemodynamic decompensation and death, but currently available prognostic tools and tests have not created a clear guidance for treatment. The mortality rate of submassive PE and subjective care guidelines currently available necessitate better prognostic tools, which have not yet been definitively described in the literature.
Shock

Hemodynamically unstable patients with pulmonary embolism, as defined in *pathophysiology*, have been associated with the greatest incidence of mortality. It is the most common cause of death from pulmonary embolism. When present it has been associated with a 25-30% mortality rate\textsuperscript{12,44,45}. The literature has demonstrated PE patients presenting with shock as having an in hospital mortality rate of 32%\textsuperscript{14}.

Right Ventricular Dysfunction

Right ventricular dysfunction has been associated with adverse outcomes in patients with PE\textsuperscript{11,35,46,47}. RVD varies in definition, but in much of the existing literature it is described as RV dilation with an RV/LV end-diastolic diameter >30mm, an RV end diastolic diameter > 1, and paradoxical septal systolic motion\textsuperscript{11,35}. A meta-analysis of 3283 patients comparing short term mortality of patients hemodynamically stable acute PE patients with right ventricular dysfunction with those with normal RV function. They found that PE patients with RVD as assessed by echocardiogram had an odds ratio of 2.29 compared to those with normal RV function\textsuperscript{48}. A 2011 meta-analysis 3 month mortality of 1249 patients with acute PE found an odds ratio of 2.36 of increased mortality in patients with RVD as assessed by echocardiogram\textsuperscript{49}. Through meta-analysis and cohort studies a clear association between right ventricular dysfunction on echocardiogram and mortality in hemodynamically stable patients with acute PE is evident.

The association between RVD and mortality has not had a large impact on treatment however, as benefit of thrombolytic therapy in hemodynamically stable patients
with RVD has not shown significant benefit over anticoagulation alone and carries a risk of intracranial hemorrhage and major bleed\textsuperscript{39-41}. This was evidenced by Konstantinides et al.\textsuperscript{50} in a 2002 randomized control trial, which showed no difference in mortality in submassive PE patients receiving thrombolytic therapy compared to those receiving heparin alone. Meyer et al.\textsuperscript{41} demonstrated an odds ratio of 0.44 in patients receiving thrombolysis developing endpoints of mortality and hemodynamic decompensation compared to those receiving heparin alone, but this was coupled with an increase risk of major bleed. Though evidence of poor RV function has been associated with increased mortality, it has not had a large impact on care. A more reliable measure of RVD, such as TAPSE, may help to better guide therapy.

1.1.6 Tricuspid Annular Plane Systolic Excursion

One measurement of right ventricular dysfunction is tricuspid annular plane systolic excursion (TAPSE). The right ventricle's muscle fibers are oriented in a longitudinal direction resulting in a longitudinal contraction of the right ventricle during systole. This physiology can be measured by transthoracic echocardiogram (echo) in a 4-chamber window as the base moves towards the apex of the heart with contraction. The m mode cursor is used along the tricuspid annulus measuring the maximum distance traveled by the tricuspid annulus during systole\textsuperscript{51,52}. There remains contention in physiological normal baseline of TAPSE but a TAPSE of greater than 17 mm is often the accepted value\textsuperscript{52,53}.

TAPSE has been shown to be an accurate predictor of right heart function\textsuperscript{52,54,55}. Kaul et al. first described this correlation in 1984, demonstrating TAPSE's association
with right ventricular ejection fraction (RVEF) as confirmed by radio nucleotide angiography\textsuperscript{51}. Ueti et al.\textsuperscript{56} built upon these findings as in a cross sectional study of 30 patients, 10 with normal RVEF and 20 with reduced RVEF due to known pathologies of pulmonary hypertension, dilated cardiomyopathy, liver cirrhosis, systemic hypertension or congenital defect. They found TAPSE was statistically significantly reduced in patients with reduced RVEF. Recent studies have shown low TAPSE to predict mortality in pulmonary hypertension\textsuperscript{57,58}, ischemic cardiomyopathy\textsuperscript{59,60}, chronic obstructive pulmonary disease (COPD)\textsuperscript{61}, and myocardial infarction\textsuperscript{62}. The cardiology literature demonstrates prognostic utility in utilizing TAPSE to risk stratify PE\textsuperscript{63-65}. These studies however often fail to control for other confounders effecting TAPS and lack uniform definition of reduced TAPSE.

Recent studies have demonstrated an association between a reduced TAPSE and mortality in patients with APE. These studies have largely been limited to the cardiology literature but have shown TAPSE of 14mm to 17mm to be associated with greater mortality in normotensive patients with pulmonary embolism\textsuperscript{63,64}. TAPSE measurement is reliable and reproducible when performed by clinicians trained in ultrasound\textsuperscript{66}. The diagnostic value of TAPSE in the ED remains contentious, but there is room for studies associating reduced TAPSE measured in the emergency department prognosis of normotensive patients presenting with acute PE based on existing literature. The existing literature regarding the prognostic utility of TAPSE in pulmonary embolism will be explored further in Chapter 2.
1.2 Statement of the Problem

The mortality rate of normotensive patients with PE is 5-10%, despite sensitive and specific diagnostic tools and effective treatments\textsuperscript{11}. Admission to the intensive care unit in this population is often inconsistent with currently available prognostic tools\textsuperscript{8}. In this patient population, anticoagulation remains the standard of care, despite this continued high inpatient mortality rate. Escalation of care beyond anticoagulation, such as thrombolytic therapy remains contentious treatment with mixed results in normotensive patient presenting with APE, and is currently considered on a case by case basis among hemodynamically stable patients presenting with acute PE and RVD\textsuperscript{11,35}. Mixed results in thrombolytic therapy in patients with submassive PE, as well as a high mortality rate on anticoagulation alone necessitate the need for more reliable prognostic guidelines informing the need for escalation of care.

Tricuspid annular plane excursion can be routinely and reliably measured in emergency departments when evaluating PE patients. Low TAPSE has been associated with poor clinical outcomes in several cohort studies\textsuperscript{63,64,67}. Clinical outcomes of hemodynamic decompensation and mortality have been associated with TAPSE values of 14mm to 20mm\textsuperscript{63,64,67}. However, there remains no standard value of TAPSE associated with presentation in the emergency department that can serve as a guide the need for escalation of care. A clear threshold value of TAPSE established with greatest association with poor clinical outcomes could help to better guide therapy of hemodynamically stable patients with acute PE in the ED.
1.3 Goals and Objectives

The goal of this study is to establish a threshold minimum value of tricuspid annular plane excursion measured with point-of-care echocardiogram in the ED, at which patients with submassive pulmonary embolism are most associated with requiring escalation of care beyond heparin alone or increased mortality. In order to do so, we will determine if a TAPSE value below 15mm is associated with hemodynamic decompensation and mortality in normotensive patients presenting in the emergency department with APE, as opposed to a TAPSE value greater than 17mm over the course of a hospital admission of up to 14 days. TAPSE will be obtained by point-of-care focused cardiac ultrasound (FOCUS) at the bedside performed, measured and read by ED physicians trained in FOCUS use. We will also compare hospital length of stay between patients with a TAPSE of less than 15mm to those with a TAPSE greater than 17mm. We will also establish if TAPSE is a more reliable prognostic indicator than RV/LV for mortality and need for escalation of care through similar method.

1.4 Hypothesis

Primary:

Pulmonary embolism (PE) patients with a tricuspid annular plane systolic excursion (TAPSE) less than 15mm measured by point-of-care echocardiogram will be independently associated with an increased higher need for escalation of care beyond heparin alone and higher mortality than PE patients with TAPSE greater than 17mm.
Secondary:

Pulmonary embolism patients with a TAPSE less than 15mm measured by point-of-care echocardiogram will be independently associated an increased hospital length of stay than PE patients with TAPSE greater than 17mm.

Pulmonary embolism patients with a TAPSE less than 15mm will have a statistically significant increased need for escalation of care beyond heparin alone and higher mortality than patients with an RV/LV ratio of greater than 1.’

1.5 References


2.1 Introduction

In this critical review of the literature, the existing evidence for and against the use of point-of-care measured tricuspid annular plane systolic excursion in prognosis of normotensive patients with acute pulmonary embolism will be examined, followed by analysis of the accuracy, reproducibility and utility of emergency department point-of-care echocardiography in the management of patients with PE, followed by a review of relevant literature regarding possible confounding variables. In order to perform this literature review, an extensive search was performed between July 2017 and May 2018 using the Scopus, Ovid MEDLINE, and PubMed databases. The following search terms were utilized in combination across each database: pulmonary embolism, submassive pulmonary embolism, right ventricle dysfunction, tricuspid annular plane systolic excursion, point-of-care ultrasound, bedside ultrasound, echocardiogram, emergency department, prognosis, hemodynamic decompensation, escalation of care, and mortality. No limit was placed on year of publication. The search was limited to English language sources and utilized articles included systematic reviews, meta-analysis, cohort studies, randomized clinical trials and case-control studies. Sources cited by selected articles were also reviewed to find additional sources.

2.2 Review of Empirical Studies About the Relationship Being Studied

2.2.1 Evidence demonstrating association of RV dysfunction and PE prognosis

A strong body of evidence exists associating increased mortality and need for escalation of care in PE with right ventricular dysfunction. The most consistent definition
of RVD used in the literature is an RV end diastolic value > 30mm, RV/LV ratio of >1, and paradoxical sepal wall motion, pulmonary hypertension > 30 mmHg, and a tricuspid regurgitant velocity >2.8m/s\(^1\). Studies vary considerably in their definitions of RVD and what measurements are included in analysis. Though the literature demonstrates an association between right ventricular dysfunction and mortality, there remains little consensus on the most accurate marker of RV dysfunction.

Ribeiro et al.\(^2\) observed an association between RV systolic dysfunction, as identified on echocardiogram in the emergency department within 1 day of PE diagnosis and death in a prospective cohort of 126 patients. In this cohort 10 of the 70 patients with RVD experienced in hospital mortality with a \(p = 0.002\). This study identified right ventricle dysfunction as qualitatively evaluated moderate and severe RV wall hypokinesis. This 1997 prospective cohort was one of the first papers to identify the relationship between RV dysfunction and PE mortality.

There were several limitations of this study. There is no identification of hemodynamic status of the patients in the study, in which 37 patients in this study received thrombolytic therapy. There is a well-defined association between hemodynamic instability and mortality in the literature\(^3,4\). This makes results less generalizable to risk stratification, as unstable patients will have increased mortality rate.

A 2000 prospective study by Grifoni et al.\(^5\) of 162 normotensive patients presenting with acute PE found an incidence of RV dysfunction of 40%. 6 of the 65 patients with RV strain and PE developed shock during admission and 3 died. This study defined RVD as RV dilation, paradox septal wall motion, and doppler evidence of
pulmonary hypertension. In this study none of the patients without RVD died, conferring a sensitivity and negative predictive value of PE related death of 100%.

There remain several limitations to the study. Statistical analysis was not completed on RVD and mortality in this study making the association only clinically significant. Patients who decompensated in this study had statistically significant lower blood pressures and age on presentation, as average blood pressures were 130 ± 17 in the stable patients, while patients with worsening clinical course and death had presenting blood pressures of 105 ± 29. 15% of stable patients were over 80 years old, while 67% of decompensating patients were. Advanced age and hypotension have been associated with worse outcomes in PE, making these differences substantial demographic differences when utilizing this study's findings.

Zhu et al. demonstrated an odds ratio of 5.23 in patients with RVD developing clinical endpoints of 14-day mortality, need for vasoactive agents, endotracheal intubation, or cardiopulmonary resuscitation in a prospective study of 520 normotensive patients diagnosed with PE. RVD was assessed on echocardiogram and defined as RVED/LVED >0.6, RV hypokinesis, loss of inspiratory collapse of IVC, or tricuspid regurgitant velocity of >2.8 m/s. Though RVD was associated with increased adverse events in this study, only RVED/LVED of >0.6 and RV hypokinesis reached statistical significance as independent predictors of mortality with odds ratios of 4.19 and 1.59 respectively.

This prospective study had several limitations. The definition of right ventricular dysfunction was very broad, which may have increased the incidence of RVD in this group. The study documented an RVD incidence of 47.7% in the study population, which
is higher other studies. Patients presenting in the RVD group were also more symptomatic on presentation with statistically significant differences in dyspnea, syncope, hypertension, and concomitant DVT than those with no RVD. The more advanced symptomology may have contributed to a greater mortality rate in the RVD group of 26.6% compared to 9.9% in the group without RVD\textsuperscript{6}. The study also failed to outline the therapy given for both groups as mortality in this study was higher than elsewhere in the literature where the mortality rate for PE 0.4-0.9 % in patients with PE but no RV dysfunction\textsuperscript{7}.

A 2014 meta-analysis by Cho et al.\textsuperscript{8} of 3283 patients comparing 30-day mortality of patients, hemodynamically stable PE patients with RVD as assessed by echocardiogram had a 2.29 increase in mortality than those with preserved right ventricle function. This corroborated the findings of Coutance et al.\textsuperscript{9} in a 2011 meta-analysis analyzing the 3-month mortality of 593 hemodynamically stable PE patients. Investigators demonstrated a 2.36 increase in mortality among patients with RVD compared to those with normal function. This study did not include TAPSE in its analysis but did use the definition of RVD as RVED/LVED of >0.9, which is a higher threshold than other studies, which often use an RVED/LVED of >1.0. This more advanced definition of RVD may have included patients in the normal RV function group, who may be classified as having RVD in other studies.

The meta-analysis by Cho et al.\textsuperscript{8} only used one database, PubMed, in its search limiting the power of its results. It did not include studies with clinical endpoints outside of its established 30-day mortality limiting he including of several studies with endpoints of 14-day, 40-day or 3-month mortality. The meta-analysis by Coutance et al.\textsuperscript{9} included
evidence of right ventricular dysfunction from CT scan. This is creates some inconsistency with measurement as most literature utilizes echocardiogram to assess RVD and there exists some variability in measurement of RD strain between CT and echo\textsuperscript{10}. Both meta-analysis were limited by an inconsistent definition of RVD in the literature, such as the value of RV/LV ranging from 0.8-1.0 in different studies.

Not all the literature supports the association between RVD and increased mortality however. In a 2017 study of 134 patients Chaudhary et al.\textsuperscript{11} found no difference in 30-day mortality between normotensive patients with RVD compared to those with preserved RV function. In this study 6 of 77 patients with RVD died, while 3 of 57 patients without RVD died. The mortality rate for patients with RVD in this study way 7.8%, which is consistent with other studies, however the mortality rate among patients with normal RV function was 5.3%, which is higher than other studies within the literature\textsuperscript{3}.

The patient population in this study had a high prevalence of malignancy, at approximately 31% and 50% in both groups respectively. Malignancy has been independently associated with mortality in patients with APE\textsuperscript{4}. This study was further limited by the high prevalence of RVD in the study population. 57% percent of patients enrolled has RVD, which is a larger prevalence than cited in most other studies\textsuperscript{1}. The greater prevalence of patients with RVD and higher mortality rate in the normal RV function group may represent enrollment of more severe patients in the study.

Overall, right ventricular dysfunction has been identified in existing literature as having a demonstrated association with PE related mortality and need for escalation of care. This association has been limited by an inconsistent definition of RVD, as
measurement thresholds and qualities of RVD differ between studies. Many studies in the existing body of literature do not include a TAPSE measurement in their designs. A review of existing literature highlights the need for a reliable and easily obtained measurement of RV function for consistent prognostic value in hemodynamically stable patients with acute PE.

2.2.2 TAPSE as a marker of RV dysfunction

Although right ventricular dysfunction has been associated with poor prognosis in normotensive pulmonary embolism patients, the definition of RVD can be met with several criteria. Tricuspid annular plane systolic excursion has been demonstrated in the literature to be a useful, reliable, and reproducible marker of right ventricular function in normotensive PE patients. In several studies reduced TAPSE has demonstrated a greater association with mortality than other markers of RVD.

In the 2014 prospective cohort study Lobo et al.\textsuperscript{12} enrolled 782 normotensive patients with APE comparing those with TAPSE > 1.6 cm to those with a TAPSE of $\leq$ 1.6 cm. Those with a TAPSE of $\leq$ 1.6 cm were found to have statistically significant increased systolic pulmonary artery pressure, RV end diastolic diameter, RV/LV end diastolic ratio and increased prevalence of RV hypokinesia. Mortality in the group with a TAPSE of $\leq$ 1.6 cm was significantly higher, as the hazard ratio (HR) was 2.3 from any cause and 4.4 from PE related death. 146 of the 782 patients enrolled in the study had a TAPSE of $\leq$ 1.6 cm representing a prevalence of 18.6\% in the study population.

This study demonstrates a significant association between TAPSE $\leq$1.6 mm and mortality, but it has several limitations. 22 of 146 (16\%) of patients with RVD had a
history of COPD and 14 (10%) patients had a history of congestive heart failure (CHF). CHF and COPD have been associated with decreased TAPSE values\textsuperscript{13-15}. Reduced TAPSE in these pathologies has also demonstrated association with poor prognosis, possibly confounding data\textsuperscript{14-16}. This study also utilized data from transthoracic echocardiogram taken within 24 hours of diagnosis. This is inconsistent with our study, as we will perform point-of-care echocardiogram in the ED upon diagnosis. Though the findings of the Lobo et al.\textsuperscript{12} study demonstrate a correlation of TAPSE of \( \leq 1.6 \) cm and mortality, its methodology does not demonstrate how TAPSE can be utilized in the ED for prognostication.

Pruszycyk et al.\textsuperscript{17} analyzed the echocardiographic parameters associated with right ventricular dysfunction in a 2014 study of 411 hemodynamically stable patients presenting with APE to the emergency department with clinical endpoints of 30-day PE related mortality and/or thrombolysis. 241 of the 411 patients enrolled were classified as having submassive PE. 21 of 411 patients reached clinical endpoints and 19 of these patients were from the submassive PE group. The average TAPSE in the clinical endpoint group was 12mm with a range of 6-20mm, while TAPSE in the remaining patients averaged 21mm with a range of 6-34mm, with a \( p \) value of \(<0.0001\). In this study TAPSE \( \leq 15 \)mm showed a hazard ratio of 27.9, and a TAPSE of \(< 16 \)mm showed an HR of 14.48. This study also found TAPSE \( \leq 15 \)mm to have a higher positive predictive value of PE related mortality and thrombolysis at 22.5\%, than an RV/LV ratio of \( >1 \) at 13.1\%.

This study demonstrates an association between a TAPSE of \( \leq 15 \)mm and PE related mortality and/or thrombolytic therapy in hemodynamically stable patients with APE. Though statistically significant associations with the clinical endpoints were also
identified with several echocardiographic parameters including RV/LV ratio of >1, HR of 7.71, McConnell's sign, HR of 3.6, these associations have frequently been identified in the literature\textsuperscript{1,7}. TAPSE of \( \leq 15\text{mm} \) remained the measurement of RVD with the strongest association with the clinical endpoints with an HR of 27.9.

This study was performed on patients admitted from the ED and the study population included 142 of 411 patients with COPD, CHF, or neoplasm, including 9 of the 21 patients reaching clinical endpoint\textsuperscript{17}. This population includes patients with conditions known to have associations with reduced TAPSE and increased mortality with TAPSE \( \leq 16\text{ mm} \)\textsuperscript{14}. Echocardiography was performed immediately on admission in 193 patients, within 24 hours in 159 patients, and between 24 and 72 hours after admission in 59 patients, showing some inconsistency in data collection. Though all echocardiograms were read by a standardized protocol, the echo may have been taken after therapy was initiated in these patients possibly confounding results.

In 2016 Paczynska et al.\textsuperscript{18} enrolled a cohort of 76 hemodynamically stable patients presenting with APE with echo obtained as soon as possible upon admission. 8 out of 76 patients had PE related mortality within 30 days of diagnosis. The average TAPSE value for the mortality group was 12.3 \( \pm 3.6 \), while in the remaining patients TAPSE was 20.3 \( \pm 5.2 \). TAPSE was the only value of RVD to have statistically significant mortality prediction, with an HR of 0.73, while RV/LV ration >1 failed to reach statistically significant association. The TAPSE \( \leq 15\text{ mm} \) showed a PPV of 43.75\% for PE related mortality and negative predictive value of 98.3\%. This study demonstrates TASPE as a powerful prognostic factor for submassive PE.
This study has several limitations. The sample size of 76 patients is small. Paczynska et al.\textsuperscript{18} also enrolled patients with comorbidities in their study. Patients with COPD, CHF, or neoplasm made up 30\% of the study population and 50\% of the mortality group, though not statistically significant, this could possibly influence TAPSE measured in this population. Mortality and survival groups had a statistically significant differences in heart rate, 110 compared to 87 bpm, and age, averaging 82 compared 66\textsuperscript{18}. Age and presenting heart rate may have been contributory as both have been associate with poor prognosis for PE previously\textsuperscript{1,3}. This study lacks a specific protocol for when to obtain echocardiography, other than obtaining it as soon as possible. Without a structured time of obtaining ultrasound, external validity is diminished as the value may have been affected by therapy up until that point.

Reduced TAPSE was associated with hemodynamic instability and shock in the 2017 study by Rabie Samra et al.\textsuperscript{19}. The prospective cohort study of 50 patients with APE placed patients into group I, hemodynamic instability, group II, hemodynamic stability with RVD and group III, hemodynamic stability with normal RV function. Group I had an average TAPSE of 13.8 ± 2.02, while group II and III had respective TAPSE measurements of 15.37± 1.7 and 19.67 ± 1.66. The difference in TAPSE among groups demonstrated a statistically significant, p= 0.0047, association between reduction in TAPSE with pulmonary embolism severity. Reduced TAPSE correlated with day 1 mortality, as 6 of the 13 patients with TAPSE ≤ 14 mm died in this study. 6 of the 16 patients in this study with a high risk PESI score, PESI >124, died, demonstrating a higher accuracy of TAPSE in prediction of acute PE mortality. Linear regression analysis
of PESI and TAPSE showed a very strong negative correlation, demonstrating a correlation between high PESI score and objectively measured reduced TAPSE.

The study by Rabie Samra et al. has several limitations. It was a single center study with a small patient population of only 50 patients in Saudi Arabia limiting its generalizability to a larger American population. The inclusion of hemodynamically unstable patients, though demonstrating an association between TAPSE and disease severity, limits the study's relevance in risk stratifying hemodynamically stable APE patients. Statistical analysis was not performed on the hemodynamically stable with RVD population alone, though the group did exhibit a 13% mortality rate and 4 of the 15 patients required thrombolytic therapy. The TAPSE of ≤ 14mm used in this study is also lower than cited in many other studies, which may result in a greater association than would be present at a higher TAPSE threshold.

Zanobetti et al. investigated how echocardiographic measurements could predict RVD, and how these measurements were affected by PE treatment. This study showed that though TAPSE is reduced in APE, RV function recovers with anticoagulation or thrombolytic therapy. In the population of 120 APE patients, the mean TAPSE on presentation was 15 ± 7mm. When remeasured after 7 days of therapy, TAPSE improved to 20 ± 6mm and improved to 22 ± 6mm after 1 month of treatment. Sub-analysis revealed that in patients with a TAPSE <15 mm and pulmonary hypertension, only patients receiving thrombolytic therapy had improved RV function, while TAPSE remained reduced in patients receiving heparin therapy alone. This study thus demonstrates that patients with TAPSE < 15mm and pulmonary hypertension may benefit from thrombolytic therapy. Investigators found no statistical correlation between
TAPSE and 7 day mortality within the study. This prospective cohort study illustrates only how RV function may be improved with therapy and treatment.

In a 2012 prospective cohort study of 50 patients with APE, Park et al. 21 found TAPSE to be a reliable marker of RV systolic dysfunction. This study identified 39 patients with RVD as assessed by right ventricular fractional area change. Investigators identified a TAPSE of < 17.5mm as an ideal cut off for identifying RVD with a sensitivity of 87% and specificity 91%. In the study 2 patients died of PE related events, which demonstrated no statistical correlation with TAPSE < 17.5mm on multivariate analysis.

This was a small study of only 50 patients. It used stored patient images for analysis, which may have affected the quality of measurements taken. RV systolic function was assessed by right ventricular fractional area change, which may not have been the most accurate control. a TAPSE of 17mm has been identified in the literature as being within physiological normal range22,23, making TAPSE <17.5mm a high definition of RVD. This high TAPSE may have played a part in there being no statistically significant relationship with mortality.

Much of the existing literature demonstrates consistent correlation between reduced TAPSE and mortality or hemodynamic decompensation, though some smaller studies have not found a significant association. There exists some inconsistency in definition of reduced TAPSE, as it has been described from $\geq 14$mm to $\geq 17.5$mm in different studies. The majority of the literature come from a cardiology perspective, but most studies attempt to take TAPSE measurements as close to presentation as possible,
usually while the patient is in the ED. Further studies outlining the prognostic utility of TAPSE as patients they are diagnosed in the ED would strengthen the existing literature.

2.2.3 Interobserver reliability of TAPSE

TAPSE has been utilized to assess right heart function since it was first identified by Kaul et al. in 1984\textsuperscript{24}. It is routinely measured in echocardiography and can be obtained through point-of-care ultrasound in the emergency department. There have been several studies performed demonstrating the interobserver reliability of point-of-care measurement of TAPSE is consistent and accurate.

Kopecna et al. compared interpretations of RV enlargement, RV/LV ratio, RV free wall hypokinesia and TAPSE on echocardiogram by central and local cardiologists in 75 patients presenting with APE. Mean TAPSE measured by both central and local cardiologists was $2.1 \pm 0.4$ cm. The intraclass observation of TAPSE was deemed very good with a kappa value of 0.85. When RV dysfunction is defined as a TAPSE of $\leq 1.6$ cm the two observers agreed whether RV dysfunction is present or not with a weighted kappa of 0.86. This demonstrates consistent measurements of TAPSE among cardiologists. The interobserver agreement for RV dilation, RV/LV ratio, and RV hypokinesia was markedly reduced compare to TAPSE with kappa values of 0.45, 0.65 and 0.70 respectively\textsuperscript{25}. This study found TAPSE to have the greatest observer reliability among echo measured values of RVD.

This study was limited by the fact that only 8 patients in the study had TAPSE $\leq 1.6$, meaning that, despite the clear consensus in interpretation, the sample size for the dysfunction group was small. The study demonstrates that among cardiologists TAPSE is
the least user dependent and most reproducible indication of RVD on echocardiogram in normotensive patients with PE. This study also highlights values of RV/LV ratio and RV dilation have lower interobserver agreement, leaving more room for error in interpretation when using the test for guiding treatment. This is a study of cardiologists, so the generalizability of the study for use in the ED is limited.

Weekes et al. demonstrated interobserver consistency when assessing RVD in a 2016 study which compared the interpretation of 9 packets of echocardiographic images taken of normotensive patients presenting with acute PE in the emergency department by 2 emergency physicians and 2 cardiologists. In this study TAPSE of <10mm with RV free wall hypokinesia was included with RV/LV ratio >1.0 and interventricular septum flattening in the definition of RV dysfunction. In this study there was 74.2% agreement on the presence of RV dysfunction with a kappa value of 0.69\textsuperscript{26}. The findings were in line with the findings of Kopecna et al., in which interobserver agreement of RV/LV ratio >1.0 was 0.65\textsuperscript{25}.

This study has several limitations. It does not look at TAPSE independently limiting the applicability of the study in validating the use of TAPSE. Though in this study TAPSE was not looked at independently its inclusion in the definition of RV dysfunction, demonstrates continued interobserver agreement when present. The definition of RVD in this study uses a TAPSE of < 10mm, which is lower than most definitions in the literature and may be easier to assess for observers to assess, but also less likely in a normotensive patient given its severity.

The use of point-of-care focused cardiac ultrasound by emergency department physicians to assess TAPSE was evaluated in the 2017 prospective cohort study by Daley
et al.. The study enrolled 150 patients, 32 of whom were PE positive, who received FOCUS. When emergency physicians performed FOCUS with an abnormal TAPSE cutoff of <1.7 cm the kappa value was 0.94, demonstrating an excellent ability of emergency physicians to accurately identify abnormal TAPSE with FOCUS. The study used intraclass correlation coefficient (ICC) to demonstrate interpreter reliability for TAPSE. Investigators found an ICC of 0.87, when comparing measurement of TAPSE by 2 emergency physicians in 30 of the study's subjects. This finding demonstrates that FOCUS performed by trained emergency physicians identifies consistent and reliable measurements of TAPSE.

This study was designed to demonstrate FOCUS measured TAPSE for diagnosing PE rather than prognosticating it, however the interobserver reproducibility and accuracy demonstrated can be applied to the use of this measurement for prognosis as well. This study utilized an abnormal TAPSE cutoff of 1.7 cm, while our study will use an abnormal TAPSE cutoff of 1.5 cm, which may affect the application of this study, as it was not designed to use this value. Daley et al. used emergency physicians with extensive training and experience in point-of-care ultrasound, which may not be consistent with the capabilities of all emergency physicians, reducing the study's generalizability.

The existing literature on the reliability of TAPSE remains sparse with 3 studies assessing interobserver reliability in measuring TAPSE. TAPSE had greater reliability and reproducibility than RV/LV ratio, RV dilation, and RV hypokinesis in the cardiology literature, favoring its use in guiding treatment for PE. Daley et al. demonstrated excellent reliability in using FOCUS to measure TAPSE in the ED. The existing literature
shows echocardiographic measurement of TAPSE to be a reliable measurement of right ventricular function.

2.2.4 Point-of-care cardiac ultrasound use in the emergency department

The literature demonstrating use of TAPSE in the emergency department to guide treatment of pulmonary embolism remains sparse. The use of point-of-care or bedside cardiac ultrasound in diagnosis and prognosis of pulmonary embolism in the ED has been addressed in several studies however. FOCUS is a routinely used and useful tool in the ED with its use recommended by the American Society of Echocardiography and American College of Emergency Physicians\textsuperscript{28}. The majority of the studies look at ultrasound performed and read by experienced and specifically trained emergency physicians. These studies have shown considerable variation in interobserver agreement, but also demonstrate benefit to their use in PE prognosis.

Taylor et al.\textsuperscript{29} analyzed the focused limited echo examinations of 411 patients presenting to the ED with suspected cardiac etiology and received consultation echocardiogram within 72 hours comparing findings of the right ventricular strain on echocardiogram in a 2014 retrospective cohort study. 69 providers performed focused limited echocardiograms in the study over a 12-month period. RV strain was noted in 6.2\% of patients on limited echo, while it was observed in 18\% of patients on consultative echo. The kappa value for agreement of RV dilation was 0.44. The agreement increased with training as fellowship-trained providers had a kappa value of 0.55.
Though agreement was not ideal in this study, the presence of RV dilation on limited echo was quite specific at 0.98, while it was not sensitive at 0.26. This demonstrates the feasibility of using limited echo to identify RV dysfunction in helping to prognosticate PE patients. While this study was not limited to patients with confirmed PE, the interobserver agreement and specificity of limited echo demonstrates its usefulness. TAPSE was not included in this study, but it is capable of being measured with limited ultrasound and could used to more clearly prognosticate echo with limited echo.

A 2013 retrospective chart review was performed on 161 patients diagnosed with PE and who received a emergency physician performed point-of-care focused cardiac ultrasound (FOCUS) in order to identify its prognostic value in predicting in hospital adverse events in PE patients. In the review right ventricular strain was defined as RV/LV ratio of $>1$, RV hypokinesia or a McConnell's sign, while adverse outcome was defined as shock, respiratory failure requiring intubation, death or recurrent VTE. 25 of the 161 patients enrolled experienced adverse events. RV strain as assessed by FOCUS had statistically significant predicative value with an odds ratio of 9.2.\textsuperscript{30}

This study did not include TAPSE in its definition of RV strain this study demonstrates the utility of FOCUS use in emergency departments in predicting adverse outcomes in PE patients. As TAPSE has been found in other studies to predict mortality better than RV/LV ratio, which was the most common finding of RV strain in this study, utilization of TAPSE in point of care ultrasound could benefit prognostication of PE. The study was limited by possible selection bias, as it only enrolled patients receiving FOCUS in the ED, which may select for more advanced patients. This study was performed by
ultrasound experienced emergency physicians, which reduces its generalizability to a broader population of providers.

Dresden et al. 31 performed a prospective observational study of 146 patients with suspected to pulmonary embolism to assess bedside echocardiography for diagnosis of PE. Researchers found an observed agreement of 100% between 4 emergency medicine physician investigators and blinded cardiologists in assessing right ventricular dysfunction measured by one of the investigators on bedside ultrasound. Though this study was not designed to demonstrate bedside echocardiography in predicting mortality, it demonstrates interobserver agreement on the measurement of right ventricular strain with bedside echo.

FOCUS and bedside echo are currently utilized in emergency departments to assess RV dysfunction in patients with pulmonary embolism. There remains some limitation of interobserver reliability in assessing RVD, but the FOCUS has shown prognostic benefit when used in the ED. TAPSE has been shown to have a greater amount of interobserver agreement in the published literature with kappa measurements of 0.85 25 and 0.9427 demonstrating greater reliability than the 0.44 assessed by Taylor et al.29. TAPSE may provide more reliable measurements than are already being utilized in the ED for evaluation of PE. The findings of our study may help point-of-care ultrasound to be more accurately, reliably, and effectively utilized in guiding therapy for APE patients.
2.3 Review of Studies to Identify Possible Confounding Variables

2.3.1 Pathologies affecting TAPSE

Our proposed study has identified a tricuspid annular plane systolic excursion of \( \leq 15 \text{mm} \) as a prognostic indicator for need for escalation of care beyond heparin alone and mortality in patients with submassive pulmonary embolism. Pulmonary embolism is not the only pathology, which can reduce TAPSE however. There have been several studies, which demonstrate COPD and CHF can reduce TAPSE. This would create an unclear clinical picture, as PE might not be the cause of reduced TAPSE in these cases.

Ghio et al.\textsuperscript{32} studied TAPSE in 140 patients with chronic congested heart failure. They identified a TAPSE of \( \leq 14 \text{mm} \) was associated with increased death from CHF. TAPSE \( \leq 14 \text{mm} \) had a hazard ratio of 2.58 and was a strong predictor of mortality, especially when coupled with NYHA class II or IV heart failure. This study also demonstrated excellent intraobserver and interobserver correlation with r-values of 0.94 and 0.93 respectively. This study demonstrates correlation of CHF and reduced TAPSE.

Kjaergaard et al.\textsuperscript{14} found in a prospective cohort of 817 patients with CHF a hazard ratio of 0.74 for every doubling of TAPSE. The most mortality was identified in patients with a TAPSE <14mm. In this study COPD was also found to increase mortality with a hazard ratio of 2.39. This study demonstrates reduced TAPSE has poor prognosis in patients with CHF. It also demonstrates COPD as being possible confounder right heart pathology.

Caso et al.\textsuperscript{16} explored the influence of COPD on TAPSE in a prospective study of 63 patients. TAPSE was reduced in only patients with COPD and pulmonary hypertension, with mean measurements of 14.0 ± 5.9 but was within physiological
normal limits of 19 ± 3.9 in COPD patients without pulmonary hypertension. As PE can raise pulmonary arterial pressure, this demonstrates possible confounding by COPD in PE patients.

The existing literature has associated COPD and CHF with reduced TAPSE. These findings have also correlated with an increased mortality in patients with reduced TAPSE. CHF and COPD may confound results as to the pathophysiology behind the reduction in TAPSE, as well with the cause for increased mortality. In previous studies CHF and COPD patients have been included in study populations, but we will exclude patients with history of these pathologies from our study to limit confounding.

2.3.2 Risk factors for hemodynamic decompensation in pulmonary embolism

There are other risk factors, such as advanced age, malignancy and concomitant disease, which put individuals at risk for adverse events when diagnosed with PE. These factors may be independently associated with mortality or contributory to PE pathology in causing mortality. In order to adequately assess the prognostic power of TAPSE, the following risk factors should be controlled for as they have been identified as contributing to increased mortality and escalation of care in PE patients.

Age

In normotensive patients presenting with acute PE, increased age has been associated with increased mortality. In analysis of clinical outcomes from the International Cooperative Pulmonary Embolism Registry (ICOPER) Goldhaber et al.\(^4\) found an association between age >70 and 3-month mortality with a hazard ratio of 1.6.
This study did not prescribe any treatment algorithms or management guidelines for patients however, and the international design of the study allows for a wide degree of treatments, possibly confounding results.

Lopez-Jiminez et al.\textsuperscript{33} found an odds ratio of 3.6 between age $>$80 and mortality, with 3.7\% mortality of the 2890 patients with age $>$80 registered in the Registro Informatizado de la Enfermedad TromboEmbólica (RIETE). This study assesses PE patients in a Spanish registry making it not entirely applicable to US populations, but the findings are consistent with other studies.

Age is a variable in the PESI and sPESI prognostication models for acute PE. This variable was derived based on the association between age $>$65 and 30-day mortality in 10,354 PE patients discharged from 186 Pennsylvania hospitals between 2000 and 2002\textsuperscript{34,35}. This study found a beta coefficient of 0.03 associated with each year of patient age associated with 30-day mortality. Age $>$65 was independently associated with mortality in this study, and have been further validated in follow up literature\textsuperscript{36,37}.

Age $>$80 was associated with increased mortality in normotensive patients with acute PE in the study by Grifoni et al.\textsuperscript{5}, though it was not associated with in hospital mortality in the cohort studied by Ribeiro et al.\textsuperscript{2,5}. Overall the literature suggests an association between increased age and mortality in acute pulmonary embolism patients. This has influenced our study as we have set our inclusion criteria to patients $<$75 years old to reduce confounding.
Malignancy

Malignancy has been associated with increased mortality in patients presenting with acute pulmonary embolism. Goldhaber et al.\textsuperscript{4} found cancer to have a hazard ratio of 2.3 when assessing 2454 patients in the ICOPER registry. As with age, the validity of this study is hurt by its lack of management guidelines in patients. The large population size however benefits this study and the findings are in line with other studies.

A 2018 retrospective cohort of 8641 patients by Alotaibi et al.\textsuperscript{38} found cancer to predict mortality in all age groups. The strongest association between cancer and < 3 month mortality was found in women and men \(\leq 50\) years old with hazard ratios of 17.85 and 2.323 respectively. This was a large study, but did have some limitations in that its retrospective nature limited researchers ability to identify cause of death, and there was no standard treatment prescribed.

Concomitant Disease

Other diseases occurring with pulmonary embolism have been associated with adverse outcomes. Goldhaber et al.\textsuperscript{4} identified CHF and COPD as being associated with increased mortality in patients with PE with hazard ratios of 2.4 and 1.8 respectively. CHF and COPD are pathologies, which have not been excluded from other studies. The presence of CHF and COPD may influence TAPSE, as well as prognosis of PE.

COPD and CHF are variables present in the PESI and sPESI scores. These diseases were associated with worse prognosis in PE patients in a study by Aujesky et al.\textsuperscript{36}. The derivation sample of the PESI score consisted of 10,354 PE patients found a beta coefficients of 0.31 and 0.30 associating CHF and chronic lung disease respectively.
with 30-day mortality. Through use of this measure in the PESI and simplified PESI scores, the association between chronic lung disease and COPD have been further validated in the literature\textsuperscript{37}.

2.4 Review of Relevant Methodology

2.4.1 Primary outcomes

Studies have correlated reduced TAPSE with poor prognosis in pulmonary embolism. These studies have previously used set values of TAPSE indicating right ventricular dysfunction. Other studies have assessed TAPSE on a continuous scale, demonstrating the mean TAPSE at which adverse events occur. Our study follows the format of the latter as it allows a clear differentiation between dysfunction defined by TAPSE and normal function. TAPSE definition of dysfunction most commonly varies between 14mm and 17mm in the literature. Our study chose a TAPSE value of 15mm to define RVD, as it has more clear association with mortality in the study by Pruszcyk et al.\textsuperscript{17} and allows for a more clearly established difference from physiologically normal TAPSE.

The literature traditionally identified the outcomes of interest as being mortality and escalation of care. Evaluation of mortality can vary in range. Studies have established a 3-month mortality tend to see a greater mortality, however this is not always due to increase PE mortality. The majority of PE related death comes during hospitalization however\textsuperscript{4,39}. For this reason and to reduce confounding with mortality from other causes we have limited our study of mortality to during hospitalization.
Care for normotensive patients presenting with acute PE begins with heparin therapy. The use of thrombolytic therapy in submassive PE patients has been contentious. Sharifi et al.\cite{40} found no statistically significant outcome in total mortality in using thrombolysis on submassive patients, though it did reduce mean length of stay from 4.9± 0.8 days to 2.2 ± 0.5 days in the group receiving thrombolysis. Meyer et al.\cite{41} found an odds ratio of 0.44 of mortality or hemodynamic decompensation when using fibrinolytics in moderate risk PE compared to placebo, but also had an odds ratio of 5.55 in major extracranial bleeding in the group receiving fibrinolysis. These findings demonstrate minimal utility in therapy beyond anticoagulation for hemodynamically stable patients with acute PE. Thrombolytic therapy and embloectomy have been identified as beneficial in hemodynamically unstable patients however\cite{3}. Our study can thus identify an endpoint being escalation of therapy beyond heparin, as an outcome if it is indicated through hemodynamic decompensation.

2.4.1 Secondary outcomes

The majority of patients diagnosed with APE in the ED are admitted to the hospital. Schissler et al.\cite{42} found 83% of patients diagnosed with PE were admitted to the hospital from emergency departments in a cross sectional study of 283 PE diagnoses made in the ED. In a study of 61,249 admissions for pulmonary embolism from 263 hospitals, Admon et al.\cite{43} found an ICU admission rate that ranged from 2.9% - 79.9% for PE patients. As low risk pulmonary emboli can be treated as outpatient it becomes increasingly important to risk stratify patients presenting with APE and understanding how their hospital course goes. Chaudhary et al.\cite{11} found a length of stay difference

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between patients with RVD and those without RVD of 7.13 days and 5.46 days respectively. Daley et al.\textsuperscript{27} found patients admitted with PE had an average length of stay of 6.3 ± 5.3 days. Cohen et al.\textsuperscript{44} found an average hospital length of stay of 5.4 days, with length of stay being longer in hospitals with greater use of transthoracic echocardiogram in prognosis of PE. Pulmonary embolism has a range of presentation and often involves hospitalizations of > 5 days. By looking at how a TAPSE ≤ 15mm influences hospital length of stay compared to a TAPSE >17mm, it will allow clinicians to better assess the care needs of patients and better plan their stay.

2.5 Conclusion

The existing evidence around the use of tricuspid annular plane systolic excursion in prognosis of pulmonary embolism demonstrates a clearly established trend in suggesting that a reduced TAPSE is associated with increased mortality and need for escalation of care. The definition of reduced TAPSE has varies from 10mm to 17mm in different studies with threshold values of 15mm and 17mm being the most common\textsuperscript{17,18}. Our study has identified 15mm as our definition of abnormal TAPSE as it is most strongly associated with mortality in the literature and as it a lower value of TAPSE it is included in a larger number of studies\textsuperscript{17}. Though this will reduce the incidence of abnormal TAPSE, we believe it will provide a more definite prognosis, given the literature reviewed.

Studies identifying the reliability of ultrasound in identifying right ventricular dysfunction have ranged from kappa values of .45 to .85 in regard to interobserver accuracy\textsuperscript{25,26,29}. There is evidence that TAPSE has the greatest interobserver consistency,
making it a more ideal echocardiographic marker of right ventricle dysfucntion\textsuperscript{25,27}.

Point-of-care echocardiography in the emergency department, though not commonly explored in the literature has demonstrated reproducible and consistent findings when obtained and read by emergency physicians\textsuperscript{29}. The majority of these studies have been done on emergency physicians specifically trained in ultrasound. Because the literature has not validated FOCUS performed by novice emergency physicians, our study will only utilize academic emergency departments with specific ultrasound curricula and emergency providers experienced in ultrasound. The use of FOCUS in measuring TAPSE will be generalizable as TAPSE measurement demonstrates reliability and point-of-care ultrasound is already utilized in the ED to identify RVD. Based on the literature, TAPSE measured by FOCUS may provide more reliable and reproducible measure of RVD with a greater association with mortality.

2.6 References


19. Rabie Samra S, Gomaa A, Shaalan A. Assessment of acute pulmonary embolism outcome in hospital through Tricuspid Annular Plane Systolic Excursion versus


CHAPTER THREE: STUDY DESIGN

3.1 Study Design

We propose a multi-center, prospective cohort study conducted in emergency departments at Yale New Haven Hospital, Boston Medical Center, and Rhode Island Hospital assessing outcomes of mortality and need for escalation of care beyond heparin alone of two cohorts with either a TAPSE $\leq 15\text{mm}$ or a TAPSE $> 17\text{mm}$ as measured by point-of-care echocardiography.

3.2 Study Population, Sampling, and Recruitment

The study will take place over twenty months, from January 2019 until August 2020. The study will use convenience sampling to screen all hemodynamically stable patients diagnosed with acute pulmonary embolism by computed tomography pulmonary angiogram as they present to participating emergency departments. Flyers (Appendix C) will be placed in participating ED's requesting that investigators be contacted for patients with acute PE on CTPA. Investigators will also monitor hospital electronic ED track board for eligible patients fitting inclusion criteria. Patients will be approached and informed consent obtained.

Inclusion criteria include age greater than 18 years old and pulmonary embolism diagnosed on CTPA. Exclusion criteria includes hemodynamic instability, as defined as a systolic arterial blood pressure of $< 90\text{mm Hg}$ or a drop of at least 40 mm Hg for at least 15 min or shock, age $> 75$ years, history of malignancy, and concomitant diagnosis of congestive heart failure, chronic obstructive pulmonary disease or pulmonary hypertension.
3.3 Subject Protection and Confidentiality

All hospitals will require approval by their own institutional review boards. We will seek approval for our research protocols from the Yale Human Research Committee Institutional Review Board. Our study will comply with all applicable criteria of the Yale University IRB Policy 100. All investigators will have evidence of institutional training in the Health Insurance Portability and Accountability Act of 1996 (HIPPA) Privacy Training and complete the National Institute of Health (NIH) Protecting Human Research Participant Training via the NIH's training website. All potential conflicts of interest will be disclosed to the institutional review board and principle investigator.

This observational study will follow chart review protocol. There is no risk to any subject in either cohort. This study will not affect treatment plans or prescriptions because of this study. Consent will be obtained by all patients participating in the study by consent form (Appendix D). Requested information from patients includes MRN, age, sex, race, past medical history, current medical problems, and records of past hospitalizations.

Patient privacy will be maintained throughout the study. Patient names on clinical data will be de-identified. Patient information will only be accessed on secure institutional servers. Computers housing patient data will be password protected requiring username and password to log in. Investigators will communicate patient sensitive data only with email encryption. Any physical copies of patient information will be kept in binders in locked file cabinets in locked offices. All members of the investigation team will maintain HIPPA compliance throughout the study.
3.4 Study Variables and Measures

This prospective cohort study will be comparing one group with a TAPSE \leq 15\text{mm} and another group with a TAPSE > 17\text{mm}. TAPSE of \leq 15\text{mm} will be the marker of right ventricle dysfunction in the study. Emergency department physicians with experience in point-of-care focused cardiac ultrasound will take TAPSE measurement within 6 hours of initiation of heparin therapy. A blinded off-site cardiologist will evaluate TAPSE measurements. Measurements will be taken in apical 4-chamber view in m mode during echocardiography. Other measurements associated with RV dilation will be taken. These will include right ventricular diameter, right ventricular end diastolic diameter to left ventricular end diastolic ratio, and RV hypokinesia.

The primary outcomes of interest are in-hospital mortality and need for escalation of care beyond heparin alone. Escalation of care beyond heparin alone is defined as the use of thrombolytic therapy, embolectomy, endotracheal intubation, or the use of vasopressors. These are markers of poor disease outcome and treatment failure of anticoagulation therapy alone. The primary outcomes are both dichotomous variables. The outcomes will be evaluated through the entire hospitalization of up to 14 days.

Our investigators are also comparing secondary outcomes of hospital length of stay between groups. This is a continuous variable, which is defined as days spent in hospital. The other secondary outcome is mortality of patients with a RV/LV end diastolic diameter of >1. This is a dichotomous outcome.
3.5 Confounding Factors

We will collect baseline data of possible confounding variables, which may influence patient outcomes. These characteristics include age, sex, BMI, blood pressure, heart rate, oxygen level, cigarette use, and history of coagulopathy, hypertension, or coronary artery disease. We will also record data on the presence of dyspnea, chest pain, syncope, cough, hemoptysis, palpitation, or concomitant DVT. These confounding factors are shown in table 1.

3.6 Data Collection

Measurement of TAPSE will be performed by emergency department physicians who are experienced in point-of-care focused cardiac ultrasound using a Phillips Sparq Ultrasound System. All investigators will be credentialed in FOCUS or complete a 1 day workshop on FOCUS. FOCUS will be performed within 6 hours of initiation of heparin therapy. After initial ultrasound, data will be performed through chart review of the participants. Investigators performing chart review will be blinded to which TAPSE group the patient belongs. Data will be collected and arranged in Excel files for statistical analysis by the sub-investigator.

3.7 Sample Size Calculation

The primary outcomes of this study are in-hospital mortality and need for escalation of care beyond heparin alone. Both outcomes are dichotomous which will be presented as incidence proportions. We will be comparing two cohorts with a sample size ratio of 5:1 using a one tailed rest with power of 80% and confidence interval of 95% for
the primary endpoint. We require an estimate sample size of 42 for the TAPSE ≤ 15mm group and 206 for the TAPSE >17mm group. Sample data was acquired from Lobo et. al.\(^1\) and Paczynska et al.\(^2\), comparing incidence of reduced TAPSE in acute pulmonary embolism patients. The sample size calculation is in Appendix E and was performed at http://www.openepi.com/SampleSize/SSCohort.htm.

3.8 Analysis

All data will be analyzed using Statistical Analysis System Software. To compare the incidence proportions of mortality and escalation of care beyond heparin alone between the TAPSE ≤ 15mm and TAPSE > 17mm groups we will use a chi square test with alpha of 0.05. Secondary outcome of hospital length of stay will be evaluated using multiple linear regression. RV/LV end diastolic diameter >1 mortality incidence proportion will be assessed using a chi square test. Incidence proportions of mortality in TAPSE ≤ 15mm and RV/LV end diastolic diameter >1 will be compared using a conditional exact test.

Baseline data for study populations will be analyzed and adjusted to control for confounding. Nominal variables such as age and presence of symptoms and medical history will be compared using chi-squared tests. Continuous variables such as systolic blood pressure and BMI will be compared using unpaired t-tests. Multiple linear regression will be used to adjust for confounding variables in primary and secondary outcomes.
3.9 Timeline and Resources

The total length of the study including recruitment, patient follow up, and data analysis will be 24 months. Recruitment will begin on January 2, 2019 and continue through August 2, 2020. Data analysis will be completed by December 2020. The primary investigator (PI) will be Christopher Moore, MD, and the co-primary investigator will be Matthew Drause, PA-SII, who will centrally handle the data analysis and statistics. Numerous staff will be required at Yale New Haven Hospital, Rhode Island Hospital and Boston Medical Center to identify participants in the ED, discuss the study and obtained informed consent. Following patient enrollment, emergency department staff will also make sure all baseline data is present in the electronic medical record (EMR). Emergency physicians trained and experienced in FOCUS will be asked to participate in the study, who will be responsible for performing and reading the echocardiogram in consented patients.

Participating hospitals were selected because they are high volume emergency departments with established emergency ultrasound fellowship programs. All participating hospitals use EPIC EMR, allowing for consistent data reference and collection. A computer programmer will design algorithms required to gather patient data. Sufficient office space and access to secured computers will be required at each site. Data analysis will take place in offices at Yale New Haven Hospital.

3.10 References

Table 1. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>TAPSE ≤ 15mm Group</th>
<th>TAPSE &gt; 17mm Group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Mean (SD)</td>
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<td>unpaired t-test</td>
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<tr>
<td>≤50</td>
<td>(%)</td>
<td>(%)</td>
<td>chi-squared</td>
</tr>
<tr>
<td>50-65</td>
<td>(%)</td>
<td>(%)</td>
<td>chi-squared</td>
</tr>
<tr>
<td>65-75</td>
<td>(%)</td>
<td>(%)</td>
<td>chi-squared</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td>BMI</td>
<td>Mean (SD)</td>
<td></td>
<td>unpaired t-test</td>
</tr>
<tr>
<td>Systolic Blood pressure</td>
<td>Mean (SD)</td>
<td></td>
<td>unpaired t-test</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>≥100</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td>Pulse oxygenation</td>
<td>&lt;90%</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td>Symptomology</td>
<td>Chest Pain</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td></td>
<td>Palpitation</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td></td>
<td>Cough</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td></td>
<td>Dypnea</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td></td>
<td>Hemoptysis</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td></td>
<td>Syncope</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td></td>
<td>Concomitant DVT</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td>Medical History</td>
<td>Hypertension</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td></td>
<td>Coronary Artery</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td></td>
<td>Disease</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td></td>
<td>Coagulopathy</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td>Social History</td>
<td>Cigarette Use</td>
<td>(%)</td>
<td>(%)</td>
</tr>
</tbody>
</table>
CHAPTER FOUR: CONCLUSION

4.1 Advantages and Disadvantages

There are several strengths to the proposed study. When compared to the existing literature our study will provide a generalizable and utilisable association between TAPSE measured by FOCUS in the ED and APE mortality and need for escalation of care beyond heparin alone. It will be the first study to use TAPSE measured by FOCUS in emergency departments to assess these clinical outcomes in hemodynamically stable patients with APE. All echocardiography will be performed by specifically trained emergency department physicians, which will reduce the interobserver variability of the measurements. ED physicians have been shown to have consistent measurement of TAPSE in previous studies\(^1,2\). As FOCUS is being increasingly utilized in emergency departments\(^3\), this study will provide direct insight into its use in measurement of TAPSE, and its utility in prognosticating patients with acute PE. Our study population will be exclude patients with age > 75 years, active malignancy, CHF, and COPD, which have been shown to independently be associated with increased mortality in APE patients and independently influence TAPSE. Our study population will be large, and as this is a multi-centered study, the results will be more generalizable to a larger population.

There will also be a few limitations to our study. The study will be carried out in 3 different hospitals, which though the hospitals follow the same treatment algorithm for APE, may affect consistency if care and introduce some confounding. Because 3 different emergency departments will be measuring TAPSE, this also requires a greater number of investigators performing FOCUS, which may introduce greater variability in measurement. This will be controlled in part by blinded cardiologists confirming TAPSE measurements. This study requires identification and enrollment of patients with
confirmed PE by ED staff, which may allow for selection bias towards patients with more severe presentation, affecting generalizability. The exclusion of patients with age > 75 years, active malignancy, CHF, and COPD will allow for a more reliable association between TAPSE and mortality, however this population makes up a large percent of PE patients making results less generalizable. Lastly, we chose the time period for mortality and need for escalation of care beyond heparin alone to be only the time in which a patient is hospitalized, which, though the most clinically relevant and frequent, may not be long enough to have captured all adverse events clinicians would deem disease relevant.

4.2 Clinical Significance

Acute pulmonary embolism is a disease with high incidence and high mortality. As outlined in Chapter 1, the first treatment for hemodynamically stable patients presenting with RVD is currently anticoagulation, which continues to carry an inpatient mortality rate of 5-10\%\textsuperscript{4,5}. As escalation of care is considered it is important to have accurate measurements to guide prognosis. Point-of-care focused cardiac ultrasound is currently utilized in the ED to assist with diagnosis and prognosis of APE\textsuperscript{3}. Reduced TAPSE has been shown to have a strong association with mortality and escalation of care in this population. This study will use FOCUS to demonstrate an association between a TAPSE \( \leq 15\text{mm} \) and mortality and escalation of care beyond heparin alone, in a way that is utilizable in emergency departments. This association will allow for clinicians to better use an existing technology to obtain a reliable and reproducible measurement of RV function to better risk stratify patients and guide their care.
4.3 References


Appendix A: Pulmonary Embolism Assessment Tools

### Wells Score

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous DVT or PE</td>
<td>1.5</td>
</tr>
<tr>
<td>Recent Surgery or immobilization</td>
<td>1.5</td>
</tr>
<tr>
<td>Cancer</td>
<td>1</td>
</tr>
<tr>
<td>Hemothysis</td>
<td>1</td>
</tr>
<tr>
<td>Heart rate &gt; 100 beats per minute</td>
<td>1.5</td>
</tr>
<tr>
<td>Clinical Signs of DVT</td>
<td>3</td>
</tr>
<tr>
<td>Alternate diagnosis less likely than PE</td>
<td>3</td>
</tr>
</tbody>
</table>

### Revised Geneva Score

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 65 years old</td>
<td>1</td>
</tr>
<tr>
<td>Previous DVT or PE</td>
<td>3</td>
</tr>
<tr>
<td>Surgery or Fracture within 1- month</td>
<td>2</td>
</tr>
<tr>
<td>Active Malignancy</td>
<td>2</td>
</tr>
<tr>
<td>Unilateral lower limb pain</td>
<td>3</td>
</tr>
<tr>
<td>Hemothysis</td>
<td>2</td>
</tr>
<tr>
<td>Heart rate 75- 04 beats per minute</td>
<td>3</td>
</tr>
<tr>
<td>Heart rate ≥ 95 beats per minute</td>
<td>5</td>
</tr>
<tr>
<td>Pain on lower limb deep palpation and unilateral edema</td>
<td>4</td>
</tr>
</tbody>
</table>

### Clinical Probability (3 Levels)

- Low - 0-1 points
- Intermediate - 2-6 points
- High - ≥ 7 points

### Clinical Probability (2 Levels)

- PE unlikely - 0-4 points
- PE likely - ≥ 4 points

### Pulmonary Embolism Rule Out Criteria (PERC Rule)

- Age < 50 years old
- Heart rate < 100 beats per minute
- Oxyhemoglobin saturation ≥95%
- No hemothysis
- No exogenous estrogen use
- No prior DVT or PE
- No unilateral leg swelling
- No Recent Surgery or Trauma

PERC > 1- Cannot rule out pulmonary embolism

### Pulmonary Embolism Severity Index (PESI)

<table>
<thead>
<tr>
<th>Age</th>
<th>Male Sex</th>
<th>History of Cancer</th>
<th>History of Heart Failure</th>
<th>History of Chronic Lung Disease</th>
<th>Pulse ≥ 110 beats/min</th>
<th>Systolic blood pressure &lt;100 mm Hg</th>
<th>Respiratory Rate ≥ 30 breaths/min</th>
<th>Temperature &lt;36°C</th>
<th>Altered Mental Status</th>
<th>Arterial oxyhemoglobin saturation level &lt;90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>+ 10</td>
<td>+ 30</td>
<td>+ 10</td>
<td>+10</td>
<td>+20</td>
<td>+30</td>
<td>+20</td>
<td>+20</td>
<td>+60</td>
<td>+20</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Class I - &lt; 66 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class II - 66 -85 points</td>
</tr>
<tr>
<td>Class III - 86-105 points</td>
</tr>
<tr>
<td>Class IV - 106- 125 points</td>
</tr>
</tbody>
</table>

### Simplified Pulmonary Embolism Severity Index (sPESI)

<table>
<thead>
<tr>
<th>Age</th>
<th>History of Cancer</th>
<th>History of Heart Failure or Chronic lung Disease</th>
<th>Pulse ≥ 110 beats/min</th>
<th>Systolic blood pressure &lt;100 mm Hg</th>
<th>Arterial oxyhemoglobin saturation level &lt;90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 80 years old</td>
<td>+1</td>
<td>History of Cancer</td>
<td>+1</td>
<td>Chronic lung Disease</td>
<td>+1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Class I - 0- Low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1- High Risk</td>
</tr>
<tr>
<td>Class V - &gt;125 points</td>
</tr>
</tbody>
</table>
Appendix B: Sample Treatment Algorithm For PE Patients

Appendix C: Recruitment Flyer

FOR YOUR INFORMATION

This hospital is currently participating in a trial examining the prognosis of hemodynamically stable patients with pulmonary embolism. Investigators will be assessing the outcomes of patients diagnosed with pulmonary embolism on computed tomography pulmonary angiogram based upon their tricuspid annular plane systolic excursion measurement on point-of-care focused cardiac ultrasound in the emergency department.

*Please contact study investigators at pager number (248) 495 6294 if you are treating a patient meeting the following characteristics.*

- New diagnosis of pulmonary embolism on computed tomography pulmonary angiogram
- Systolic Blood Pressure >90 mm Hg
- Heparin therapy initiated for less than 5 hours
- Age <75 years
- No known medical history of active malignancy, congestive heart failure, chronic obstructive pulmonary disease or pulmonary hypertension.
Appendix D: Informed Consent Form

CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT
200 FR. 1 (2016-2)

YALE UNIVERSITY SCHOOL OF MEDICINE – YALE-NEW HAVEN HOSPITAL, BOSTON MEDICAL CENTER, RHODE ISLAND HOSPITAL.

Study Title: Prognostic utility of point-of-care ultrasound of tricuspid annular plane systolic excursion in pulmonary embolism patients in the emergency department
Principal Investigator: Dr. Christopher Moore, MD: Matthew Drause, PA-SII
Funding Source: YCCI

Invitation to Participate and Description of Project
You are invited to participate in a research study designed to look at the effect a reduced tricuspid annular plane systolic excursion has on the outcomes of hemodynamically stable patients with acute pulmonary embolism. You have been asked to participate because you have been diagnosed with an acute pulmonary embolism, have a systolic blood pressure greater than 90 mmHg, are younger than 75, with no active malignancy or history of congestive heart failure or chronic obstructive pulmonary disease. This study aims to enroll approximately 214 individuals at 3 emergency departments to determine if a tricuspid annular plane systolic excursion of < 15mm influences mortality or need for escalation of care beyond heparin alone.

In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the research study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures and possible benefits. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Description of Procedures

➢ You will be given a bedside transthoracic echocardiogram by an emergency department physician, which will measure the size of your right ventricle, the movement of your right ventricle and the movement of your tricuspid valve.
➢ An echocardiogram is an image of your heart. It is taken over your skin and has no exposure to radiation or toxins.
➢ Transthoracic echocardiograms are routinely taken in the emergency department but are not always taken for every patient with a pulmonary embolism. You will be given a bedside echocardiogram to measure your right ventricle.
➢ Based on the measurement of the movement of the tricuspid valve of your right ventricle you will be put into either the TAPSE < 15mm or TAPSE >17mm groups.
➢ You will receive IV heparin for medical management of your pulmonary embolism initially, as is the standard treatment in the emergency department, but all further medical decisions will be made by your internal medicine team while in the hospital.

➢ Your medical records will be reviewed by your research clinician for the following information: medical history, medicines administered while in the hospital, vital signs while in the hospital, bedside echocardiogram images and reading, notes regarding rapid response events, and clinical team notes while admitted.

If you agree to participate in this study, you will be asked to receive a bedside transthoracic echocardiogram that will measure the function of the right side of your heart, the movement of your tricuspid valve, and the size of your right ventricle. You will also grant us access to your electronic medical record to monitor your hospital course. This study will not effect your treatment.

A description of this clinical trial will be available on [http://www.ClinicalTrials.gov](http://www.ClinicalTrials.gov), as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

You will be told of any significant new findings that are developed during the course of your participation in this study that may affect your willingness to continue to participate.

**Risks and Inconveniences**

➢ There is no risk associated with echocardiogram. Incidental findings outside of the scope of the study will be reported to you and directed to your physician at your request.

**Benefits**

➢ There will be no direct benefit for your participation in this study. We hope that the information obtained in this study will increase our understanding of how tricuspid annular plane systolic excursion measured in the emergency department with point-of-care echocardiogram is associated with mortality and escalation of care, and it may be beneficial to provide patients with a TAPSE < 15mm a higher level of care.

**Economic Considerations**

➢ The bedside echocardiogram will be provided at no cost.

**Confidentiality**

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as required by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. All patient information will be de-identified by removing, name, date of birth and MRN. Patient information will be kept on a secure server access only password-protected computers. All physical copies of patient data will be kept in locked cabinet in a locked office. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained.
Representatives from the Yale Human Research Protection Program, the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects) may inspect study records during internal auditing procedures. However, these individuals are required to keep all information confidential.

**In Case of Injury**

If you are injured while on study, seek treatment and contact the study doctor as soon as you are able.

Yale School of Medicine Yale-New Haven Hospital, Boston Medical Center, Rhode Island Hospital do not provide funds for the treatment of research-related injury. If you are injured as a result of your participation in this study, treatment will be provided. You or your insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available.

You do not give up any of your legal rights by signing this form.

**Voluntary Participation and Withdrawal**

Participating in this study is voluntary. You are free to choose not to take part in this study. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health care, and your health care benefits). However, you will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow use of your information as part of this study.

**Withdrawing From the Study**

If you do become a subject, you are free to stop and withdraw from this study at any time during its course.

To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part.

The researchers may withdraw you from participating in the research if necessary.

Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. It will not harm your relationship with your own doctors or with Yale-New Haven Hospital, Boston Medical Center, or Rhode Island Hospital.

When you withdraw from the study, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to insure the integrity of the study and/or study oversight.
Questions

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully – as long as you feel is necessary – before you make a decision.

Authorization

I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of my involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

Name of Subject: ______________________________

Signature: ____________________________________

Relationship: _________________________________

Date: _______________________________________

____________________________________________________________________________________

Signature of Principal Investigator _____________________ Date

or

____________________________________________________________________________________

Signature of Person Obtaining Consent _____________________ Date

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator Matthew Drause 248-495-6294.

If, after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at 203-432-5919. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688.
Appendix E: Sample Size Calculation

<table>
<thead>
<tr>
<th>Sample Size: X-Sectional, Cohort, &amp; Randomized Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two-sided significance level (1-alpha): 95</td>
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<tr>
<td>Power (1-beta, % chance of detecting): 80</td>
</tr>
<tr>
<td>Ratio of sample size, Unexposed/Exposed: 5</td>
</tr>
<tr>
<td>Percent of Unexposed with Outcome: 5</td>
</tr>
<tr>
<td>Percent of Exposed with Outcome: 21</td>
</tr>
<tr>
<td>Odds Ratio: 5</td>
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<tr>
<td>Risk/Prevalence Ratio: 4.2</td>
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<td>Risk/Prevalence difference: 16</td>
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<table>
<thead>
<tr>
<th></th>
<th>Kelsey</th>
<th>Fleiss</th>
<th>Fleiss with CC</th>
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</thead>
<tbody>
<tr>
<td>Sample Size - Exposed</td>
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<td>34</td>
<td>42</td>
</tr>
<tr>
<td>Sample Size - Nonexposed</td>
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<td>170</td>
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</tr>
<tr>
<td>Total sample size:</td>
<td>160</td>
<td>204</td>
<td>248</td>
</tr>
</tbody>
</table>

References
Kelsey et al., Methods in Observational Epidemiology 2nd Edition, Table 12-15
Fleiss, Statistical Methods for Rates and Proportions, formulas 3.18 & 3.19
CC = continuity correction
Results are rounded up to the nearest integer.
Print from the browser menu or select, copy, and paste to other programs.

Results from OpenEpi, Version 3, open source calculator--SSCohort
Print from the browser with ctrl-P
or select text to copy and paste to other programs.
BIBLIOGRAPHY


