Pulmonary embolism in the Intensive Care Unit

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SUMMARY

The aim of this paper was to identify the major causes, risk factors, diagnostic procedures and treatment of pulmonary embolism in the setting of ICU. It was oriented swell toward highlighting how treatment implications influence the mortality rates of pulmonary embolism patients in the ICU.

The objectives were to evaluate the effectiveness of treatment variations implemented in the setting of the ICU for PE patients. In addition, to shed light on the advantages of thrombolysis and anti-aggregant therapy. And finally, to identify the outcomes and mortality rates that emerge after applying both assisted and non-assisted mechanical ventilation therapy in for PE patients residing in the intensive care unit.

Results revealed that In terms of mortality, thrombolytic therapy is a gold standard and has shown efficacy in reduction of RVD in patients that are both hemodynamically stable and those after an acute PE. There is a higher impact on mortality reduction, minimised risk of pulmonary embolism recurrence and reduction in time till hospital discharge when thrombolytic therapy is combined with anticoagulants. Thrombolytic therapy showed to minimise the risk of hemodynamic decompensation but elevate the possibility of a stroke and/or haemorrhage in patients that were hemodynamically unstable in the ICU setting. On the other hand, the mortality rates of those on mechanical ventilation in the ICU setting range between 60-80% respectively.

Conclusion: The evidence after a decade of accumulation reveals a low rates of improvement and high rates of mortality with Mechanical ventilation. In terms of mortality, thrombolytic therapy is a gold standard that has been widely adopted in the treatment and prophylaxis after a PE has taken place. It remains to be controversial in respect to having sudden bleeding and strokes. The best outcomes of thrombolytic therapy are seen when it is combined with anticoagulants.
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CONFLICT OF INTEREST

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SOURCES OF FUNDING

None.

ETHICS COMMITTEE CLEARANCE

It was not required.
ABBREVIATION LIST

RV( RIGHT VENTRICLE) , LV ( LEFT VENTRICLE), CT( COMPUTER TOMOGRAPHY) , ECG( ELECTROCARDIOGRAPHY) , BNP( BRAIN NATRIURETIC PEPTIDE), CTA( CT PULMONARY ANGIOGRAPHY), EU( EUROPEAN UNION), PA(PULMONARY ANGIOGRAPHY), ER( EMERGENCY ROOM) , PESI( PULMONARY EMBOLISM SEVERITY INDEX), CPR( CARDIO PULMONARY RESUSCITATION), APACHE ( ACUTE PHYSIOLOGIC ASSESSMENT AND CHRONIC HEALTH EVALUATION) ,LMWHs( LOW MOLECULAR WEIGHT HEPARINS) , TT(THROMBOLYTIC THERAPY), UFH(Unfractionated HEPA-RIN)

TERMS

CTEPH(CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION) COPD(CHRONIC OBSTRUCTIVE PULMONARY DISEASE)
DVT(DEEP VEIN THROMBOSIS) PE(PULMONARY EMBOLISM)
PI(PULMONARY INFARCTION)
VTE( VENOUS THROMBOEMBOLISM), RVD(RIGHT VENTRICLE DYSFUNCTION) RAD( RIGHT ATRIAL DYSFUNCTION)
INTRODUCTION

The study of Pulmonary embolism in the ICU setting has been debated for over a decade. The mortality rates have been greatly attributed to responses issued by the medical care givers. These responses tend to be centered around thrombolysis, anticoagulant therapies and mechanical ventilation around others. Various articles and researches have been published during the years to study the phenomenon of mortality among patients being put on these therapies. It has always been a point of debate whether mechanical ventilation is more useful to a patient that is rapidly decompensating or has it become a contributing factor to the heightened mortality rates of pulmonary embolism. Mechanical ventilation is usually indicated for patients whose cardio-respiratory systems have started to wane due to a decompensated pulmonary embolism. The drawbacks of mechanical ventilation seen in the ICU setting are heightened risks for another pulmonary embolism and a consequential worsened cardio-respiratory state. Thrombolysis has been regarded as the cornerstone of rapid therapy in the emergency department and the ICU setting. Various studies have shown how thrombolytic therapy is able to shift the tides in the realm of mortality of pulmonary embolism patients. Thrombolytic therapy is thought to work the most optimal with anticoagulant therapy. It also raises to question the option of the usage of anticoagulants alone. Mortality is thought to be increased in the ICU setting with the usage of thrombolytics due to the risk of bleeding and especially intracranially. Not only are thrombolytics thought to decrease the mortality in patients with an acute pulmonary embolism rather it is postulated that it is able to diminish mortality in patients residing in a controlled ICU environment. Anticoagulants when used alone tend to affect mortality and diminishing it as well. However, when used together with a thrombolytic the impact on mortality tend to be more accentuated and the risks of adverse effects or pulmonary embolism recurrence to become significantly less. Whether it’s thrombolytic therapy alone or mechanical ventilation coupled with the treatment strategy, the risks and positive impact that both tend to have are interesting to debate and to study. Bleeding remains the drawback of thrombolytic therapy and cardiopulmonary decompensation remains that of mechanical ventilation. The usage of either is nonetheless quintessential for the current age and the questioning of benefit versus risk in the ICU setting remains a question mark encircled with the lack of a concrete alternative. The trend nowadays seems to be shifting toward the usage of thrombolytic therapy and the general abstinence from mechanical ventilation until all other alternatives have been exhausted. The mortality rates of patients on mechanical ventilation do not seem to be improving over the decades of data that has been collected.
AIMS

To identify the major causes, risk factors, diagnostic procedures and treatment of pulmonary embolism in the setting of ICU, and how treatment implications influence the mortality rates of pulmonary embolism patients.

OBJECTIVES

- To evaluate the effectiveness of treatment variations implemented in the setting of the ICU for patients suffering from pulmonary embolism

- To light out on the advantages of thrombolysis and anti-aggregant therapy, and how the combination therapy (thrombolytics+antiaggregants) influences the mortality rates of pulmonary embolism patients.

- To identify the outcomes and mortality rates that emerge after applying assisted mechanical ventilation therapy in the treatment of Pulmonary embolism patients.
LITERATURE REVIEW

Pulmonary embolism (PE) is a cardiovascular disorder that has amongst highest mortality rates in the acute settings and that of the controlled hospital settings. [8] Despite the advances in medicine, it has continued to lure the diagnostic and therapeutic advances for over thirty years. PE obstructs the pulmonary vascular bed and leads to an acute state of right ventricular failure which carries one of the highest risks of mortality [8]. Patients usually encounter death in a manner of hours when emergency aid is not administered and even with the latest advancements in resuscitation and treatment tactics it remains a complicated condition to treat [8]. Therefore, patients stand the highest chance when these emergency procedures are delivered as soon as possible. Initial treatment is usually directed toward the restoration of blood flow in an adequate manner to the pulmonary vascular bed and to minimise the risk of recurrences [8]. Therefore, the type of therapy is dependant on the risk stratification that is assembled from assessment of hemodynamic impact (best marker for short-term prognosis). After which, the extent of the morphological mark the PE has left behind and the status of the pulmonary and the cardiovascular systems are evaluated. Finally, the patient’s neuro-humoral system and its adaptation to the PE with the subsequent risks that come with the different types of therapy that could be applied are all assessed [3].

Incidence and Mortality of PE

According to the European guidelines for diagnosis and management report of PE, the incidence of PE ranges between 60 to 70 per 100,000 of the general population and 124 per 100,000 in regards to venous thrombosis [4]. These numbers can fluctuate and vary to become in reality much higher due to the fact that silent PE can be an outcome in 40% to 50% of patients with deep vein thrombosis (DVT) [4]. Only 30% to 45% of patients whom are actually diagnosed with PE are discovered on autopsy, meaning that the greater percentage of PE victims are left undiagnosed nor treated prior to their deaths. Contrary to clinical data which situates PE in the 60 to 70 years age group, the data gathered from autopsies indicate PE with the highest occurrence in the 70 to 80 years age group. The mortality rate carried with acute PE when left untreated is around 30% which is quite high [4]. In comparison, when PE is both diagnosed and treated, the rates of mortality plunge to 8% and although is still elevated remains significantly less than when patients are not treated. Approximately 10% of acute PE patients succumb to an instantaneous death, 2 out of 3 patients that survive a PE attack die within a timeframe of 2 hours after presentation [11]. Those with Massive pulmonary embolism carry an overall mortality rate of 18% to 65%, 20% of the overall Massive PE victims have received treatment [11]. Sub-massive PE victims succumb to a
mortality rate of 5% to 25% whereas those with a PE with a mobile thrombi in the right-heart chambers carry a mortality rate as high as 27% [4].

Risk Factors, Medical History, Pathphysiology, Clinical Presentation and Risk Stratification

Diagnosing PE is rarely a task that is deemed simple, it often includes a multitude of clinical experience, quick thinking and efficiency when it comes to analysing clinical and physiological presentations [8,9,11]. It is therefore important to always consider a PE when symptoms are slightly leaning in that direction. The diagnosis of PE unfortunately grows difficult in accuracy as the age of patients increase [8,9,11]. Comorbidities such as chronic obstructive pulmonary disease (COPD), asthma, broncho-pneumonia or chronic fibrotizing pulmonary processes make the diagnosis of PE ever more elusive and difficult [8,9,11]. Patients presenting with DVT are a red flag risk factor for the development of PE. In fact, up to 85% of the PE registered cases are due to DVT, after which comes thrombosis of the iliac and renal veins, and then the inferior vena cava. Therefore, the most common sources of PE are in the lower limb regions, the upper limb is not commonly a source of major PE [8,9,11].

Common Risk Factors

In broad terms, it’s the interaction of each patient’s risk factors and the cumulative circumstances affecting each patient that lead up to a venous thromboembolism (VTE) [2,3]. Therefore, it is essential to state that the patient-associated risk factors are usually fixed and common between all patients, whereas the cumulative circumstances where the VTE occurs vary between patients [2]. Patient-associated risk factors include commonly age, prior history of VTE, cardio-pulmonary failures, active malignancy, coagulation disorders, placement on hormonal or oral contraceptive therapy [2,3]. These risk factors are usually classified according to the British Thoracic Society into major and minor categories. Major risk factors include post-operative states such as abdominal or pelvic surgeries, obstetric factors such as late pregnancy and c-section [2,3]. Other major risk factors include malignancies, limited mobility such as hospitalisation and other factors such as puerperal venous thromboembolism [3]. Risk factor that fall under the minor category include cardiovascular (heart failure, hypertension), humoral (estrogen use whether it’s for oral contraception or hormone replacement therapy) and many other factors that play a role in influencing cardiovascular and humoral settings [3]. Patients placed in the intensive care ward are under the population labelled with a risk for developing VTE.
Patient Symptoms

Over 85% of PE patients illustrate initially the sudden-onset of resting dyspnea that worsens and some express that symptoms dyspnea began during periods of exercise [9]. Interestingly a significant percentage of patients display symptoms of chest pain and discomfort that could be elusive as in to misdiagnose a patient upon first glance with angina of ischemic origin [9]. One of the differentiating factors in PE is that pain is sharp and connected with respiratory dynamics. Common PE presentation includes coughing, syncope and less commonly hemoptysis (indicative of possible lung infarction) [9]. It is however less likely to see patients with a triad of dyspnea, chest pain and hemoptysis, the rate of this triad is around 5% to 7% [5]. Therefore the most common symptoms seen clinically are dyspnea, tachypnea and chest pain [9]. The outcome of a grave PE attack can be shock, hypotension and ultimately cardiac arrest. Patients impacted with a central PE plus a major hemodynamic condition are more likely to develop isolated and a rapidly progressing dyspnea [11]. These symptoms can indicate right ventricle (RV) ischemia or infarction in the RV due to the overload this ventricle has to endure [11]. Minor embolisms that occlude the peripheral branches of pulmonary arteries usually present with very minimalistic symptoms to no symptoms at all [11]. Interestingly however, over 30% of PE’s tend to occur without any prior identifiable risk factor and are labeled as idiopathic [9].

Pathphysiological processes and outcomes

The hemodynamic impact left behind an acute PE determines its severity and is usually presented as acute pulmonary hypertension [1]. Both the cardiovascular functional status; otherwise known as cardiovascular reserve and the adaptation ability of the pulmonary and neurohormonal systems hold a substantial role in determining the hemodynamic consequences [4]. Interestingly, the size of the PE doesn’t necessarily have to determine the hemodynamic impact [4]. A morphologically substantial PE can illustrate itself with minor hemodynamic outcomes and the opposite is true as well. Patients with a comorbidity factor that includes heart or lung disease require only a minor obstruction to the circulation in the pulmonary bed to cause acute pulmonary hypertension [5]. In patients whom are otherwise free from cardio-pulmonary diseases the magnitude of pulmonary bed obstruction required to illicit pulmonary hypertension is between 30% to 50% [9]. Due to the acute pulmonary hypertension that the PE subdues, RV after-load increases and morphologic dilation of the RV takes place and right-heart failure might occur. Sudden death can occur when the pulmonary vascular resistance reaches a threshold beyond which the RV can no longer adapt to [9]. At this stage, the acute PE results in sudden pulseless electric
activity in the heart [2]. If however the PE causes a more gradual decline in RV this causes a chain process of diminished left ventricular (LV) filling with a diminished LV diastolic functionality due to the morphological bulging of the now congested RV (ventricular interdependence) [3]. The result is inter-ventricular bulging toward the LV. The overload faced by the RV coupled with the decrease in coronary blood flow can lead to sub-endocardial RV ischemia or infarction [1]. The consequence of these events is a drop in blood pressure which can appear as hypotension, syncope or even cardiogenic shock [54]. If a patient survives the initial episodes of right-heart failure they are more likely to have developed a series of compensatory mechanisms involving the activation of the sympathetic nervous system [54]. The coupling of the Frank-Starling mechanism to intropic and chronotropic stimulation and systemic vasoconstriction that maintains the needed pulmonary artery blood flow, blood pressure and organ function. In a previously healthy individual, an acute PE generates a RV overload that does not allow the RV to produce more than 40 mmHg of mean pulmonary arterial pressure. Respiratory insufficiency is yet another outcome with an incidence of 10% among patients [4]. The reason this occurs is due to a low cardiac output and ventilation-perfusion mismatch. The low cardiac output causes mixed venous blood desaturation and an eventual reverse blood flow back into the pulmonary capillaries [55]. It is estimated that 1 in every 3 patients develop a right to left shunt through the patent foramen oval (PFO). This takes place due to inverse pressures in the right and left atria which tightens the risk of paradoxical embolisation [51].

Nonthrombotic PE

This type of PE includes fat or air embolism, foreign body embolisation, amniotic fluid embolism, septic emboli and tumorous mass embolisation [4].

Foreign body embolisation is mainly due to improper handling of the medical instruments such as guidance wires, pieces of catheters, caval filters and other types of invasive devices that move through the blood vessels [32].

Fat embolism is associated with mainly with long bone and pelvis fractures. Traumatic fractures, and especially invasive orthopaedic procedures are series risk factors of fat embolism. In addition to lipo-suction, lipid or propofol infusion, even extensive necrosis of a steatotic liver [47].

Septic embolisation is frequently linked to tricuspid endocarditis especially in drug addicts, cases of endocarditis due to catheters and foreign bodies in general. Patients with the high risk are especially those presenting with fever, cough, hemoptysis and sepsis [47].
Air embolisms are prone to take place when there’s an open wound or any exposure between the external environment and the vascular system and most commonly during cranial surgeries were the patient is placed in a sitting position [10]. Both arteries and veins are locations where air embolisms can develop. The symptoms occur rapidly and systemically with the degree of presentation varying depending on the amount of air that entered the vascular system. 200 ml or 3 ml/kg to 5 ml/kg of body wight is approximately the lethal amount of air required to induce a fatal PE [10]. If air penetrates into the venous system, it blocks the RV outflow passage or clogs the pulmonary arteries. In either case, the result is an obstruction to the circulatory system and eventual circulatory failure [47,10].

The number one counteractive procedure should be to prevent any more from entering the circulatory system. The second step is maximise hemodynamic support while positioning patients on their left side and maintaining their heads in a tilted down position. Hyperbaroxia has at times proven to be successful in minimising the damage when an air emboli reaches the brain [51].

Amniotic fluid embolism poses as a serious risk factor in pregnancy where the incidence rate is 1 in every 8000 to 80000 pregnancies [67]. It can happen during labor, caesarean section, dilatation and evacuation or in the postpartum period. If amniotic embolism was not detected or was not treated it will eventually lead to fulminant pulmonary edema, Disseminated intravascular coagulation, intractable convulsions, arrhythmias, and cardiac arrest [67]. And The effect is transcended to fetal mortality as well. It can result in non-fatal complications such as organ dysfunction and coagulopathy. Supportive therapy is currently the therapy available. Early diagnosis and applying early resuscitative measures has shown to significantly increase survival rate after Amniotic fluid embolism [67].

Clinical presentation and diagnosis

The PE clinical presentation is mainly based on the classifications set by the 2008 European Society of Cardiology (ESC) and are named The 2008 European guidelines on the diagnosis and management of pulmonary embolism [67]. The system is based on the assessment of individual risks that are associated with the PE. Patients are divided based on risk stratification markers of high, intermediate and low risk. Patients are divided into symptomatic RV dysfunction(shock and hypotension) as massive or (high risk
PE), normal RV function (low risk PE) and asymptomatic dysfunction and/or RV over-load (intermediate-risk PE). CT, angiography, ventilation-perfusion scans and the presence of syncope are important markers [67].

PESI (pulmonary embolism severity index) is used to distinguish between LOW risk PE (PESI class I or II), and Intermediate risk PE (PESI > or equal to III).

Silent PE are very common and they were published in results of a study by Meagan et al that involved 622 patients with proximal DVT. 40% to 50% of the patients involved reported a silent PE that was caught by routine lung perfusion scans [1,3].

Pulmonary infarction (PI) on the other hand is caused by distal and small embolizing thrombi that lead to alveolar haemorrhages, pleuritis or pleural exudates that may be hemorrhagic. Clinically, pleural pain, irritating cough, fever, hemoptysis and friction rub are all common signs of a PI. Triangle shaped infiltrates occasionally appear on CT scans and X-rays. It can prove difficult at times to differentiate PE from acute pneumonia. The patients whom are most prone to PI are those with chronic heart failure and PE [4].

Chronic thromboembolic pulmonary hypertension (CTEPH) is when pulmonary artery pressure grown beyond the 24 mmHg mark while maintaining normal capillary wedge pressure and angiographic signs of pulmonary bed obstruction that has persisted 6 months after the PE [41]. It’s worth noting that most CTEPH patients have no prior PE attacks [13]. Clinically, progressive exertional dyspnea, syncope, RV hypertrophy, accentuated second sound over the pulmonary artery, ECG changes (will be discussed below) and hypertrophy on the echocardiography of the RV free wall [52]. Treatment is through surgical procedures that will be discussed further.

Diagnosis

A gold standard of assessing PE patients is **spiral CT pulmonary angiography (CTA)** and works to confirm or exclude the presence of a thrombi in the pulmonary bed [8]. It visualises the pulmonary bed by highlighting a partly or completely occluded hypodense defect/lung infarction [8]. A negative CTA scan indicates a low risk for a PE and improves the risk stratification in PE patients. Patients that carry a right-to-left ventricular dimension ratio >0.9 carry a 16% mortality risk after 30 days versus those without RV overload that have a risk of 8% [64]. Interventricular septum shape, pulmonary artery width,
pulmonary artery -to-aorta width ratio, decreased width of the left atrium and the back flow reflux into the inferior vena cava and azygos veins are some of the signs seen on CTA. The obstruction index set by Qandali et al and Mastora et al are standards that determine the degree of obstruction. Whereby values of obstruction <40% carry a good prognosis [67]. Spiral CTA on the other hand is the most accurate diagnostically encompassing detailed imaging of the central segments of the pulmonary reaching segmental arteries with a specificity and sensitivity of 95% [52]. Various analyses revealed that negative results of CT scans indicate low PE risk subsequently. Thus, this technique invariably creates a risk stratification strategy that involves PE patients. According to the EU guidelines, RV dilation that has been detected and confirmed by CTA is a critical sign in risk stratification [64]. There are even analysis that indicated an increase risk prognosis of 5 times if a CTA indicates a positive result [52]. The structures visualised on a CT and analysed thoroughly involve the lung parenchyma, mediastinum, pleural cavity, pericardial space and the thoracic aorta. The screening involves inflammation, tumours, emphysema, pneumomediastinum, pneumothorax, pericardial tumours, aortic dissections and coarctation of the aorta. A Triple rule-out approach involves exclusion principles using the radiological elements to assess a patient with acute chest pain [8]. This involves the CTA to rule out coronary syndrome, Pulmonary angiography to rule out PE and Thoracic aorta aortography to rule out aorta dissection [2].

**Pulmonary angiography**

This technique has withstood the test of time to prove itself as a gold standard in the diagnosis of PE. The CTA has however replaced it due to the quality of production and sensitivity. Pulmonary angiography (PA) is used in order to conduct pressure measurements in right-heart chambers, the pulmonary artery and has the capacity to initiate a thrombus management approach whether by a thrombolytic agent or through fragmentation. PA can still be used in emergency situations to exclude PE especially in situations of acute coronary syndrome.

**Echocardiography**

In acute PE, the echocardiography is still considered one of the go-to approaches in acute PE in the ER environment. It presents as a risk stratification strategy that mirrors the hemodynamic impact that is left over in the imminent aftermath of the PE [13]. It is also used in situations where it is not possible to conduct CT angiography or ventilation-perfusion scans. In case a patient is detected to be hemodynamically unstable, a more sensitive and accurate diagnostic approach is then implemented only after a bedside echocardiography confirms the suspicion on admission to the ICU [13]. Echocardiography is one of the most go-to approaches when it involves differentiating a small PE from a submassive one that is
intermediate risk. This is very important since each of them carry a different prognosis. The signs presented on the echocardiography are summarised in the guidelines set by the European Society of Cardiology [64]. They present with RV dilation, RV free wall hypokinesia with an increase in the right-to-left ventricular dimension ratio that is witnessed in diastole [64]. In addition, the D shape assumed by the left ventricle in parasternal projection to the short axis. Supplementary testing includes Doppler echocardiography that documents the tricuspid-mitral valve excursions [64]. Echo in low small PE can still identify valuable information specially the detection of mobile thrombi in the right chambers which is %4 to %18 [13].

**Electrocardiography and chest x-ray**

In particularly recent PE the ECG points out with general signs of RV overload which are illustrated in the T-wave inversion seen in the V1-V4 leads, an S1Q3 display and a QR in V1 lead. In addition, a right bundle-branch block that may be complete or incomplete is visualised [47]. An ST-segment elevation is also noticeable in the V1 lead almost exclusively, with great resemblance to a myocardial infarction ST-segment elevation [47]. Chest x-ray is helpful in establishing the presence of differential factors that could explain acute dyspnea and chest pain. Though it neither confirms nor rebuttals the presence of a PE in the images it reproduces, it may help through the clues it offers to guide the physicians towards the right diagnosis [48]. The clues are represented as diaphragm elevation on the effected side, a prominence of the pulmonary artery and the hilus, not to mention a pleural exudate with Westermark sign (oligemia) as well [8].

**Laboratory**

D-dimers are produced as an after-product of plasmin-mediated fibrin degeneration and are elevated in situations of acute blood clot. The reason for the rise in D-dimers during a clot is the increase of fibrinolysis associated with the activation of the coagulation system [25]. Thus when lab values turn up with D-dimer levels in the normal range, it is not likely that a DVT or a PE has occurred. D-dimers can also be high in situations of inflammation, malignancies, infections or aortic dissections for instance [25]. This is due to the fact that D-dimers are fibrin specific and thus not VTE specific thereby carry a chance of being misleading if the patient has other causes that might elevate fibrin levels [32]. In addition, patients who are long term known for increased risk of thromboembolism tend to carry a persistent elevated level of D-dimer [10]. Myocardial injury markers are those such as cardiac troponins (T and I) are very important and are often coupled with overload markers such as natriuretic peptides [24]. Natriuretic peptides include brain natriuretic peptide (BNP) and N-terminal pro-hormone BNP (NT-proBNP). The role
that these markers assume is one that aims to reflect the bodily biochemical response to PE [24]. That is an important point since the rise of these markers in a PE patient are not related to a coronary manifestation. In hemodynamically stable and normotensive patients, the fluctuation of cardiac troponin are suggestive of severity or risk stratification [8]. Interestingly, elevation of these enzymes is thought to indicate an elevated risk of mortality in PE patients, regardless if they’re affected by coronary illness or not [25]. Troponin should be evaluated after admitting the patient and afterwards with an optimal time frame of 6 to 8 hours. Beyond the 72 hour mark, the value of troponin is of no clinical significance [60]. BNP and NT-proBNP illustrate in PE an RV overload or dysfunction and thereby have a role in raising the mortality scale [63]. They can also be elevated in other cases beyond PE such as pulmonary arterial hypertension, CTEPH, pulmonary hypertension in lung and heart diseases. Relative to mortality, elevation in BNP and NT-proBNP carry a significant increase in mortality [63,25]. Some meta analyses and studies interpret a 6-9 fold increase in mortality between normotensive patients [5]. In patients whose overload markers do not decrease within a 24 hour time frame, their mortality risk is significant and require rapid and aggressive intervention [5]. Other laboratory factors involve blood gases and thereby the use of arterial and venous blood sampling for their analysis. In acute PE, the classical clinical picture of hypoxemia, hypocapnia and respiratory alkalosis due to a reactive compensatory mechanism by the nervous system to induce hyperventilation is apparent [5]. Blood gas analysis allows for a more accurate approach toward identifying risk stratification individually for the patients, especially when monitoring for organ dysfunction along the course of the illness and treatment [5,10,64]. The main impact that PE leaves behind on organs such as heart, lungs and the kidneys can be monitored and quickly detected [4]. Outcomes such as low cardiac output syndromes and a ventilation-perfusion mismatch can take place [67]. Blood clotting tests are important for determining whether the individual is suffering from any thromophilias and coagulation irregularities [64]. Interesting to note is that almost 50% of all PE patients are those without any clinical or laboratory risk factors [63]. The importance of blood clotting tests is for us not to expose patients to thrombolytic therapy while suffering from a condition such as thrombophilia [24]. Those with the highest risk factors are those with antithrombin therapy, with protein C and S deficiency and in addition to factor V Leiden mutation [10]. In such cases, it’s efficient to administer a reduced dose of thrombolytic agent and await the results of the tests.

**Ventilation Perfusion Scintigraphy**

This is a highly sensitive and non-specific technique that is used to rapidly and efficiently rule out PE in patients whose risk is medium to negative [8]. The technique is done by using a compilation of lung perfusion and an aerosol that is inhaled in order to detect any defects caused by COPD, pneumonia,
bullies emphysema and others [63]. The test carries an impressive negative predictive value of 100% [8]. Chest x-rays can be used at times to complement the scintigraphy [4]. It is interesting that even after periods of 6months scintigraphy is still able to detect residual variances in the lungs in around 20% of the patients [4].

Management

Anticoagulation therapy
This type of therapy is one that is worldwide considered as the essence of PE therapy. It is initiated during the diagnosis procedure even when the clinical diagnosis is highly oriented toward a PE. Intravenous unfractioned heparin or low-molecular heparins (LMWHs) are initiated, with at times fondaparinux is the drug used [45]. Usually a bolus of 5000U is initiated and then soon followed by an infusion rate of 18 U/kg/h [45]. Assessment of therapeutic efficacy is by partial thromboplastin time and that should be double to triple the normal control of plasma levels [64]. A routine 6h check up of the partial thromboplastin time is maintained so that the values don’t drop down to the normal ranges [11]. Unfractioned heparin (UFH) is used over a period of various days and at times replaced with LMWH which as stated in various studies carries somehow of an equally efficacy in therapy as that of intravenous (IV) unfractioned heparin therapy [12]. PE that is graded medium to low risk is usually set for a therapy for LMWHs whereas IV unfractioned heparin is oriented more towards those a massive PE that could have reduced or affected their ability to resorb LMHWs subcutaneously [12]. LMHs are given in a dose dependent fashion and is monitored by anti-Xa activity after 4 hours of LMWH administration to be certain that a value of 0.6 to 1.0 u/ml is achieved after receiving the medicine as a double dose [64]. After such therapy, a minimum 3 month followup therapy with vitamin k antagonist should be maintained for a patient that has been receiving unfractioned or LMWHs [45]. The international normalised ratio (INR) of 2.0 to 3.0 in first time PE patients is a risk factor. Long term therapy with vitamin K antagonists is important especially in patients with coagulative disorders and recurrent episodes of PE [23]. The American College of Chest Physicians’ guidelines set in 2008 recommend ICU admitted patients with a PE receive a bolus of UFH if no contraindications of anticoagulation are present [12]. This should be done until bedside diagnostic tests such as echocardiography are done.

Thrombolysis
This happens to be the primary type of management that is targeted toward a massive PE [15, 52]. In short it helps by restoring the unstable hemodynamic and ventilatory systems into controllable states
[18]. It works in addition to substantially decreases the chances of conditions such as multi organ dysfunction syndrome and systemic inflammatory syndromes from taking place [22, 7]. If cardiac arrest takes place, studies revealed a higher chance to achieve return of spontaneous circulation (ROSC) after a rapid and intense initiation with thrombolytic therapy (TT) [31, 56]. In a trial conducted by Jan Bělohlávek in 2013, they noticed that patients receiving a bolus injection of 50 mg alteplase 15 min after non-successful CPR had a higher chance of walking out of the hospital [8]. In addition, an increase in CPR-related bleeding in patients receiving the TT was not marked [8]. The mortality rate, though less than the 100% rate a patient would suffer with if affected with a PE and cardiac arrest outside the hospital remained to be high with a 90% mark. In his trial Jan Bělohlávek concluded that patients who expirence an out-of-hospital cardiac arrest would have a higher chance of survival and ROSC with a rapid TT initiation [8]. TT according to the trial and specifically alteplase as a titrated and repeated bolus injection is useful when CPR fails to achieve spontaneous circulation and should be used as a last resort.

If no cardiac arrest accompanies a PE, circulatory and ventilatory support can temporarily sustain the patient’s deteriorating state till a more concrete treatment strategy is set forth [37, 53]. Before implementing a TT strategy a concise set of diagnostic procedures must take place [18, 62]. Among of which are the ECG, physical exam and echocardiography which allows the diagnostic team to draw a baseline assessment of the patient’s status and differential [19, 58]. In addition, absolute contraindications for TT must be ruled out, such elements include right-heart overload [21, 61]. TT could be fathomed as a treatment for patients arriving with ventilatory and hemodynamic instability in addition to hypotension with catecholamine administration [28, 29]. Other factors that allow TT are the PE patients also suffering from hypoxia and requiring mechanically ventilation as life support since this on its own widens the margin for an exacerbated embolism to develop and evolve [60, 30, 35]. It is however worth mentioning that according to the European guidelines, TT is avoided in case the patient is in a stable condition and is able to breath spontaneously [64, 40, 41]. The diagnosis in such a case is verified with a CT angiography and the patient is placed under supervision [27, 29, 43]. A meta-analysis of 5 studies revealed that with TT included in the medicament strategy for patients diagnosed with massive PE there was a 55% decrease in mortality [45, 46, 44, 49, 50]. A significantly higher 90-day mortality was discovered in patients suffering from a massive PE (52.4%) in comparison to those who suffered from a non-massive PE (14.7%) [45, 46, 44, 49, 50]. The 90-day mortality rate of patients receiving TT and heparin was 46.3% in comparison to the patients receiving heparin only 55.1% [45, 46, 44, 49, 50].

In patients suffering from submassive PE, the European guidelines dictate the use of TT to be limited to patients without contraindications to treatment [64, 17, 18]. A study dubbed the Management Strategy and Prognosis of Pulmonary Embolism Trial (MAPPET)-3 trial indicated in 2002 that the use of TT for
patients diagnosed with submassive PE is safe in compared to heparin [11, 23]. The importance in this conclusion lies in the fact that TT in submassive PE is second to heparin with no further indications set in place [65, 26]. In massive PE, TT resumes the first place as part of the early treatment strategy since a delay appears to raise the mortality rate significantly [14, 19].

The protocols of administering and initiating TT illustrate a therapy that could start as late as two weeks after the first symptoms appear [42, 66]. Seeing that it is not diagnosed as a massive PE, an anticoagulant therapy is set in first with usually a bolus of 80U/kg unfractioned heparin and thereafter a 18U/kg/h continuous infusion [39, 41]. Alteplase 10mg IV bolus 1-2 min and then a 90mg infusion for 2h is the recombinant tissue plasminogen activator of choice [43, 38]. It is given in conjunction with a continuous heparin infusion [43, 21]. A less aggressive bolus dose of 0.6mg/kg can be given over 15 min in cases where patients are diagnosed with contraindications for TT therapy [54, 51]. It is suspected by researchers and some practitioners that alteplase carries an earlier reduction of pulmonary bed obstruction in relation to streptokinase [50, 30]. Streptokinase carries contraindications in its own specifically and not limited to patients that have received streptokinase earlier [15, 12]. Streptokinase cannot be used in addition with heparin that is stopped during the treatment period and then reinstated when streptokinase is stopped [62, 60].

**Supportive care**

Supportive care includes ventilation support, oxygen therapy, mechanical ventilation, volume expansion therapy, RV function support, bronchodilators, antibiotics and pulmonary circulatory support [4, 1]. In the acute setting, volume expansion therapy can be a double edge sword since it can deteriorate RV function or vitally improve cardiac output [11]. This is mainly because a sudden a volume expansion can trigger a RV overload and deterioration in function [11, 3]. At the same time, if well controlled and given in the right amounts, volume expansion can prove itself to act as a therapy in normotensive PE patients [10, 67]. This is due to improvement seen in cardiac output once the VET (volume expansion therapy) is introduced correctly and to the suitable patients [67]. RV function support and pharmacological support consist of elements such as vasopressors and positive intrepid agents [52]. As an example, Dopamine and Dobutamine that act as positive inotrope are used quite often in the setting of acute RV failure [57]. They work by increasing cardiac output, oxygen supply and tissue oxygenation [64]. It is important to note that dobutamine if administered incorrectly such as at improper doses will increase the perfusion to non-ventilated areas of the lungs and actually worsen the respiratory insufficiency due to a ventilation-perfusion mismatch [52]. The dosages used and those which are advisable are 10ug/kg/min
Noradrenaline should be used in severely hypotensive patients due to a rise in pulmonary vascular resistance. Adrenaline faces the same issues although it doesn’t have vasodilator effects [10,1,67].

**Mechanical ventilation**

Mechanical ventilation (MV) is of two types; both invasive an non-invasive [67]. Initially hypoxemia is controlled by oxygen inhalation and then shifted toward a mechanical ventilation scheme with usage of small volumes and low inspiratory pressure [52]. Due to the adverse effects on the RV function, low positive and expiratory pressures are implemented. Mechanical ventilation is associated with elevated risks of deep venous thrombosis regardless of the thromboprophylaxis measures implemented [11]. In the ICU setting, PE is reportedly found in 7-15% of postmortem patients [1]. Mechanical ventilation is thought to play a role in those figures as will be discussed further in this paper. It is speculated that pulmonary fibrin turnover is altered by mechanical ventilation [47]. In a study conducted by Hatisma and colleagues, the demonstrated pulmonary injuries caused by the mechanical ventilation increased coagulopathy and resulted eventually in a systemic coagulation. It is thought to be the result of a diminished inhibition of coagulation with a decrease in fibrinolysis [4,6].

Changes in RV after-load are common in patients without a pre-existing cardiopulmonary disease who are ventilated to a normal residual capacity [63, 52]. Even with a positive end-expiratory pressure (PEEP) of < 10 cm H2O the RV changes are still present [57]. In cases when patients are with limited cardiopulmonary reserve and are concomitantly affected by a PE, even the smallest fluctuations in lung volume can exacerbate the PVR and eventually lead to a worsened RV function [57]. The consequence is unfortunately an affected hemodynamic system [64, 57].

Therefore MV could be a risk factor attributor in the ICU setting. Some of the contributing causes are the decrease in the right and left ventricular preload and the eventual increase in right ventricular after load and diminishing in left ventricular afterload [2, 52]. Cardiac output is exposed to a rapid decrease in cardiac output that is further exacerbated by hypovolemia and a reduced state of cardiovascular reflexes [2, 3, 52].

In mechanically ventilated patients residing in the ICU environment, a series of bedside studies should be consistently taking place. In a literature review conducted in 2013, researchers illustrated results of bedside diagnostic studies such as chest x-ray (CXR), ECG, arterial blood gas (ABG) analysis, late pulmonary dead space fraction (F'fd-late) and echocardiography [25]. CXR and ABG are important though non-specific markers of a potential PE in the ICU setting. Late dead space fraction is showing...
recent promise in the detection of acute PE in the ICU [63]. It is calculated determining the end-tidal carbon dioxide at a point on the volumetric capnogram equal to 15% of the total lung capacity [63]. This results in the determination of the arterial-alveolar pCO2 gradient to late expiration [63, 52]. Studies are revealing that Fd-late has a high speciality and sensitivity to a PE [25, 63, 52]. This may prove in the future to be a more credible and reliable diagnostic tool when it comes to bedside PR screening in mechanically ventilated patients. The advantage is that it is both cost effective and can indirectly monitor the efficacy of thrombolytic therapy [25]. Echocardiography is useful in mechanically ventilated patients due its ability to detect RV strain that is caused both by an impending PE and the underlying factors such as chronic obstructive pulmonary disorder, pulmonary hypertension and right-sided myocardial infarction [64, 52, 67]. Mechanical ventilation increases the difficulties of obtaining clear results in the case of trans-thoracic echocardiography (TTE) due to the interposition of the inflated lung between the heart and patient’s chest wall. Other factors include the presence of cardiopulmonary disease [64, 52, 67]. Therefore it has been recently debated regarding the usage of transoesophageal echocardiography (TOE) that could help better detect a central PE and visualise the pulmonary arteries [4, 52, 67]. TOE is especially recommended in the bedside environment of a patient that has been mechanically ventilated due to the high specificity for PE [4, 52, 67]. It carries certain drawbacks due to the risk of injury to the gastrointestinal tract in a ventilated patient in comparison to a patient non-sedated [4, 52, 67]. TOE is risky to be performed in the patients that are cardiopulmonary compromised due to a high risk for laryngeal and bronchial spasms in addition to an unwanted and dangerous vagal/sympathetic response [1, 52, 64]. Spiral computed tomographic pulmonary angiography (CTPA) is able to detect with high accuracy an RV dysfunction and allow physicians to better judge the severity [63,52]. CTPA is more sensitive than the conventional pulmonary angiography and carries less of the complications, time consumption and invasiveness [63, 52, 67]. Therefore CTPA is currently the gold-standard diagnostic tool for PE detection in a mechanically ventilated patient [63, 52, 67]. The limitation of CTPA is the need of transporting the patient and thus is not always ideal [4, 5, 67].

The dangers of Mechanical ventilation lie in the difficulty to evaluate the patients for new PE’s [4, 11, 67]. In addition, patients that have been diagnosed with a massive PE and RV failure and are kept on PEEP are done so with extreme caution [1, 11, 67]. This is due to the reduction of venous return, worsening of RV function and elevation of RV after-load that PEEP can induce [1, 11, 52].

Catheter management of PE is indicated when the thrombus is out of the thrombolytic agent’s reach with IV infusion alone [11,9]. It’s a therapy dedicated to delivering the anti-thrombus medication to areas of the pulmonary bed that have been walled of by proximally impacted thrombus
Though it carries risk factors and dangerous aftermaths of its own, this procedure in the acute setting of a massive PE can save the patient’s life [11,9]. It is usually a temporary therapy until the patient achieves relative hemodynamic stability [11, 9, 52]. In some literatures, it has been described as a possible alternative to the also invasive surgical embolectomy [11, 9, 52]. This is a procedure that carries a relative high success rate that staggers above 80% [11]. Though like any other procedure that breaks the sanctity of the flesh, it has its own shares of risks [67]. Catheter-based therapy carries along with it the implantation of a vena cava filter [11, 9, 52]. This is especially indicated in those who are contraindicated for a TT [51,27]. The filter is established in order to minimise the recurrence of a PE especially in patients with thrombosis residues in the femoral or the iliac veins [51,27]. The filter is however not full-proof and with drawback of its own [51,27].
RESEARCH METHODOLOGY

The research was carried mainly through three online databases: The National Library of Medicine(Pub-Med), European society journal, and Uptodate.

We built our research by making 3 basic entities: first, gathering the terms referring to mortality rates of Pulmonary embolism ( “pulmonary embolism” OR “PE” ), cross matched with another one gathering terms referring to the Intensive care unit ( “intensive care unit” OR “ICU” ), and also cross matched with terms referring to (“Treatment”)

We limited our search and results by adding filters. The studies carried out were mainly in the past ten years (2008-2018), done on humans, and the ones only written in English language were included. After searching in both electronic databases we deducted 721 relevant papers.

Assesment Of Eligibility

We performed our articles selection according to: Title, abstract and full text, meeting the eligibility criteria. The majority of the articles were excluded. The most exclusions were done due to following reasons: Inaccessible, Not performed on ICU patients, duplicates, done on very small number of patients.

Inclusion Criteria

The articles meeting the inclusion criteria were eligible to our systemic review: English language, published between 2008 and 2018, performed in the ICU, done on Humans, included both gender, contained enough quantitative and qualitative data.

Exclusion Criteria

Articles thats were excluded met the following criteria: published before 2008, articles that did not discuss treatment strategies, articles that were not free accessible, articles with not enough quantitative and qualitative information.

Included Articles: Finally, a total of 35 articles were included according to the eligibility criteria and they were considered to be the most relevant ones from the initial pool of the obtained results.
**ARTICLE SELECTION PROCESS:**

721 relevant articles identified in literature search using the search terms

471 articles were excluded after title review.
Duplicates, publication date criteria

250 articles were obtained for further review

130 articles excluded after abstract review

95 full-texts were obtained for full-text review

60 articles excluded after Full-text review

35 relevant articles included after primary research

**IDENTIFICATION**

**SCREENING**

**ELEGIBILITY**

**INCLUDED**
RESULTS

In a study conducted by Begum Ergan et al. in 2016, they reviewed the mortality-related risk factors in high-risk PE patients in the ICU [6]. The diagnosis was implemented using computerised tomography pulmonary angiography (CTPA). The study involved 56 patients with 46.4% male and the average age being 70.5 years old. Patients were placed on low molecular weight heparin (enoxaparin 1mg/kg x 2 per day subcutaneously). All patients were on oxygen or mechanical ventilation therapy depending on the degree of respiratory failure. Chi-square tests and Fisher’s tests were compared with student’s t-test or Mann-Whitney U test. Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II Scoring System was 18.0 and the comorbidities were hypertension 51.8% and diabetes 26.8% [6]. The risk factors that were associated with the patients in the study were immobilisation, recent operation, cancer, congestive heart failure, previous venous thromboembolism, chronic respiratory disease and obesity. The patients were all diagnosed with main pulmonary vasculature. 41 patients were classified into group 1 whereas 15 patients were classified into group 2. 19 patients in group 1 and 11 patients in group 2 were placed on oxygen therapy. 7 patients in group 1 and 3 in group 2 were set up on non-invasive ventilation. 15 patients in group 1 and 1 patient in group 2 were on mechanical ventilation as well. In group 1, 28 patients were on vasopressors whereas none were on vasopressors in group 2 [6]. When it comes to mortality, 13 patients in group 1 and 2 patients in group 2 passed away during their stay in the ICU.

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted odds ratio</th>
<th>95% CI</th>
<th>Adjusted odds ratio</th>
<th>95% CI</th>
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<tr>
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<td>1.15-19.65</td>
<td>16.67</td>
<td>0.79-350</td>
</tr>
<tr>
<td>APACHE II score &gt;18</td>
<td>13.75</td>
<td>2.47-76.43</td>
<td>42.47</td>
<td>1.5-1201</td>
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<tr>
<td>Invasive mechanical ventilation</td>
<td>33.</td>
<td>5.23-208</td>
<td>30.10</td>
<td>1.96-463</td>
</tr>
<tr>
<td>Thrombolytic therapy</td>
<td>0.53</td>
<td>0.13-2.18</td>
<td>0.03</td>
<td>0.01-0.98</td>
</tr>
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**APACHE**: acute physiology and chronic health evaluation; **CI**: confidence interval

Table excerpt from results collected in the Ergan et al. 2016 study
In this relevantly recent study, the examiner Winterton et al. 2016 aimed to investigate the impact that mechanical ventilation can have on PE victims residing in the ICU [9]. A retrospective, cross-sectional study was conducted for PE patients that were admitted to Australia’s and New Zealand’s ICU between the years 2005 and 2013. They conducted a comparison between those who survived and those who unfortunately did not. In addition, they compared those placed on mechanical ventilation as opposed to those that were non-ventilated. Their study was ultimately guided toward understanding the variation in incidence and mortality over time [9]. 2797 patients were studied in total and overall mortality was 14.1%. Surprisingly though, 41% of those that did not survive were on mechanical ventilation. It was worth noting that during their study the illness severity - adjusted mortality rate remained the same during the period of study [9]. Ucgun et al. conducted a study that was published in the European Respiratory Journal in 2016 and involved multiple variables and subtypes of treatment and diagnostic methods that patients with PE were placed on [5]. The study aimed to gain a better perspective of the risk factors that promote mortality among patients that have been diagnosed with his risk pulmonary embolism and admitted concurrently to the ICU [5]. It involved 60 patients that were closely followed during their ICU residency, all of which had been previously diagnosed with a high pulmonary embolism [5]. 31 of the patients otherwise 51.7% were women with the mean age being 67.1 years. The most common co-morbidities that patients were affected by were heart failure, malignancy and being in a post-op condition [5]. 32 patients were diagnosed with a high risk PE whereas 28 were diagnosed with an intermediate risk PE. Signs of cor pulmonare (RVD, RAD) were established in 37 of the patients using bedside ECHO [5]. Out of these 37 patients diagnosed with acute cor pulmonale, 32 were set on thrombolytic therapy (rtPA) [5]. Respiratory failure was detected in 31 patients out of the 60 and 13 out of the 31 were placed on non-invasive ventilation whereas 16 patients were set on mechanical ventilation [5]. In 2016, Recai et al. This aimed to better comprehend the risk factors connected with a worsened prognosis in patients admitted to the ICU on the basis of a PE [10]. It involved a total of 28 patients out of which 46.4% were male and the average age was 68.5 years [10]. Out of the 28, 22 came with at least one predisposing factor for PE such as dyspnea and pleuritic pain [10]. The types of PE were two; high risk PE, and intermediate risk PE they were confirmed with computerised tomography and the demographic, clinical, radiological and therapeutic datas were all recorded [10].

In 2002, Janata et al. compared and acknowledged what comparisons over a decade ago suspected and detected regarding the issue of Mechanical ventilation for PE patients in the ICU setting [68]. The study span over a number of years involved a substantial number of 283 patients that have been diagnosed with PE and whose demographic data, risk factors related to thromboembolic diseases and symptoms were all documented [68]. All these patients had undergone a variety of diagnostic and therapeutic pro-
cedures such as lactate and D-dimer determination, ECG, echocardiography, spiral computer tomography (spiral CT) and ventilation/perfusion lung scintigraphy otherwise V/Q-Scan [68]. Therapeutic and resuscitative measures such as thrombolytic therapy, cardiopulmonary resuscitation and mechanical ventilation were separately accounted for. The interesting aspect of the study was that it involved recording the mortality rates after the third day of admission into the ICU. The results displayed an overall mortality rate of 15%, otherwise 42 patients out of the 283 that were included in the study. 80% of the 50 patients placed on Mechanical ventilation passed away and 77% of the 48 patients who were in need of cardiopulmonary resuscitation during the first 24 hours [68]. Out of those who perished, 21 patients were admitted with cardiac arrest and those had a mortality rate of 95% since 22 patients in total had cardiac arrest on admission [68]. 30% of the 87 patients placed on thrombolytic therapy were some of the patients that did not survive as well. In 2010, Berghaus conducted a single-centre study regarding the effects of thrombolysis on the clinical outcome of intermediate risk PE patients are studied [7]. It was oriented toward better understanding the length of ICU stay (LOS) as well. Out of 202 patients that were studied 84 received alteplase and heparin. Thrombolysis was given to the patients in the form of 100 mg alteplase. In addition, 118 patients were treated with anticoagulants alone [7]. The patients were all hemodynamically stable with a blood pressure above 90 mmHg. In all the cases, there was an immediate initial therapy of both fractionated and unfractionated heparin once the diagnosis of PE was made [7]. The time difference concerning ICU stay in comparison was 10 to 12 days shorter for the alteplase group. All patients on oral anticoagulants were also on a vitamin K antagonist regimen and sustained at an international normalised ratio (INR) of more than 2.0 at their time of discharge from the hospital [7]. No difference was marked in between genders in either group and those that were treated with both alteplase and heparin were younger than the others treated just by heparin [7]. In addition, those treated with alteplase + heparin had a lower comorbidity than the heparin solo group [7]. In the alteplase group however, a presence of minor bleeding was detected with a higher incidence in comparison to the other group. The most important result concerned mortality and the group with the higher mortality rate was that of the heparin alone group [7]. It was registered that patients receiving heparin in addition to alteplase were discharged more frequently from the hospital and without further treatment planned in the short run.

The Khemasuwan et al. 2015 study was directed toward summarising the influence of thrombolysis and mechanical ventilation on the echocardiographic predictors of severe pulmonary embolism and for better risk stratification [69, 70]. The cohort study involved 211 patients that were admitted to the ICUs all on the basis of acute pulmonary embolisms. The relation in study was between the clinical picture and outcome of these patients and their echocardiographic diagnostic results [69, 70]. The eventual goal was to tie the echocardiographic results with the clinical picture in order to better understand how they relate
to long-term mortality in the ICU for PE patients on thrombolysis and/or mechanical ventilation [69, 70]. 19 of the 211 patients included in the study, otherwise 9% got intravenous thrombolytic therapy and 55 patients (26%) were on mechanical ventilation.

The Otair et al. 2009 study entailed a gross study of patients with pulmonary embolism that were admitted to the intensive care unit [1]. It consisted of 56 patients between the year 2000 and 2007. 43% of the patients were female and the mean age of the patients was 40.6 +/- 10.6 years [1]. Of these 56 patients 7 were diagnosed with PE and 15 patients were diagnosed with intermediate PE [1]. Out of the 56 patients, eventually 44 patients were ultimately diagnosed with a form of PE by spiral CT and eight patients were diagnosed with a V/Q scan [1]. 39 of the patients presented with initial symptoms of dyspnea, 35 of the patients showed presenting signs of cough and 33 of the patients revealed initial signs of chest pain [1]. Chest X-ray appeared normal in 41 of the patients and 13 of them had signs of cardiomegaly. Thrombolysis with tissue plasminogen activator (t-PA) was initiated for 4 of the 7 patients diagnosed with a High risk PE [1]. In addition, all 7 patients that were diagnosed with high risk pulmonary embolisms were placed on mechanical ventilation for a duration of 45.5 +/- 12.4 hours. Due to thrombolysis, one patient developed gastro-intestinal bleeding and did not survive. Soon after 3 of the 6 surviving patients left on thrombolysis died within 48 hours after their admission to the ICU [1]. The 3 patients that survived the first 48 hours in the ICU did not make it past the 72 hour mark [1]. The MAPPET-3 trial remains to be one of the cornerstones of the studies done on the efficacy and possible drawbacks of thrombolytic therapy in PE patients with intermediate risk pulmonary embolism to be specific [8,11]. In this trial, a comparison of heparin plus alteplase 100 mg with heparin with a placebo was conducted. These two groups of combinations were both introduced over a period of 2 hours [8,11]. The examiners were closely monitoring whether the patients would reach the primary endpoint of deterioration thus requiring alternate therapy or in some cases death would presume. It was detected that incidence of the endpoint was more pronounced in the latter group that were administered heparin plus a placebo (P=0.006) [8,11]. In addition, the probability that a certain group of patients would survive 30 days without succumbing to any events that declined their state of health was observed to be higher in the heparin-plus-alteplase group (P=0.005). Interestingly, when it came to mortality, it was observed that the number of in-hospital deaths between the two groups was the same [8,11]. The MOPPET trial involved a total of 121 patients that were selected having been diagnosed with intermediate risk PE [37]. Each of the patients in the trial received a low dose of heparin and 50 mg of alteplase combined or alteplase 50mg alone [37]. In this study, the endpoints that were monitored were the development of pulmonary hypertension and the risk of developing another PE during a timeframe of 28 months. Interestingly, the occurrence of pulmonary hypertension was recorded in 9, otherwise 16% of the 58 patients taking heparin in combination with 50 mg alteplase [37]. On the other hand, 32 (57%) of the 56 patients
on solely 50mg of alteplase were diagnosed with pulmonary hypertension in the before-mentioned timeframe (P<0.001) [37].

The PEITHO double-blind, randomised trial aimed to compare the effect of heparin-plus-tenecteplase with heparin-plus-placebo in 1,005 patients that were diagnosed with intermediate-risk pulmonary embolism [64, 52]. The primary endpoint in this trial was patients experiencing hemodynamic decompensation or passing away within a timeframe of 7 days after the randomisation has taken place [64, 52]. It is noteworthy mentioning that all of the patients had right-ventricular dysfunction (RVD). The results illustrated a primary endpoint in 2.6% of the patients placed on heparin-plus-tenecteplase, otherwise 13 of 506 patients experienced either hemodynamic decompensation or death [64, 52]. In comparison, 28 of the 499 patients in the heparin-plus-placebo group succumbed to a primary endpoint fate (P=0.02) [64, 52]. The revelation of extra-cranial haemorrhage was detected in 32 patients of the heparin-plus-tenecteplase group and in only 6 out of the 499 patients in the heparin-placebo group (6.3% vs. 1.2% respectively) [64, 52]. In addition, 12 of the heparin-tenecteplase patients were inflicted by a stroke (2.4%) and 10 of those 12 were diagnosed with a stroke that was hemorrhagic [64, 52]. In stark comparison, only 1 patient from the heparin-placebo group sustained a stroke and it happened to be hemorrhagic as well (0.2% of the 499 patients, P= 0.003) [64, 52]. The TIPES trial involved 58 patients [38]. The trial was randomised, double-blind and placebo-controlled [38]. It aimed to study the impact that tenecteplase; a thrombolytic agent, had on right-ventricular dysfunction in patients that are hemodynamically stable and concurrently diagnosed with a pulmonary embolism [38]. The patients were divided into two groups and randomly chosen to receive either a single-bolus of tenecteplase (23 patients chosen) or a placebo (28 patients) [38]. Both groups received unfractioned heparin (UFH) in conjunction with the treatment they were on. The end-point in this study was the detection of a reduction in right ventricular dysfunction during and up-till a period of 24 hours since initiation of treatment [38]. The tenecteplase-UFH group exhibited a 0.31 reduction in the right-to-left ventricle end-diastolic dimension ratio. The placebo-UFH group revealed a 0.10 reduction ratio in comparison (P= 0.04) . Regarding the recurrence of PE in either groups during the trial period, 1 patient in the tenecteplase-UFH group sustained a PE recurrence and 3 patients in the placebo group were affected in comparison [38]. Bleeding was not a stranger to this trial either, 2 patients in the tenecteplase group sustained a non-fatal though major bleed; one of which was intracranial. In comparison, the placebo group recorded a single bleeding incident that was non-fatal. The TOPCOAT double-blind trial included 83 patients that were diagnosed with intermediate pulmonary embolism, right ventricular strain and are all normotensive [71]. The patients were divided into two groups and randomly chosen to receive either a single weight-bolus of tenecteplase (40 patients chosen) or a placebo (28 patients). Both groups received low molecular weight heparin (LMWH) in conjunction with the treatment they were on. The question in study was whether the patients
on tenecteplase would exhibit better outcomes than those on LWMH alone. After a time period of 5 days, 3 of the placebo patients began exhibiting negative signs and regression, one of which passed away [71]. The tenecteplase group had a patient that succumbed to acute intracranial hemorrhage within 5 hours after the drug was given but did not perish. In fact, after the patients were discharged, they remained on a 90-day probation period under which no patients died. After the 90-day mark, 16 (37%) of the 43 patients that were on a placebo were reportedly affected by an adverse outcome. In comparison, 6 (15%) of the 40 patients that were treated initially with a bolus of tenecteplase in conjunction with low molecular weight heparin endured at least 1 adverse event afterwards (two-sided P=0.017) [71].
DISCUSSION

It was remarked in the Ergan et al. 2016 study that more patients in the non-survivor segment needed vasopressor therapy and mechanical ventilation [6]. Additionally, the length stated in the hospital for patients who survived the ICU was longer than those who did not. Their results came in showing that the male gender having an APACHE II score > 18 in addition to invasive mechanical ventilation carried a higher risk of mortality. In contrast, thrombolytic therapy assumed a protective role for the patient [6]. Mechanical support is established to combat severe hypoxemia, increase in the alveolar-arterial gradient and hypocapnia that are commonly seen in PE. In the study discussed above, hypoxemia was recorded with a presence of 81%, increased alveolar-arterial gradient at 80% and hypocapnia was recorded with a presence of 74% [6]. The conductors of the above study were surprised to find the staggering need of mechanical ventilation to support the patients [6, 10]. 36.6% of high-risk patients were on mechanical ventilation support and 17.1% were on non-invasive ventilation therapy. The conductors assumed the high demand for mechanical ventilation was due to the high severity of the condition these patients were in [6, 10]. They deduced that invasive mechanical ventilation increase the mortality rates for high-risk PE patients [6, 10]. One of the main causes for this high mortality could have been the negative effect that positive pressure puts on the cardiac output. It allows for a stark decrease in venous return and preload [6, 10]. Studies such as Kheasuwan et al. and Soh et al. claimed that mechanical ventilation increases both the risk for death in the ICU and hospital settings. Interestingly, in the Ergan et al. study, 70% of patients in the first group received thrombolytic therapy and gained evidence enough to show that heparin alone was able to induce a faster rate of lysis [6, 10]. In addition, it showed sound capability to improve variably the patients’ hemodynamic statuses and RV functional capacities. They also add that early timing of the thrombolytic therapy was of the essence [6, 10]. The overall gender that had the highest mortality was male. Interestingly, in this study and that of others they noticed that the female gender had a higher severity of illness whereby their clinical and diagnostic picture was bleaker than the males [6, 59, 60]. Nonetheless, the males came out with a higher rate of mortality though not significantly [6, 59, 60].

The Winterton et al. study concluded that ICU admitted PE patients have increased over time and though the mortality rate of PE patients is generally high, it is especially so and has not improved among those placed on mechanical ventilation [9]. Uçgun et al. results indicated that the mortality rates of those suffering from a high risk PE was 25.0% whereas those diagnosed with intermediate risk PE had a mortality rate of 32.1% [5]. Those suffering from a malignant disease had a mortality rate of 43% whereas those whom suffered from respiratory failure and were mechanically ventilated had a 51.6% mortality
rate [5]. It is difficult to ascertain whether it was mechanical ventilation itself that exacerbated the deterioration of patient’s condition so that the mortality rate was escalated [5]. It could be argued even by the examiners that the mere fact of respiratory compromise is enough to degrade a patient’s condition and chances of recovery. Mechanical ventilation sets itself as a possible factor that more research about is needed in order to gain more perspective on its role as an advocate of worsening mortality rates [5, 64]. Recai et al. results illustrated that all the patients respectively had a form of ventricular dysfunction and an average pulmonary artery (PA) pressure of 50mmHg [10]. Interestingly, those that did not eventually survive had a recorded mean pulmonary artery pressure around 62.5mmHg [10]. All the patients involved in the study required oxygen therapy but only 9 required mechanical ventilation [10]. Out of those 9 patients on mechanical ventilation 5 received ventilation invasively and 4 non-invasively. In addition, 18 out of the total 28 patients received thrombolytic therapy. Toward the end of the study, four patients passed away and were in more need of hemodynamic and mechanical respiratory support compared to those that survived. They concluded that patients that had a higher PA pressure and a need for hemodynamic support and mechanical ventilation endured a worse outcome. That conclusion is growing to appear within various studies not to be a mere coincidence [10].

The Janata et al. study concluded at that time that among the PE patients that passed away during their study, those on mechanical ventilation, CPR and thrombolytic therapy had a lower chance of survival in comparison to those outside those parameters [68]. It is of particular interest how the view toward thrombolytic therapy has shifted after more than a decade. Whereby, thrombolytic therapy is now a gold standard regarding treatment and maintenance of acute PE patients. Mechanical ventilation remains to this day undoubtedly a point of controversy, whereby mortality rates of those on mechanical ventilation have yet to decline in retrospect to all the advancements 15 years of ICU control had to offer.

The conclusion of the Berghaus study revolved around the shorter median hospital stay and mortality that PE patients receiving thrombolytic patients were exhibiting [7]. It was worth mentioning that comorbidities added to the mortality and the length of the ICU stay in both groups. This was a univariate and multivariate case, it was ultimately demonstrated to the conductors that thrombolysis and specifically with the use of 100 mg alteplase is associated with a significant decrease of in-hospital mortality and stay [7]. A recommendation of close monitoring for patients receiving thrombolysis in comparison to those receiving anticoagulants alone [7]. This is due to potential side effects of bleeding that was observed in previous papers and experiments [7]. Their data analysis revealed 9% risk for major bleeding and a 22% risk for minor bleeding. Another important constitution is that a treatment of heparin and alteplase together shows better hemodynamic benefits within the first few days to a week of hospital treatment [7, 49, 50]. The observation seems to be that 1 week after a thrombolytic treatment in addition
to anticoagulants the hemodynamic benefits and changes observed with patients receiving anticoagulants alone were similar [7]. Finally, the study deemed treatment with thrombolytic agents to be the most effective when the patients are normotensive, with acute PE, signs of RVD and detected by biomarkers and echocardiography [7]. According to the Khemasuwan et al. 2015 stud, certain factors such as left ventricular end-diastolic diameter (hazard ratio per centimeter, 0.54; 95% confidence interval [CI], 0.38–0.77) and left ventricular ejection fraction were important predictors of lower states of long-term mortality in patients who received thrombolytic therapy (hazard ratio per 10%, 0.75; 95% CI, 0.60–0.95) [69, 70]. This is in reference to age and gender as well. Other important variables included tricuspid annular plane systolic excursion values (hazard ratio per centimeter, 0.56; 95% CI, 0.32–0.99) [69, 70]. Mechanical ventilation was associated with significant elevated values of ICU mortality, whereby 12 out of the 55 patients passed away in the ICU [69, 70]. Their results were supplemented by APACHE IV evaluation and the Pulmonary Embolism Severity Index scores (PESI) [69, 70]. The MOPPET trial revealed the sequelae of developing another pulmonary embolism within a 28 month period was similarly detected in 16% (nine) of the 58 patients in the heparin-plus-alteplase group. In comparison, the group whose patients were only receiving alteplase without heparin had a much higher pulmonary embolism recurrence rate of 63%, in other words 35 of the 56 patients (P<0.001) [37]. Even the duration of hospital stay was different between patients of the two groups. The heparin/alteplase group had an average duration of hospital stay that ranged around 2.2 days. In comparison, the alteplase-only group had a longer average hospital stay of 4.9 days (P<0.001). The mortality rate including the recurrence of PE was estimated 1.6% for the heparin-plus-alteplase group in comparison to the alteplase-only group whose mortality + PE recurrence was remarkably higher at 10.0% (P=0.0489) [37]. Interestingly, none of the patients in either groups exhibited bleeding during the trial. The PEITHO double-blind, randomised trial deducted that thrombolytic therapy revealed to minimise the risk of hemodynamic decompensation But elevate the possibility of a stroke and/or haemorrhage. The TIPES trial examiners deduced that a single-bolus tenecteplase in conjunction with UFH can reduce RVD during a 24 hour time frame in patients that are hemodynamically stable and concurrently affected by a pulmonary embolism [38].
CONCLUSION

In terms of mortality, thrombolytic therapy is a gold standard that has been widely adopted in the treatment and prophylaxis after a PE has taken place. Though controversial in respect to having sudden bleeding and strokes.

The best combination of success in that realm is when thrombolytic therapy is combined with anticoagulants. Whereby when used together, the impact on mortality reduction, minimised risk of pulmonary embolism recurrence and reduction in time till hospital discharge are apparent. In patients that were hemodynamically unstable in the ICU setting, thrombolytic therapy showed minimise the risk of hemodynamic decompensation but elevate the possibility of a stroke and/or haemorrhage.

Mechanical ventilation is still used and could be seen continuously used at the time being. Though the mortality rates are significantly high, it remains to this day the considered approach in acute PE patients that have reached critical cardio-respiratory instability. The difficulty lies in whether the same patient that is subjected to a decline in cardiopulmonary status would fare better without mechanical ventilatory support. The evidence after a decade of accumulation reveals a low rates of improvement and high rates of mortality.
REFERENCES


