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Pulmonary Embolism – Adherence to Diagnostic Protocol and Prognostic Markers

Juha Kauppi

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ABSTRACT

The aim of this study was to comprehensively evaluate the adherence to an externally validated diagnostic pulmonary embolism (PE) protocol. In addition, the long-term prognostic value of biomarkers such as N-terminal pro-B-type natriuretic peptide (NT-proBNP), C-reactive protein (CRP), D-dimer and cardiac troponin T (cTnT) were assessed in patients undergoing computed tomography pulmonary angiography (CTPA) for a suspected PE. Furthermore, this study analyzed the predictive performance of CTPA-derived markers of right ventricular (RV) dysfunction, including contrast agent (CA) reflux, for determining early mortality risk.

In total 1001 patients suspected of PE underwent CTPA in the emergency department (ED) in this retrospective study, of whom 22.2% of patients had PE. Firstly, this study found that CTPA was frequently performed even in patients with low to intermediate pre-test probability without D-dimer testing. Secondly, biomarker profiles demonstrated prognostic significance: in confirmed PE, elevated NT-proBNP (>1000ng/L) and CRP (>50mg/L) predicted poor long-term survival, whereas in patients without PE, increases in multiple biomarkers (NT-proBNP, CRP, D-dimer, cTnT) were associated with worse outcomes. Finally, CA reflux into inferior vena cava (IVC) observed in CTPA and elevated NT-proBNP levels emerged as a potential early markers of poor prognosis in PE.

These results emphasize the need for consistent use of validated risk scores and D-dimer testing to reduce unnecessary imaging. Furthermore, RV dysfunction markers in CTPA and biomarker assessment could help identifying patients at higher risk for adverse outcomes.

KEYWORDS:Pulmonary embolism; CTPA; contrast agent reflux; biomarkers, prognosis.

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TIIVISTELMÄ

Tutkimuksen ensimmäisenä tavoitteena oli arvioida diagnostisten hoito-ohjeiden noudattamista keuhkoemboliaepäilyissä. Erityisesti tarkasteltiin keuhkojen varjoainetehosteisen viipalekuvauksen käyttöä suhteessa potilaiden keuhkoembolian ennakkotodennäköisyyteen ja D-dimeeri-testauksen suosituksiin sekä erilaisten biomerkkiaineiden hyötyä potilaan ennustearvioinnissa. Lisäksi arvioitiin, miten tietokonetomografisissa keuhkoangiografioissa (CTPA) (*engl. computed tomography pulmonary angiography*) todettavat sydämen oikean puolen kuormitusmuutokset vaikuttavat keuhkoemboliapotilaiden ennusteeseen.

Tässä retrospektiivisessä tutkimuksessa analysoitiin 1001 päivystyspoliklinikan potilasta, joille oli tehty CTPA-tutkimus keuhkoemboliaepäilyn takia. Heistä 22,2 prosentilla todettiin keuhkoembolia. Tutkimuksessa havaittiin, että hoito-ohjeiden vastaisesti D-dimeeri-testi jäi usein ottamatta, ja että CTPA-tutkimus tehtiin tarpeettomasti matalan ja keskisuuren keuhkoemboliariskin omaavilta potilailta. Lisäksi tutkimuksessa todettiin ennustearvoa eri biomarkkereilla: keuhkoemboliapotilailla kohonnut NT-proBNP (>1000ng/L) ja CRP (>50mg/L) ennustivat heikompaa pitkän aikavälin selviytymistä, kun taas potilailla, joilla keuhkoemboliaa ei ollut, useiden biomarkkereiden kohoaminen liittyi huonompaan ennusteeseen. Lisäksi CTPA:ssa havaittu varjoaineen takaisinvirtaus alaonttolaskimoon sekä NT-proBNP arvojen kasvu nousivat esiin mahdollisena varhaisen huonon ennusteen merkkinä.

Tulokset korostavat systemaattisen riskinarvion ja D-dimeeri tutkimisen merkitystä tarpeettoman kuvantamisen vähentämiseksi sekä biomarkkereiden ja kuvantamislöydösten hyödyntämistä kliinisessä päätöksenteossa ja seurannassa.

AVAINSANAT: Keuhkoembolia; CTPA; varjoaine; biomarkkerit; ennuste.

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Abbreviations

APS	Antiphospholipid syndrome
AUC	Area under curve
Bpm	Beats per minute
CA	Contrast agent
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CT	Computed tomography
cTnI	Cardiac troponin I
cTnT	Cardiac troponin T
CTPA	Computed tomography pulmonary angiography
DASH	D-dimer, Age, Sex, Hormonal therapy
DOAC	Direct oral anticoagulant
DVT	Deep vein thrombosis
ECG	Electrocardiography
ED	Emergency department
ESC	European Society of Cardiology
HERDOO2	Hyperpigmentation, Edema, Redness, D-dimer, Obesity, Old age
HL	Hodgkin lymphoma
INR	International normalized ratio
IVC	Inferior Vena Cava
IQR	Interquartile range
MM	Multiple myeloma
NSCLC	Non-small cell lung carcinoma
NT-proBNP	N-terminal pro-B-type natriuretic peptide
LMWH	Low-molecular-weight heparin
LV	Left ventricle
PE	Pulmonary Embolism
PEACT	Pulmonary Embolism And Computed Tomography
PESI	Pulmonary Embolism Severity Index
ROC	Receiver operating characteristic
RV	Right ventricle

SCLC	Small-cell lung carcinoma
SD	Standard deviation
sPESI	Simplified Pulmonary Embolism Severity Index
TAPSE	Tricuspid Annular Plane Systolic Excursion
TIA	Transient ischemic attack
TTE	Transthoracic echocardiography
VKA	Vitamin K antagonists
VTE	Venous thromboembolism
V/Q	Ventilation-perfusion

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Juha Matias Kauppi, K.E. Juhani Airaksinen, Juuso Saha, Anton Bondfolk, Jussi-Pekka Pouru, Petra Purola, Samuli Jaakkola, Jarmo Lehtonen, Tuija Vasankari, Markus Juonala, and Tuomas Kiviniemi. Adherence to risk-assessment protocols to guide computed tomography pulmonary angiography in patients with suspected pulmonary embolism. European Heart Journal - Quality of Care and Clinical Outcomes, 2022, 461-468, doi:10.1093/ehjqcco/qcab02028461

II Juha Matias Kauppi, K.E. Juhani Airaksinen, Joonas Lehto, Jussi-Pekka Pouru, Juuso Saha, Petra Purola, Samuli Jaakkola, Jarmo Lehtonen, Tuija Vasankari, Markus Juonala, and Tuomas Kiviniemi Performance of D-dimer, cardiac troponin T, C-reactive protein, and NT-proBNP in prediction of long-term mortality in patients with suspected pulmonary embolism. European Heart Journal Open, 2024, Volume 4, Issue 5:oeae079, doi 10.1093/ehjopen/oeae07

III Juha Matias Kauppi, K.E. Juhani Airaksinen, Laura Nummijärvi, Joonas Lehto, Jussi-Pekka Pouru, Juuso Saha, Petra Purola, Samuli Jaakkola, Kalle M. Mattila, Tuija Vasankari, Markus Juonala, and Tuomas Kiviniemi. Title of the submitted manuscript: Refining the risk stratification in patients with pulmonary embolism: The prognostic role of CTPA-derived Contrast Agent Reflux. Submitted manuscript.

1 Introduction

Pulmonary Embolism (PE) is a potentially life-threatening condition characterized by the obstruction of the pulmonary arteries, most commonly by thrombi originating from the deep veins of the lower extremities. As a major manifestation of venous thromboembolism (VTE), PE represents a significant cause of cardiovascular morbidity and mortality. The clinical spectrum of PE is broad, ranging from silent, incidental findings to sudden cardiac death, making timely recognition and appropriate management essential.

The incidence of PE varies widely across populations, influenced by age, comorbidities, and diagnostic practices. While rare in children (Navanandan et al., 2019), the incidence of PE increases exponentially with age, particularly in individuals over 80 (Wendelboe and Raskob, 2016; Konstantinides et al., 2020). Numerous risk factors contribute to the development of PE, including major trauma, surgery, cancer, pregnancy, immobilization, and inherited thrombophilias (Bahloul, et al., 2020; Mahmoud et al., 2022; Godzik et al., 2014; Parvizi et al., 2014; Pottier et al., 2009; Dado et al., 2018; Prandoni et al., 2005). These risk factors are often cumulative, and their presence guides both diagnostic evaluation and therapeutic decisions.

PE diagnosis remains a clinical challenge due to its nonspecific symptoms. Tools such as the Wells score and Geneva rule, combined with D-dimer testing and imaging—most notably CTPA—form the diagnostic protocol (Konstantinides et al., 2020; Creager et al., 2026). However, the rising use of CTPA has led to concerns about overdiagnosis and unnecessary exposure to radiation and contrast agents (Smith-Bindman et al., 2012).

Risk stratification using scores like simplified Pulmonary Embolism Severity Index (sPESI) (Righini et al., 2011; Yamashita et al., 2020) and biomarkers, such as troponin and NT-proBNP, has enabled more nuanced management strategies, including the safe outpatient treatment of selected low-risk patients. Treatment primarily involves anticoagulation, with thrombolysis and mechanical thrombectomy reserved for high-risk or hemodynamically unstable patients. Despite advances in diagnosis and treatment, PE continues to pose diagnostic and therapeutic challenges, underscoring the importance of adherence to evidence-based guidelines for optimal patient outcomes. (Konstantinides et al., 2020; Creager et al., 2026).

2 Review of the Literature

2.1 Pulmonary Embolism

2.1.1 Epidemiology

PE is a potentially life-threatening condition resulting from the obstruction of pulmonary arteries by thromboembolic material. This chapter explores the epidemiology of PE, focusing on its incidence, prevalence, most common risk factors, pathophysiology clinical presentation and diagnosis.

PE is a common manifestation of VTE, which includes both deep vein thrombosis (DVT) and PE. The annual incidence of pulmonary embolism varies across populations, with estimates ranging from 50-112.3 per 100 000 (Spencer et al., 2009; Wiener et al., 2009; Pastori et al., 2023). However, PE incidence increases exponentially with age. While PE is rare in children, approximately 0.9 per 100 000 (Stein et al., 2004), the incidence doubles approximately every decade after the age of 40 (Konstantinides et al., 2016). Among individuals over 70 years, the incidence can be up to 700 cases per 100,000 per year (Raskob et al., 2014). However, determining the prevalence of PE is challenging due to its acute nature and reliance on diagnostic confirmation. Postmortem studies suggest that a significant number of cases go undiagnosed during life, highlighting the condition´s silent burden (Sweet III et al., 2013).

2.1.2 Risk factors

Numerous risk factors have been identified as contributors to the development of PE, and these are summarized in Table 1. Significant provoking factors include major trauma, surgical procedures, especially orthopedic surgeries such as hip and knee replacements and spinal cord injuries, all of which carry heightened risk of PE (Rogers et al., 2012).

Table 1. Risk factors of PE (Pastori et al., 2023; Anderson and Spencer, 2003; Ageno et al., 2008). PE, pulmonary embolism; OR, odds ratio; VTE; venous thromboembolism.

Risk category	Risk factor
Strong risk factors (OR >10)	Major trauma (e.g. spinal cord injury or hip or leg fracture)
	Hip or knee replacement or other major general surgery
	Hospitalization for heart failure or atrial fibrillation/flutter
	Myocardial infarction (within 3 months)
	Previous VTE (moderate to strong risk)
Moderate risk factors (OR 2–9)	Thrombophilia (moderate to strong risk)
	Central venous lines or catheters
	Congestive heart failure or respiratory failure
	Hormone replacement therapy, oral contraceptive therapy, in vitro fertilization
	Chemotherapy
	Infection (pneumonia, HIV)
	Paralytic stroke
	Superficial vein thrombosis
	Cancer (especially metastatic)
	Inflammatory bowel disease
Weak risk factors (OR <2)	Increasing age
	Obesity
	Pregnancy, postpartum
	Laparoscopic surgery
	Varicose veins
	Diabetes mellitus
	Hypertension
	Immobilization (bed rest > 3 days)

2.1.2.1 Major trauma

Major trauma is a well-established and significant risk factor for the development of PE, primarily due to its strong association with VTE (Bahloul et al., 2020; Geerts et al., 1994). Several studies have demonstrated that patients with major trauma, especially those with pelvic or lower limb fractures, traumatic brain injury, or spinal cord injury, are at particularly elevated risk for PE (Mahmoud et al., 2022; Godzik et al., 2014; Bahloul, et al., 2011). The incidence of PE in trauma patients ranges from 0.2% to over 5%, depending on the population studied and diagnostic intensity

(Mahmoud et al., 2022; Paffrath et al., 2010). Notably, PE may occur despite thromboprophylaxis, especially in high-risk individuals, underscoring the importance of early risk assessment and appropriate anticoagulation strategies (Bahloul et al., 2020).

2.1.2.2 Surgical procedures

PE is a significant postoperative complication associated with substantial morbidity and mortality. Surgical procedures, particularly major operations such as orthopedic (e.g., hip or knee arthroplasty), and neurosurgical interventions, are well-established risk factors for PE (Parvizi et al., 2014; Anderson et al., 2019; Falck-Ytter et al., 2012). Also, longer surgeries under general anesthesia directly increase the risk of VTE (Kim et al., 2015). While symptomatic VTE seems extremely rare after laparoscopic cholecystectomy – below 0.1% – its incidence can reach roughly 10% in high-risk procedures such as emergency open total proctocolectomy (Lavikainen et al., 2024).

Both pharmacological agents, such as low-molecular-weight heparin and direct oral anticoagulants, and mechanical devices, such as graduated compression stockings, intermittent pneumatic compression and foot pumps, have been shown to significantly reduce the risk of PE in the perioperative period (Zurawska et al., 2007). Importantly, elevated PE risk persists for several weeks postoperatively, often extending beyond the duration of hospital stay (Caron et al., 2019). Therefore, comprehensive risk assessment and individualized thromboprophylaxis protocols remain critical in surgical care to mitigate this preventable complication.

2.1.2.3 Immobilization

Immobilization is a well-established risk factor for DVT and PE. Patients confined to bed during hospital stays particularly in medical wards and post-surgical settings, are at significantly higher risk for VTE. Studies show that up to 60% of hospital-associated VTE occurs in non-surgical patients, largely due to immobility (Pottier et al., 2009).

Long distance travel (>4 hours), is associated with increased risk of PE, especially in individuals with other VTE risk factors (e.g. thrombophilia, obesity, use of oral contraceptives) (McKerrow et al., 2022; Anderson and Spencer, 2003). Long-haul flights are particularly associated with an elevated risk of VTE, primarily due to venous stasis and activation of the coagulation cascade. Additionally, the hypobaric hypoxia encountered at high altitude contributes to thrombin generation and impairs fibrinolysis, further promoting thrombogenesis (Pastori et al., 2023).

2.1.2.4 Previous VTE

Patients with a history of DVT or PE have an increased risk of recurrent VTE (Hansson et al., 2000). The risk is higher when the initial VTE event is unprovoked, with cumulative recurrence rates of 32% and 44% at 10 and 20 years of follow-up, respectively (Kyrle et al. 2016). However, recurrence seems to be lower in VTE patients receiving extended anticoagulant therapy (Khan et al., 2021). Therefore, current ESC guidelines recommend extending oral anticoagulation beyond the standard 3 months in patients with a first unprovoked episode of PE (Konstantinides et al., 2020).

2.1.2.5 Myocardial infarction

There remains a general consensus that recent (< 3 months) myocardial infarction is associated with increased risk of PE, likely due to venous stasis and elevated systemic venous pressure (Sørensen et al., 2011; Anderson and Spencer, 2003). Furthermore, also other cardiac conditions may also increase the risk of PE due to similar pathophysiology (Prandoni et al., 2009). In these situations, thrombosis may develop intracardially, meaning that patients may develop PE without preceding DVT (Sørensen et al., 2011). However, the management of myocardial infarction has undergone substantial changes in recent decades, including advances in reperfusion therapies, antithrombotic strategies, and shorter periods of immobilization, all of which reduce the risk of thrombus formation (Byrne et al., 2023). Additionally, patients with VTE are at an increased risk of developing myocardial infarction (Sørensen et al., 2007).

2.1.2.6 Atrial fibrillation/flutter

Although atrial fibrillation is linked to arterial embolism such as stroke (Van Gelder et al., 2024), growing evidence suggests that it is associated also with an increased risk of venous thromboembolism especially in the first months after diagnosis of atrial fibrillation (Pastori et al., 2023; Saliba and Rennert, 2014). The underlying mechanism remains incompletely understood. Some evidence suggests a stronger association between atrial fibrillation and PE than with DVT (Enga et al., 2015). However, other study reports similar associations for atrial fibrillation with both PE and DVT, indicating that the underlying mechanism may involve a systemic procoagulant state or shared risk factors rather than an intracardiac origin (Lutsey et al., 2018).

2.1.2.7 Malignancy

Cancer-associated thrombosis is a notable concern, with malignancies accounting for approximately 20% of all VTE cases. The highest risk for VTE among different cancer types is in pancreatic cancer (Lyman, 2011). The risk of VTE in cancer patients is increased by tumor-related factors (e.g., procoagulant release, inflammatory cytokines), patient-related factors (e.g., immobility, comorbidities), and treatment-related factors (e.g., chemotherapy, surgery, central venous catheters) (Wan et al., 2025).

Certain cancer types – such as pancreatic, liver, ovarian and lung cancers (Figure 1), as well as haematological malignancies – are associated with particularly high thrombotic risk. The incidence of VTE is highest during periods of active treatment and advanced disease. Clinical prediction tools, such as the Khorana score, have been developed to identify patients at high risk of VTE and guide thromboprophylaxis decisions. (Wan et al., 2025)

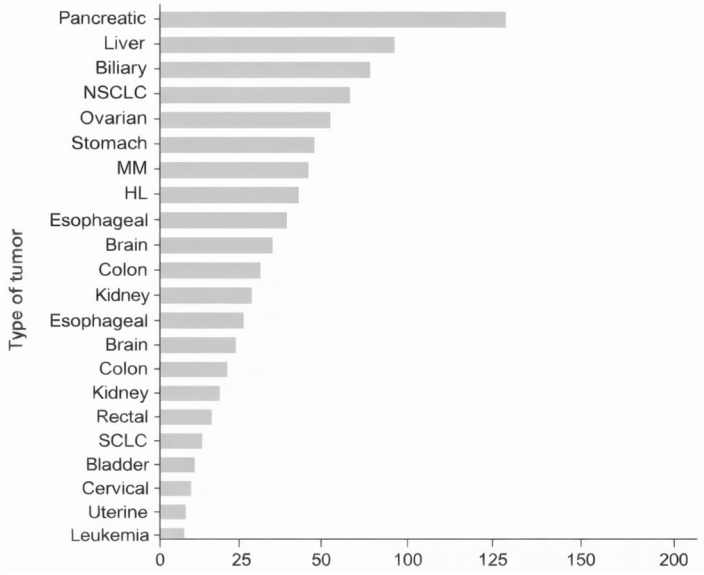

Figure 1. Incidence rate of VTE in the first 6 months after cancer diagnosis by tumor type (per 1000 person-years with 95% confidence interval). Figure is modified from its original article (Wan et al. 2025). NSCLC, non-small cell lung carcinoma; MM, multiple myeloma; HL, Hodgkin lymphoma; SCLC, Small-cell lung carcinoma; VTE, venous thromboembolism.

2.1.2.8 Pregnancy and hormonal therapy

Pregnancy and hormonal therapy are also associated with an elevated risk of developing PE and are highly relevant due to the large patient population. The risk

of VTE is highest during the postpartum period, particularly in the first six weeks after delivery, but may persist for 12 weeks postpartum (Dado et al., 2018). Additional risk factors include obesity, advanced maternal age, thrombophilia, cesarean delivery, prolonged immobility, and a personal or family history of VTE. Due to the potential for severe maternal morbidity and mortality, early identification and prophylactic management of high-risk individuals are critical components of obstetric care. (Scheres et al., 2020)

Menopausal hormone therapy, particularly combined estrogen–progestin therapy, is associated with an increased risk of VTE, including PE. Thus, hormone therapy should not be used for prevention of cardiovascular diseases, but rather reserved for woman <60 years with menopausal symptoms, with careful assessment of VTE risk. (Manson et al., 2024)

2.1.2.9 Inherited and acquired thrombophilia

Thrombophilia, whether inherited or acquired, is a hematological condition characterized by an increased tendency of the blood to form thrombi. Therefore, patients with thrombophilia are at higher risk for VTE, encompassing both DVT and PE. While both genetic and environmental factors contribute to the development of thrombophilia, inherited forms represent a significant subset, particularly among younger patients or those with recurrent or unexplained thrombotic events. (Stern et al., 2019)

The most common inherited thrombophilia is Factor V Leiden, which is associated with 3–4-fold increased risk of VTE. Despite this heightened risk, many carriers remain asymptomatic throughout life, and clinical manifestations often occur in the presence of additional risk factors such as surgery, immobilization or pregnancy. (Stern et al., 2019) Other inherited cause of thrombophilia include prothrombin gene mutation and antithrombin deficiency (each with a 3–4-fold increased risk), as well as protein C and protein S deficiencies (associated with a 7-30-fold increased risk) (Anderson and Spencer, 2003).

The most common acquired thrombophilias include antiphospholipid syndrome (APS) and myeloproliferative neoplasms, such as polycythemia vera and essential thrombocythemia.

2.1.3 Pathophysiology

The pathophysiological basis for VTE is rooted in Virchow's Triad, which includes endothelial injury, venous stasis, and a hypercoagulable state. Risk factors often affect at least one of the components of Virchow's Triad. However, the evolution of

VTE is multifactorial including additional mechanisms involving platelet activation and inflammatory pathways. (Pastori et al., 2023)

All the elements of Virchow's Triad are frequently present following major trauma as direct vascular injury and tissue damage contribute to endothelial dysfunction, while prolonged immobilization — common in trauma patients due to fractures, spinal injuries, or postoperative recovery — promotes venous stasis. Additionally, the systemic inflammatory response following trauma can lead to a prothrombotic state, further predisposing individuals to thrombus formation (Imiela et al., 2025; Anderson and Spencer, 2003).

Heightened risk in pregnancy is due to physiological changes that occur during gestation, such as increased levels of procoagulant factors, reduced fibrinolytic activity, and venous stasis resulting from mechanical compression of the inferior vena cava (IVC) and pelvic veins by the gravid uterus. Hormonal influences also contribute to vascular endothelial changes that favor thrombosis (Scheres et al., 2020). Also, post-partum endothelial injury due to delivery or C-section plays a major role with heightened risk of VTE (James et al., 2009).

Cancer affects all the components of Virchow´s triad inducing a prothrombotic and hypercoagulable state through multiple mechanisms including altered platelet function and heightened platelet activity, endothelial damage, and abnormal tumour-driven angiogenesis (Lip et al., 2002; Leiva et al., 2020).

2.1.4 Clinical presentation of PE

The clinical presentation of PE is highly variable, ranging from asymptomatic cases to sudden death. Common symptoms include dyspnea, pleuritic chest pain and tachypnea. Additional signs may include hemoptysis, fatigue and syncope. The clinical manifestations of PE exist along a continuum determined by the extent of vascular obstruction and the patient’s physiological response. Small subsegmental emboli may be clinically silent, whereas large or multiple emboli involving the main pulmonary arteries can cause acute right ventricular failure and hemodynamic instability. (Goldhaber and Bounameaux 2012)

2.1.5 Diagnosis

The nonspecific nature of symptoms often complicates diagnosis, necessitating the use of pre-test scores, laboratory tests and imaging modalities such as CTPA and ventilation-perfusion scans for confirmation.

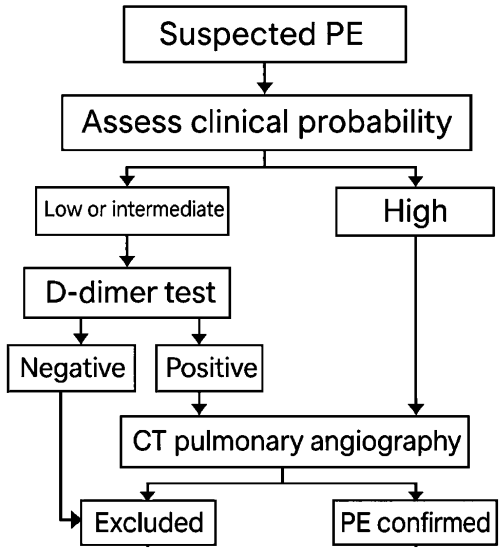

Figure 2. Simplified diagnostic protocol adapted from ESC PE guidelines (Konstantinides et al., 2020). ESC, European Society of Cardiology; PE, pulmonary embolism; CT, computed tomography.

2.1.5.1 Wells score and revised Geneva score

Assessing the pre-test probability of PE is a cornerstone of clinical decision-making. Clinical prediction rules stratify patients into low-intermediate, or high probability categories based on clinical criteria (Konstantinides et al., 2020).

Wells score for PE is a widely used clinical score to estimate the probability of PE based on specific criteria (Table 2).

Table 2. Wells score criteria (Wells et al., 2001). Bpm, beats per minute; PE, pulmonary embolism; DVT, deep vein thrombosis.

Clinical Criteria	Points
Clinical signs and symptoms of DVT	3
PE is the most likely diagnosis	3
Heart rate > 100 bpm	1,5
Immobilization ≥ 3 days or surgery in the previous 4 weeks	1,5
Previous DVT or PE	1,5
Hemoptysis	1
Malignancy (on treatment, treated in past 6 months, or palliative)	1

Patients are categorized into low (0-1 points), moderate (2-6 points), or high (7 or more points) pre-test probability groups. These thresholds guide subsequent diagnostic steps, including D-dimer testing and imaging studies. For instance, a high Wells score warrants immediate imaging with CTPA, while a low score combined with a negative D-dimer test can effectively exclude PE (Figure 2). These strategies aim to balance diagnostic accuracy with the risks and costs associated with unnecessary imaging and anticoagulation.

Revised Geneva score is another validated clinical prediction tool used to assess the pre-test probability of PE. It evaluates both clinical and demographic factors (Table 3).

Table 3. Revised Geneva score criteria (Le Gal et al., 2006). DVT, deep vein thrombosis; bpm, beats per minute; PE, pulmonary embolism.

Clinical Feature	Revised Geneva Score
Clinical signs of DVT (leg swelling, pain on palpation)	3 points
Heart rate	
75–94 bpm	3 points
≥ 95 bpm	5 points
Recent surgery or lower limb fracture in past month	2 points
Previous DVT or PE	3 points
Hemoptysis	2 points
Malignancy (recent/active)	2 points
Age > 65 years	1 point

Patients are stratified into low (Score 0-3 points), intermediate (4-10 points), or high (>10 points) pre-test probability groups based on their score. The Geneva rule simplifies decision-making and aligns well with diagnostic pathways, often serving as an alternative to the Well Score. When combined with a negative D-dimer test in low- or intermediate-risk patients, it can safely exclude PE, reducing the need for further testing.

2.1.5.2 YEARS algorithm

YEARS algorithm was developed to simplify the diagnostic process for suspected PE. It was specifically validated in pregnant women (Pol et al., 2019) and is a guideline preferred approach for suspected PE in pregnancy (Konstantinides et al., 2020; Creager et al., 2026). YEARS algorithm combines D-dimer testing with three clinical criteria: signs of DVT, haemoptysis and whether PE is the most likely diagnosis. PE is excluded, if D-dimer is <1.0 mg/L and none of the three clinical

criteria is present. If one or more criteria is present, D-dimer <0.5mg/L excludes PE. If either of these situations are not met, CTPA is performed. (Van Der Hulle et al., 2017)

2.1.5.3 Electrocardiography (ECG)

ECG is a critical examination in patients presenting with acute symptoms such as dyspnea, palpitations and chest pain. It is widely used in pre-hospital services and EDs because it is fast to perform, non-invasive, and highly informative in acute care settings. Although ECG cannot confirm PE, it may reveal abnormalities that raise suspicion of the condition in symptomatic patients. Typical findings include sinus tachycardia (>100 beats/min), T-wave inversions in leads V1-V4, the S1Q3T3 pattern, and complete right bundle branch block (Shopp et al., 2015).

2.1.5.4 D-dimer in diagnosis of PE

D-dimer is a fibrin degradation product that reflects ongoing clot formation and breakdown (Gaffney, 1993). Elevated levels indicate recent or ongoing thrombus formation, making it a useful marker for VTE, including PE (Keeling et al., 2004). To minimize unnecessary imaging, plasma D-dimer has become an essential component of diagnostic algorithms for suspected PE, particularly excluding PE in patients with low or intermediate clinical probability (Konstantinides et al., 2020; Creager et al., 2026).

Traditionally a threshold of <0.5mg/L or age-adjusted cut-offs for patients over 50 years, calculated as age x 0,01mg/L, are used to exclude PE in low and intermediate risk patients (Konstantinides et al., 2020; Marc Righini et al., 2014; Creager et al., 2026). More recent data support using D-dimer <1.0mg/L in low-risk patients to exclude PE (Van Der Hulle et al., 2017).

However, D-dimer is not specific for PE and can be elevated in many conditions such as infection, inflammation, trauma, pregnancy, and cancer (Esmailian et al., 2022; Lippi et al., 2014; Lee et al., 1999; Franchini et al., 2024). Similarly, D-dimer is frequently elevated in hospitalized patients, reducing its specificity and diagnostic value (Richardson et al., 2025). Furthermore, the use of D-dimer is not recommended in patients with high clinical probability (Konstantinides et al., 2020; Creager et al., 2026). Over time, the breakdown of fibrin decreases, which reduces the reliability of D-dimer testing in patients whose symptoms have persisted for a longer duration (De Bastos et al., 2006). However, only limited data are available regarding the optimal cut-off value based on the duration of symptoms.

2.1.5.5 Evolution of PE imaging

Previously diagnosing PE relied on indirect methods such as chest radiography, ECG and arterial blood gas analysis, which lacked sensitivity and specificity. Ventilation-perfusion (V/Q) scintigraphy emerged as a non-invasive alternative in the mid 20th century, but its interpretative limitations often resulted in indeterminate findings. The definite diagnostic tool was conventional pulmonary angiography, an invasive catheter-based procedure that provided direct visualization of emboli but carried procedural risks and required specialized expertise. (Triggiani et al., 2025)

The introduction of helical CT technology in the early 1990s revolutionized thoracic imaging. With this technique it was possible to visualize the pulmonary arteries in a single breath-hold. Soon CTPA came superior in diagnostic accuracy compared to V/Q scanning as sensitivity and specificity exceeding 90% (Stein et al., 2007; Triggiani et al., 2025).

2.1.5.6 Computed Tomography Pulmonary Angiography

CTPA has become the primary imaging modality for diagnosing PE due to its high sensitivity and specificity, but also due to its availability, as it is easy and fast to execute, and it provides immediate results (Donohoo et al., 2008). Over recent decades, along with technical advancements (Triggiani et al., 2025), there has been a notable increase in the utilization of CTPA (Wittram et al., 2004; Weir et al., 2010; Donohoo et al., 2008; de Boer et al., 2022; Chandra et al., 2013). For instance, a study conducted at a single center observed a 27-fold rise in CTPA usage over an eleven-year period (Chandra et al., 2013).

Despite the increased use of CTPA, the diagnostic yield for PE has not proportionally improved. Research indicates that many CTPA scans result in negative findings for PE (de Boer et al., 2022). The rising use of CTPA has also led to concerns about overutilization and the associated risks, including radiation exposure and potential nephrotoxicity from contrast agents. Moreover, incidental findings unrelated to PE are frequently detected, which can lead to additional investigations and increased healthcare costs (Chandra et al., 2013).

2.1.5.7 Adherence to diagnostic protocol

Adherence to established diagnostic protocols for PE is crucial for accurate diagnosis and optimal patient outcomes. The ESC has developed comprehensive guidelines to standardize the diagnostic approach to PE (Konstantinides et al., 2020).

Despite the availability of the ESC guidelines, studies have indicated variability in their application (Crichlow et al., 2012; Perera et al., 2017). For instance, an audit revealed that only a small percentage of cases had documented clinical probability

scores prior to undergoing diagnostic imaging for PE (Anwar et al., 2017). This underutilization of clinical prediction rules can lead to unnecessary imaging, increased healthcare costs, and potential patient harm due to radiation exposure.

2.1.6 Risk assessment

2.1.6.1 Early mortality risk

The early mortality risk classification was part of the risk stratification protocol in the ESC PE guidelines. This approach has not been formally validated and is based on a combination of multiple different clinical variables such as haemodynamic instability, PESI, RV dysfunction in CTPA or transthoracic echocardiography (TTE) and cardiac biomarkers such as troponin and NT-proBNP levels. (Konstantinides et al., 2020)

Table 4. Early mortality risk by ESC guidelines (Konstantinides et al., 2020). ESC, European Society of Cardiology; RV, right ventricle; sPESI, simplified pulmonary embolism severity index.

Risk category	Clinical presentation	Estimated risk of early death
High	Hemodynamic instability	High (> 15%)
Intermediate-high	Normotensive + RV dysfunction + elevated cardiac troponin	Intermediate (3–15%)
Intermediate-low	Normotensive + either RV dysfunction OR elevated cardiac troponin	Intermediate (3–15%)
Low	sPESI 0 + Normotensive + No RV dysfunction + normal cardiac troponin	Low (< 1%)

2.1.6.2 PESI and Spesi

PESI is a validated clinical scoring tool developed to predict the 30-day mortality risk in PE patients (Aujesky et al., 2005; Elias et al., 2016). It incorporates 11 clinical factors (Table 5) to stratify patients into different risk categories (Table 6).

Table 5. Clinical variables of the PESI. PESI, pulmonary embolism severity index; COPD, chronic obstructive pulmonary disease; BP, blood pressure.

Variable	Points
Age	(=age)
Male sex	10
Cancer	30
Chronic heart failure	10
Chronic lung disease (e.g., COPD)	10
Heart rate ≥ 110/min	20
Systolic BP < 100 mmHg	30
Respiratory rate ≥ 30/min	20
Temperature < 36°C	20
Altered mental status	60
0^2 saturation <90%	20

Table 6. The different risk classes by PESI and the 30-day mortality in different classes. PESI, pulmonary embolism severity index.

PESI Class	Score	30-day Mortality (%)
I	≤ 65	< 1%
II	66–85	1–3%
III	86–105	3–7%
IV	106–125	7–11%
V	> 125	10–24%

Low-risk patients (classes I-II) may be considered for outpatient management, but higher classes (III-V) generally require inpatient care, and very high-risk patients may need ICU or advanced therapies.

The sPESI is an adaptation of the original PESI designated to provide a quick and practical assessment of mortality risk in patients with acute PE including only six easily obtainable clinical parameters: age over 80 years, history of cancer, chronic cardiopulmonary disease, heart rate of at least 110 beats per minute, systolic blood pressure below 100mmHg, and arterial oxygen saturation under 90%. Each positive criterion adds one point, and patients with a score of zero are considered low risk with an estimated 30-day mortality of less than 1%, making them potential candidates for outpatient management. A score of one or more indicates higher risk and generally warrants inpatient care. Despite multiple validation studies evaluating risk stratification based on clinical variables alone (Righini et al., 2011; Jiménez et

al., 2010), ESC PE guidelines also recommend assessing the RV dysfunction using imaging or laboratory biomarkers (Konstantinides et al., 2020).

2.1.6.3 Prognostic value of biomarkers

The integration of biomarkers in the management of PE is essential for accurate diagnosis, effective risk stratification, and treatment decisions. These indicators help clinicians make informed decisions about excluding pulmonary embolism and the prediction of potential complications. Biomarkers are typically used in conjunction with clinical risk scores (e.g. Wells score) and imaging tests such as CTPA. By combining these tools, clinicians can better rule out PE, but also classify PE patients into low, intermediate, or high-risk categories guiding the treatment from outpatient management to more aggressive treatment. (Konstantinides et al., 2020; Leidi et al., 2022; Brailovsky et al., 2021; Moumneh et al., 2020; Creager et al., 2026)

2.1.6.4 Cardiac troponin

Cardiac troponin I (cTnI) and cTnT are widely recognized as reliable biomarkers for detecting myocardial tissue damage (Katus et al., 1991). In the context of acute PE, elevated levels of cTnI and cTnT are strongly associated with increased mortality and serious adverse outcomes (Bajaj et al., 2015; Becattini et al., 2007). This correlation is primarily due to right ventricular dysfunction, which occurs due to elevated pulmonary artery pressure and increased strain on the heart. A systematic review and meta-analysis further confirmed that higher troponin concentrations are linked to increased all-cause mortality within three months, even among patients classified as low–risk PE patients by PESI or sPESI (Barco et al., 2019).

Research has explored multiple troponin cut-off values, ranging from 10 to 200ng/L across different PE populations (Becattini et al., 2007; Sanchez et al., 2008). One notable study introduced age-adjusted thresholds for high-sensitivity troponin T (hsTnT): ≥14ng/L for patients <75years and ≥45ng/L for patients ≥75years old. These age-specific cut-offs were associated with adverse outcomes during a 30-day follow-up period (Kaeberich et al., 2015). Despite these findings, ESC PE guidelines emphasize the high negative predictive value of cTnT levels below 14ng/L for ruling out in-hospital complications. The guidelines recommend using troponin measurements together with clinical assessment and imaging results, without suggesting any universal cut-off value beyond those determined by the specific assay in use. (Konstantinides et al., 2020)

2.1.6.5 NT-proBNP

NT-proBNP is another key biomarker in the evaluation of patients with acute PE. It is released in response to increased ventricular wall stress, making it a valuable indicator of RV strain. Elevated levels of NT-proBNP have been consistently associated with higher short-term mortality and an increased risk of serious adverse events in PE patients (Coutance et al., 2008; Sanchez et al., 2008; Luijten et al., 2024). Evidence from meta-analyses suggests that patients with elevated NT-proBNP levels have a more than sixfold increased risk of death (Coutance et al., 2008).

Similarly to cardiac troponins, NT-proBNP demonstrates high sensitivity and a strong negative predictive value, meaning that normal levels can reliably identify patients with a favorable prognosis. While NT-proBNP is useful for risk stratification, a universally accepted and clinically practical cut-off value has yet to be established. Current practice involves interpreting NT-proBNP levels alongside other clinical findings and imaging results to guide decision-making. (Konstantinides et al., 2020)

2.1.6.6 C-reactive protein

CRP is an acute-phase reactant, that reflects systemic inflammation and tissue injury (Rahali et al., 2024). Its role is not fully understood in venous thrombosis. CRP is not included in the ESC PE guidelines for diagnostic or risk stratification protocol (Konstantinides et al., 2020). However, elevated CRP levels have been associated with a higher risk of short-term mortality and recurrent thromboembolic events (Galeano-Valle et al., 2021). In a prospective study, CRP was found to predict 30-day mortality and bleeding in patients with venous thromboembolism (Demelo-Rodríguez et al., 2020). Patients with higher CRP levels had worse outcome, indicating that CRP can serve as a useful marker for identifying high-risk patients who may require closer monitoring and more aggressive treatment. Its prognostic value, however, is limited by its non-specific nature, as CRP can be elevated in various inflammatory and infectious conditions.

2.1.6.7 Role of D-dimer in prognosis

D-dimer, widely used as a diagnostic marker, has also been investigated for its prognostic significance. Some evidence suggests that elevated D-dimer levels might correlate with disease severity rather than long-term survival. In a study cohort of 200 patients, those in the highest D-dimer quartile were significantly more likely to present with hypotension, tachycardia, hypoxemia, and higher pulmonary arterial obstruction index values (Geissenberger et al., 2019). In addition, a recent study

suggests that ratios such as D-dimer/cTnT can improve short term mortality prediction (Urfalioglu et al., 2024). However, due to insufficient evidence, D-dimer was not incorporated into the guideline-recommended risk stratification protocol (Konstantinides et al., 2020).

2.1.7 RV dysfunction with imaging

RV dysfunction is a critical prognostic marker in acute PE, strongly associated with short-term mortality and adverse outcomes. The ESC guidelines recommend incorporating RV assessment into risk stratification, particularly for intermediate-risk patients (Konstantinides et al., 2020).

2.1.7.1 RV dysfunction findings in TTE

TTE is considered the first-line imaging modality for evaluating RV function in patients with suspected or confirmed PE. This preference is due to its rapid availability, non-invasive nature and widespread use in both emergency and inpatient settings. TTE provides a real-time visualization of cardiac structures and hemodynamics, allowing clinicians to identify RV dysfunction promptly, which is a critical prognostic marker in acute PE.

Several TTE parameters have been validated for detecting RV dysfunction. These include measurements of RV size, systolic function, and interventricular septal motion, as well as indirect signs such as elevated pulmonary artery pressure. Table 7 summarizes commonly used TTE parameters, their abnormality thresholds, and associated risk ratios for adverse outcomes.

Table 7. TTE parameters with thresholds that are used to detect RV dysfunction in PE patients (Cimini et al., 2023; Kanwal et al., 2022). TAPSE, Tricuspid Annular Plane Systolic Excursion; RV, right ventricle; LV, left ventricle.

Parameter	Abnormality threshold	Risk ratio (95% CI)
TAPSE	< 16 mm	2.3 (1.5-3.6)
RV/LV ratio	> 1.0	1.6 (1.1-2.4)
RV hypokinesis	Abnormal if present	1.6 (1.1-2.3)
RV diameter (4 chamber view)	> 50 mm	5.9 (1.5-23.2)
LV diameter (4 chamber view)	< 36 mm	7.0 (1.7-27.9)

Beyond these parameters, additional findings such as McConnell´s sign (regional RV dysfunction with preserved apical contractility) and elevated pulmonary artery pressure further support the diagnosis of RV strain (Cimini et al., 2023). However,

it is important to interpret these findings in the clinical context, as RV dysfunction can also occur in other conditions such as chronic pulmonary hypertension or RV infarction.

2.1.7.2 RV dysfunction findings in CTPA

CTPA is the gold standard for diagnosing PE, but it also provides valuable information about RV function. Among the most widely studied markers is the right-to-left ventricular (RV/LV) diameter ratio, which has been consistently identified as an independent predictor of mortality (Kanwal et al., 2022; Ghuysen et al., 2005; van der Meer et al., 2005; Meinel et al., 2015).

Several studies have explored additional CT indicators of RV strain. Bach et al. demonstrated that CA reflux into the IVC had prognostic value in acute PE (Bach et al., 2015), in accordance with other studies (Meinel et al., 2015; Aviram et al., 2012). Kang et al. investigated various CT signs of RV dysfunction including interventricular septal position and three-dimensional ventricular volume measurement. Interestingly, while volumetric analysis emerged as a strong predictor of early death in acute PE, traditional markers such as RV/LV ratio >1.0, septal bowing and IVC contrast reflux did not reach statistical significance for predicting 30-day mortality (Kang et al., 2011). A large meta-analysis involving over 13,000 patients confirmed that the RV/LV diameter ratio on transverse CT sections remains the most robust predictor of short-term mortality and major adverse events. Additional markers, including RV/LV ratio on four-chamber view, septal bowing or straightening, and contrast reflux into the IVC, were also significantly associated with all-cause mortality within 0.5–3 months of follow-up ($p < 0.01$) (Meinel et al., 2015). These findings underscore the importance of incorporating RV assessment into routine CTPA interpretation, as it provides critical information beyond the mere presence of emboli.

2.1.8 Management

The management of PE has evolved from surgical embolectomy to modern risk-adapted strategies integrating anticoagulation, reperfusion therapies, and interventional approaches. Anticoagulation remains the cornerstone of treatment, with direct oral anticoagulants (DOACs) replacing vitamin K antagonists (VKA) as the preferred option, while mechanical thrombectomy, systemic and catheter-directed thrombolysis are reserved for high-risk patients (Creager et al., 2026). Successive ESC guidelines (2000, 2008, 2014, 2019) have refined risk stratification, emphasized care for special populations, and endorsed outpatient management for

selected low-risk patients, reflecting a shift toward individualized, evidence-based therapy (Konstantinides et al., 2020).

2.1.8.1 Anticoagulation

Anticoagulation is the cornerstone of PE management, aiming to prevent further clot formation and facilitate clot resolution. Initial therapy often involves rapidly acting agents such as low-molecular-weight heparin (LMWH), and DOACs, while VKA is nowadays reserved for specific clinical situations for long-term management. The choice of agent and duration of therapy depend on factors such as the presence of provoking factors, risk of recurrence, and patient-specific considerations. For instance, in cancer-associated PE, LMWH is often preferred due to lower rate of VTE recurrence with similar bleeding complications than VKA. (Konstantinides et al., 2020) Also, some studies have suggested that LMWH may have antitumor effects (Kuderer et al., 2007; Lazo-Langner et al., 2007). However, this has not been consistently confirmed in subsequent analyses (Sanford et al., 2014; Taghizadeh Kermani et al., 2019).

The optimal duration of anticoagulation varies according to the underlying clinical context. For patients with a major transient provoking factor (e.g. recent surgery, immobilization), current guidelines recommend a minimum of three months of therapy, as this duration effectively reduce the recurrence risk while limiting bleeding complications. In contrast, for patients with unprovoked PE or a persistent risk factor, anticoagulation should generally be extended beyond three months, with individual reassessment of the risk–benefit ratio (Creager et al., 2026). In cases of recurrent VTE or certain high-risk conditions such as active malignancy, indefinite or extended anticoagulation may be indicated. (Konstantinides et al., 2020)

DOACs, including rivaroxaban, apixaban, edoxaban, and dabigatran, are now preferred for most patients due to their predictable pharmacokinetics, reduced need for monitoring, and favorable safety profile compared to VKAs. LMWH remains the standard of care in cancer-associated thrombosis, although accumulating evidence supports the use of certain DOACs in this population as well. VKAs, such as warfarin, are now typically reserved for patients with contraindications to DOACs, severe renal impairment, or limited drug availability. (Riaz et al., 2023)

Long-term management further requires a risk-adapted approach, balancing recurrence risk against bleeding risk. Tools such as the DASH score or HERDOO2 rule may assist in identifying candidates for extended anticoagulation, while concomitant comorbidities, patient preferences, and drug tolerability remain crucial determinants in shared decision-making. (Tosetto et al., 2017; Rodger et al., 2012)

2.1.8.2 Thrombolysis

Thrombolysis involves the administration of fibrinolytic agents to dissolve existing clots and is typically reserved for patients with high-risk PE presenting with haemodynamic instability, such as sustained hypotension or shock. Systemic thrombolysis can rapidly restore pulmonary perfusion and improve right ventricular function but carries a significant risk of major bleeding, including intracranial hemorrhage. Therefore, its use is carefully considered, weighting the potential benefits against the risks. In certain scenarios, catheter-directed thrombolysis, delivering lower doses of thrombolytic agents directly to the site of the clot, may be employed to mitigate bleeding risks. (Carroll et al., 2023)

2.1.8.3 Mechanical thrombectomy

Mechanical thrombectomy refers to the physical removal of thrombi from the pulmonary arteries and is considered in patients with contraindications to thrombolysis or when thrombolytic therapy has failed. Percutaneous mechanical thrombectomy offers an invasive approach to rapidly reduce thrombus burden and alleviate right ventricular strain. This intervention is particularly beneficial for patients with high-risk PE who are not candidates for thrombolysis due to bleeding risks or other contraindications. (Carroll et al., 2023)

3 Aims

The specific aims of this study were to:

1) Comprehensively evaluate the adherence to externally validated diagnostic protocols and ESC guidelines for the use of CTPA in the diagnosis of PE. Specifically, study sought to investigate the alignment of CTPA utilization with pre-test probability assessments and D-dimer testing recommendations.

2) Assess the long-term prognostic value of biomarkers such as NT-proBNP, CRP, D-dimer and cTnT in patients undergoing CTPA for suspected PE.

3) Systematically analyze the predictive performance of CTPA-derived markers of RV dysfunction, including CA reflux, for determining early mortality risk as defined by ESC guidelines.

4 Materials and Methods

4.1 Study design

This PEACT (Pulmonary Embolism And Computed Tomography) study was set to investigate the indications for CTPA at Turku University Hospital ED. The data of 1001 patients were retrospectively collected from the medical records over the period from 1 January 2014 to 31 December 2016. The study included 1001 adult patients undergoing CTPA with any indication in the ED during the study period. If a patient had several CTPAs over the study period, only the first CTPA was included. Because of the observational nature of the study, the Ethics Committee of the Hospital District of Southwest Finland waived written informed consent.

4.2 Data collection

The data were extracted from electronic medical records using a structured case report form by trained research personnel. Collected variables included demographics and medical history (comorbidities, medications), clinical examination findings, laboratory results, ECG, chest X-ray, and CTPA imaging reports. Uncertain cases were reviewed by senior investigators. CTPA was performed according to the hospital protocol and interpreted by emergency radiologists. For deceased patients date and cause of death were obtained from Statistics Finland for follow-up until December 31, 2019.

4.3 Biomarker analysis

The cTnT and NT-proBNP values were analysed with electrochemiluminescence immunoassay (Elecsys, Roche Diagnostics; ranges 3–10 000ng/L and 5–35 000ng/L, respectively). NT-proBNP cut-off level of <300 (ng/L) was selected, and the upper limit cut-off level of 1000ng/L was chosen based on PARADIGM-HF substudy (Zile et al. 2016). Extensive research has studied cTnT cut-off levels in short-term prognosis of PE patients. In this study, the established lower and upper cut-off thresholds for cTnT were 50 and 100ng/L.

C-reactive protein values were analysed with particle-enhanced immunoturbidimetric assay (Tina-quant CRP IV, Roche Diagnostics; range <1–700mg/L). The minimum threshold for CRP was set at 10 mg/L. The upper limit was set at 50mg/L) based on studies where C-reactive protein levels of 48–50 (mg/L) were identified as an optimal cut-off value for predicting short-term mortality in PE patients. (Abul Y et al., 2011; Demelo-Rodriguez et al., 2020)

The D-dimer values were analysed with particle-enhanced immunoturbidimetric assay (Tina-quant D-dimer Gen. 2, Roche Diagnostics; analytical range 0.2–21.6 mg/L, Supplementary Table 1). The minimum cut-off value for D-dimer was set at 0.5 mg/L and upper limit was set to 4mg/L. In addition, age-adjusted cut-offs were used, if needed.

4.4 Computed tomography

CTPA was performed according to institutional protocol using 320-multidetector CT scanner (Canon Aquilion One, Canon Medical Systems, Otawara, Japan). A total of 60 mL of iodinated contrast agent (Omnipaque® 350, GE HealthCare) was administered intravenously at 4.0 mL/s. Bolus tracking was triggered at 120 Hounsfield units in the pulmonary trunk. Imaging parameters included 100 kVp, 100–460 mAs, 1 ms rotation time, 0.5 mm slice thickness, and a pitch of 1.39.

An experienced radiologist, blinded to the clinical findings, reviewed all CTPAs of PE patients focusing on the quantitation of CA reflux, septal deviation and diameters of LV and RV (Supplementary Figure 1). The CA reflux was evaluated using a 3-point scale: no CA reflux, CA reflux filling IVC and CA reflux reaching into hepatic veins (Supplementary Figures 1: panels A–C).

The RV and LV measurements were performed by identifying the maximum distance between the endocardium of the ventricular free wall and the interventricular septum, measured at the long axis of each ventricle (Supplementary Figure 1: D). Septal deviation was considered positive if flattening of the interventricular septum was observed (Supplementary Figure 1: E).

Patients with septal deviation or RV/LV ratio ≥1 on CTPA were categorized as patients with RV dysfunction in the early mortality risk calculations.

4.5 Clinical endpoints

Clinical primary endpoints included short-term all-cause mortality and PE-related mortality at 30-day follow-up. Long-term all-cause mortality follow-up was for up to 5 years. Causes of death were collected from the death certificates, which were acquired from Statistics Finland, the official national statistics agency of Finland. Date of death for patients who were deceased between 1 January 2014 and 31

December 2019 were collected from the death certificates but also from the medical records. Secondary endpoints included thrombolysis or mechanical thrombectomy within 30-day follow-up.

4.6 Research ethics

The Ethics Committee of the Wellbeing Services County of South-West Finland exempted the study subjects from providing consent due to the retrospective observational nature of the study.

4.7 Artificial intelligence (thesis)

Artificial intelligence tools were employed during the grammatic review of this thesis to enhance readability.

4.8 Statistical analysis

Data were analyzed with SPSS v27 and v29 and R (2023.9). Continuous variables were expressed as mean ± standard deviation (SD) or median (IQR), categorical variables as counts and percentages. Normality was tested with Kolmogorov–Smirnov and Shapiro–Wilk tests. Group comparisons used Pearson x2 and Fisher's exact and appropriate parametric/non-parametric tests. Prognostic performance was evaluated using Receiver operating characteristic (ROC) analysis and area under the curve (AUC) values. Kaplan-Meier survival analysis with log-rank test assessed long-term outcomes. Two-sided P-values <0.05 were considered significant.

5 Results

5.1 Study population

A total of 1001 patients underwent CTPA for a suspected PE. PE was confirmed in 222 patients (22.2%) Baseline characteristics, comorbidities, symptoms and the use of medications are summarized in Table 8. Patients with PE more frequently presented with unilateral leg pain and swelling, an elevated heart rate, had a higher prevalence of prior PE/DVT and bleeding/thrombotic diathesis, and a lower prevalence of asthma, chronic obstructive pulmonary disease (COPD), coronary artery disease, and decompensated heart failure. Most frequent diagnoses for patients, who underwent CTPA without having PE in the ED are presented in Supplementary Table 2.

Table 8. Baseline characteristics of the study population. CTPA, computed tomography pulmonary angiography; DVT, deep vein thrombosis; PE, pulmonary Embolism; ED, emergency department; COPD, chronic obstructive pulmonary disease; TIA, transient ischemic attack.

	Finding in CTPA		
	PE Count (%)	No PE Count (%)	P-value
Female	126 (56.8)	463 (59.3)	0.474
Clinical signs and symptoms of DVT	73 (32.9)	123 (15.8)	<0.001
PE is #1 diagnosis OR equally likely	210 (94.6)	330 (42.4)	<0.001
Heart rate >100	59 (26.6)	134 (17.2)	0.002
Immobilization ≥3 days OR surgery in previous 4 weeks	34 (15.3)	125 (16.0)	0.793
History of DVT or PE	54 (24.3)	83 (10.7)	<0.001
Fracture or operation within 4 weeks	14 (6.3)	61 (7.8)	0.447
At least 3 days immobilization within 4 weeks	23 (10.4)	93 (11.9)	0.517
Hemoptysis	2 (0.9)	16 (2.1)	0.254
Cancer (treatment ≤6 months or palliative)	20 (9.0)	67 (8.6)	0.601
Age >65 years	127 (57.2)	423 (54.3)	0.443
Recent surgery or lower limb fracture	8 (3.6)	48 (6.2)	0.143
Cancer (treatment ≤12 months or palliative)	21 (9.5)	73 (9.4)	0.968

	Finding in CTPA		P-value
	PE Count (%)	No PE Count (%)	
Unilateral lower limb pain	48 (21.6)	71 (9.1)	<0.001
Pain on lower limb palpation + unilateral edema	24 (10.8)	28 (3.6)	<0.001
Heart rate <75 bpm	61 (27.5)	288 (37.0)	0.007
Heart rate 75–94 bpm	81 (36.5)	260 (33.4)	0.418
Heart rate ≥95 bpm	77 (34.7)	216 (27.7)	0.049
Flight within 4 weeks	12 (5.4)	33 (4.2)	0.458
Previous ED visit within 4 weeks	40 (18.1)	145 (18.6)	0.856
Asthma or COPD	24 (10.9)	177 (22.8)	<0.001
Hypertension	105 (47.3)	387 (49.7)	0.52
History of heart failure	11 (5.0)	87 (11.2)	0.006
Atrial fibrillation	21 (9.5)	95 (12.2)	0.265
Diabetes	37 (16.7)	140 (18.0)	0.647
Previous stroke or TIA	16 (7.2)	71 (9.1)	0.368
Coronary artery disease	21 (9.5)	129 (16.6)	0.009
History of myocardial infarction	16 (7.2)	64 (8.2)	0.622
Arteriosclerosis obliterans	3 (1.4)	30 (3.9)	0.067
Pregnancy	0 (0.0)	10 (1.3)	0.91
Childbirth within 3 months	1 (0.5)	3 (0.4)	0.287
Bleeding or thrombotic diathesis	18 (8.1)	23 (3.0)	0.001
Previous medications			
Aspirin	40 (18.0)	165 (21.3)	0.287
Clopidogrel or ticagrelol	7 (3.2)	32 (4.1)	0.506
Enoxaparin	6 (2.7)	37 (4.8)	0.179
Warfarin	3 (1.4)	42 (5.4)	0.009
Direct oral anticoagulants	2 (0.9)	19 (2.3)	0.277
Manifested symptoms			
Dyspnea	190 (85.6)	576 (73.9)	<0.001
Fatigue	44 (19.9)	195 (25.1)	0.111
Chest pain	58 (26.1)	241 (30.9)	0.167
Syncope or presyncope	29 (13.1)	114 (14.6)	0.555
Altered level of consciousness	15 (6.8)	55 (7.1)	0.876

5.2 Clinical prediction rules

By the Wells score, 382/1001 (38.2%) patients were classified as low risk (<2 points), 527 (52.6%) as intermediate risk (2–6 points), and 92 (9.2%) as high risk (>6 points). The prevalence of PE increased progressively across these categories: 2.4% in low-risk, 31.5% in intermediate-risk, and 52.2% in high pre-test risk patients.

Using the revised Geneva score, 955/1001 (95.4%) patients were categorized as low-intermediate risk (0-10 points) and 46 (4.6%) as high risk (>10 points), with PE detected in 200 (20.9%) and 22 (47.8%) patients in these groups, respectively. ROC analysis demonstrated superior discrimination for the Wells score vs. revised Geneva score (AUC 0.78 (0.75-0.81) vs AUC 0.63 (0.59-0.67); Figure 3).

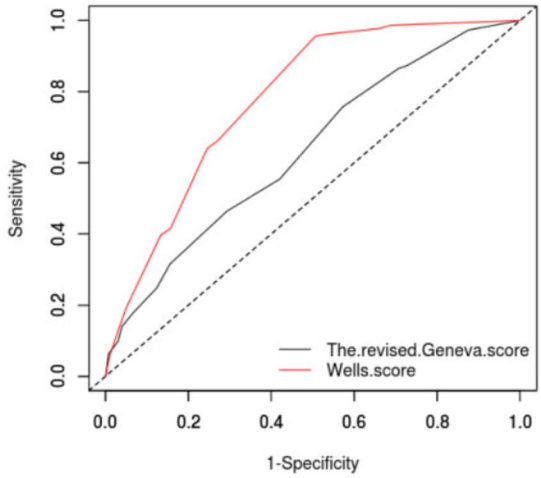

Figure 3. ROC analysis for determining the predictive performance of Wells score and revised Geneva score to exclude PE. ROC, receiver operating characteristic; PE, pulmonary embolism.

5.3 D-dimer testing and pre-test probability

D-dimer testing was performed in 568/909 (62.5%) and 597/955 (62.5%) patients with low or intermediate pre-test probability by Wells and revised Geneva score, respectively. Among these (n=107 for Wells score, and n=109 for revised Geneva score), PE was diagnosed in only two patients with negative age-adjusted D-dimer values; both had additional clinical signs not captured by the scoring systems. In contrast, PE was detected in 139/461 (30.2%) and 155/488 (31.8%) patients with positive D-dimer results and low-intermediate pre-test probability by Wells and revised Geneva score. Furthermore, 105/909 (18.5%) and 107/955 (17.9%) patients in these pre-test probability groups had negative age-adjusted D-dimer but underwent CTPA inappropriately (Table 9).

Notably, 341 (34.1%) and 358 (35.8%) low- and intermediate-risk patients underwent CTPA without prior D-dimer testing, and only 34/341 (10.0%) and 43/358 (12.0%) of these had PE. In high-risk patients by Wells and revised Geneva score, D-dimer was measured in 54/92 (58.7%) and 25/46 (54.3%) patients. PE occurred in 27/54 (50.0%) and 11/25 (44%) patients with positive D-dimer results,

while none with negative D-dimer had PE. Among high-risk patients with unknown D-dimer status 20/38 (52.6%) by Wells and 11/21 (52.4%) by revised Geneva score had PE. Furthermore, pre-test likelihoods of patients with asthma or COPD, decompensated heart failure and coronary artery disease are separately reported in Supplementary Table 3.

Table 9. Pre-test likelihood combined with D-dimer testing. CTPA, computed tomography pulmonary angiography; PE, pulmonary embolism.

Wells score	**D-dimer (age-adjusted)**	**Finding in CTPA**	
		PE Count (%)	No PE Count (%)
Low - Intermediate	Negative	2 (1.9)	105 (98.1)
Low - Intermediate	Positive	139 (30.2)	322 (69.8)
Low - Intermediate	Unknown	34 (10.0)	307 (90.0)
High	Negative	0 (0)	5 (100)
High	Positive	27 (55.1)	22 (44.9)
High	Unknown	20 (52.6)	18 (47.4)
Revised Geneva score	**D-dimer (age-adjusted)**	**Finding in CTPA**	
		PE Count (%)	No PE Count (%)
Low - Intermediate	Negative	2 (1.8)	107 (98.2)
Low - Intermediate	Positive	155 (31.8)	333 (68.2)
Low - Intermediate	Unknown	43 (12.0)	315 (88.0)
High	Negative	0 (0)	3 (100)
High	Positive	11 (50)	11 (50)
High	Unknown	11 (52.4)	10 (47.6)

5.4 Transthoracic echocardiography

TTE was reported in 21 PE patients (9.5%) during ED evaluation. RV dysfunction was reported in 19 (90%) of these patients. Among patients with a sPESI score ≥1, 15/16 (93.8%) had RV dysfunction. RV dysfunction was observed in 66.7% of patients classified as intermediate–low risk, and in all patients classified as intermediate–high (13/13) and high risk (4/4) by ESC criteria.

5.5 Patients on anticogulation treatment

Details of anticoagulation use are provided in Table 8. Among patients receiving warfarin, the international normalized ratio (INR) was below the therapeutic range in 9/46 (19.6%), and one of these patients developed PE.

5.6 Short-term prognosis

Baseline characteristic of patients with confirmed PE and 30-day outcomes are presented in Table 10. Fourteen (6.4%) PE patients died within 30-days, nine due to PE and five due to malignancy. Survivors were younger than non-survivors (67 vs 85 years). In addition, patients with asthma/COPD and atrial fibrillation appeared to have a significantly poorer prognosis. Eleven patients received reperfusion therapy, and none of them died within 30-days. Supplementary Tables 4 and 5 present the main causes of death in patients with and without PE in index imaging during the 30-day follow-up.

Table 10. Baseline characteristics of study population with PE based on 30–day all-cause mortality. PE/DVT, pulmonary embolism/deep vein thrombosis; COPD, chronic obstructive pulmonary disease; sPESI, simplified pulmonary embolism severity index; cTnT, cardiac troponin T; NT-proBNP, N-terminal pro-brain natriuretic peptide; RV, right ventricle; CTPA, computed tomography pulmonary angiography; CA, contrast agent; IVC, inferior vena cava; LV, left ventricle.

	Non-survivors n=14	**Survivors** n=208	**p value**
Age (years)	85.0 ± 8.6	67.0 ± 16.4	<0.001
Female	8 (57.1)	118 (56.7)	0.98
History of PE/DVT	1 (7.1)	53 (25.5)	0.20
Asthma/COPD	5 (35.7)	19 (9.1)	0.01
Prior heart failure	2 (14.3)	9 (4.3)	0.15
History of cancer	5 (35.7)	36 (17.3)	0.14
Atrial fibrillation	6 (42.9)	15 (7.2)	<0.001
sPESI-score ≥ 1.0	12 (85.7)	138 (66.3)	0.24
Early mortality risk score			
Low	1 (7.1)	32 (15.4)	0.70
Intermediate-low	5 (35.7)	101 (48.6)	0.35
Intermediate-high	3 (21.4)	62 (29.8)	0.76
High	5 (35.7)	13 (6.3)	0.003
Biomarkers			
cTnT (ng/L) (n=212)	32.5 [18-52]	19.0 [9-53]	0.09
NT-proBNP (ng/L) (n=156)	12270 [2398-26800]	518 [155-1957]	<0.001
CTPA markers of RV dysfunction			
CA reflux (n=211)			
No CA reflux	5 (35.7)	136 (69.0)	0.026
CA reflux into IVC	4 (28.6)	35 (17.8)	0.30
CA reflux into hepatic veins	5 (35.7)	26 (13.2)	0.031
Septal deviation (n=217)	2 (14.3)	43 (21.2)	0.74
RV/LV ratio ≥ 1.0 (n=213)	5 (50.0)	91 (44.8)	0.76

Cox multivariable regression analysis of mortality or need for thrombolysis or catheter-based intervention in PE patients according to ESC early mortality risk category, sPESI-score, and RV dysfunction findings on CTPA are presented in Supplementary Table 6.

5.6.1 Biomarkers

NT-proBNP levels were significantly higher in non-survivors compared to survivors (median 12 270 ng/L [IQR 2 398–26 800] vs. 518 ng/L [IQR 155–1 957]; p<0.001). cTnT was elevated (≥14 ng/L) in 123 patients (55.4%); there was no significant differences between survivors and non-survivors (p=0.09; Table 10).

The optimal NT-proBNP cut-off for predicting 30-day mortality (Youden index) was 6 380 ng/L yielding a positive predictive value (PPV) 0.37 (95% Cl 0.23–0.85), and negative predictive value (NPV) 0.99 (95% Cl 0.93–0.99).

5.6.2 Markers of CTPA-derived RV dysfunction

Septal deviation and RV/LV ratio ≥1 on CTPA were not significantly associated with 30-day mortality. In addition, in PE patients classified as intermediate-low risk by ESC criteria, the presence of CA reflux was associated with higher 30-day mortality compared to those without reflux (15.0% vs. 2.5%, p=0.022). No significant difference was observed in the intermediate-high risk group by reflux status. Kaplan-Meier analysis of 30-day all-cause survival in PE patients with or without CA reflux into IVC are presented in Supplementary Figure 2.

A model incorporating continuous NT-proBNP values and CA reflux into the IVC yielded an AUC of 0.800 (95% CI: 0.68–0.92), compared to 0.742 (95% CI: 0.62–0.87; p=0.15) for the model without these variables (Figure 4).

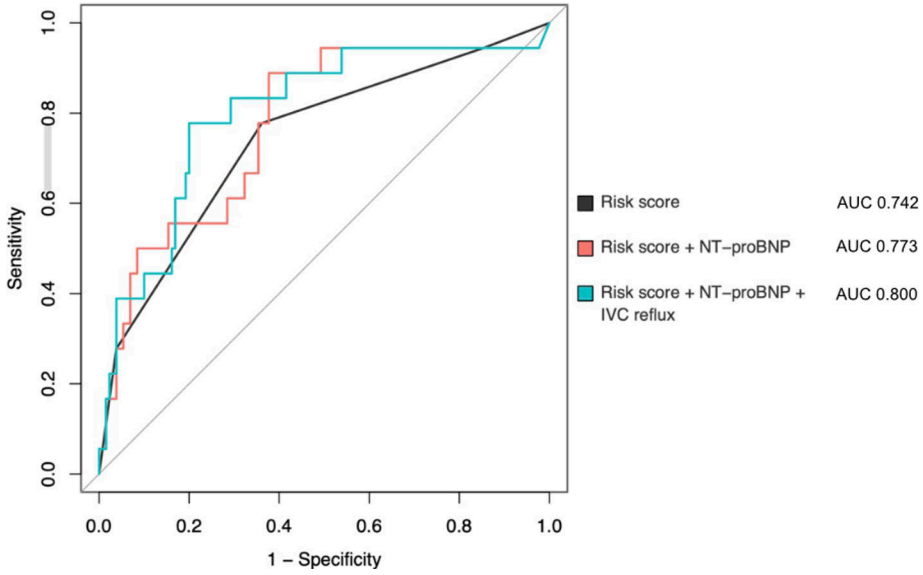

Figure 4. ROC analysis of ESC early mortality risk category combined with and without NT-proBNP and CA reflux into IVC. ROC, receiver operating characteristic; NT-proBNP, N-terminal pro-brain natriuretic peptide; CA, contrast agent; IVC inferior vena cava.

5.7 Long-term prognostic value

During the median of 3.9 [IQR 2.9-4.9] year follow-up, all-cause mortality was 24.8% in patients with PE and 31.7% among those without PE (p=0.047). PE-related death occurred in 3.2% of patients with PE and 0.5% of those without. Underlying and contributing causes of death for both groups are shown in Supplementary Table 7. Among patients with PE on index imaging, cancer (27.2%), dementia (21.8%), and PE (12.7%) were the most common underlying and contributing causes of death. In patients without PE, cancer (31.6%), obstructive coronary disease (19.4%) and COPD (8.9%) were the most common causes.

Biomarkers were measured based on clinical judgement: NT-proBNP in 155/222 (69.8%) PE patients and 411/779 (52.8%) non-PE; cTnT in 212 (95.5%) and 717 (92.0%); CRP in 219 (98.6%) and 758 (97.3%), and D-dimer in 165 (74.3%) and 443 (56.9%), respectively. In prognostic analyses among PE patients, elevated CRP (>50mg/L) and NT-proBNP (>1000ng/L) were associated with worse long-term survival (Figure 5). In patients without PE, higher NT-proBNP (>1000ng/L), cTnT (>50ng/L), CRP (>10mg/L), and D-dimer (>4.0mg/L) predicted poorer outcomes (Figure 6). Cox multivariable regression analysis adjusted with age, sex, cancer diagnosis are presented in Table 11.

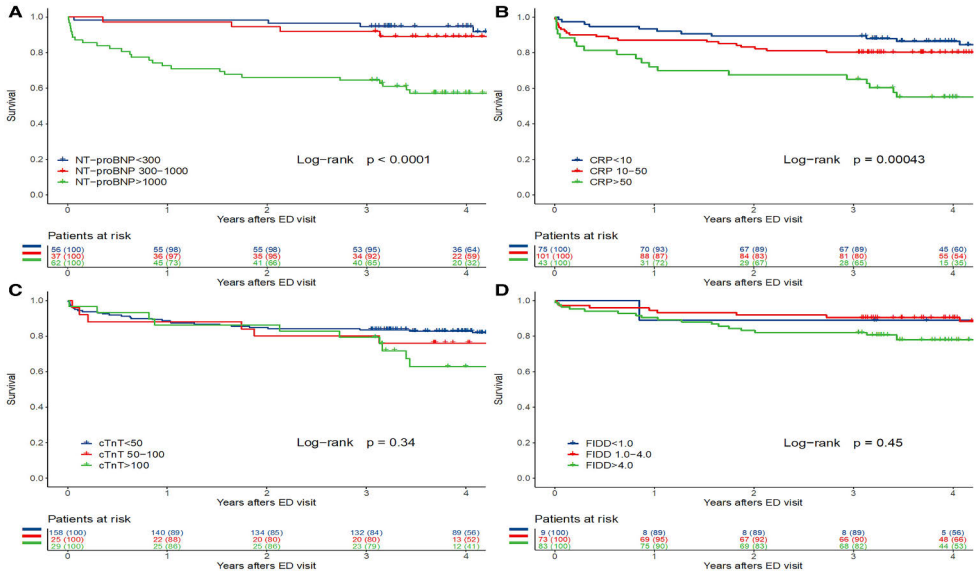

Figure 5. Kaplan-Meier survival analysis of patients with PE in CTPA according to NT-proBNP, CRP, cTnT and D-dimer. PE, pulmonary embolism; CTPA, computed tomography pulmonary angiography; NT-proBNP, N-terminal pro-brain natriuretic peptide; CRP, C-reactive protein; cTnT cardiac troponin T.

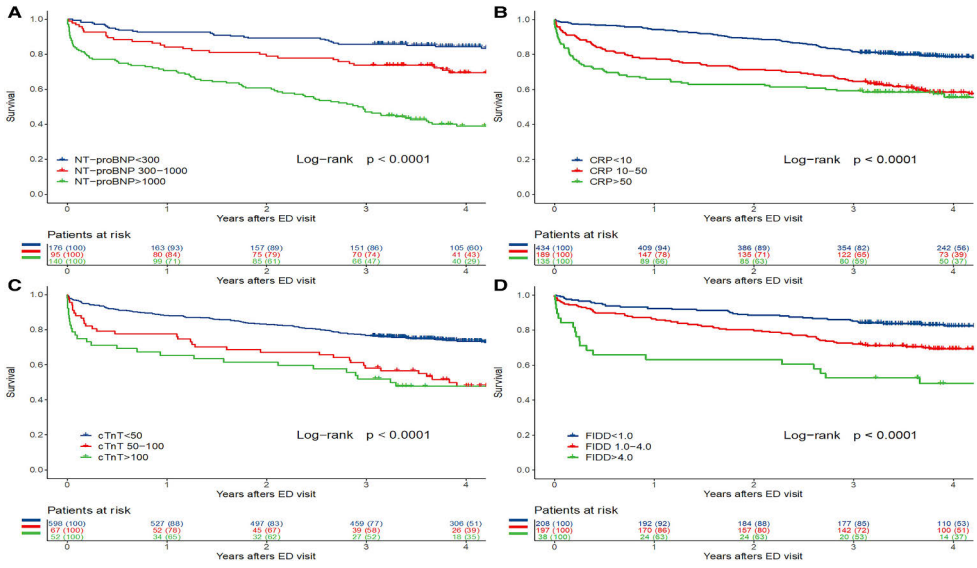

Figure 6. Kaplan-Meier survival analysis of patients without PE in CTPA according to NT-proBNP, CRP, cTnT and D-dimer. PE, pulmonary embolism; CTPA, computed tomography pulmonary angiography; NT-proBNP, N-terminal pro-brain natriuretic peptide; CRP, C-reactive protein; cTnT cardiac troponin T.

Table 11. Cox multivariable regression analysis adjusted with age, sex, and cancer diagnosis and various biomarker. HR, hazard ratio; PE, pulmonary embolism; CTPA, computed tomography pulmonary angiography; NT-proBNP, N-terminal pro-brain natriuretic peptide; CRP, C-reactive protein; cTnT cardiac troponin T.

	PE			No PE		
Variable	HR	95% CI	P value	HR	95% CI	P value
Age	1.1	1.0–1.1	<0.001	1.0	1.0–1.1	<0.001
Sex (male)	1.5	0.7–3.0	0.26	1.4	1.0–1.9	0.05
Cancer diagnosis	3.0	1.5–6.3	0.003	2.3	1.6–3.2	<0.001
NT-proBNP <300 ng/L	Ref			Ref		
NT-proBNP 300–1000 ng/L	0.7	0.2–2.3	0.5	1.7	1.0–2.8	0.05
NT-proBNP >1000 ng/L	3.1	1.2–6.3	0.02	3.5	2.2–5.4	<0.001
Age	1.1	1.1–1.1	<0.001	1.1	1.0–1.1	<0.001
Sex (male)	1.2	0.7–2.1	0.5	1.3	1.0–1.7	0.04
Cancer diagnosis	2.3	1.2–4.3	0.008	1.8	1.4–2.4	<0.001
cTnT <50 ng/L	Ref			Ref		
cTnT 50–100 ng/L	0.9	0.4–2.2	0.8	1.9	1.3–2.7	<0.001
cTnT >100 ng/L	1.1	0.5–2.3	0.9	2.4	1.6–3.6	<0.001
Age	1.1	1.1–1.1	<0.001	1.1	1.0–1.1	<0.001
Sex (male)	1.4	0.8–2.5	0.22	1.4	1.1–1.8	0.02
Cancer diagnosis	2.2	1.3–4.0	0.006	1.9	1.5–2.6	<0.001
CRP <10 mg/L	Ref			Ref		
CRP 10–50 mg/L	1.5	0.7–2.9	0.3	2.2	1.6–2.9	<0.001
CRP >50 mg/L	2.6	1.3–5.2	0.007	3.0	2.1–4.1	<0.001
Age	1.1	1.1–1.2	<0.001	1.0	1.0–1.1	<0.001
Sex (male)	1.5	0.7–3.2	0.3	1.5	1.0–2.1	0.04
Cancer diagnosis	1.9	0.9–4.1	0.1	1.8	1.2–2.8	0.005
D-dimer <1.0 mg/L	Ref			Ref		
D-dimer 1.0–4.0 mg/L	0.55	0.07–4.5	0.58	1.5	0.97–2.2	0.07
D-dimer >4.0 mg/L	0.49	0.06–3.9	0.50	2.9	1.7–5.0	<0.001

Increasing age and cancer were consistently associated with a poorer prognosis. Markedly elevated NT-proBNP >1000ng/L and CRP >50mg/L showed strong and independent associations with adverse outcomes in patients with and without PE. CRP >10mg/L, D-dimer >4.0mg/L and cTnT >50ng/L were linked to a significantly worse prognosis in non-PE patients (Table 11). Cox multivariable regression analysis adjusted with age, sex and cancer diagnosis and various biomarkers as continuous variables are shown in Supplementary Table 8.

The ROC analysis of NT-proBNP, CRP, D-dimer, and cTnT confirmed NT-proBNP as the strongest prognostic marker, improving predictive performance beyond age, sex, and cancer in PE (AUC 86.7 vs 81.8, p=0.071) and non-PE patients (AUC 80.2 vs 76.1, p<0.05) during the 3–year follow-up (Figure 7).

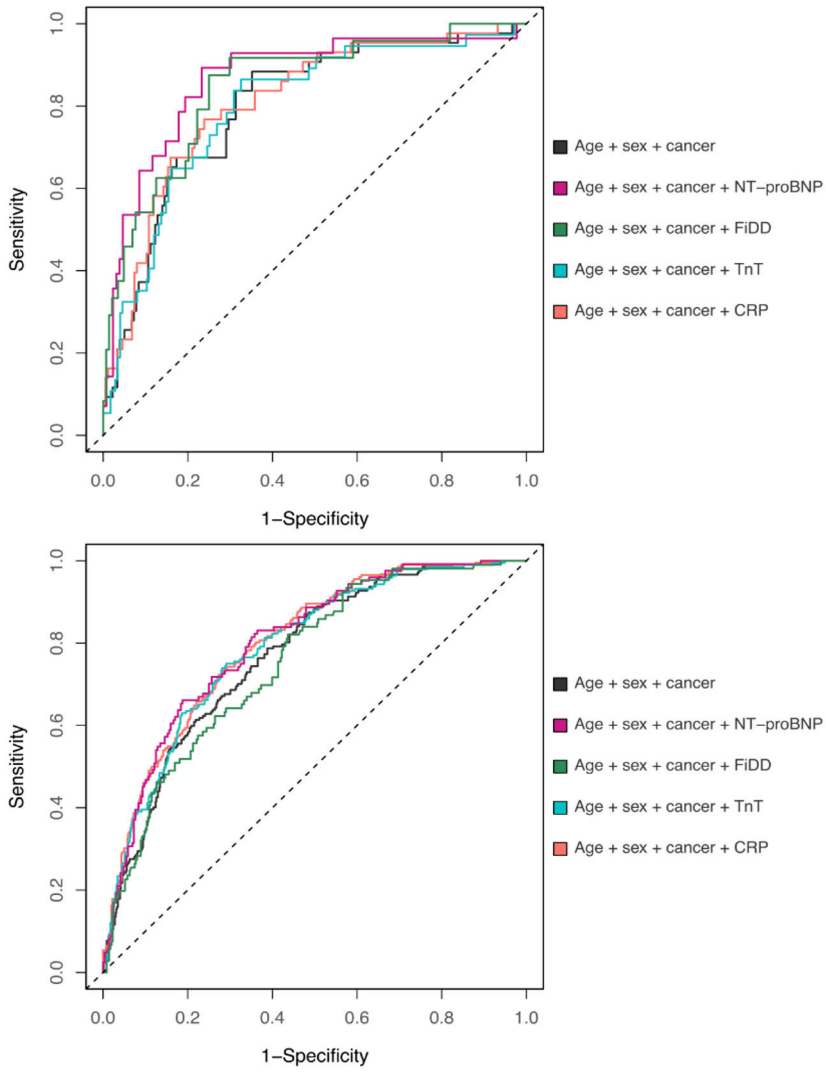

Figure 7. ROC analysis of patients with (A) and without (B) PE in CTPA and levels of NT-proBNP, CRP, D-dimer, and cTnT. PE, pulmonary embolism; CTPA computed tomography pulmonary angiography; NT-proBNP, N-terminal pro-brain natriuretic peptide; CRP, C-reactive protein; cTnT, cardiac troponin T.

Among non-PE patients, adding NT-proBNP [AUC 80.2 (95% Cl 75.8–84.6) vs. 76.1 (95% Cl 71.3–80.8), N=412], CRP [AUC 80.0 (95% Cl 76.6–83.3) vs. 77.1 (95% Cl 73.6–80.7), N=759], and cTnT [AUC 78.9 (95% Cl 75.3–82.5) vs. 77.0 (95% Cl 73.3–80.7), N=718] significantly enhanced prediction compared with the baseline model ($P<0.05$ for all comparisons). Supplementary Figure 3 presents AUC analysis of continuous cTnT levels over a 3-year follow-up period, categorized by mortality in patients with (A) and without (B) PE.

6 Discussion

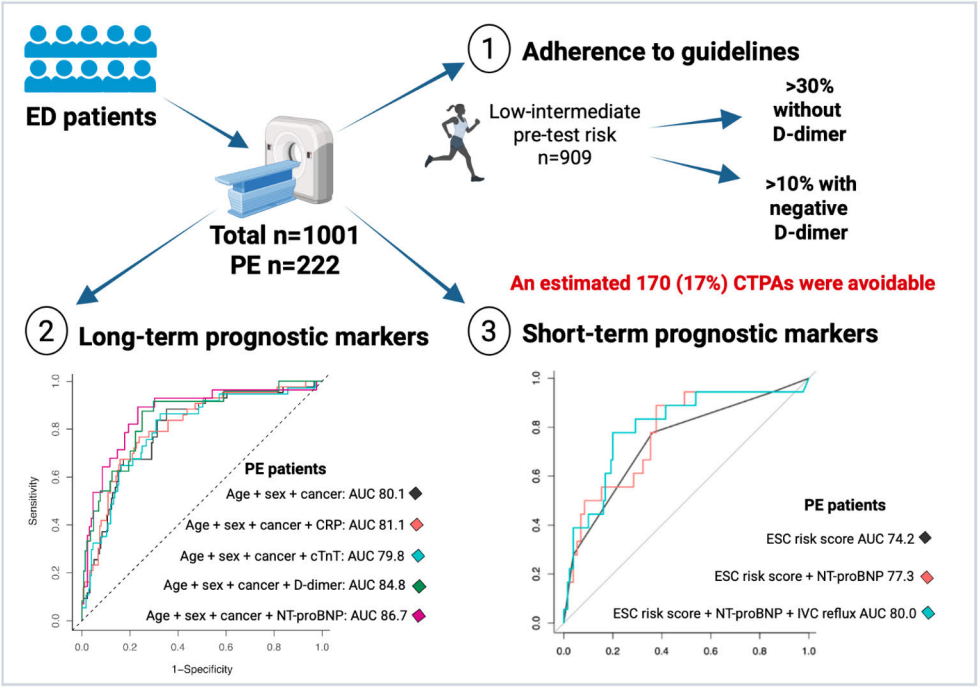

Figure 8. Main findings of the PEACT study. AUC, Area Under the curve; ED, Emergency department; ESC, European Society of Cardiology. Created in BioRender.com.

The study population consisted of 1001 adults who underwent CTPA for a suspected PE during emergency care. The first objective of this study was to evaluate adherence to externally validated diagnostic protocols (Konstantinides et al., 2020) focusing on pre-test probability assessment and D-dimer use. Results revealed only partial compliance with guideline-based diagnostic algorithms. D-dimer testing — an essential step for excluding PE in low–intermediate-risk patients— was taken only in less than two-third of cases in this risk group. Furthermore, among patients with low–intermediate pre-test probability and an unknown D-dimer level, the estimated prevalence of PE was 10%, compared to 30% when the D-dimer test was positive in this risk group. Consequently, 17% of CTPAs were deemed avoidable, as

they were also performed in low–intermediate risk patients with negative age-adjusted D-dimer or without D-dimer testing. Only two patients (2%) with a negative age-adjusted D-dimer in the low-intermediate group had PE –and both had atypical features not captured by scoring systems– supporting the safety and reliability of guideline-recommended pathways. Collectively, these data underscore an opportunity for improved clinician awareness and stricter adherence to validated algorithms to reduce unnecessary imaging, contrast agent and radiation exposure.

On the other hand, in patients with a high clinical probability of PE, measuring D-dimer is not protocol-recommended (Konstantinides et al., 2020). Nevertheless, D-dimer testing was performed in 54-58% of these high-risk patients. Measuring D-dimer in high-risk patients can lead unnecessary delays in confirming the diagnosis and initiating urgently needed therapy. Since treatment decisions in this group should be based on clinical probability and imaging rather than D-dimer results, this practice may compromise timely management.

Around the turn of the millennium, PE incidence increased 81% after introduction of CTPA with only a minimal change in mortality (Wiener et al., 2011). Thus, overutilization of CTPA (Osman et al., 2018; Costantino et al., 2008) and the rising annual costs of imaging (Smith-Bindman et al., 2012) are well-recognized issues in the literature. When physicians were asked to explain the reasons behind the overutilization of CTPA several factors were highlighted, including availability and speed to execute, providing the exclusion of a wide range of differential diagnoses, but also the fear of missing PE (Thurlow et al., 2022). Furthermore, excessive use of CTPA has led to the detection of findings such as subsegmental emboli and incidentalomas – conditions for which optimal management remains uncertain. In addition, due to the fast-paced environment of the ED, where decisions are often made under significant time pressure, clinicians may prioritize rapid decision-making over structured assessments (Thurlow et al., 2022). Proper education, improvements in healthcare systems, and integration of artificial intelligence could significantly simplify and accelerate risk evaluation, ensuring that emergency physicians can make timely and well-informed decisions.

When considering other strategies to reduce unnecessary CTPA utilization, it is important to identify specific patient groups that could be targeted for alternative diagnostic approaches. Based on the observed data, patients with a history of asthma or COPD, coronary artery disease or heart failure demonstrated a significantly lower prevalence of PE on CTPA ($p<0.05$; Table 10). This observation may be attributed to the overlap in clinical symptoms between these conditions and PE. Nevertheless, these diseases differ substantially in their diagnostic protocols, and symptom similarity alone does not justify the excessive use of CTPA. Targeting these groups could help minimize overuse of imaging while maintaining diagnostic accuracy.

The second aim was to assess the long-term prognostic value of biomarkers, including NT-proBNP, CRP, D-dimer, and cTnT, in patients undergoing CTPA for suspected PE. First clinically interesting finding was that patients with suspected PE had poor survival during 3.9 years follow-up. Specifically, patients without PE had increased mortality (31.7%) compared with PE patients (24.8%). In those patients who died, cancer was reported as an underlying or contributing cause of death in 27.2% of PE patients and 31.6% non-PE patients. Furthermore, other prominent causes of death included obstructive coronary artery disease (PE patients: 9.1% vs. non-PE: 19.4%), dementia (PE: 21.8% vs. non-PE: 5.3%), PE (PE:12.7% vs. non-PE 1.6%), and chronic pulmonary disease (PE: 5.5% vs. non-PE 8.9%). In particular, the higher prevalence of obstructive coronary artery disease and chronic pulmonary disease as causes of death in non-PE patients suggests a greater burden of cardiopulmonary comorbidity in this group, which may partly explain the observed difference in mortality.

Kaplan-Meier survival analysis showed that PE and non-PE patients with NT-proBNP value over 1000 ng/L had significantly worse outcome during follow-up. These findings align with previous research linking NT-proBNP elevations to RV strain and hemodynamic compromise in acute PE (Januzzi et al., 2006; Zile et al., 2016; Lankeit et al., 2014).

Patients without PE and cTnT <50ng/L had significantly better prognosis compared to those whose cTnT was elevated. Elevation of cTnT levels did not correlate significantly with mortality in PE patients. This discrepancy suggests that NT-proBNP, reflecting sustained ventricular overload, may be a more sensitive and specific biomarker for prognostic assessment in PE compared to troponin. In this cohort, cTnT levels were measured 96% and 92% patients with or without PE, reflecting the routine use of troponins in the ED. This frequent testing underscores the role of troponins as a rapid and accessible biomarker for myocardial injury, which clinicians often utilize in the initial evaluation of patients presenting with chest pain, dyspnea or haemodynamic instability. While cardiac troponins are typically used as biomarkers for myocardial infarction, they can also indicate myocardial injury in other diseases such as PE, sepsis and endocarditis (Lidija et al., 2025). While different studies have applied various troponin thresholds to predict mortality, a meta-analysis concluded that elevated troponin is associated with up to a fivefold increase in short-term all-cause mortality (Bajaj et al., 2015). However, elevated troponin in non-coronary conditions may prompt unnecessary investigations or interventions if not assessed within the correct clinical context. In PE, guidelines suggest using troponins as integrated part of a broader risk assessment strategy, guiding on monitoring intensity and potential invasive or thrombolytic therapies (Konstantinides et al., 2020).

The strong concordance between negative age-adjusted D-dimer and absence of PE in low–intermediate risk groups highlights the reliability of this biomarker in safely ruling out PE without imaging (Righini et al., 2014). In the present study non-PE patients with D-dimer >4.0mg/L had worse outcomes in 3.9 years of follow-up, consistent with some previous studies that have shown association of elevated D-dimer levels in short-term mortality (Becattini et al., 2012). Furthermore, previous study has suggested that D-dimer may have prognostic relevance in cancer-associated thrombosis (Himeno et al., 2023), but evidence for its role in other patient populations is limited. Similarly to cTnT, no specific cut-off values for D-dimer have been universally endorsed for risk stratification or prognosis of PE. Routine use of D-dimer for risk stratification in patients with confirmed PE is not recommend at the moment (Konstantinides et al., 2020). In conditions known to elevate D-dimer, such as cancer, baseline levels could provide additional information into the presence of acute thrombosis. Yet, their interpretation would be challenging in those conditions as disease progression could still independently raise D-dimer without the presence of thrombosis.

In the present study CRP >50mg/L was associated with mortality in patients with and without PE ($p<0.001$), and CRP values 10-50mg/L with non-PE patients ($p<0.001$) during four-year follow-up. Comparable findings have been reported in previous studies investigating short-term adverse outcomes across different CRP levels (Demelo-Rodríguez et al., 2020; Galeano-Valle et al., 2021; Abul et al. 2011). Because CRP can be elevated by numerous underlying conditions, its clinical utility as a prognostic marker in thrombosis is limited. Prospective studies are needed to determine whether incorporating CRP into risk stratification algorithms improves clinical decision-making outcomes. Additionally, research should explore whether dynamic changes in CRP during treatment provide incremental prognostic information.

When NT-proBNP, CRP, D-dimer, and cTnT were added to the baseline clinical predictors (age+sex+cancer) in PE patients, only NT-proBNP showed a tendency to enhance predictive performance in ROC analysis (AUC 86.7, 81.8; $p=0.071$). In non-PE patients all the biomarkers reach $p<0.05$ when compared to base model, and substantially improved AUC values. These findings summarize the key findings in the second part of the study. The next step is indeed to determine how these insights can be translated into clinical practice and, through future research, establish appropriate cut-off values.

The third aim of this study was to systematically analyze the predictive value of CTPA-derived markers of RV dysfunction, particularly CA reflux, for determining early mortality risk, as outlined in ESC guidelines. The study findings demonstrate that CA reflux into the IVC and hepatic veins was significantly associated with increased all-cause and early mortality. While traditional CTPA indicators of RV

dysfunction such as septal deviation and an RV/LV ratio ≥1 were not significantly correlated with mortality, CA reflux provided a robust, easily identifiable imaging marker of hemodynamic compromise matching the previous results (Bach et al., 2015). TTE remains the gold standard for dynamic assessment, including parameters such as tricuspid regurgitation and TAPSE. However, limitations in CTPA-based RV assessment must be acknowledged. Unlike TTE, CTPA is not routinely ECG-gated, and ventricular measurements are obtained at unsynchronized points during the cardiac cycle (Gopalan et al., 2017). Additionally inadequate contrast opacification of the left ventricle may hinder reliable RV/LV ratio assessment (Foley et al., 2021). In contrast, CA reflux may be less affected by these technical limitations and could serve as a more robust indicator of elevated right-sided pressures. It is also important to consider that RV dysfunction observed on CTPA may not be attributable solely to the index PE event. CA reflux is an indirect marker of dysfunction and may also occur in other conditions such as chronic pulmonary hypertension or RV failure. In addition, higher injection rates of CA tend to increase the incidence of IVC reflux (Aviram et al., 2012).

NT-proBNP emerged as the more powerful prognostic marker, showing an association with short-term mortality, whereas cTnT levels did not differ significantly between groups. While ESC guidelines recommend troponin as part of the prognostic work-up, the role of NT-proBNP is not that clear as spesific cut-off level for NT-proBNP for excluding or predicting poor outcome are yet to be established (Konstantinides et al., 2020).

Among patients categorized as intermediate–low risk according to ESC criteria, the presence of CA reflux was associated with an increase in 30-day mortality. This finding could have clinical implications, suggesting that such patients may benefit from closer monitoring or early escalation of therapy, particularly as CTPA results are available at the time of initial ED evaluation. Routine evaluation of CA reflux on CTPA could therefore enhance clinical risk stratification, particularly among intermediate-risk patients who might otherwise be underestimated using clinical or biomarker criteria alone.

6.1 Limitations

Some limitations of this thesis study should be noted. First, this is an observational, single-center study and the data was collected from the available medical records and a possibility for residual confounding exists. Nevertheless, trained research personnel used a structured case report to collect data consistently.

Retrospective study design was chosen as being appropriate approach for evaluating the real-world diagnostic practices and prognostic factors related to PE. The absence of exclusion criteria makes the study more generalizable as it reflects

true clinical heterogeneity and unselected patient flow, allowing a fair assessment of how guidelines are followed in practice. However, due to retrospective nature of the study, medical records often lacked important details such as symptoms or clinical context, or documented Wells score. Laboratory or imaging results were sometimes missing as well. These gaps reduce data completeness and may weaken statistical power. Also, biomarker testing and imaging were performed based on clinical judgment rather than a standardized protocol, which may limit comparability across patients and introduce uncontrolled factors that affect interpretation. As a single-center study, findings reflect local practice patterns and may not be generalizable to other settings. Although the Wells score showed better discrimination than the Geneva score in ROC analysis, this finding should be interpreted with caution. The study was retrospective, and Wells scoring was rarely documented in the medical records. In many cases, the item "PE is the most likely diagnosis" had to be judged by the data collector based on available notes, which introduces potential bias. To address this limitation, revised Geneva score – based entirely on objective variables – was also calculated to provide a more standardized comparison. Both scoring systems generally produced comparable results across different patient groups.

It is also noteworthy that the pre-test probability scores do not take into account the bradycardic effect of beta blockers which may lead to misclassification in this patient group. In addition, CTPA was not routinely ECG-gated, which have effect on the measured diameters of RV and LV. Despite these potential limitations, this contemporary data represents well a relatively large volume centralized ED with half a million-inhabitant's catchment area. The harms of over- and underdiagnoses are well-recognized. Our findings underscore the use of guideline-recommended risk-stratification tools to reduce unnecessary CTPA.

6.2 Future considerations

The observed underuse of guideline-recommend diagnostic algorithms, particularly the D-dimer testing in low and intermediate-risk patients, highlights the need for prospective studies evaluating the impact of structured diagnostic algorithms on clinical outcomes and resource utilization.

Secondly, the strong prognostic performance of NT-proBNP compared to other biomarkers in this study suggest that its role in risk stratification needs further investigation. Future research should focus on validating NT-proBNP thresholds for mortality in short-term and long-term. There is also a special need to explore, if adding NT-proBNP and CA reflux guided management strategies can help to identify patients at risk and who may benefit from closer monitoring or early escalation of care especially in intermediate-risk patients.

Future studies should aim to develop and validate a model that integrates the clinical scores, biomarkers, and imaging findings into a single prediction tool that could evaluate the patient's individualized risk. Long-term follow-up studies are also needed to identify predictors of chronic thromboembolic pulmonary hypertension and post-PE syndrome, thereby addressing the full spectrum of patient outcomes beyond the acute phase.

The future of healthcare is increasingly data-driven. With the increasing growth of electronic health records, imaging data, laboratory results, genomic information and real-time monitoring from wearable devices, clinicians face an overwhelming amount of information. Artificial intelligence has the potential to revolutionize how we identify and manage patients at risk by providing fast and reliable insights into individual risk profiles.

7 Conclusions

The following conclusions can be drawn from this thesis:

CTPA was often performed in patients with low or intermediate pre-test probability and D-dimer testing was underutilized. This indicates suboptimal adherence to ESC recommendations, as nearly one-sixth of CTPAs could have been avoided with proper risk stratification.

Biomarker analyses revealed that in confirmed PE, elevated NT-proBNP and CRP predicted poor long-term survival. In patients without PE, increases in multiple biomarkers were associated with worse outcomes, highlighting their value for risk assessment beyond diagnostic purposes.

CA reflux into the IVC emerged as a potential early marker of poor prognosis in acute PE, particularly in intermediate-risk patients, suggesting its utility for refining risk stratification and guiding close monitoring or escalation of care.

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List of Figures, Tables and Appendices

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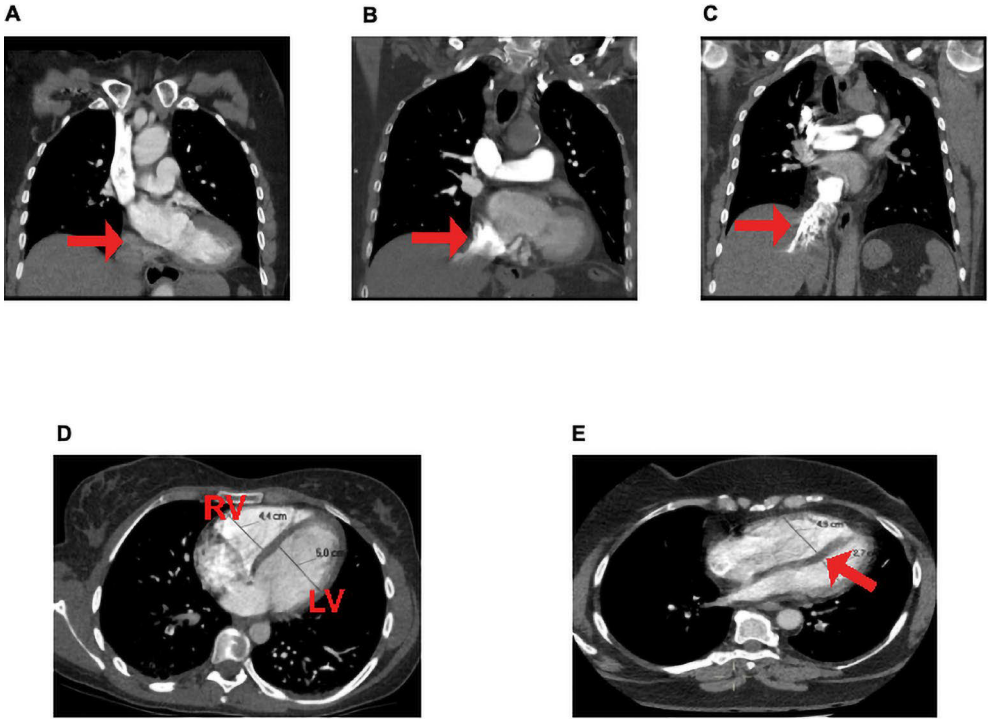
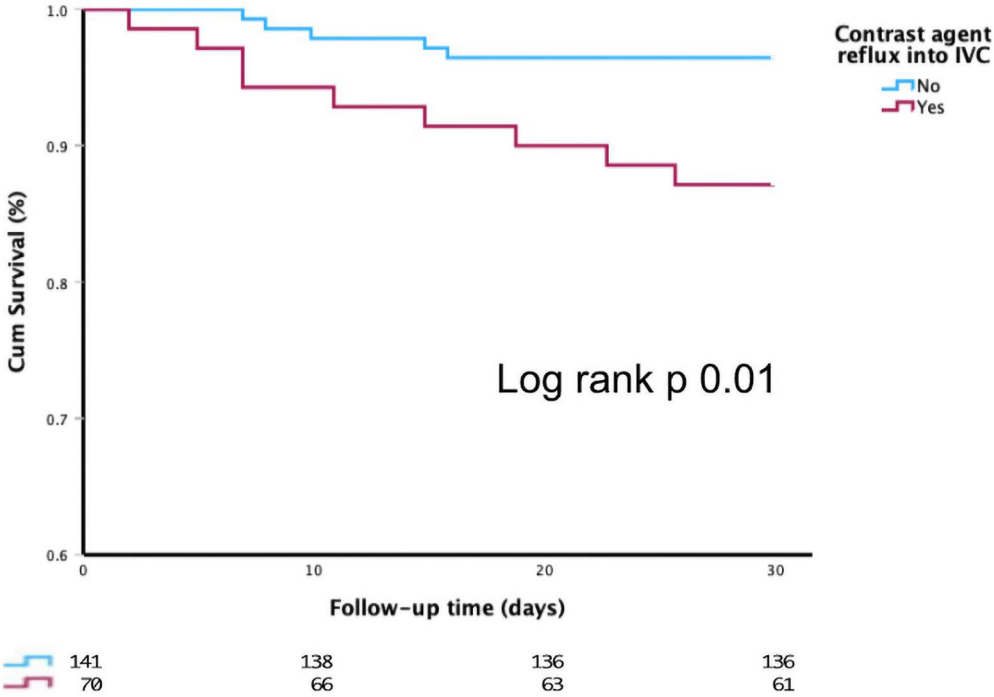
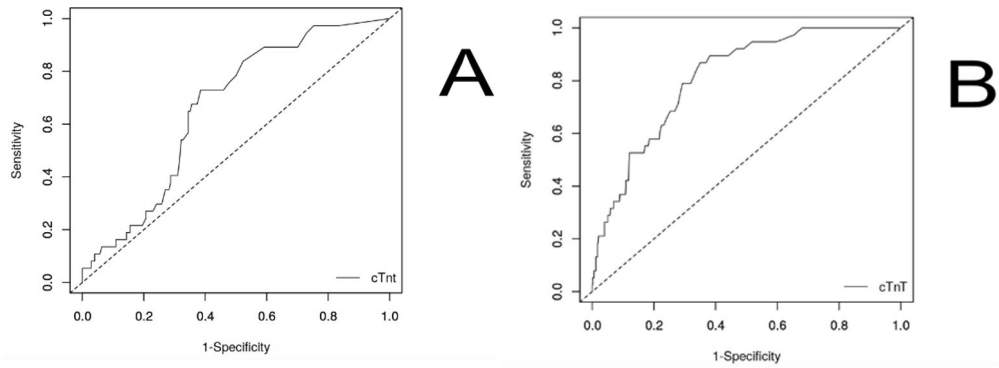


Supplementary Figure 1. Categories of CA reflux; no reflux (A), CA reflux into IVC (B), and CA reflux into hepatic veins (C), and the axial RV/LV diameters on CTPA (D), and deviation of the interventricular septum (E).



Supplementary Figure 2. Kaplan-Meier analysis of 30-day all-cause survival in PE patients with or without CA reflux into IVC. CA, contrast agent; IVC, inferior vena cava.



Continuous cTnT	PE	Non PE
Deaths (%)	37/212 (17.5)	191/718 (26.6)
AUC	0.66	0.73
Sensitivity	0.73	0.87
Specificity	0.62	0.65
Positive Predictive Value	0.29	0.12
Negative Predictive Value	0.92	0.99
Positive Likelihood Ratio	1.90	2.48
Negative Likelihood Ratio	0.44	0.20

Supplementary Figure 3. AUC analysis of continuous cTnT levels over a 3-year follow-up period, categorized by mortality in patients with (A) and without (B) PE. PE, pulmonary embolism; AUC, area under curve.

Supplementary Table 1. The D-dimer precision as reported by the manufacturer Roche Diagnostics: “Precision was determined using human samples and controls in an internal protocol with repeatability (n=21) and intermediate precision (3 aliquots per run, 1 run per day, 10 days). The following results were obtained:”

Repeatability	**Mean**	**SD**	**CV**
	µg FEU/mL	µg FEU/mL	%
Control 1	0.882	0.010	1.1
Control 2	3.99	0.04	0.9
Human plasma A	0.278	0.010	3.5
Human plasma B	1.74	0.01	0.6
Human plasma C	7.12	0.10	1.4
Intermediate precision	**Mean**	**SD**	**CV**
	µg FEU/mL	µg FEU/mL	%
Control 1	0.87	0.03	3.8
Control 2	3.48	0.04	1.3
Human plasma A	0.42	0.02	4.7
Human plasma B	0.98	0.02	1.7
Human plasma C	2.65	0.03	1.3

Supplementary Table 2. Pre-test likelihoods of patients with asthma or COPD, decompensated heart failure and coronary artery disease.

Pre-test likelihood of patients with asthma or COPD		**Finding in CTPA**	
Wells score	D-dimer (age-adjusted)	PE Count (%)	No PE Count (%)
Low–Intermediate	Negative	0 (0)	26 (100)
Low–Intermediate	Positive	14 (15.7)	75 (84.3)
Low–Intermediate	Unknown	5 (6.8)	68 (93.2)
High	Negative	0 (0)	0 (0)
High	Positive	5 (50)	5 (50)
High	Unknown	0 (0)	3 (100)
Pre-test likelihood of patients with asthma or COPD		**Finding in CTPA**	
Revised Geneva score	D-dimer (age-adjusted)	PE Count (%)	No PE Count (%)
Low–Intermediate	Negative	0 (0)	25 (100)
Low–Intermediate	Positive	17 (18.3)	76 (81.7)
Low–Intermediate	Unknown	4 (5.5)	69 (94.5)
High	Negative	0 (0)	1 (100)
High	Positive	2 (33.3)	4 (66.7)
High	Unknown	1 (33.3)	2 (66.7)
Pre-test likelihood of patients with decompensated heart failure		**Finding in CTPA**	
Wells score	D-dimer (age-adjusted)	PE Count (%)	No PE Count (%)
Low–Intermediate	Negative	0 (0)	8 (100)
Low–Intermediate	Positive	3 (7.9)	35 (92.1)
Low–Intermediate	Unknown	4 (9.3)	39 (90.7)
High	Negative	0 (0)	0 (0)
High	Positive	2 (66.7)	1 (33.3)
High	Unknown	2 (33.3)	4 (66.7)
Pre-test likelihood of patients with decompensated heart failure		**Finding in CTPA**	
Revised Geneva score	D-dimer (age-adjusted)	PECount (%)	No PE Count (%)
Low–Intermediate	Negative	0 (0)	7 (100)
Low–Intermediate	Positive	4 (10.3)	35 (89.7)
Low–Intermediate	Unknown	5 (11.9)	41 (89.1)
High	Negative	0 (0)	1 (100)
High	Positive	1 (50)	1 (50)
High	Unknown	1 (33.3)	2 (66.7)

Pre-test likelihood of patients with coronary artery disease		**Finding in CTPA**	
Wells score	D-dimer (age-adjusted)	PE Count (%)	No PE Count (%)
Low–Intermediate	Negative	2 (14.3)	12 (85.7)
Low–Intermediate	Positive	11 (16.4)	56 (83.6)
Low–Intermediate	Unknown	5 (8.5)	54 (91.5)
High	Negative	0 (0)	0 (0)
High	Positive	3 (42.9)	4 (57.1)
High	Unknown	0 (0)	3 (100)
Pre-test likelihood of patients with coronary artery disease		**Finding in CTPA**	
Revised Geneva score	D-dimer (age-adjusted)	PE Count (%)	No PE Count (%)
Low–Intermediate	Negative	2 (15.4)	11 (84.6)
Low–Intermediate	Positive	11 (16.2)	57 (83.8)
Low–Intermediate	Unknown	5 (8.5)	54 (91.5)
High	Negative	0 (0)	1 (100)
High	Positive	3 (50)	3 (50)
High	Unknown	0 (0)	3 (100)

Supplementary Table 3. Most frequent diagnoses for patients, who underwent CTPA without having PE in the ED.

Diagnosis (ICD10)	N (%)
R06 Dyspnea	111 (14.2%)
J18 Pneumonia	64 (8.2)
I50 Heart failure	63 (8.1)
R07 Pain in throat and chest	31 (4.0)
R55 Syncope and collapse	26 (3.3)
J44-J45 Asthma and COPD	25 (3.2)
I21 Acute myocardial infarction	20 (2.6)
I48 Atrial fibrillation and flutter	17 (2.2)
Z03 Medical observation and evaluation of suspected diseases and conditions ruled out	13 (1.7)
I46 Cardiac arrest	10 (1.3)
Total (n=779)	380 (48.7)

Supplementary Table 4. Main causes of death in patients with PE identified in index imaging within 30-day follow-up. Data was gathered from the death certificates.

Main causes of death	N (%)
C34-C83 Malignant neoplasm	5 (35.7)
I26 Pulmonary Embolism	2 (14.3)
G30 Alzheimer's disease	2 (14.3)
I25 Chronic ischemic heart disease	1 (7.1)
E11 Type 2 diabetes mellitus	1 (7.1)
I42 Cardiomyopathy	1 (7.1)
I63 Cerebral infarction	1 (7.1)
W01 Fall on same level slipping, tripping and stumbling	1 (7.1)
Total (n=14)	14 (100)

Supplementary Table 5. Main causes of death in patients without PE identified in index imaging within 30-day follow-up.

Main causes of death	N (%)
C16- C92 Malignant neoplasm	10 (25.0)
I25 Chronic ischemic heart disease	9 (22.5)
J84 Interstitial pulmonary disease	3 (7.5)
I11 Hypertensive heart disease	2 (5.0)
I21 Acute myocardial infarction	2 (5.0)
Total (n=40)	26 (57.8)

Supplementary Table 6. The underlying and contributing causes of death (%) in patients with and without PE in computed tomography pulmonary angiography during 3-year follow-up.

Disease	PE (n=55)	No PE (n=247)
Cancer	15 (27.2)	78 (31.6)
Obstructive coronary disease	5 (9.1)	48 (19.4)
Pulmonary embolism	7 (12.7)	4 (1.6)
Infection	2 (3.6)	14 (5.7)
Dementia	12 (21.8)	13 (5.3)
Chronic pulmonary disease	3 (5.5)	22 (8.9)
Accident/suicide	5 (9.1)	9 (3.6)
Hypertension	1 (1.8)	12 (4.9)
Diabetes	1 (1.8)	4 (1.6)
Stroke	1 (1.8)	8 (3.2)
Renal failure	0 (0)	1 (0.4)
Other reason	3 (5.5)	25 (10.1)

Supplementary Table 7. Cox multivariable regression analysis adjusted with age, sex and cancer diagnosis and various biomarkers as continuous variables. HR, hazard ratio; CI, confidence interval.

	PE			No PE		
Variable	HR	95%-CI	P value	HR	95%-CI	P value
Age	1.1	1.0-1.1	<0.001	1.0	1.0-1.1	<0.001
Sex (male)	1.4	0.72-2.7	0.33	1.5	1.2-2.2	0.005
Cancer diagnosis	2.8	1.3-5.9	0.007	2.0	1.4-2.9	<0.001
NT-proBNP (ng/L)	1.0	1.0-1.0	0.006	1.0	1.0-1.0	<0.001
Age	1.1	1.0-1.1	<0.001	1.1	1.0-1.1	<0.001
Sex (male)	1.2	0.65-2.1	0.59	1.4	1.1-1.8	0.02
Cancer diagnosis	2.3	1.2-4.3	0.008	2.0	1.5-2.6	<0.001
cTnT (ng/L)	1.0	1.0-1.0	0.25	1.0	1.0-1.0	<0.001
Age	1.1	1.1-1.1	<0.001	1.1	1.0-1.1	<0.001
Sex (male)	1.5	0.85-2.6	0.17	1.4	1.1-1.9	0.006
Cancer diagnosis	2.2	1.3-4.0	0.006	2.1	1.6-2.8	<0.001
CRP (mg/L)	1.0	1.0-1.0	0.005	1.0	1.0-1.0	0.005
Age	1.1	1.1-1.2	<0.001	1.0	1.0-1.1	<0.001
Sex (male)	1.5	0.72-3.1	0.27	1.5	1.1-2.2	0.02
Cancer diagnosis	1.8	0.80-4.0	0.14	1.8	1.2-2.9	0.005
D-dimer (mg/L)	1.0	0.94-1.0	0.65	1.1	1.0-1.1	<0.001

Supplementary Table 8. Cox multivariable regression analysis of mortality or need for thrombolysis or catheter-based intervention in PE patients according to ESC early mortality risk category, sPESI-score, and RV dysfunction findings on CTPA.

PE patients	N (%)	Exp	95% CI	p value
ESC early mortality risk category				
Low	2 (6.1)			Ref
Intermediate-low	5 (4.7)	0.8	0.2–4.0	0.77
Intermediate-high	10 (15.8)	2.5	0.6–11.6	0.23
High	8 (44.4)	9.3	2.0–43.8	0.005
sPESI-score				
0	5 (6.9)			Ref
≥ 1	20 (13.3)	1.9	0.7–5.1	0.20
Contrast Agent reflux				
No reflux	9 (6.4)			Ref
CA reflux into IVC	7 (17.9)	3.0	1.1–8.0	0.031
CA reflux into hepatic veins	9 (29.0)	5.0	2.0–12.5	<0.001
Septal deviation				
No	15 (8.7)			Ref
Yes	10 (22.2)	2.5	1.1–5.5	0.027
RV/LV				
< 1.0	6 (5.1)			Ref
≥ 1.0	15 (15.6)	3.1	1.2–7.9	0.021

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