UNIVERSITÀ DEGLI STUDI DI PAVIA

DIPARTIMENTO DI SCIENZE CLINICO-CHIRURGICHE,
DIAGNOSTICHE E PEDIATRICHE
DOTTORATO DI RICERCA IN MEDICINA SPERIMENTALE

SUSPECTED PULMONARY EMBOLISM IN THE EMERGENCY DEPARTMENT: A NEW DIAGNOSTIC ALGORITHM INTEGRATING CLINICAL PROBABILITY SCORES, D-DIMER AND ULTRASONOGRAPHY

A Monocentric Retrospective Study on 889 Patients

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Anno Accademico 2021-2022

1. Introduction

1.1 Definition

Venous thromboembolism (VTE) is a pathology characterised by the formation of blood clots inside the venous blood circulation.[1]

1.2 Epidemiology

VTE manifests clinically as deep vein thrombosis (DVP) and pulmonary embolism (PE) and amongst acute cardiovascular diseases it occupies the third place for incidence, after acute myocardial infarction and stroke.[2] Annual incidence is equal to 39-115 for 100000 inhabitants for PE and 53-162 for 100000 for DVT.[3]

In recent years, incidence has increased for PE but a decrease in mortality rate has also been recorded for the same pathology. This could be explained by the ageing society, especially in the Western world, but also by an increased sensitivity of imaging techniques, in particular Computed Tomography Pulmonary Angiography (CTPA).[4] However, it appears difficult to precisely determine epidemiological data regarding PE as sometimes it remains silent clinically and diagnosis is made when imaging is required for other reasons.

1.3 Predisposing factors

VTE results from the interaction amongst different risk factors that can be relative to the patient or his environment, the former exerting a chronic effect whilst the latter being often transient.

We define an episode of VTE as "provoked" when it occurs in the presence of reversible and transient risk factors such as surgery, complete bed rest, pregnancy, oral contraception, hormone replacement therapy in the last 6-12 weeks.[5] Other strong risk factors include traumas, lower limbs fractures, spinal cord injury, hip or knee replacement, hospitalisation for atrial fibrillation/flutter or heart failure in the last 3 months, myocardial infarction in the last 3 months. [3,6,7] Relatively to limb immobilization, 72 hours are needed for the related risk to develop.[8] Another relevant predisposing factor for VTE is cancer, to which it seems that 20 to 30% of first episode VTE are related but with a risk that varies according to the type of malignancy, which seems highest for the following: pancreatic cancer, haematological malignancy, lung cancer, gastric cancer and cerebral neoplasms. A relatively lower risk is associated to breast cancer and prostate cancer.[9] In general, it seems that patients with cancer have double the risk of VTE compared to patients without cancer.[10] However, the risk stands only if the malignancy is active and not when cancer is in remission, after treatment has been completed.

Considering young women in reproductive age, oral contraception represents the biggest risk factor for TVP.[11] More specifically, the so called combined contraceptives, which contain both oestrogen and progesterone, of the third generation are linked to a higher risk.[12,13] Conversely, intrauterine

hormone-releasing systems and some progesterone-only oral contraceptive pills do not seem to be associated with an increased VTE risk and for this reason, they are often used as first choice in women with a positive family or personal history for VTE. Finally, infections, blood transfusions and erythropoiesis stimulating agents also represent VTE risk factors.[6]

If VTE occurs without such risk factors and situations, it can be defined as "unprovoked VTE".[5]

Some unmodifiable and chronic risk factor appear to play a role for VTE including age (due to a decrease in circulating anticoagulants proteins such as proteins C and S and an increase in the procoagulants ones), venous insufficiency (which produces venous stasis and blood pooling), family history of VTE, autoimmune disorders such as antiphospholipid syndrome and inflammatory bowel disease, hereditary thrombophilia (Factor V Leiden, Antithrombin III deficiency, protein C deficiency, protein S deficiency, Prothrombin mutation).[10]

1.4 Natural history

DVT usually originates at the level of the venous system of the calf and from there it can extend to more proximal veins up to the venous lung circulation causing PE, which can be life-threatening. Thrombosis at each of these levels can be associated to symptoms or not, according to its entity and to the level of vascular occlusion, to the presence of a collateral circulation and to the degree of inflammation that it causes. The ability of the patient to tolerate the thrombotic event can vary, indeed an otherwise healthy patient can be asymptomatic or only mildly symptomatic when presented with a moderate PE, whilst a patient with severe cardiovascular disease can show severe symptoms up to even death, when facing PE of the same entity.[14]

After surgery, the risk of VTE is highest in the first two weeks but it remains consistent for the following three months. Fatal post-operative PE seems to be linked to the first 3 to 7 days after surgery. These data show how fundamental post-operative anti-thrombotic prophylaxis is in reducing VTE risk. Incidence has been shown to be reduced by increasing the duration of anticoagulation therapy for what regards orthopaedics and cancer surgery, but the same has not been found for abdominal surgery. A study has been carried out regarding the recurrence risk of VTE in patients under anticoagulation therapy: 2% at 2 weeks, 6,4% at 3 months and 8% at 6 weeks. Over the long period and after stopping anticoagulation treatment the following has been reported: 13% at 1 year, 23% at 5 years and 30% at 10 years.[15]

The frequency of recurrence do not seem to be linked to the initial clinical presentation of VTE (either PE or DVT), however, it has been shown that recurrence tends to show the same clinical features as the first episode. The risk of fatal PE after a first episode of PE is 2 to 3 times higher than with a first episode of DVT. Indeed, when the first episode is PE there is a 60% recurrence rate in the form of PE whilst only 20% of initial DVT will recur as PE.[14]

It is important to note that the risk of recurrency for VTE is higher for the "unprovoked" episodes or for VTE provoked by ongoing at risk situations such as active malignancy as opposed to "provoked"

VTE by transient risk factor such as recent surgery (10% risk each year vs 3%, after stopping anticoagulation treatment).[14] Recurrent episodes are most common for women who continue hormone replacement therapy after the first episode of VTE and for patients who experienced PE secondary to proximal DVT as opposed to distal DVT. For reference, a proximal DVT is considered to involve iliac, femoral or popliteal veins, whilst distal DVT involves veins distal to the popliteal ones. Other factors linked to late recurrence which are still under study are age, male sex,[16,17] family history for PE and increased BMI.[15,18] High levels of D-dimer measured in blood both during and after stopping anticoagulation therapy also suggests higher risk of recurrence.[19] Finally, it has been demonstrated that inherited thrombophilia is linked to a low predictive value for VTE recurrence and therefore it appears not indicated to test for it or start anticoagulation therapy on its basis, after a single episode of VTE.[20]

1.5 Physiopathology

The triad of factors which appear to participate in the process of thrombus formation as stated by R. Virchow in 1856 still appears valid and includes a state of hypercoagulability, venous stasis and local trauma to the vessel wall. In general, procoagulant factors must prevail over anticoagulant and fibrinolytic ones for a thrombus to form. Thrombotic PE most frequently arises when a thrombus which has formed in the peripheral venous circulation detaches and migrates up to the pulmonary circulation to obstruct pulmonary arteries or their branches. The obstruction can thus involve segmental or subsegmental lung arteries or be right at the pulmonary arteries bifurcation forming the so called “saddle PE”.[10] Depending on the entity of the mechanical obstruction and provided that at least 30-50% of the arterial lung circulation is involved, an increase in pulmonary pressure is triggered, which can generate strain on the right heart up to right heart failure, which is one of the most common causes of death due to PE.[21] This process is exacerbated by the fact that thrombi are physiologically active and release vasoconstricting factors such as thromboxane A2 and serotonin, which contribute to the increase in pulmonary vascular resistance (PVR).[22]

According to the Frank-Starling law, an increase in PVR causes an increase in end-diastolic ventricular volume which corresponds to an increase in wall tension with a relative lengthening of cardiomyocytes. This causes an increase in contraction force. Parallelly, there are also neurohumoral factors which behave as positive chronotropes and inotropes. These compensatory mechanisms bring a further increase in pulmonary arterial pressure, which increase blood flow through obstructed vessels and, even if momentarily, stabilize systemic blood pressure. This process continues until a threshold pressure is reached, at this point the right ventricle (RV) will not be able to cope anymore with the increased pressure and it will begin to fail. The RV increased systolic time causes a leftwards movement of the interventricular septum during left ventricular diastole,[23] possibly resulting in LVEF reduction and CO reduction. This mechanism explains why systemic hypotension and haemodynamic instability can occur in severe PE.[24] The appearance of a RBBB at ECG also appears to be related to

acute RV failure and in particular to the inhibition of blood flow to subendocardial vessels in the right bundle that occurs upon acute dilation of RV in severe PE.[25]

It has been shown that acute PE causes myocarditis and an increased concentration of epinephrine, as found upon dissection in the heart muscle of patients who died of PE. This inflammatory response can contribute to explain the already mentioned haemodynamic instability that can occur 24 to 48 hours after the acute event.[26] A link between elevated cardiac biomarkers and early death from PE has also been found, underlying the importance of RV ischemia in the pathophysiology of acute PE.[27]

Even if it is rare to experience RV infarction due to PE, it is likely that the mismatch between oxygen demand and supply causes cardiomyocytes damage and reduction in contractile force.

During an episode of PE, the respiratory insufficiency is mostly related to the haemodynamic instability. A decreased EF causes desaturation of blood which added to the decreased flow in obstructed vessels and increased flow in open capillaries, causes a V/Q mismatch that increases the hypoxia.[28]

To conclude, it is worth noticing how small emboli in distal arterial pulmonary branches do not alter the haemodynamic balance but concur to the pathophysiology by creating areas of alveolar haemorrhage and pulmonary infarction. This translates clinically with haemoptysis, pleuritis and pleural effusion.

1.6 Clinical presentation

PE can be symptomatic or silent, depending on its extent and on patient characteristics, including age and possible pre-existing cardiopulmonary conditions. PE is sometimes diagnosed accidentally in the workup of other clinical conditions. More frequently, it is suspected in patients presenting with dyspnoea, chest pain, pre-syncope or syncope, haemoptysis.[29] Dyspnoea can be absent or mild if the clot is distal in the pulmonary vascularisation, or acute and severe in case the clot is proximal and central. Dyspnoea is perceived by patients due to the hypoxic state but also related to the increased respiratory rate that the acute condition imposes. Chest pain is a frequent symptom, it is related to pleural irritation caused by distal emboli that generate lung infarctions[30] or can also be angina-like pain related to the increased work of the heart that causes RV ischemia. Some cases of central PE manifest themselves with chest pain that mimics closely the presentation of acute coronary syndrome (ACS) or aortic dissection (AD) and, indeed, the differential diagnosis of PE includes these two conditions. According to a recent study, PE frequently presents with syncope.[31] The most common PE-related syncope is the reflex syncope due to vasovagal response, but syncope could also be hypotension-related or an arrhythmic syncope. Hypotension and shock are more rarely the initial clinical presentation of PE but they are relevant considering that they are linked to central PE or to PE associated with severely reduced haemodynamic reserve. Shock is of the obstructive-distributive type: tissue hypoperfusion due to pulmonary artery clot, together with hypotension and reduced venous return to the LV reduce the CO. Finally, sudden death is also a possible presentation of PE other than

the most severe one, it can be related to the obstructive shock or be underlined by a malignant arrhythmia.

To increase the level of accuracy in suspecting PE, it is always important to consider the presence (or absence) of the specific predisposing conditions, which closely correlate with the risk. However, it is worth mentioning that according to the literature in up to 50% of cases, no predisposing factor can be identified.[32]

Considering the cases of asymptomatic PE, they can sometimes be linked to an already existing clinical DVT, therefore it could be useful to investigate for subtle signs of PE when the diagnosis of DVT is manifest.

Hypoxia is considered typical, but a relevant proportion of patients present with normal arterial blood saturation. Hypocapnia is another common finding at arterial blood analysis. However, literature does not support arterial blood gas analysis alone as a mean to exclude PE, even if it remains a valid instrument in overall patient evaluation.[33]

Other than the classic imaging techniques, and especially in severe cases, ECG can be extremely useful and show pathological patterns such as RBBB either uncomplete or complete, T wave inversion in V1 to V4, the QR pattern in V1 or the S1Q3T3 pattern which could be quite evocative.[34] When PE is not as severe, the most common ECG presentation is sinus tachycardia. Finally, some rarer cases of PE are linked to supraventricular tachycardias such as atrial fibrillation.

1.7 Diagnosis

1.7.1 Diagnostic approach in the Emergency Department

According to the latest ESC Guidelines released in 2019,[3] the diagnostic algorithm when suspecting PE changes according to whether the patient suffers from haemodynamic instability or not. The ESC guidelines also precisely define the concept of haemodynamic instability. *(Table 1)*

If the patient is haemodynamically unstable, it is recommended to perform transthoracic echocardiography (TTE) to evaluate for the possibility of RV dysfunction. If TTE is negative for RV dysfunction, the physician should focus on finding other possible causes of haemodynamic instability. On the contrary, if signs of right heart failure are found, the suspicion of PE grows posing direct indication for performing CTPA. According to the imaging result, if PE is confirmed, treatment is started following the guidelines for high-risk PE. If CTPA is not available within a short delay, it is recommended to start treatment as if the diagnosis of high-risk PE was confirmed. Lastly, if CTPA is negative for PE, the clinical suspicion is rejected and other causes of shock must be considered and investigated.

If the patient is haemodynamically stable, pre-test probability is evaluated (*paragraph "1.7.2 Pre-test probability"*) using currently available scores to decide the level of clinical probability or, in other terms, the likelihood of PE being the correct diagnosis. *(Figure 1).*

If there is low to intermediate clinical probability, or PE is unlikely, there is indication to measure blood D-dimer levels. According to the latest ESC 2019 Guidelines, D-dimer levels are considered adjusted to age (age x 10 ng/ml) for patients older than 50 years old, whilst the cut off is considered to be 500 ng/ml for patients younger than 50 years old. If the patient's D-dimer measurement is lower than the patient-specific cut off, no treatment is needed and the diagnosis of PE is rejected. Conversely, if the D-dimer measurement is higher than the patient-specific cut off, the clinical suspicion of PE cannot be excluded and therefore there is indication to perform CTPA, which is the only investigation that can confirm or reject the clinical hypothesis with certainty. If the diagnosis of PE is confirmed by CTPA, treatment for PE can then be started.

If the pre-test probability for PE is high, or PE is likely, it is possible to directly run CTPA without testing D-dimer levels beforehand. If CTPA is positive for PE, treatment for PE is started. If CTPA is negative for PE, a discordance between high pre-test probability and CTPA result has been found, therefore it is suggested to either exclude the possibility of treating for PE or to investigate further *(figure 2).*

(1) Cardiac arrest	(2) Obstructive shock	(3) Persistent hypotension
Need for cardiopulmonary resuscitation	Systolic BP <90 mmHg, or vasopressors required to achieve a BP ≥90 mmHg despite adequate filling status	Systolic BP <90 mmHg, or systolic BP drop ≥40 mmHg, either lasting longer than 15 minutes and not caused by new-onset arrhythmia, hypovolaemia, or sepsis
	And	
	End-organ hypoperfusion (altered mental status; cold, clammy skin; oliguria/anuria; increased serum lactate)	

Table 1: Definition of haemodynamic instability (from ESC 2019 Guidelines)

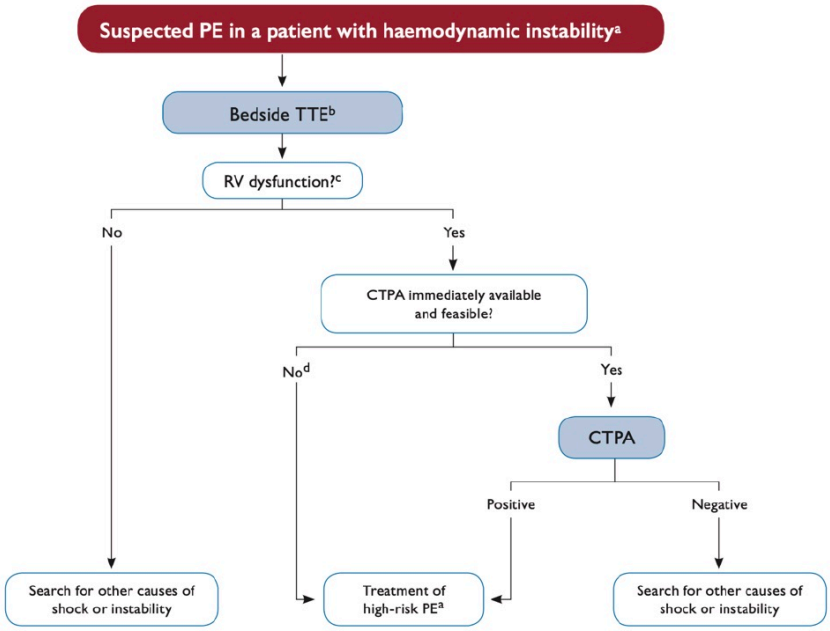

Figure 1: Algorithm for suspected PE in a patient with haemodynamic instability (from 2019 Guidelines on acute PE)

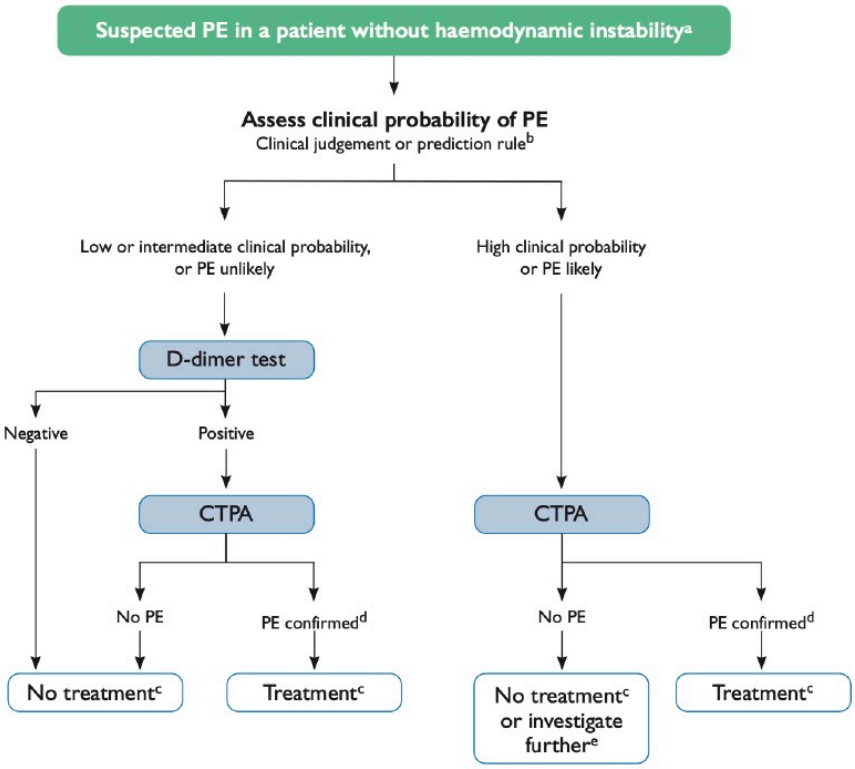

Figure 2: Algorithm for suspected PE in a patient without haemodynamic instability (from 2019 Guidelines on acute PE)

1.7.2 Pre-test probability

In the diagnostic algorithm for PE, the evaluation of pre-test probability (PTP) is crucial. PTP is obtained by a combining different clinical findings and measurements with PE predisposing factors in patients' anamnesis. This allows to stratify patients according to the relative clinical probability of suffering from PE, which corresponds to the effective increasing prevalence of confirmed PE.

Pre-test evaluation can be performed through investigations such as chest radiography or ECG or by using clinical prediction rules such as Wells score or Geneva revised score *(table 2)*.[35] Originally they were both divided into three levels (low, intermediate, high), later modified to two levels ("PE likely", "PE unlikely"). A simplified version of these decision tools also exist which is particularly helpful in the emergency setting.[36]

If one utilises the three levels scheme prediction scores, the percentage of correctly diagnosed patients is 10% for the low probability category, 30% for the intermediate probability category and 65% for the high probability category.[37] Considering the two levels scheme scores, a correct diagnosis is reached in 12% of cases if patients are classified as "PE unlikely" and in 30% of cases for "PE likely" patients.

Considering PE as a possible diagnosis in every patient with chest pain or dyspnoea comes with high cost and with the realisation of unreasonable testing in some instances. For this reason, some criteria

defined as “PERC” (Pulmonary Embolism Rule-out Criteria) were developed in order to identify patients for which the benefit of testing overcomes the risk of it *(table 3)*.

These criteria include eight clinical items that should be considered only for patients which fall in the low clinical PTP of having PE.[38,39]

The sensibility of PERC is estimated to be between 96 and 100% whilst specificity is between 15 and 27%.

According to the existing literature, by combining a low PPT and the presence of all PERC items, it is possible to safely exclude the possibility of PE. On the contrary, if at least one item of PERC is not respected, it is not possible to safely exclude PE and therefore, at least D-dimer measurement is indicated. However, it must be noted that the overall low prevalence of PE in these studies does not really support the generalisation of the result.

Items	Clinical decision rule points	
Wells rule	**Original version[95]**	**Simplified version[107]**
Previous PE or DVT	1.5	1
Heart rate ≥100 b.p.m.	1.5	1
Surgery or immobilization within the past four weeks	1.5	1
Haemoptysis	1	1
Active cancer	1	1
Clinical signs of DVT	3	1
Alternative diagnosis less likely than PE	3	1
Clinical probability		
Three-level score		
Low	0–1	N/A
Intermediate	2–6	N/A
High	≥7	N/A
Two-level score		
PE unlikely	0–4	0–1
PE likely	≥5	≥2
Revised Geneva score	**Original version[93]**	**Simplified version[108]**
Previous PE or DVT	3	1
Heart rate 75–94 b.p.m. ≥95 b.p.m.	 3 5	 1 2
Surgery or fracture within the past month	2	1
Haemoptysis	2	1
Active cancer	2	1
Unilateral lower limb pain	3	1
Pain on lower limb deep venous palpation and unilateral oedema	4	1
Age >65 years	1	1
Clinical probability		
Three-level score		
Low	0–3	0–1
Intermediate	4–10	2–4
High	≥11	≥5
Two-level score		
PE unlikely	0–5	0–2
PE likely	≥6	≥3

Table 2:PTP scores (from ESC 2014 Guidelines on acute PE)

Pulmonary embolism rule-out criteria (PERC)	
Criteria	Points
Age > 50 years	1
Heart rate > 100/min	1
Oxygen saturation < 95%	1
Hemoptysis	1
Estrogen use	1
Prior history of DVT or PE	1
Recent surgery or trauma in the past 4 weeks	1
Unilateral lower limb edema	1
Clinical pretest probability • Total score 0: pretest probability < 1%; no further testing needed • Total score ≥ 1: PE is not ruled out; further testing needed	

Table 3: PERC (from Amboss)

1.7.3 D-dimer test

Blood D-dimer increase in patients with VTE due to activation of both coagulation cascade and fibrinolytic pathway. The negative predictive value of such test is high, therefore normal blood D-dimer renders VTE highly unlikely. Conversely, the positive predictive value of high D-dimer is low, considering that fibrin levels increase even in conditions such as cancer,[40] hospitalization,[41] severe inflammatory state, sepsis, pregnancy,[42] bleeding, trauma and surgery. As a consequence, it appears insufficient to confirm acute VTE but useful in ruling it out whenever it is low or negative.[43]

Age is another unmodifiable condition for which D-dimer levels increase physiologically. Indeed, it has been demonstrated how D-dimer testing specificity decreases of 10% in patients older than 80 years old.[44] However, recent studies have shown that applying an age-adjusted D-dimer threshold (age x 10microg/L, if > 50 years old) results in increased efficiency in testing older patients for which VTE is clinically suspected. Consequently, according to the literature and to the latest ESC Guidelines, it is now considered safe to rule out PE in patients with low to intermediate pre-test probability and a negative D-dimer blood level considering the age-adjusted patient-specific D-dimer threshold.[3,45]

Even more recently, some studies have suggested that the age-adjusted D-dimer threshold is too permissive and that a great number of CTPA could be spared by applying an even higher thresholds for D-dimer testing.

In 2019, a scientific prospective study has been published on the NEJM which showed how on a cohort of 2017 patients, using a D-dimer cut off of 1000 ng/dl for patients with low clinical pre-test probability, it has been possible to rule out PE in 93% of cases without further testing needed.[46]

Another study published in JAMA in 2021 proposed a combination of the YEARS rule (1pt if PE is the most likely diagnosis, 1pt for hemoptysis and 1pt for clinical signs of DVT) and a D-dimer level of 1000 ng/ml for patients with low subjective clinical probability with 1 or more PERC items. According to this strategy, only patients with YEARS > 0 and D-dimer > 1000 ng/ml should undergo chest imaging, otherwise PE can be excluded.[47]

1.7.4 CTPA, CXR and V/Q scan imaging

CTPA is considered the standard of care imaging technique for the diagnosis of PE. It studies the lumen of pulmonary arteries until the subsegmental/segmental level to look for intraluminal filling defects that could partially or completely occlude the vessel *(figure 3)*. Some peculiar findings are the so called longitudinal "railway track" sign or transversal "polo mint" sign that correspond to a partial filling defect surrounded by contrast on the sides. The significance of incidentally-found single subsegmental emboli at CTPA remains controversial, especially because these patients are often asymptomatic; it is currently recommended to carry out compression venous ultrasonography and withhold treatment for these patients in the absence of specific risk factors.[48]

CTPA allows to rule out other possible causes that could account for the patient symptoms, such as aortic dissection, pneumonia or pneumothorax. It has excellent positive and negative predictive values (respectively 86% and 95% according to the PIOPED II trial)[49] and it now widely available in hospitals.[50]

Often the first line imaging technique ordered for patients with dyspnea or chest pain is Chest Radiography (CXR) but it has limited utility for suspected PE. Some specific findings at CXR that could suggest PE are the Westermark sign (paucity of distal vascular branches) and the Fleischner sign (focal enlargement of the central pulmonary artery) that are both related to the presence of the clot in the lumen of the artery. Another quite specific sign is the Hampton's hump which is a peripheral wedge-shaped opacity that corresponds to an area of pulmonary infarction *(figure 4)*. Unfortunately, these signs are inconsistent and more often patients show atelectasis or lung opacity at CXR, which are unspecific, despite suffering from PE.[50]

A valid alternative to CTPA is the ventilation and perfusion (V/Q) scanning to screen for a V/Q mismatch, which, in the specific case of PE, corresponds to an area of altered perfusion with conserved ventilation. V/Q scanning has very good positive and negative predictive value when combined to, respectively, high and low clinical probability. However, it was found that the positive predictive value is only 56% in patients with low clinical probability[50] and that there are more undiagnostic results with V/Q scanning than with CTPA[49]. On the contrary, V/Q scanning has the advantage of exposing patients to lower quantity of radiation, which could be relevant especially in pregnant women or younger patients, as well as patient allergic to contrast agents or with chronic renal failure.[51] Therefore, it is currently believed that V/Q scanning should be reserved for patients for which CTPA appears disadvantageous[52] whilst for the general population, CTPA remains the currently recommended standard of care imaging technique for the diagnosis of PE.[53]

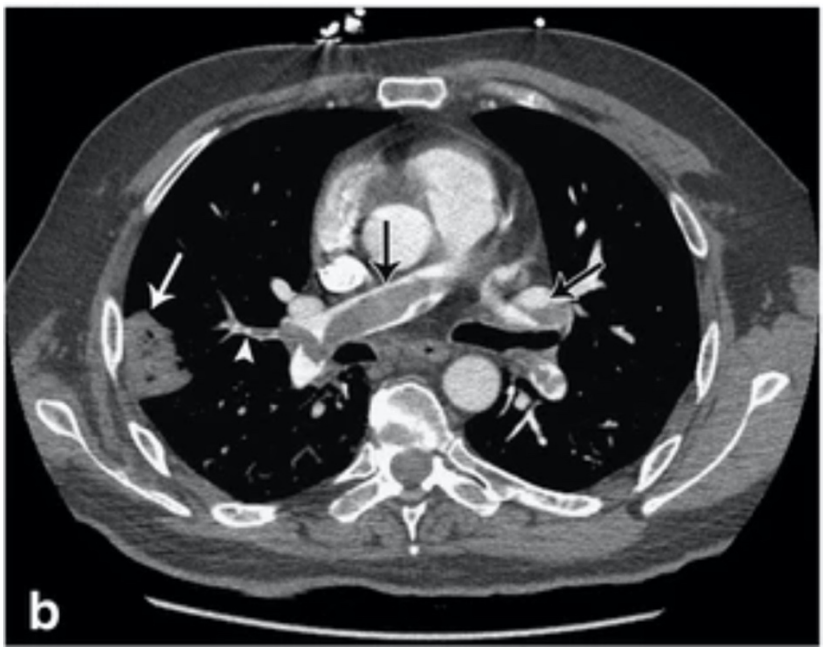

Figure 3: Bilateral PE (from "Imaging of acute pulmonary embolism" nota 49)

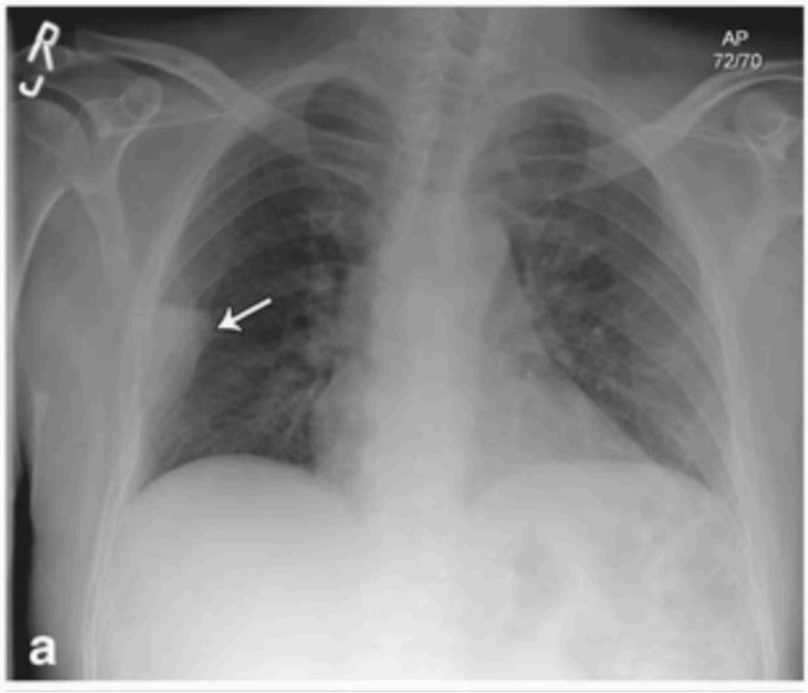

Figure 4: Hampton's hump (from "Imaging of acute pulmonary embolism" nota 49)

1.7.5 Ultrasonography

Ultrasonography of the venous circulation of the lower limbs, combined with compression maneuvers (Compression Ultrasound, CUS) and transthoracic echocardiography (TTE) represent two important imaging modalities in patient with suspected PE. TTE is included in the 2019 ESC Guidelines on Acute PE[3] as a mean to evaluate patients with hemodynamic instability before recurring to CTPA;[3]

however, its role, even if not yet standardized, is recognized in the evaluation of hemodynamically stable patients suspected to have PE too.

In the specific case of hemodynamically unstable patients, TTE is able not only to identify signs of PE but also provide information on the differential diagnosis of shock, such as evaluate for the presence of cardiac tamponade, acute valvular dysfunction, aortic dissection or hypovolemia. For this category of patients, it is enough to find RV dysfunction at TTE, without another possible explanation, for the patient to be treated with emergency reperfusion, in case CTPA is not available shortly, as the diagnosis of PE is already established.[54] Lastly, also atrial thrombi, even if a rare finding, can confirm the diagnosis of PE and are associated with RV dysfunction and early mortality.[55]

Considering now hemodynamically stable patients, according to a systematic review and meta-analysis, there are numerous signs that can be found in TTE and possibly point toward PE with high specificity but low sensitivity, making it a good test in the emergency setting to rule in hemodynamically stable patients, but not adequate to safely exclude the possibility of PE,[56] considering that in up to 71% patients with PE no significant abnormalities were found.[57]

TTE signs of PE are mostly related to the RV, that becomes acutely distended and possibly dyskinetic *(figure 5)*. It must be noted that other pathologies could lead to the same echocardiographic picture, such as right acute myocardial infarction or pulmonary diseases, therefore careful differential diagnosis should be conducted.

According to the meta-analysis, the most common indicator of PE at TTE is an undefined "right heart strain" with a specificity of 83% and a sensitivity of 53%.[56] A more specific description of RV enlargement can be found in at least 27% of patients with PE whilst interventricular septal flattening was found in 18% of patients.[57] Furthermore, the combination between pulmonary ejection acceleration time <60 ms with a tricuspid regurgitation peak systolic gradient < 60 mmHg (60/60 sign) and the presence of McConnell sign, has turned out indicative of PE and the most useful criterion to define RV dysfunction.[58] As opposed to global movement dyskinesis in the setting of chronic RV dysfunction, this specific sign called McConnel sign describes the coexistence of RV free wall akinesia with conserved apical contractility. In case of hypo/akinesia of the RV free wall in the presence of previous RV myocardial infarction, which could mimic McConnell sign,[59] other echocardiographic signs of RV volume overload are necessary in order not to be mistaken, such as measuring the TAPSE, which would be reduced in the specific case of a patient with PE.[60] Another finding that correlates with RV overload is a distended inferior vena cava (IVC, > 2 cm) together with its failure to collapse during inspiration, when observed from the subcostal window *(figure 6)*.

Considering the data already present in literature regarding echocardiographic findings in hemodynamically stable patients but taking into account their low sensitivity for PE when evaluated singularly, it would be interesting to study their possible usefulness when combined to other indicators of PE, such as PTP scores or clinical and laboratory findings that are also classically associated with

PE. In this way, a more sensitive patient evaluation to find patients that would benefit the most from CTPA could be done.

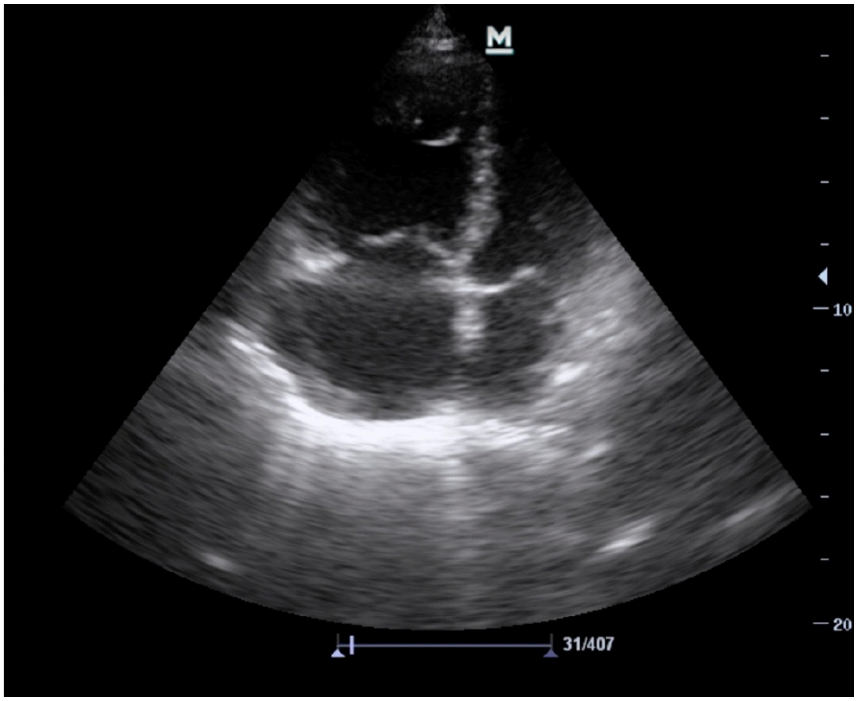

Figure 5: distended right ventricle as seen with bedside echocardiography, with Mindray Ultrasound Machine (see Materials and Methods)

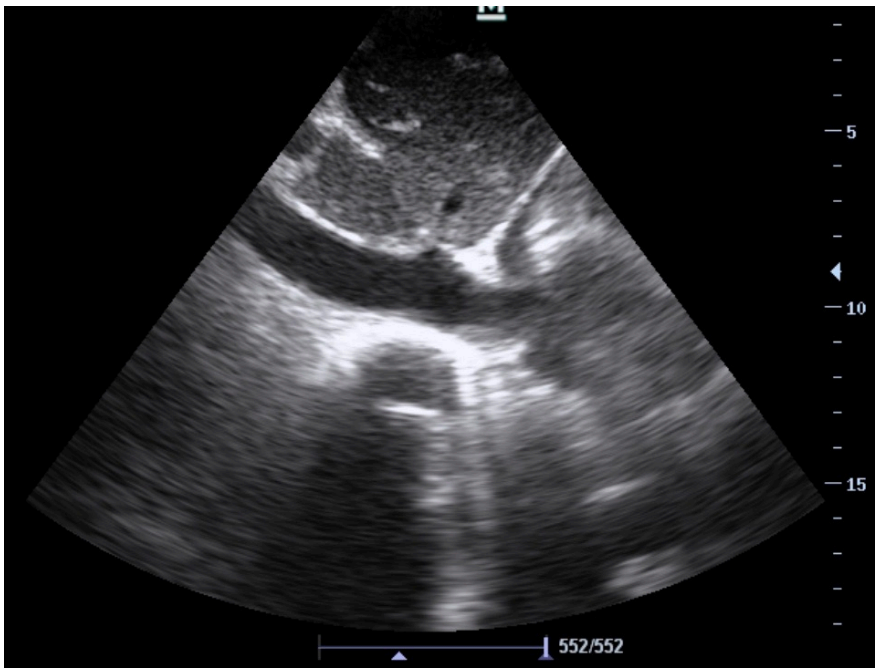

Figure 6: distended IVC as seen in the subcostal window with Mindray Ultrasound Machine (see Materials and Methods)

Venous compression ultrasonography (or CUS), as previously mentioned, is a relevant imaging technique that consists in finding incomplete collapsibility of venous vessels upon compression exerted with the ultrasound probe. This technique allows to recognize DVT in symptomatic patients with a positive predictive value of around 97% and to exclude it, whenever complete compressibility is achieved, with a negative predictive value of 98%.[61] Nowadays, CUS has replaced venography for the diagnosis of TVP.

In the majority of cases, PE originates from an inferior limb DVT, more rarely from an upper limb DVT (especially as a consequence of venous catheterization). CUS has been found to show DVT in 30-50% of patients with PE,[62] and the finding of proximal DVT in patients with suspected PE is sufficient to mandate anticoagulation treatment as the diagnosis of PE is ruled in, without further more demanding tests needed.[63]

When clinical suspicion of PE arises, it is necessary to conduct four points CUS (bilateral inguinal and popliteal) to investigate for the presence of DVT. The only criterion for the diagnosis of DVT at CUS is the absence of complete collapsibility of the venous vessel taken into consideration, which indicates the presence of a blood clot. Furthermore, it has also been found that the possibility of finding a positive CUS is higher if the patient has symptoms for DVT.[61]

Thoracic ultrasound (LUS) includes the ultrasound study of the lung parenchyma and the pleural space. The lung parenchyma has long been considered an inadequate acoustic window as the air contained therein compromises the morphological evaluation of the organs. Recently, lung ultrasound has instead proved to be useful for excluding or confirming the suspicion of various pathologies, such as pneumothorax, pulmonary embolism, pneumonia, pericardial effusion and heart failure. [62]

Lung, indeed, shows different acoustic windows in pathological conditions, useful for analyzing the artifacts generated by the interaction between air and water inside the parenchyma (A lines and B lines).[63]

Lung parenchyma study is conducted through longitudinal and transversal scans of the lung fields, moving the probe from the top to the bottom until the complete exploration of the parenchyma was done. In detail, longitudinal scans are preferred for their panoramic view and are generally conducted along standard lines (parasternal, half clavicle, middle axillary). If an equivocal finding is found during this type of scan, transverse scans are performed by moving the probe along the intercostal space, allowing a better evaluation.[64] However, there are lung areas hidden by particular anatomical structures, such as the posterior regions covered by the scapulae, the periclavicular regions and the apices, the portion of the thoracic wall corresponding to the axilla and the precordial region, that make their study difficult or impossible.

The image that emerges in the longitudinal B-mode scan is called the bat sign, where the wings indicate the costal shadow cones. In the center there is the pleural line formed by two layers, parietal and visceral, which slide over each other during respiratory excursions. Sonographically, this

movement appears as a single movement and is defined as "gliding" or "sliding sign". The presence of pleural sliding is an index of pulmonary excursion.

LUS has several advantages in the diagnosis of PE. First, the pathological changes seen in PE are the result of a dynamic process. For example, an embolus can decrease in size within 48 hours and even disappear completely after two days due to local fibrinolysis: so it is not uncommon, for some pulmonary thrombi, to go undetected by CTPA due to diagnostic delay. However, using LUS, which is a non-invasive methodic that can be applied early and repeatedly at the bedside, this dynamic process can be captured more easily. Secondly, US resolution in the subpleural region of the lung parenchyma is better than CTPA. Thus, the smallest pulmonary embolus, which is located in the peripheral lung parenchyma near the pleural surface, can be detected by LUS; it can therefore have a particular application also for patients presenting with non-severe PE.[65] Thirdly, ultrasound is recognized as the most sensitive tool for detecting pleural effusions, which are a common feature of PE and are detectable in up to 57% of cases on CT. This will increase the diagnostic accuracy of LUS. Nevertheless, LUS has some limitations; in fact, it is able to detect parenchymal lesions caused by emboli only when these lesions have affected the peripheral portion of the lung parenchyma. As noted above, nearly one third of the peripheral lung areas are covered by bone structures and are not accessible to LUS. Most emboli, yet, occur in the lower lobes, which are easily accessible. Another limitation is the subjectivity of results interpretation and its dependence on operator that perform LUS.[66]

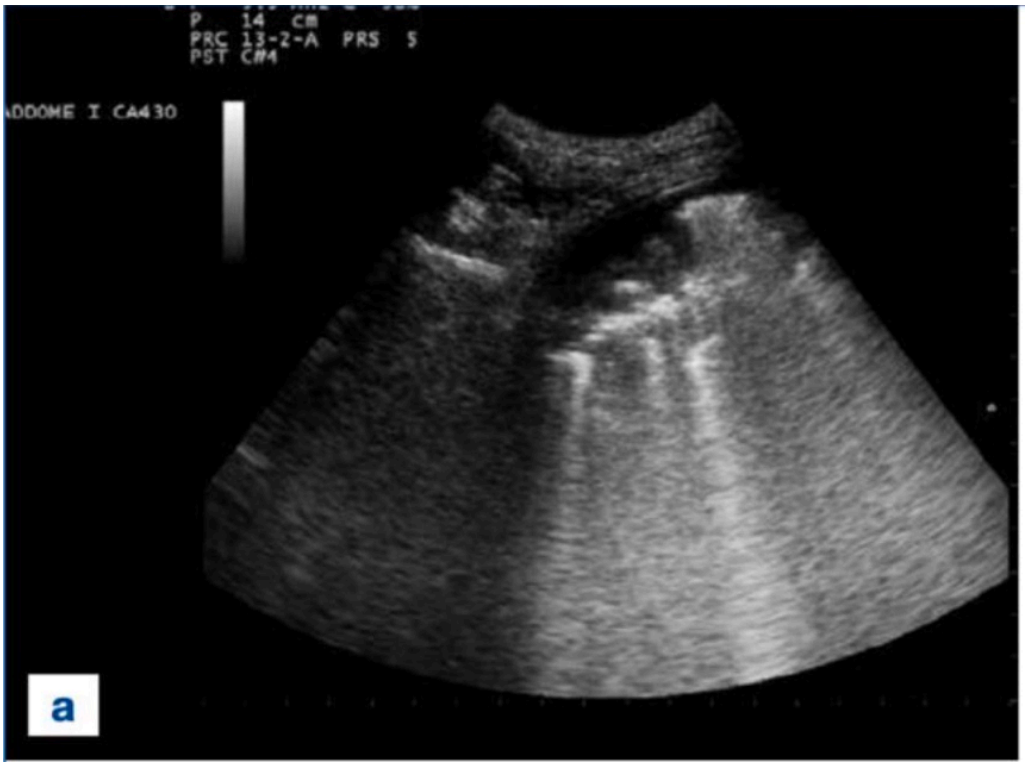

Figure 7: subpleural infarction caused by embolism (41)

In Emergency Department patients with hemodynamic instability for which PE is suspected to be the cause, a combination of CUS with TTE appears to further increase the specificity. On the contrary, it has been demonstrated that combining in the same patient a TTE negative for RV dysfunction to negative CUS, it is possible to exclude PE with a high negative predictive value (96%).[67]
Another study has demonstrated the usefulness of a combination of Multiorgan Ultrasonography (meaning heart, leg vein and lung) in the assessment of patient suspected to have PE, when combined to PTP scores and D-dimer testing, without the need to recur to CTPA. Multiorgan ultrasonography was found to have a sensitivity of 90% and specificity of 86%, furthermore whenever a negative multiorgan ultrasonography was coupled to either an alternative US diagnosis or a negative D-dimer result, PE was never the correct diagnosis eventually.[68]

1.8 Prognosis

Once the diagnosis of PE has been established, it is mandatory to perform risk stratification to correctly identify the appropriate treatment modality. Initially, it is necessary to identify patients who show severe symptoms and signs of hemodynamic instability, since both indicate high risk of early mortality. Alternatively, patients are identified as not hemodynamically unstable and thus need further risk stratification considering other prognostic factors: firstly, clinical, imaging and laboratory signs of PE severity; secondly, presence of comorbidities or aggravating circumstances that could negatively affect the prognosis. These prognostic factors are of little use when considered singularly, for this, combined strategies and composite scores have been developed to allow standardized and trustworthy patient prognostic assessment.

1.8.1 Clinical markers of severity

Acute RV dysfunction is an important determinant of prognosis in acute PE. Some sign and symptoms such as tachycardia, low systolic blood pressure, respiratory insufficiency (tachypnea and/or low SaO2) and syncope, alone or in combination, have been associated to worse prognosis in the short term. These clinical conditions are all undermined by RV dysfunction and can be rapidly deteriorating.[69]

1.8.2 Imaging markers of severity

As already mentioned, PE severity is mostly determined by the presence and degree of RV dysfunction, which can be visualized by different imaging modalities.[70]
Considering ultrasonography, RV dysfunction as seen by echocardiography is found in >25% of patients with acute PE. Studies have shown that its positive predictive value is low but it is a reliable marker or short term mortality in hemodynamically stable patients. Echocardiographic signs that correlate the most with unfavorable prognosis are RV/LV ≥ 1.0 (RV that is as big as or bigger than

LV) and TAPSE < 16.[60] Other signs that ultrasonography can identify which is associated with increased mortality is a right to left shunt through a patent foramen ovale, as well as the presence of floating thrombi in the right heart.[73,74]

RV enlargement can also be visualized by CTPA and it corresponds to a RV/LV > 0,9, which is quite a frequent finding in hemodynamically stable patients (>50% of acute PE patients). The value of this ratio is inversely proportional to mortality, meaning that the higher the value of this ratio, the worse the prognosis.[75] Other prognostic elements studied by CTPA are contrast agent reflux in the IVC and obstructive thrombus distribution: the former has shown good results in correlating with 30-days mortality risk whilst thrombotic obstruction scores have demonstrated to be poor risk stratification tools.[76]

1.8.3 Laboratory markers of severity

Laboratory markers of severity in acute PE patients are mainly two: troponin (myocardial damage marker) and plasma natriuretic peptide levels (RV dysfunction marker).

There are different types of troponins and assays to be used, such as conventional - cTnT vs high sensitivity troponin – hsTnT and TnT vs TnI.

HsTnT cut off values have been studied corrected for age (<14 pg/ml if younger than 75 years old and > 45 pg/ml if older than 75) to further improve patient risk assessment.[77] A significant number of acute PE patients has been found to have elevated troponin levels: up to 60% using hsTnT, which correlated well with their adverse 30-days outcome; however, up to 50% of patients would have been misclassified as low risk with a low-risk level of cTnT when actually they experienced adverse early outcome.[78] According to a meta-analysis, increased hsTnT levels are correlated with acute PE at high risk of short term death and adverse outcome events (meaning death, need for catecholamines, endotracheal intubation or cardiopulmonary resuscitation),[79] thus being able to improve risk stratification of non-high risk PE.[78]

Plasma levels of natriuretic peptides, such as BNP and NT-proBNP, are severity markers that indicate RV dysfunction.[80] They are abundantly released because acute PE causes stretching of myocardial fibers, consequently to RV volume and pressure overload. Cut off for NT-proBNP has been set to <500 pg/ml as to indicate patients who are not at high risk and could benefit from ambulatory treatment,[81] even if it seems that a higher cut-off (NT-proBNP $\geq$ 600 pg/ml) would enable to increase prognostic specificity for an early adverse outcome.[82]

A meta-analysis showed that patients with increased BNP or NT-proBNP have 10% risk of short term mortality and 23% risk of adverse clinical outcome, however, the same study suggested this marker should not be used alone in order to decide treatment strategy.[83]

Another study showed that both natriuretic peptides and troponins have high negative predictive value whenever found low in plasma, thus allow correct identification of low-risk acute PE patients, for which echocardiography may not even be necessary. On the contrary, if high levels of both markers

are found, echocardiography may be used to further study RV dysfunction, before deciding for more aggressive treatment vs anticoagulation alone. [84]

1.8.4 Scores to assess prognosis

Single markers are of little use to evaluate prognosis in day-to-day clinical practice. Combined strategies including clinical, laboratory and ultrasonographic techniques, could have higher power to perform a semi-quantitative mortality risk assessment correlated with PE.

Considering hemodynamically unstable acute PE patients, no further risk assessment is necessary and, as mentioned before, reperfusion strategies are to be implanted straightaway after CTPA, or even TTE only, confirm the diagnostic suspect *(paragraph 1.7.1 Diagnostic approach in the Emergency Department)*.

Contrarily, risk assessment is key in hemodynamically stable patients with confirmed PE, in order to select appropriate treatment strategy combined with home vs hospital observation. One proven approach for risk stratification in this population of patients can be done through PESI or sPESI (simplified version of PESI), which stands for "Pulmonary Embolism Severity Index" *(table 4)*. PESI is the clinical score with bigger validation that provides 30-days mortality risk. It is widely used because it integrates clinical indicators of PE severity as well as patient anamnestic data that also contribute to increase mortality risk.

Since PESI is a quite complex score with 11 items, a simplified version has been created.[85,86] If sPESI = 0, it accurately identifies patient with low risk (a probability of 1,0 % of early mortality), whilst sPESI ≥ 1 indicates 10,9% risk of intra-hospital 30-days mortality. On the contrary, PESI divides patients in five categories, from lower to highest 30-days mortality risk. PESI categories I and II correspond to sPESI = 0 and they are both reliable indicators of low risk acute PE, whilst PESI > II and sPESI ≥ 1 correspond to intermediate to high risk acute PE.

If patients have intermediate risk at PESI or sPESI with concurrent evidence of RV dysfunction at TTE or CTPA as well as elevated cardiac enzymes, they are considered at intermediate to high risk. In these cases hospitalization and strict monitoring is advised to allow early diagnosis of hemodynamic instability and consequently, the need of urgent reperfusion therapy.[87] Patients without signs of RV failure and negative troponins, can be considered at low to intermediate risk.

A recent meta-analysis has studied a total of 3295 patients with low risk PE (PESI I or II): in 34% of cases signs of RV dysfunction were reported. Since RV dysfunction as well as elevated troponin are markers of adverse outcome, until clinical implication of such discrepancies will not be clarified,[88] patients with RV dysfunction or increased troponin levels should be considered as intermediate to low risk, and not low risk, despite a low PESI or sPESI = 0. Therefore, it is possible to conclude that a combination of sPESI with troponin levels has ameliorated prognostic assessment,[89] especially for patients which are initially considered at low risk to identify those who will benefit the most from out-of-hospital treatment.[27] *Figure 8* provides a summary of these considerations.

Parameter	Original version[214]	Simplified version[218]
Age	Age in years	1 point (if age >80 years)
Male sex	+10 points	–
Cancer	+30 points	1 point
Chronic heart failure	+10 points	1 point
Chronic pulmonary disease	+10 points	
Pulse rate ≥110 b.p.m.	+20 points	1 point
Systolic blood pressure <100 mm Hg	+30 points	1 point
Respiratory rate >30 breaths per minute	+20 points	–
Temperature <36 °C	+20 points	–
Altered mental status	+60 points	–
Arterial oxyhaemoglobin saturation <90%	+20 points	1 point
	Risk strata[a]	
	Class I:≤65 points very low 30-day mortality risk (0–1.6%) **Class II: 66–85 points** low mortality risk (1.7–3.5%) **Class III: 86–105 points** moderate mortality risk (3.2–7.1%) **Class IV: 106–125 points** high mortality risk (4.0–11.4%) **Class V: >125 points** very high mortality risk (10.0–24.5%)	**0 points**= 30-day mortality risk 1.0% (95% CI 0.0%–2.1%) **≥1 point(s)**= 30-day mortality risk 10.9% (95% CI 8.5%–13.2%)

Table 4: PESI (from ESC 2014 Guidelines on Acute PE)

1.9 Therapy

1.9.1 Treatment strategies

According to current guidelines, management of acute PE depends upon risk stratification: treatment strategy is well characterized for low risk and high risk acute PE, whilst for intermediate risk patients, optimal treatment strategy is currently unknown and careful considerations is needed.[90] In general, risk assessment is necessary to decide for pharmacologic anticoagulation vs reperfusion strategies, according to the severity of the case.

In hemodynamically unstable patients, also known as high risk (massive) acute PE, it is necessary to urgently start anticoagulation therapy with Unfractioned Heparin (UFH); then, reperfusion is indicated through systemic thrombolysis. Whenever thrombolysis is contraindicated i.e. high bleeding risk or unsuccessful, percutaneous catheter-based reperfusion or surgical embolectomy will be the treatment of choice. For this category of patients, Low Molecular Weight Heparin (LMWH) and Fondaparinux have not proven their efficacy yet. Studies have also shown that delayed anticoagulation is an important prognostic factor of poor outcome in high-risk acute PE patients.[91]

In hemodynamically stable patients with acute PE, treatment of choice is represented by subcutaneous LMWH or Fondaparinux, provided the absence of renal failure.

Patients belonging to PESI classes I and II or sPESI = 0, can be started on subcutaneous anticoagulation treatment and possibly benefit from early discharge *(paragraph 1.9.4 Early discharge and out-of-hospital treatment)*. For the remaining classes of patients with intermediate risk acute PE, further risk stratification through TTE and serum troponin measurement is needed, in order to decide

whether they fall in the intermediate to high-risk category (whenever at least one of these two severity marker is positive) or intermediate to low risk category (negativity of these severity markers).
For patients with intermediate to low acute PE, pharmacologic treatment alone is indicated (i.e. subcutaneous LMWH or Fondaparinux). Patients with intermediate to high risk can be treated with parenteral anti-coagulation too or, alternatively, with thrombolysis, according to the bleeding risk and to the severity of the clinical picture. Indeed, as previously mentioned, guidelines are not conclusive for this category of intermediate-risk patients. As for high risk patients, surgical embolectomy or catheter-based techniques also represents a therapeutical choice in case both thrombolysis and parenteral anticoagulation are contraindicated in intermediate to high risk patients.

1.9.2 Anticoagulant therapy in the acute phase

1.9.2.1 Pharmacologic anticoagulation

Anticoagulants are the cornerstone of acute PE treatment and should be started as soon as possible. This is especially true for high-risk patients,[91] in which parenteral anticoagulation should be initiated while waiting for diagnostic tests results if clinical probability is intermediate to high. For all patients with a diagnosis of PE, it is then recommended to continue anticoagulation for at least for three months, in order to reduce the risk of short-term mortality and fatal VTE.
Available parenteral drugs include LMWH, which is usually the drug of choice, Fondaparinux and UFH. Simultaneously, oral treatment with Vitamin K-Antagonists (VKA) is usually started, which will be the only treatment after 5-10 days since parenteral drugs will be stopped as soon as the wanted INR is reached.[92] Alternatively to these drugs, New Oral Anticoagulants (NOACs) can be used and have proven to have a similarly rapid anticoagulant effect.[93] Furthermore, studies have shown that switching from heparin (either LMWH or UFH) to Dabigatran (a NOAC) after 72h only, resulted in safe and effective anticoagulation for patients with intermediate risk acute PE.[90]
When starting anticoagulation treatment, it appears that LMWH and Fondaparinux perform better than UFH, since they are associated to lower bleeding risk and lower risk of Heparin-Induced Thrombocytopenia (HIT).[94] The use of UFH is mostly reserved for patients with hemodynamic instability or at risk for it, since they will need primary reperfusion therapy, or for patients with severe renal failure (Creatinine Clearance $\leq$ 30 ml/min), since LMWH and Fondaparinux would then be contraindicated.
LMWH is administered subcutaneously every 12 hours, the most commonly used molecules are Enoxaparin and Dalteparin. Fondaparinux, on the contrary, is administered every 24 hours. LMWH activates antithrombin III which will subsequently inactivate thrombin and FXa whilst Fondaparinux is an inhibitor of FXa.

VKA have been for decades the gold standard of oral anticoagulation; those recommended for VTE include Warfarin and Acenocoumarol. They antagonize Vitamin K-related coagulation factors II, VII, IX, X as well as protein C and S.

NOACs are indirect inhibitors of activated coagulation cascade factors, more specifically thrombin for Dabigatran and FXa for Apixaban, Edoxaban and Rivaroxaban. Studies involving NOACs have demonstrated not only non-inferiority in the treatment of acute VTE in the acute phase and for the first six months, but also lower major bleeding events, when compared to LMWH + VKA.[95] NOACs do not need activity monitoring, can be administered at fixed doses and, compared to AVK, show minor drug-drug interactions with other drugs.[93]

1.9.2.2 Reperfusion therapy

Reperfusion can be obtained in three ways, which are usually reserved for patients at intermediate to high risk of adverse outcome: thrombolytic therapy, surgical embolectomy or percutaneous catheter-based therapy. These treatments are more efficient as they re-establish pulmonary perfusion in a more rapid way compared to anticoagulation treatment, as they act directly on already formed thrombi.[96] RV function and distension quickly ameliorates, since resistance in pulmonary artery drops upon removal of the obstructive clot.[97]

Thrombolysis is usually performed endovenously with a recombinant tissue plasminogen activator (rtPA), such as Alteplase. It is known that maximum benefit is achieved when treatment is started within 48 hours from the first symptoms, however, it can be useful even in patients who have been symptomatic for 6-14 days.[98] The percentage of failed thrombolysis performed in high risk acute EP patients is 8%.[99]

Percutaneous catheter-based procedures can vary, some of them involve thrombus fragmenting strategies or thrombus aspiration (catheter embolectomy). These techniques can be especially useful in patients with absolute contraindication to thrombolysis due to high bleeding risk.[45]

Whenever thrombolysis or percutaneous techniques fail or are contraindicated in intermediate to high risk acute PE patients, surgical embolectomy can be performed.[100]

Finally, caval filter is not a proper reperfusion technique but can be used in the acute phase to reduce mortality correlated to acute PE, in patients for which anticoagulation is strictly contraindicated or for those with recurrent VTE. [101]

1.9.3 Supportive measures

In the acute phase, it is important to prevent and treat the state of acute heart failure, mostly related to RV pressure overload, which is the first cause of mortality. Hemodynamic support can be given through fluids, even if it seems that volume expansion bigger than 0,5 L is not only not beneficial, but could even worsen RV dysfunction.[102] In order to have an indication of Central Venous Pressure

(CVP), to guide the amount of fluids to give to the patient, evaluation of Central Venous Pressure (CVP) through TTE by visualization of IVC collapsibility can be carried out.

Parallelly to reperfusion therapy, vasopressors are often inevitably given to hemodynamically unstable patients. Noradrenaline is indicated in hypotensive patients; dobutamine and dopamine are used in normotensive patients with low Cardiac Index; finally, adrenaline is indicated in patients with shock.[102,103]

As already mentioned *(paragraph 1.6 Clinical presentation)*, often patients are hypocapnic and hypoxic, mandating oxygenation therapy up to mechanical ventilation in severe cases.

In extreme cases, it is possible to support both circulation and oxygenation through ECMO (ExtraCorporeal Membrane Oxygenation), even if no clinical study has ever been published regarding its efficacy and safety in the treatment of massive acute PE. Actually, its therapeutical use coupled with anticoagulation is controversial,[104,105] and other therapies should be taken in consideration as well, such as surgical embolectomy.

1.9.4 Early discharge and outpatient management

According to guidelines, patients at low risk for adverse events are started on anticoagulants and could benefit from out-of-hospital treatment if three main criteria are respected: low risk of short-term death and adverse outcome correlated to acute PE, absence of severe comorbidities and aggravating circumstances, adequate healthcare and social system to support proper care and outpatient anticoagulation treatment.

Two major sets of criteria exist to then accurately select this population of patients: “Hestia Clinical Decision Rule”, which is a list of exclusion criteria, and PESI/sPESI > 85 *(paragraph 1.8.4 Scores to assess prognosis)*. Hestia criteria include hemodynamic instability, need for IV pain medications for > 24 hours, risk of bleeding, need for invasive procedures or hospitalization for other reasons, O2 needs for > 24 hours, pregnancy, severe liver or kidney impairment, history of HIT and PE diagnosed while on anticoagulants.[106]

Both Hestia Clinical Decision Rule and PESI/sPESI have proven to safely identify patients who are at low risk of adverse events correlated to PE.[106,107]

Current guidelines on acute EP summarize not only risk assessment (especially important for low to intermediate cases) but also therapeutical indications, according to said risk, with an algorithm *(figure 8)*.

1.9.5 Long term patient management

According to guidelines, anticoagulation treatment should be continued for at least 3 months after the acute episode.[3] After three months, patients who developed PE consequently to proximal DVT should

benefit from extended anticoagulation. Indeed, extended anticoagulation has proven to reduce the risk for recurrent VTE by ≤ 90%.[3]

Life-long treatment is recommended for patients with a second episode of DVT or PE,[108] as it is known that anticoagulants do not continue to prevent recurrency after discontinuation.[109] As in the case of extended anticoagulation, it is necessary to continuously re-assess the bleeding risk (for example, through the HAS-BLED score),[110] to evaluate the risk-benefit ratio of anticoagulation.

In case of high bleeding risk but also high risk of recurrent VTE, aspirin has shown to reduce recurrency risk of 30-35%,[111] which is actually half of the benefit that anticoagulants would give, but with a lower bleeding risk.

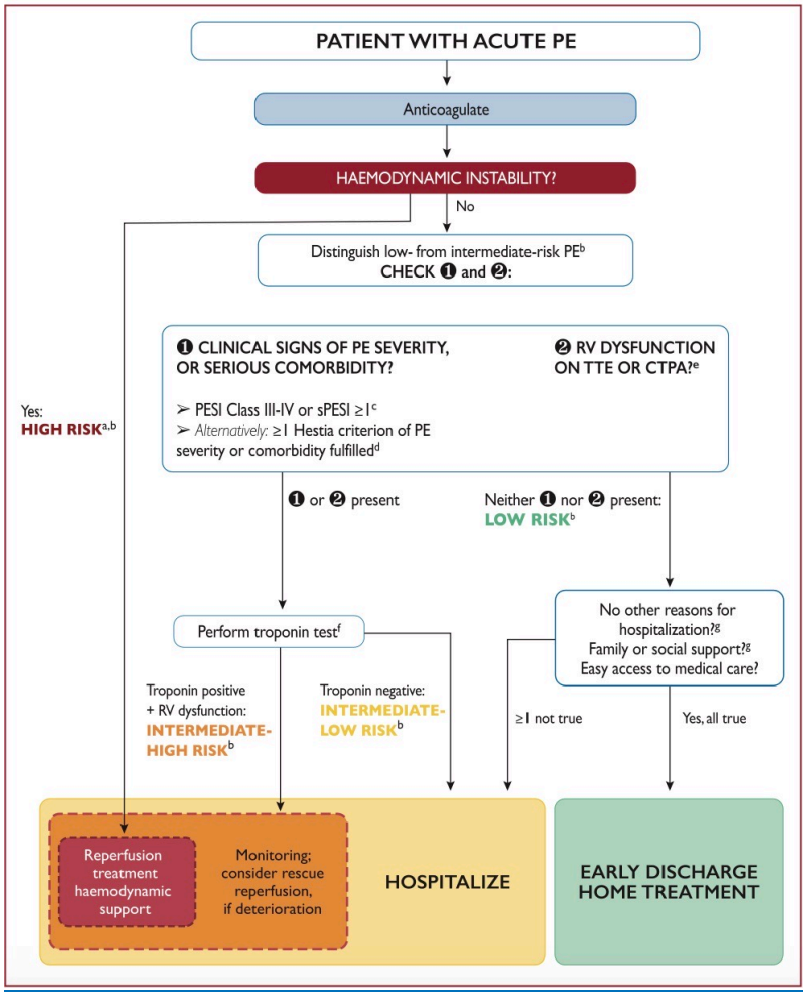

Figure 8: Integrated risk-adapted management for acute PE (from 2019 Guidelines on acute PE)

2. Aim of the study

The aim of this study is to investigate the diagnostic approach to patients with clinically suspected acute PE in the Emergency Department, for which CTPA was performed, firstly according to 2019 ESC Guidelines and subsequently, according to an alternative algorithm that combines TTE, CUS and LUS with higher D-dimer cut offs.

3. Materials and Methods

3.1 Study design

The study is monocentric and retrospective, carried out analysing clinical charts of a consecutive series of patients, who consulted the Emergency Department of the I.R.C.C.S University Hospital Policlinico San Matteo, Pavia, between January 1st 2021 and December 31st 2021.

3.1.1 Inclusion criteria

Patients included in the study were older than 15 years old, which is the minimum age to gain access to our ER and received CTPA during the diagnostic work-up in the ER owing to the clinical suspect of PE.

3.1.2 Exclusion criteria

Patients were excluded from the study if CTPA was performed for reasons other than the clinical suspect of PE or if it was performed elsewhere other than our Emergency Department. Other reasons for exclusion were patient with negative age-adjusted D-dimer which ruled out PE before recurring to CTPA as well as patients for whom too little data was available in the charts.

3.2 Collection of data

Patient data were collected with the use of the electronic softwares "PIESSE" and "Portale di reparto" (client software by CBIM).

More specifically, patients' demographic and anamnestic characteristics were collected, together with the reason for consult, physical examination, vital parameters and oxygenation therapy at presentation. Then, laboratory tests results were analysed (through the software "Spartito": ABG, CBC, biochemistry and coagulation panels), imaging reports (TTE, CUS, LUS and CTPA; all findings included, regardless of coherency with the diagnosis of acute PE or not), final diagnosis (both acute PE and other diagnosis) and therapy administered while in the Emergency Department (anticoagulant therapy, antiaggregant therapy, O2 therapy). Both pre-test clinical probability scores and PESI were evaluated. Finally, for patients diagnosed with acute PE through CTPA, it was studied whether they were admitted or not and in which ward, as well as 30-day mortality (score = 0 if deceased, score = 1 if alive).

These findings were reported using the following ultrasound machines, which were available in the Emergency Department: Mindray M7 Premium, Esaote MYLAB 25 and ESAOTE MYLAB 80. The echocardiographic probe was used (frequency: 2-4 MHz), linear probe with a frequency of 10-12 MHz

for CUS, convex probe with a frequency of 2-5 MHz and linear probe with a frequency of 7-12 MHz for LUS

3.2.1 TTE

Echocardiography reports were considered and points were given according to whether nothing abnormal was found (score = 0) or whether signs of acute PE were present. More specifically, a score of 1 was assigned if RV was abnormal in its kinetics or dimension, if VCI was distended or did not collapse in inspiration, if McConnel sign or paradoxical septal motion were appreciated.

3.2.2 CUS

Venous circulation of the lower (or upper) extremities was studied through CUS and results were reported according to where the obstruction was found:

0. Absence of thrombi
1. Unilateral femoral vein thrombosis
2. Unilateral femoro-popliteal veins thrombosis
3. Unilateral popliteal vein thrombosis
4. Bilateral vein thrombosis
5. Distal vein thrombosis
6. Right/left femoro-popliteal + left/right popliteal vein thrombosis
7. Unilateral subclavian vein thrombosis

3.2.4 LUS

The ultrasound images analyzed during data collection were divided according to the prevailing pattern found, which was assigned a score among the following:

0. Negative
1. Unilateral Pattern B
2. Unilateral pleural effusion
3. Bilateral pattern B
4. Bilateral pleural effusion
5. Subpleural consolidation
6. Parenchymal consolidation

Plus, other scores coming from association of different pattern.

3.2.5 CTPA

Considering CTPA reports, patients were stratified according to where the obstruction was found in pulmonary arteries.

0. Absence of pulmonary arteries embolism
1. Unilateral subsegmental/segmental embolism
2. Bilateral subsegmental/segmental embolism
3. Unilateral central embolism
4. Bilateral central embolism
5. Right/left central embolism + left/right subsegmental/segmental embolism

3.2.6 Pre-test probability scores

Pre-test clinical probability scores were applied as recommended in the diagnostic algorithm of 2019 ESC Guidelines on acute PE. Therefore, patients were stratified according to original Wells score, simplified Wells score and revised Geneva score (*table 2*, all items applied as reported). Original Wells and Geneva scores consider three levels of risk (low, intermediate and high) as well as a two-level classification ("PE likely", "PE unlikely"). Conversely, simplified Wells score only considers the two-level stratification.

3.3 Statistical analysis

Statistical analysis of collected data was performed through the program "SPSS Statistics" (version 26.0.0). Chi-squared test, variance analysis through Kruskal Wallis test and ROC analysis were carried out.

3.4 Limitations of the study

The following limitations can be identified:

- Exclusion of patients with low risk of acute PE according to pre-test clinical probability scores and negative age-adjusted D-dimer, who did not benefit from CTPA;
- Pre-test clinical probability scores were calculated retrospectively for each patient, on the basis of data collected from the charts;
- TTE, CUS, LUS and CTPA results were not elaborated from the same physician at all times;
- CTPA results are qualitatively only and not reported according to a specific quantitative radiologic score;
- Ultrasonography was at times conducted but not reported in the charts, significantly reducing the amount of data available to be integrated with pre-test clinical probability scores.

4. Results

4.1 Population analysis

From January 1st 2021 to December 31st 2021, 45248 patients consulted the Emergency Department of the I.R.C.C.S University Hospital Policlinico San Matteo, Pavia, all complaints included. This retrospective study included 889 patients, who fulfilled the inclusion criteria.

Considering the population under study, as reported in *Table 5*, 394 patients out of 889 were men (44%) and 495 women (56%).

Patients (N=889)	**Number**	**Frequency (%)**
Men	394	44
Women	495	56

Table 5: Population M/F

Mean age was 68,4 ± 17,9 [16;100].

For each patient of the 889 included in the study, medical charts were analysed to evaluate: medical history, chief complaint, physical examination as well as blood tests results and vital parameters.

In *Table 6*, all types of patients' medical history with respective absolute frequencies are reported. Patients with Factor V Leiden mutation, MTHFR mutation, lupus anticoagulant antibodies-positive (LAC+) and protein S deficiency were considered in the same category called "Pro-coagulatory genetic conditions".

Medical history	**Number (N)**	**Frequency (%)**
No past medical history	138	15,5
Cardiovascular	526	59,2
Respiratory	152	17,1
Cancer	157	17,7
Pro-coagulatory genetic conditions	7	0,8
Other	193	21,7

Table 6: Patients' medical history

Table 7 shows data regarding findings at physical examination, both in absolute number and frequency. The term "cardiovascular" and "respiratory abnormalities" at physical examination was used to indicate, respectively, findings such as heart murmur or arrhythmic heart sounds for the former and decreased breath sounds, crackles or wheezes for the latter.

Physical examination abnormal findings	**Number (N)**	**Frequency (%)**
No abnormalities	326	36,7
Cardiovascular	141	15,9
Respiratory	358	40,3
Edema	85	9,6
Signs of DVT	75	8,4
Vascular (ischemic)	4	0,4
Other	75	8,4

Table 7: Patients' physical examination

Table 8 shows patients' chief complaint, which is the presenting symptom that led them to consult the Emergency Department. If there was more than one, they were all considered (for example, both chest pain and dyspnea).

Chief complaint	**Number (N)**	**Frequency (%)**
Chest pain	217	24,4
Dyspnea	300	33,7
Syncope/pre-syncope	132	14,8
Palpitations/arrhythmia	37	4,2
Signs of DVT/limb edema	57	6,4
Limb pain (upper or lower, unilateral)	20	2,2
Cough, fever and other infectious disease signs	147	16,5
Hypotension	3	0,3
Neurological symptoms	16	1,8
Cardiac arrest/ROSC	8	0,9
Other	106	11,9

Table 8: Patients' chief complaint

The following table (*Table 9*) shows the result of the nasopharyngeal search of SARS-CoV-2 through PCR analysis.

SARS-CoV-2 PCR Results	Number (N)	Frequency (%)
Positive	90	10,1
Negative	627	70,5
No data	172	19,3

Table 9: Patients' SARS-CoV-2 PCR results

Vital parameters at admission were also considered to stratify patients according to the 2019 ESC Guidelines on acute PE *(table 1)*. Therefore, enrolled patients were divided into two groups: haemodynamically stable and haemodynamically unstable.

Hemodynamically stable (N; %)	Hemodynamically unstable (N; %)
884 (94,9%)	45 (5,1%)

Table 10: Hemodynamic state

	Total	Mean	Standard Deviation	Variance
Systolic BP	883	137,84	24,77	613,35
Diastolic BP	883	79,88	14,99	224,82
Mean Arterial Pressure (MAP)	883	99,2	18,25	354,33
HR	883	89,56	24,46	598,49
SpO2	882	95,35	5,49	30,19
P/F	460	331,67	100,95	10191,44
Serum lactates	65	2,05	2,16	4,67

Table 11: Vital parameters and ABG results

At admission to the Emergency Department, all patients are assigned a color to indicate four levels of priority. This assessment stratifies patients from top priority requiring immediate evaluation (color red), to intermediate priority requiring medical attention within 60 minutes (yellow), to patients whose pathology is not assumed to be time-dependent and thus will be evaluated according to the time of arrival, theoretically after all yellow codes have been seen. "Low intensity yellow" ("*giallo bassa intensità*") is in-between yellow and green, these patients should be seen before those assigned color green. Finally, "white" priority is assigned to cases which are not recognized as urgent and that would not have needed Emergency Department consultation (but rather, referral to the Family Doctor).

Color	Number (N)	Frequency (%)
White	3	0,3
Green	383	43,1
"Low intensity" Yellow	31	3,5
Yellow	446	50,2
Red	26	2,9

Table 12: Colour code priority at admission

The following statistical analyses were carried out to evaluate the different diagnostic tools for acute PE: clinical probability scores and D-dimer testing.

In *figure 14*, the distribution trend of acute PE at CTPA ("TEP") vs no acute PE at CTPA ("No TEP") is represented for the classes of risk identified by the Simplified Wells score (from low risk – classes 0 and 1, to high risk, classes from 2 on). On the x axis the different levels of the score can be found, from 0 to 4, whilst on the y axis the acute PE percentage is displayed.

The following figures 15 and 17 show the same analysis carried out for the other two clinical probability scores: original Wells score and revised Geneva score.

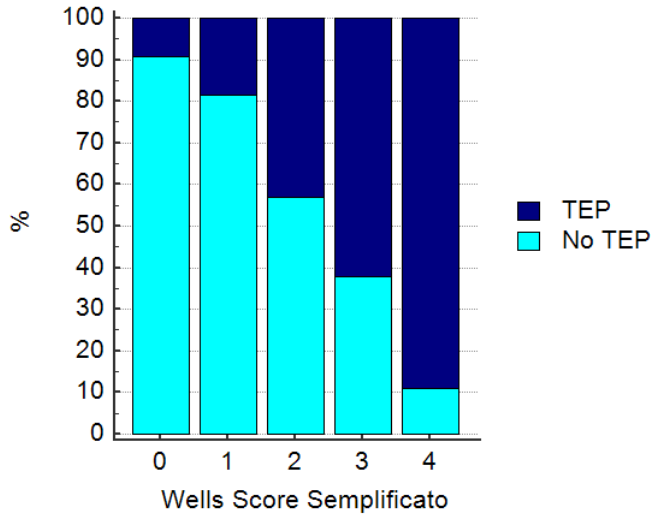

Figure 9: Percental distribution of acute PE diagnosis with progressively higher risk scores (low to high) with Simplified Wells score

	Wells_Score_semplificato					
diagnosi_TEP__0_no__1_si_	0	1	2	3	4	
0	364	249	79	14	1	707 (79,3%)
1	37	57	60	23	8	185 (20,7%)
	401 (45,0%)	306 (34,3%)	139 (15,6%)	37 (4,1%)	9 (1,0%)	892

Test del chi-quadrato

Chi-quadrato	139,736
DF	4
Livello di significatività	P < 0,0001

Test del chi quadrato per trend

Chi-quadrato (trend)	131,334
DF	1
Livello di significatività	P < 0,0001

Figure 10: Statistical analysis

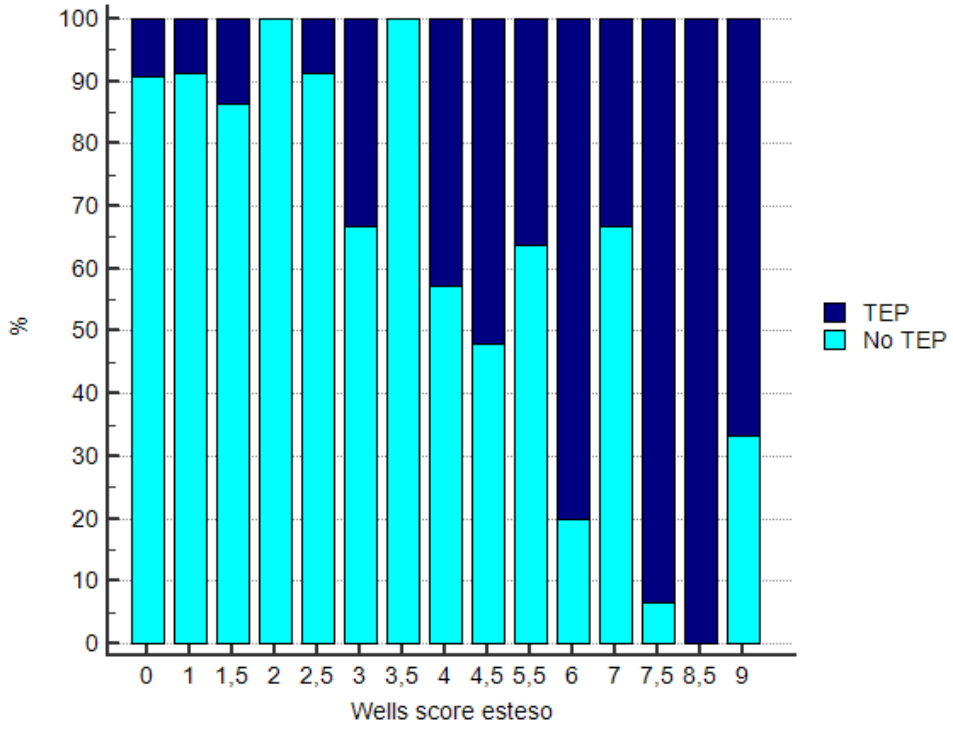

Figure 11: Percental distribution of acute PE diagnosis with progressively higher risk scores (low to high) with Original Wells score

	Wells_score_esteso															
diagnosi_TEP__0_no__1_si_	0	1	1,5	2	2,5	3	3,5	4	4,5	5,5	6	7	7,5	8,5	9	
0	364	53	139	1	31	66	2	12	23	7	6	2	1	0	1	708 (79,3%)
1	37	5	22	0	3	33	0	9	25	4	24	1	14	6	2	185 (20,7%)
	401 (44,9%)	58 (6,5%)	161 (18,0%)	1 (0,1%)	34 (3,8%)	99 (11,1%)	2 (0,2%)	21 (2,4%)	48 (5,4%)	11 (1,2%)	30 (3,4%)	3 (0,3%)	15 (1,7%)	6 (0,7%)	3 (0,3%)	893

Test del chi-quadrato

Chi-quadrato	231,697
DF	14
Livello di significatività	P < 0,0001

Test del chi quadrato per trend

Chi-quadrato (trend)	200,815
DF	1
Livello di significatività	P < 0,0001

Figure 12: Statistical analysis

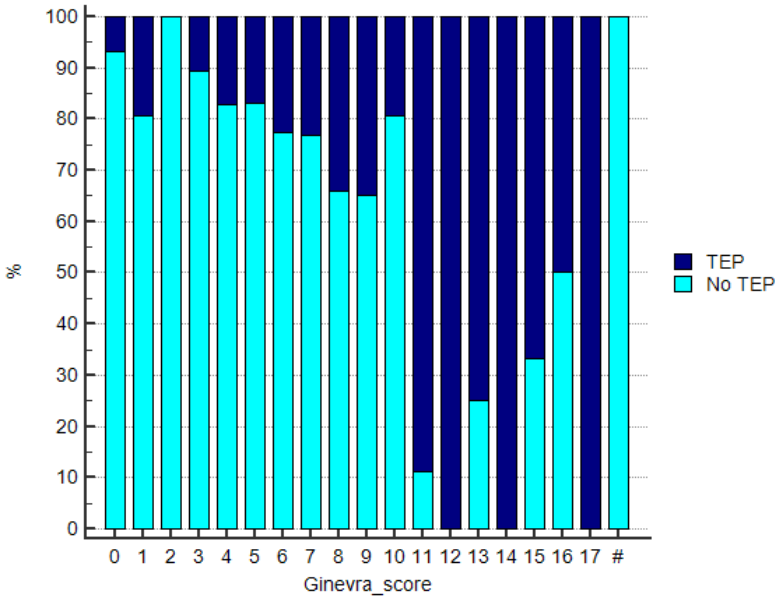

Figure 13: Percental distribution of acute PE diagnosis with progressively higher risk scores (low to high) with revised Geneva score

X Ginevra_score
Y diagnosi_TEP__0_no__1_si_

	Ginevra_score																			
_0_no__1_si_	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	#	
	41	84	4	110	140	99	120	33	37	15	21	1	0	1	0	1	1	0	1	709 (79,3
	3	20	0	13	29	20	35	10	19	8	5	8	6	3	2	2	1	1	0	185 (20,7
	44	104	4	123	169	119	155	43	56	23	26	9	6	4	2	3	2	1	1	894
	(4,9%)	(11,6%)	(0,4%)	(13,8%)	(18,9%)	(13,3%)	(17,3%)	(4,8%)	(6,3%)	(2,6%)	(2,9%)	(1,0%)	(0,7%)	(0,4%)	(0,2%)	(0,3%)	(0,2%)	(0,1%)	(0,1%)	

percentuali

adrato

	98,062
	18
ativit	P < 0,0001
	0,314

Figure 14: Statistical analysis

Figure 15: Comparison of the three scores

Dimensione campione	892
Gruppo positivo [a]	185 (20,74%)
Gruppo negativo [b]	707 (79,26%)

[a] diagnosi_TEP__0_no__1_si_ = 1
[b] diagnosi_TEP__0_no__1_si_ = 0

Variabile	AUC	SE [a]	CI del 95% [b]
Wells_score_esteso <= 4	0,677	0,0186	0,645 a 0,708
Ginevra_score <= 5	0,608	0,0204	0,575 a 0,640
Wells_Score_semplificato <=1	0,679	0,0195	0,648 a 0,710

[a] DeLong et al., 1988
[b] Binomiale esatto

Confronto a coppie delle curve ROC

Wells_score_esteso <= 4 ~ Ginevra_score <= 5	
Differenza tra le aree	0,0695
Errore standard [a]	0,0223
Intervallo di confidenza del 95%	0,0258 a 0,113
Statistica z	3,120
Livello di significatività	P = 0,0018
Wells_score_esteso <= 4 ~ Wells_Score_semplificato <=1	
Differenza tra le aree	0,00235
Errore standard [a]	0,0113
Intervallo di confidenza del 95%	-0,0198 a 0,0245
Statistica z	0,208
Livello di significatività	P = 0,8349
Ginevra_score <= 5 ~ Wells_Score_semplificato <=1	
Differenza tra le aree	0,0719
Errore standard [a]	0,0209
Intervallo di confidenza del 95%	0,0309 a 0,113
Statistica z	3,440
Livello di significatività	P = 0,0006

Figure 16: Statistical analysis

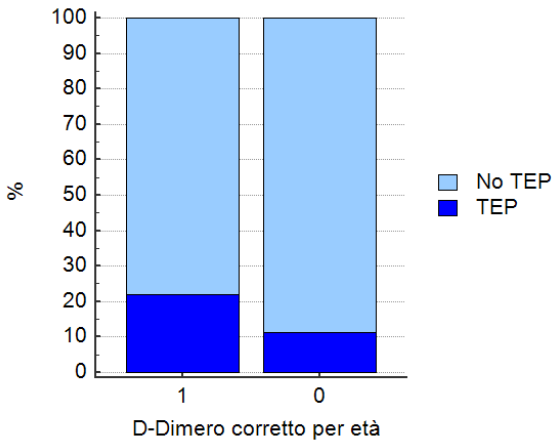

Figure 17: Percental distribution of the acute PE diagnosis in case of age-adjusted D-dimer positivity (1) or negativity (0)

	D_dimero_corretto		
diagnosi_TEP__0_no__1_si_	0	1	
0	55	543	598 (78,8%)
1	7	154	161 (21,2%)
	62 (8,2%)	697 (91,8%)	759

Test del chi-quadrato

Chi-quadrato	3,972
DF	1
Livello di significatività	P = 0,0463
Coefficiente di contingenza	0,072

Figure 18: Statistical analysis

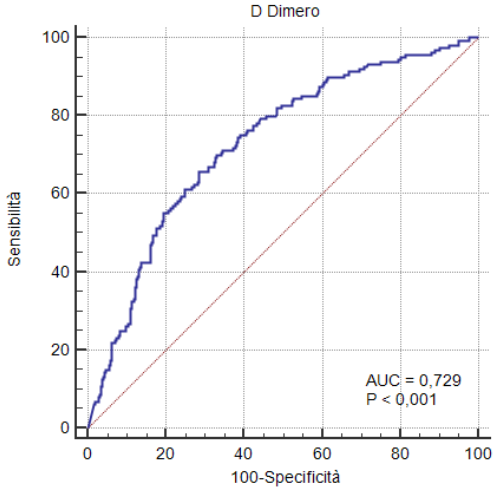

Figure 19: ROC curve with sensitivity and specificity, D-dimer

Variabile	D_dimero
Variabile di classificazione	diagnosi_TEP__0_no__1_si_

Dimensione campione	745
Gruppo positivo [a]	160 (21,48%)
Gruppo negativo [b]	585 (78,52%)

[a] diagnosi_TEP__0_no__1_si_ = 1
[b] diagnosi_TEP__0_no__1_si_ = 0

Prevalenza malattia (%)	sconosciuto

Area sotto la curva ROC (AUC)

Area sotto la curva ROC (AUC)	0,729
Errore standard [a]	0,0222
Intervallo di confidenza del 95% [b]	0,695 a 0,760
Statistica z	10,313
Livello di significatività P (Area=0,5)	<0,0001

[a] DeLong et al., 1988
[b] Binomiale esatto

Indice di Youden

Indice di Youden J	0,3708
Criterio associato	>3460
Sensibilità	65,62
Specificità	71,45

Figure 20: Statistical analysis

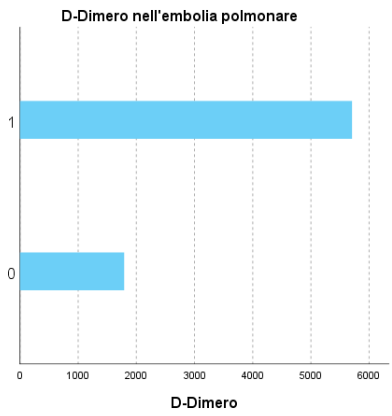

Figure 21: D-dimer concentration distribution according to acute PE diagnosis (y=1) or not (y=0)

Dimensione campione	745

Statistiche descrittive

Fattore	n	Minimo	25° percentile	Mediana	75° percentile	Massimo
0	585	0,0000	1038,500	1790,000	3874,000	35000,000
1	160	313,0000	2302,000	5707,500	12654,500	35000,000

Test di Kruskal-Wallis

Statistica test	78,8249
Corretto per valori equivalenti Ht	78,8265
Gradi di libertà (DF)	1
Livello di significatività	P < 0,000001

Figure 22: Statistical analysis

Considering a total of 889 patients for which CTPA was carried out in the Emergency Department suspecting acute PE, 45 of them (5.1%) fulfilled the criteria for haemodynamic instability set by 2019 ESC Guidelines on acute PE, whilst the remaining 844 fell into the "haemodynamically stable" category. Of these, PERC was calculated and came out as 0 for 54 of them, whilst > 0 for the remaining part (790 patients).

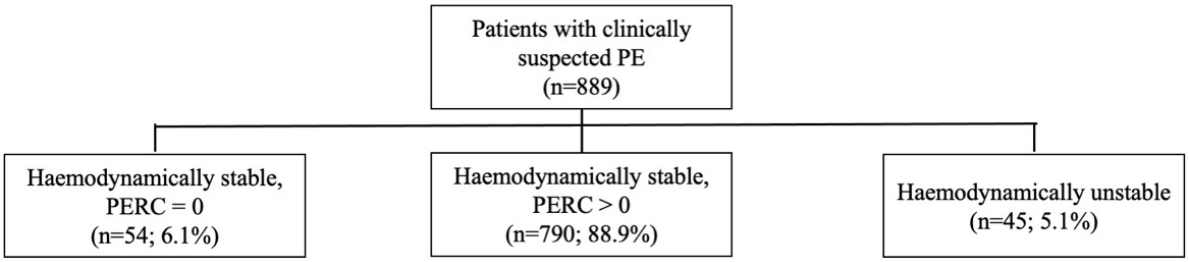

Figure 23: Patient subdivision according to haemodynamic state

This subdivision is relevant because diagnostic algorithms are different according to the haemodynamic state.

The same three-tier distinction was obtained for patients who tested negative for Covid-19 at the time of consultation.

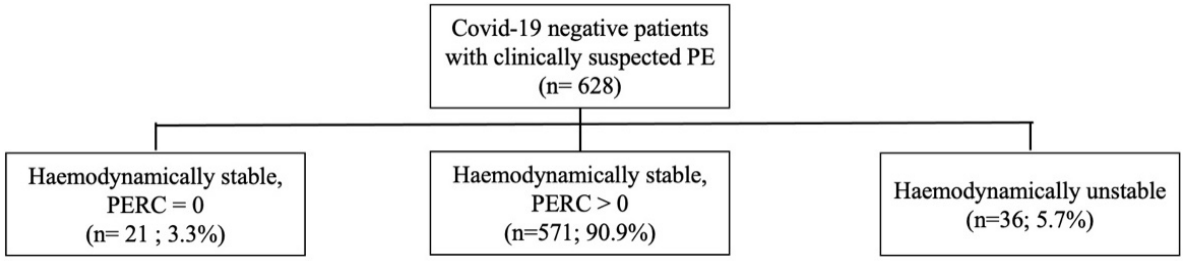

Figure 24: Patient subdivision according to haemodynamic state, considering Covid-19 patients only

4.2 Haemodynamically unstable population analysis

The same statistical analysis regarding sex, medical history, physical examination, chief complaint, SARS-CoV-2 search was carried out for specific patients' sub-populations, starting with haemodynamically unstable patients. Vital parameters and the priority colour code was also evaluated. The following tables show these results.

Patients (N=45)	Number	Frequency (%)
Men	18	40
Women	27	60

Table 13: Hemodynamically unstable patients' M/F proportion

Mean age was 70,4 ± 16,09.

Medical history	Number (N)	Frequency (%)
No past medical history	4	8,9
Cardiovascular	27	60
Respiratory	11	24,4
Cancer	7	15,5
Pro-coagulatory genetic conditions	0	0
Other	7	15,5

Table 14: Hemodynamically unstable patients' medical history

Physical examination abnormal findings	Number (N)	Frequency (%)
No abnormalities	12	26,7
Cardiovascular	8	17,7
Respiratory	20	44,4
Edema	6	13,3
Signs of DVT	2	4,4
Vascular (ischemic)	0	0
Other	9	20

Table 15: Hemodynamically unstable patients' physical examination

Chief complaint	Number (N)	Frequency (%)
Chest pain	4	8,9
Dyspnea	16	35,6
Syncope/pre-syncope	5	11,1
Palpitations/arrhythmia	1	2,2
Signs of DVT/limb edema	1	2,2
Limb pain (upper or lower, unilateral)	0	0
Cough, fever and other infectious disease signs	7	15,6
Hypotension	3	6,6
Neurological symptoms	0	0
Cardiac arrest/ROSC	7	15,6
Other	5	11,1

Table 16: Hemodynamically unstable patients' chief complaint

SARS-CoV-2 PCR Results	Number (N)	Frequency (%)
Positive	6	13,3
Negative	36	80
No data	3	6,6

Table 17: Hemodynamically unstable patients' SARS-CoV-2 search

	Total	Mean	Standard Deviation	Variance
Systolic BP	44	110,11	33,28	1104,01
Diastolic BP	44	61,3	16,26	264,4
Mean Arterial Pressure (MAP)	44	77,57	21,93	544,27
HR	44	94,68	27,26	743,15
SpO2	43	92,16	16,07	258,36
P/F	25	310,16	156,78	24579,89
Serum lactates	3	8	4,58	21

Table 18: Hemodynamically unstable patients' vital parameters and ABG

Color	Number (N)	Frequency (%)
White	0	0
Green	10	22.2
"Low intensity" Yellow	1	2.2
Yellow	9	20
Red	25	55.6

Table 19: Colour code priority at admission for hemodynamically unstable patients

According to the Guidelines, TTE should be performed for haemodynamically unstable patients and if positive, CTPA is mandated (when available shortly). The diagnostic flowchart for haemodynamically unstable patients was recreated retrospectively considering the population of this study.

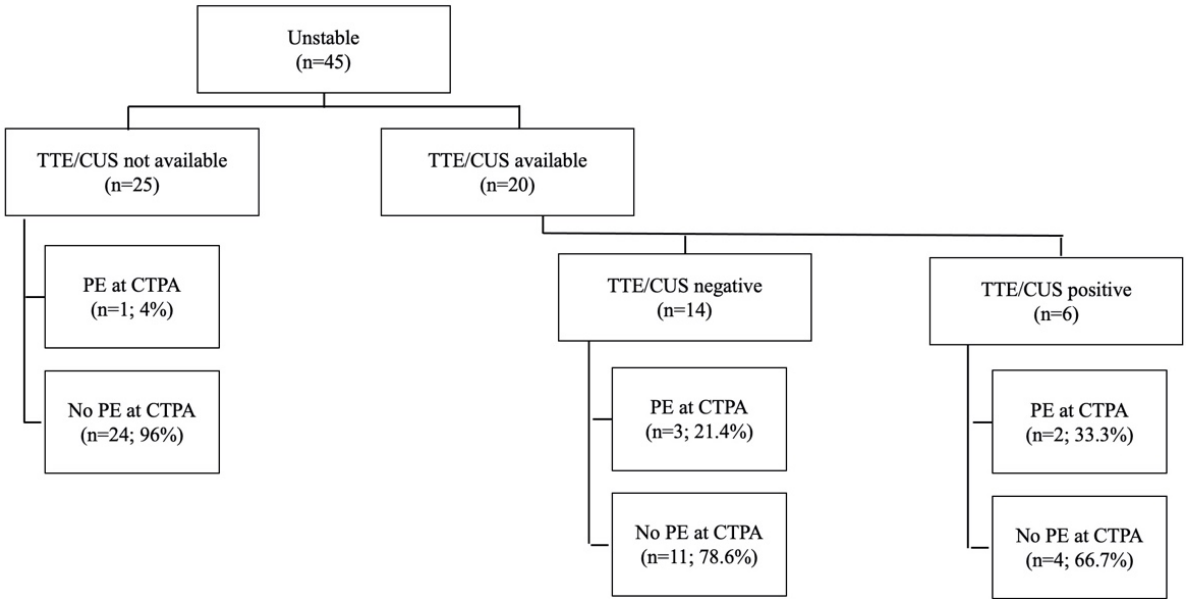

Figure 25: Hemodynamically unstable patients' flowchart

In this analysis, for patients with negative or not available ultrasonography examination, a pre-test score (Simplified Wells Score) was applied retrospectively for statistical purposes. In this way, it was found that amongst patients with negative TTE/CUS (n=14), only 1 would have fallen into the "PE likely" Wells score category (and for this patient CTPA confirmed acute PE) whilst for the remaining 13 patients classified as "PE unlikely", 2 would have been diagnosed with acute PE at CTPA. Then, considering patients without TTE/CUS (n=25) and applying again a pre-test clinical probability score (Simplified Wells score), 3 patients would have been classified as "PE likely", but with zero acute PE diagnosed at CTPA, whilst for the remaining 22 patient classified as "PE unlikely", one patient would have shown acute PE at CTPA.

4.2.1 Covid-19 negative haemodynamically unstable population analysis

The same statistical analysis regarding patients' characteristics obtained from medical charts (sex, age, medical history, physical examination, chief complaint) was performed for the subpopulation which includes haemodynamically unstable patients who tested negative for SARS-CoV-2 at the time of consultation.

Patients (N=36)	**Number**	**Frequency (%)**
Men	15	42
Women	21	58

Table 20: Covid 19-negative hemodynamically unstable patients' sex

Mean age was 73,2 ± 14,3.

Medical history	**Number (N)**	**Frequency (%)**
No past medical history	3	8,3
Cardiovascular	22	61,1
Respiratory	8	22,2
Cancer	7	19,4
Pro-coagulatory genetic conditions	0	0
Other	6	16,6

Table 21: Covid-19-negative hemodynamically unstable patients' medical history

Physical examination abnormal findings	**Number (N)**	**Frequency (%)**
No abnormalities	8	22,2
Cardiovascular	6	16,6
Respiratory	17	47,2
Edema	5	13,9
Signs of DVT	2	5,6
Vascular (ischemic)	0	0
Other	9	25

Table 22: Covid-19-negative hemodynamically unstable patients' physical examination

Chief complaint	Number (N)	Frequency (%)
Chest pain	3	8,3
Dyspnea	12	33,3
Syncope/pre-syncope	4	11,1
Palpitations/arrhythmia	0	0
Signs of DVT/limb edema	1	2,8
Limb pain (upper or lower, unilateral)	0	0
Cough, fever and other infectious disease signs	3	8,3
Hypotension	3	8,3
Neurological symptoms	0	0
Cardiac arrest/ROSC	7	19,4
Other	5	13,9

Table 23: Covid-19-negative hemodynamically unstable patients' chief complaint

As for the total of hemodynamically unstable patients *(figure 11)*, the same algorithm was applied considering patients who tested negative for SARS-CoV-2 at the time of consultation only.

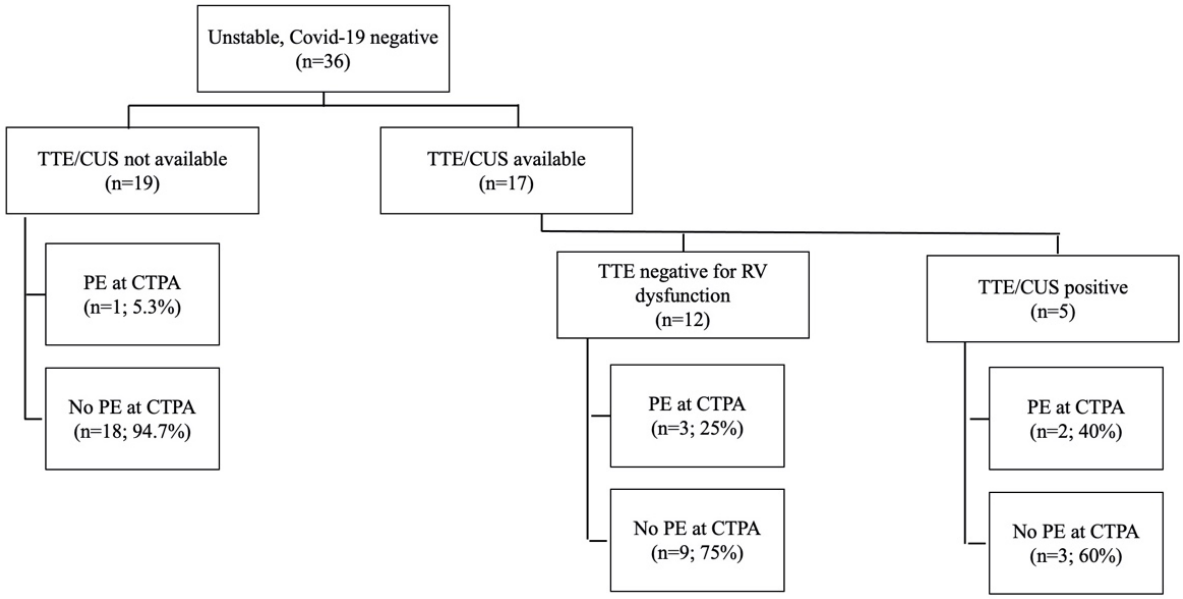

Figure 26: Covid-19 negative hemodynamically unstable patients' flowchart

4.3 Haemodynamically stable population analysis

Patients (N=844)	Number	Frequency (%)
Men	376	45
Women	468	55

Table 24: Hemodynamically stable patients' sex

Mean age was 68,3 ± 17,9.

Medical history	Number (N)	Frequency (%)
No past medical history	134	15,8
Cardiovascular	499	59,1
Respiratory	141	16,7
Cancer	150	17,8
Pro-coagulatory genetic conditions	7	0,8
Other	172	20,4

Table 25: Hemodynamically stable patients' medical history

Physical examination abnormal findings	Number (N)	Frequency (%)
No abnormalities	314	37,2
Cardiovascular	133	15,7
Respiratory	338	40
Edema	79	9,4
Signs of DVT	73	8,6
Vascular (ischemic)	4	0,5
Other	66	7,8

Table 26: Hemodynamically stable patients' physical examination

Chief complaint	Number (N)	Frequency (%)
Chest pain	213	25,2
Dyspnea	284	33,6
Syncope/pre-syncope	127	15
Palpitations/arrhythmia	36	4,3
Signs of DVT/limb edema	56	6,6
Limb pain (upper or lower, unilateral)	20	2,3
Cough, fever and other infectious disease signs	140	16,6
Hypotension	0	0
Neurological symptoms	16	1,9
Cardiac arrest/ROSC	1	0,1
Other	101	11,9

Table 27: Hemodynamically stable patients' chief complaint

	Total	Mean	Standard Deviation	Variance
Systolic BP	839	139,3	23,37	546,42
Diastolic BP	839	80,86	14,28	203,96
Mean Arterial Pressure (MAP)	839	100,34	17,31	318,11
HR	839	89,29	24,3	590,335
SpO2	839	95,51	4,27	18,24
P/F	435	332,9	96,9	9391,07
Serum lactates	62	1,76	1,54	2,38

Table 28: Hemodynamically stable patients' vital parameters and ABG

SARS-CoV-2 PCR Results	Number (N)	Frequency (%)
Positive	84	9,9
Negative	591	70
No data	169	20

Table 29: Hemodynamically stable patients' SARS-CoV-2 search

Color	Number (N)	Frequency (%)
White	3	0,4
Green	373	44.2
"Low intensity" Yellow	30	3,6
Yellow	437	51.8
Red	1	0,1

Table 30: Colour code at admission for hemodynamically stable patients

Table 31 shows the number of acute PE diagnosis (identified as 1 in the graph) for patients with high-risk Simplified Wells score ("PE likely").

Diagnosi TEP emodinamicamente stabili, PERC > 0 e sWells > 1

		Frequenza	Percentuale	Percentuale valida	Percentuale cumulativa
Valido	0	88	49,7	49,7	49,7
	1	89	50,3	50,3	100,0
	Totale	177	100,0	100,0	

Table 31: Acute PE diagnosis for PERC>0 and sWells >1

The following tables *(tables 32 to 35)* correlate the number of acute PE diagnoses with different D-dimer concentrations thresholds.

Diagnosi TEP per emodinamicamente stabili, PERC > 0 e sWells <= 1

D-dimero corretto per età	diagnosi TEP	Numero di casi validi (listwise)
= si	Positivo[a]	77
	Negativo	428
= no	Positivo[a]	3
	Negativo	32
Valido		540
Mancante		68
Totale		608

Dei valori più grandi della variabile o delle variabili dei risultati del test indicano una maggiore prova di uno stato effettivo positivo.

a. Lo stato effettivo positivo è 1.

Table 32: Acute PE diagnosis for PERC>0 and sWells <=1

Diagnosi TEP emodinamicamente stabili, PERC > 0, sWELLS <= 1

D-dimero	Diagnosi TEP	Numero di casi validi (listwise)
< 1000,00	Positivo[a]	6
	Negativo	91
>= 1000,00	Positivo[a]	74
	Negativo	365
Valido		536
Mancante		72
Totale		608

Dei valori più grandi della variabile o delle variabili dei risultati del test indicano una maggiore prova di uno stato effettivo positivo.

a. Lo stato effettivo positivo è 1.

Table 33: Acute PE diagnosis for PERC>0 and sWells <=1

Diagnosi TEP emodinamicamente stabili, PERC > 0, sWELLS <=1

D-dimero	diagnosi TEP (0=no, 1=si)	Numero di casi validi (listwise)
< 1500,00	Positivo[a]	15
	Negativo	180
>= 1500,00	Positivo[a]	65
	Negativo	276
Valido		536
Mancante		72
Totale		608

Dei valori più grandi della variabile o delle variabili dei risultati del test indicano una maggiore prova di uno stato effettivo positivo.

a. Lo stato effettivo positivo è 1.

Table 34: Acute PE diagnosis for PERC>0 and sWells <=1

Diagnosi TEP emodinamicamente stabili, PERC > 0 e sWELLS <=1

D-dimero	diagnosi TEP (0=no, 1=si)	Numero di casi validi (listwise)
< 2000,00	Positivo[a]	21
	Negativo	239
>= 2000,00	Positivo[a]	59
	Negativo	217
Valido		536
Mancante		72
Totale		608

Dei valori più grandi della variabile o delle variabili dei risultati del test indicano una maggiore prova di uno stato effettivo positivo.

a. Lo stato effettivo positivo è 1.

Table 35: Acute PE diagnosis for PERC>0 and sWells <=1

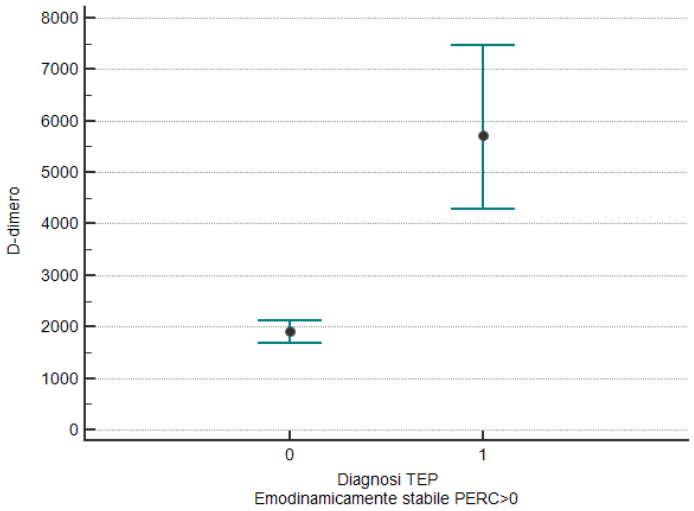

Figure 27: D-dimer concentration distribution for hemodynamically stable patients PERC>0

Dimensione campione	664

Statistiche descrittive

Fattore	n	Minimo	25° percentile	Mediana	75° percentile	Massimo
0	511	0,0000	1094,750	1909,000	4001,000	35000,000
1	153	313,0000	2343,250	5729,000	12175,750	35000,000

Test di Kruskal-Wallis

Statistica test	69,5860
Corretto per valori equivalenti Ht	69,5877
Gradi di libertà (DF)	1
Livello di significatività	P < 0,000001

Fattore	n	Rango medio
(1) 0	511	298,52
(2) 1	153	445,99

Figure 28: Statistical analysis

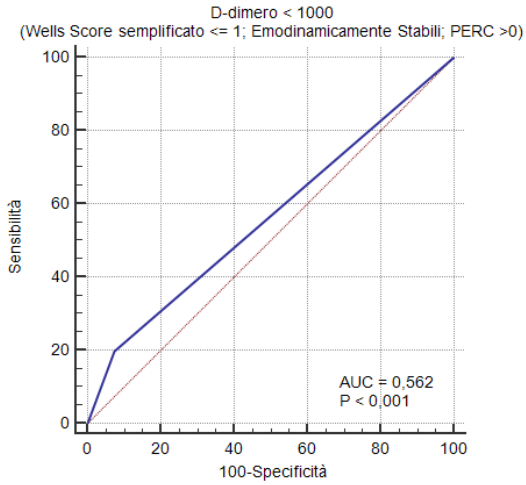

Figure 29: ROC curve sensitivity and specificity, D-dimer < 1000 ng/ml

Dimensione campione	536
Gruppo positivo [a]	456 (85,07%)
Gruppo negativo [b]	80 (14,93%)

[a] diagnosi_TEP__0_no__1_si_ = 0
[b] diagnosi_TEP__0_no__1_si_ = 1

Prevalenza malattia (%)	sconosciuto

Area sotto la curva ROC (AUC)

Area sotto la curva ROC (AUC)	0,562
Errore standard [a]	0,0175
Intervallo di confidenza del 95% [b]	0,519 a 0,605
Statistica z	3,553
Livello di significatività P (Area=0,5)	0,0004

[a] DeLong et al., 1988
[b] Binomiale esatto

Indice di Youden

Indice di Youden J	0,1246
Criterio associato	>0
Sensibilità	19,96
Specificità	92,50

Figure 30: Statistical analysis

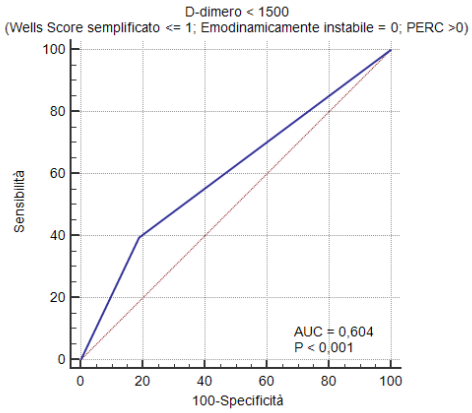

Figure 31: ROC curve sensitivity and specificity, D-dimer < 1500 ng/ml

Variabile	D_dimero < 1500
Variabile di classificazione	diagnosi_TEP__0_no__1_si_
Filtro	AND(Wells_Score_semplificato <= 1; Emodinamicamente_instabile = 0; PERC >0)

Dimensione campione	536
Gruppo positivo [a]	456 (85,07%)
Gruppo negativo [b]	80 (14,93%)

[a] diagnosi_TEP__0_no__1_si_ = 0
[b] diagnosi_TEP__0_no__1_si_ = 1

Prevalenza malattia (%)	sconosciuto

Area sotto la curva ROC (AUC)

Area sotto la curva ROC (AUC)	0,604
Errore standard [a]	0,0248
Intervallo di confidenza del 95% [b]	0,561 a 0,645
Statistica z	4,184
Livello di significatività P (Area=0,5)	<0,0001

[a] DeLong et al., 1988
[b] Binomiale esatto

Indice di Youden

Indice di Youden J	0,2072
Criterio associato	>0
Sensibilità	39,47
Specificità	81,25

Figure 32: Statistical analysis

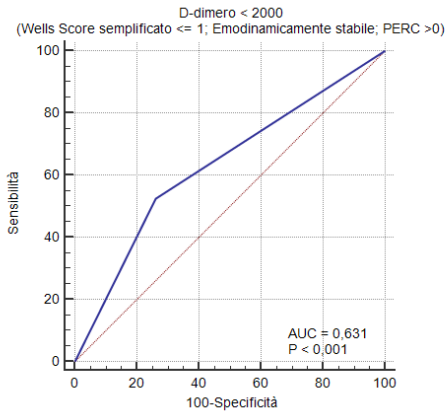

Figure 33: ROC curve sensitivity and specificity, D-dimer < 2000 ng/ml

Variabile	D_dimero < 2000
Variabile di classificazione	diagnosi_TEP__0_no__1_si_
Filtro	AND(Wells_Score_semplificato <= 1; Emodinamicamente_instabile = 0; PERC >0)

Dimensione campione	536
Gruppo positivo [a]	456 (85,07%)
Gruppo negativo [b]	80 (14,93%)

[a] diagnosi_TEP__0_no__1_si_ = 0
[b] diagnosi_TEP__0_no__1_si_ = 1

Prevalenza malattia (%)	sconosciuto

Area sotto la curva ROC (AUC)

Area sotto la curva ROC (AUC)	0,631
Errore standard [a]	0,0274
Intervallo di confidenza del 95% [b]	0,588 a 0,672
Statistica z	4,778
Livello di significatività P (Area=0,5)	<0,0001

[a] DeLong et al., 1988
[b] Binomiale esatto

Indice di Youden

Indice di Youden J	0,2616
Criterio associato	>0
Sensibilità	52,41
Specificità	73,75

Figure 34: Statistical analysis

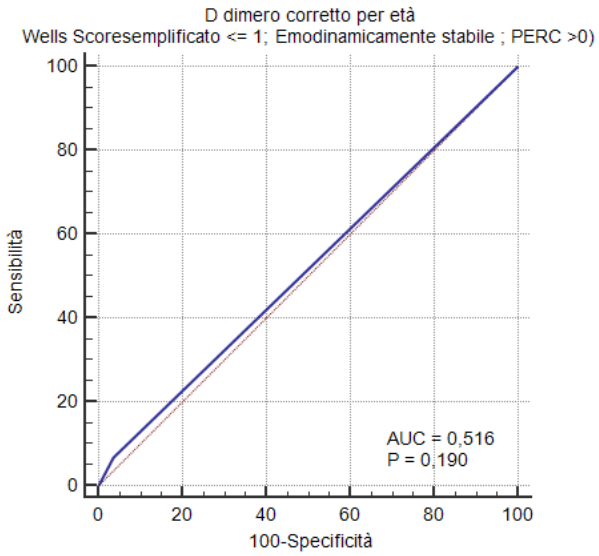

Figure 35: ROC curve sensitivity and specificity, age-adjusted D-dimer

Variabile	D_dimero_corretto
Variabile di classificazione	diagnosi_TEP__0_no__1_si_
Filtro	AND(Wells_Score_semplificato <= 1; Emodinamicamente_instabile = 0; PERC >0)

Dimensione campione	540
Gruppo positivo [a]	460 (85,19%)
Gruppo negativo [b]	80 (14,81%)

[a] diagnosi_TEP__0_no__1_si_ = 0
[b] diagnosi_TEP__0_no__1_si_ = 1

Prevalenza malattia (%)	sconosciuto

Area sotto la curva ROC (AUC)

Area sotto la curva ROC (AUC)	0,516
Errore standard [a]	0,0122
Intervallo di confidenza del 95% [b]	0,473 a 0,559
Statistica z	1,311
Livello di significatività P (Area=0,5)	0,1897

[a] DeLong et al., 1988
[b] Binomiale esatto

Indice di Youden

Indice di Youden J	0,03207
Criterio associato	≤0
Sensibilità	6,96
Specificità	96,25

Figure 36: Statistical analysis

The following flowcharts were created at first following the 2019 ESC Guidelines on acute PE for the diagnosis of haemodynamically stable patients. Then, some D-dimer cut offs different from those suggested by the Guidelines were applied.

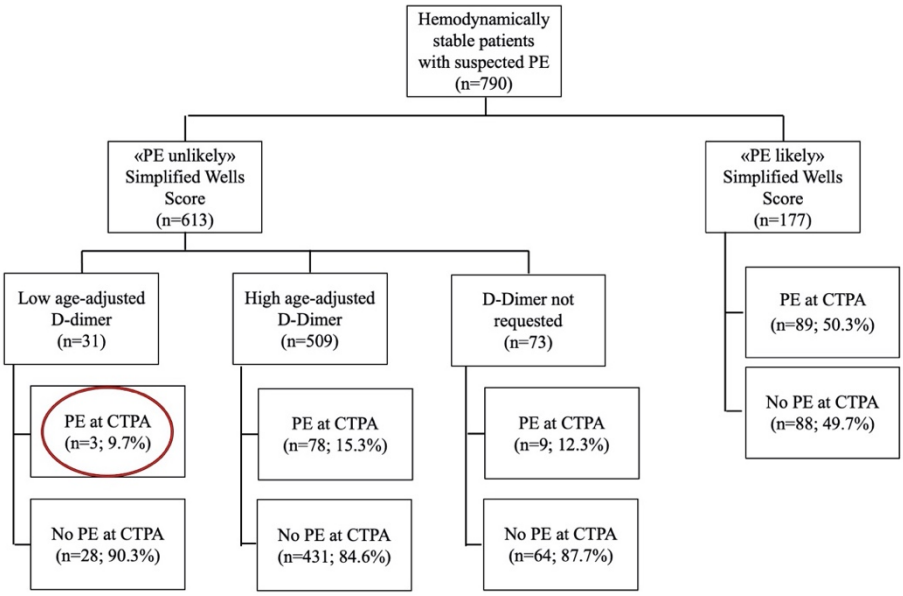

Figure 37: Hemodynamically stable patients' flowchart with age-adjusted D-dimer

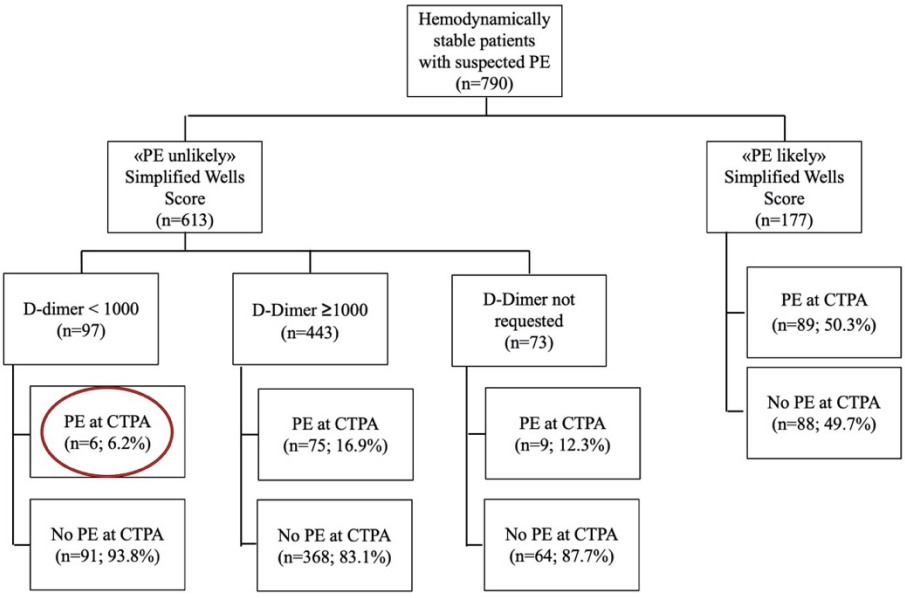

Figure 38: Hemodynamically stable patients' flowchart with D-dimer < 1000 ng/ml

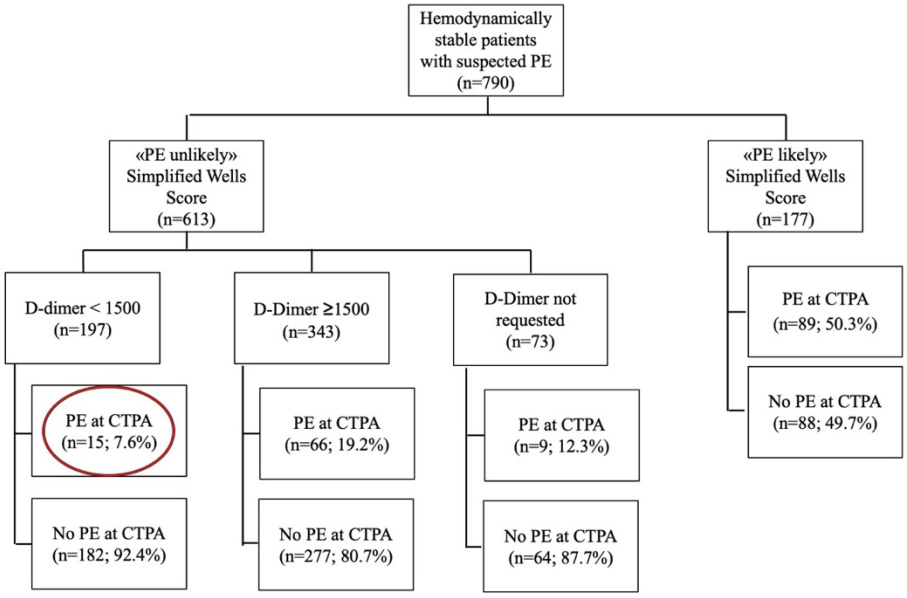

Figure 39: Hemodynamically stable patients' flowchart with D-dimer < 1500 ng/ml

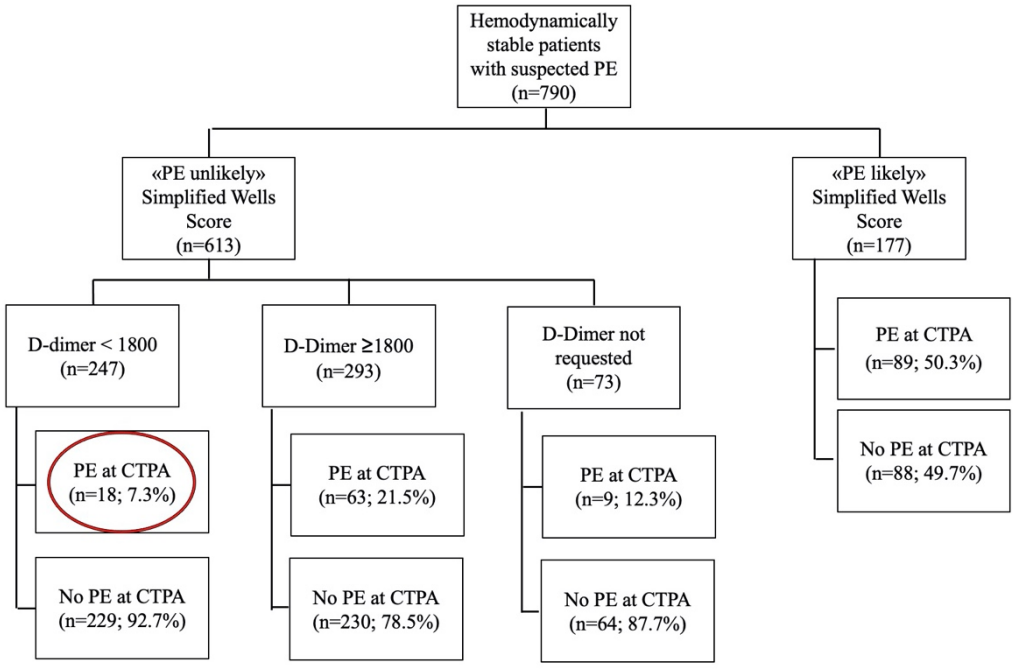

Figure 40: Hemodynamically stable patients' flowchart with D-dimer < 1800 ng/ml

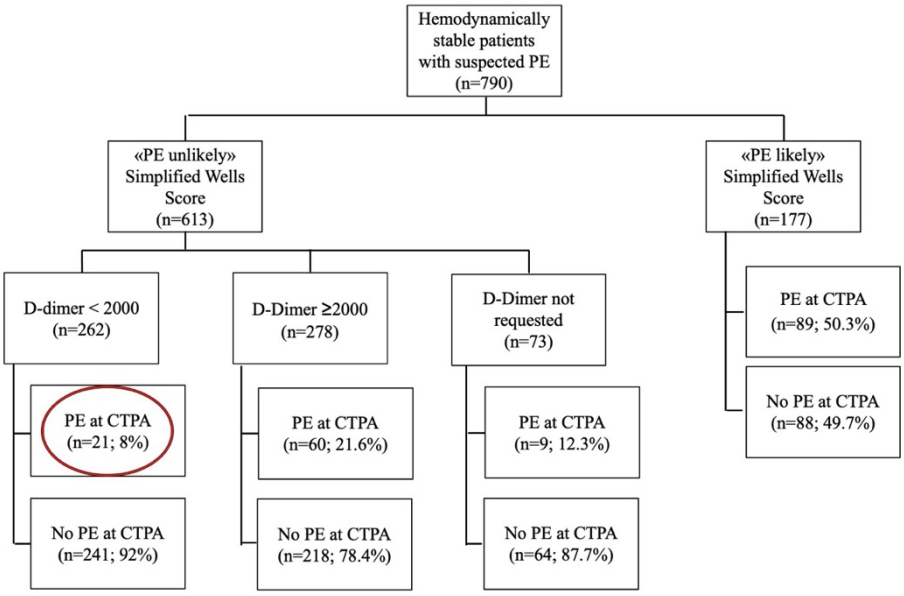

Figure 41: Hemodynamically stable patients' flowchart with D-dimer < 2000 ng/ml

4.4 Covid-19 negative haemodynamically stable population

The same statistics and flowcharts were calculated considering the subpopulation of Covid-19 negative patients belonging to the haemodynamically stable group.

Patients (N=591)	**Number**	**Frequency (%)**
Men	259	44
Women	331	56

Table 36: Covid-19-negative hemodynamically stable patients' sex

Mean age was 70,9 ± 16,7.

Medical history	**Number (N)**	**Frequency (%)**
No past medical history	65	10,9
Cardiovascular	372	62,9
Respiratory	109	18,4
Cancer	125	21,2
Pro-coagulatory genetic conditions	4	0,7
Other	121	20,5

Table 37: Covid-19-negative hemodynamically stable patients' medical history

Chief complaint	Number (N)	Frequency (%)
Chest pain	134	22,7
Dyspnea	204	34,5
Syncope/pre-syncope	86	14,6
Palpitations/arrhythmia	24	4
Signs of DVT/limb edema	49	8,3
Limb pain (upper or lower, unilateral)	14	2,3
Cough, fever and other infectious disease signs	97	16,4
Hypotension	0	0
Neurological symptoms	15	2,5
Cardiac arrest/ROSC	1	0,2
Other	75	12,7

Table 39: Covid-19-negative hemodynamically stable patients' chief complaint

Physical examination abnormal findings	Number (N)	Frequency (%)
No abnormalities	192	32,5
Cardiovascular	108	18,3
Respiratory	246	41,62
Edema	64	10,8
Signs of DVT	61	10,3
Vascular (ischemic)	3	0,5
Other	49	8,3

Table 38: Covid-19-negative hemodynamically stable patients' physical examination

Diagnosi TEP stabili, COVID -, PERC >0 e sWells <= 1

D-dimero corretto	Diagnosi TEP	Numero di casi validi (listwise)
= 1	Positivo[a]	61
	Negativo	399
= 0	Positivo[a]	1
	Negativo	23
Valido		484
Mancante		71
Totale		555

Dei valori più grandi della variabile o delle variabili dei risultati del test indicano una maggiore prova di uno stato effettivo positivo.

a. Lo stato effettivo positivo è 1.

Table 40: Acute PE diagnosis for Covid-19 negative patients with PERC>0, Wells <= 1

Diagnosi TEP stabili, COVID -, PERC > 0 e sWells <=1

D-dimero	Diagnosi TEP	Numero di casi validi (listwise)
< 1000,00	Positivo[a]	3
	Negativo	82
>= 1000,00	Positivo[a]	59
	Negativo	340
Valido		484
Mancante		71
Totale		555

Dei valori più grandi della variabile o delle variabili dei risultati del test indicano una maggiore prova di uno stato effettivo positivo.

a. Lo stato effettivo positivo è 1.

Table 41: Acute PE diagnosis for Covid-19 negative patients with PERC>0, Wells <= 1

Diagnosi TEP Covid - PERC >0 e sWells <= 1

D-dimero	diagnosi TEP (0=no, 1=si)	Numero di casi validi (listwise)
< 1500,00	Positivo[a]	9
	Negativo	163
>= 1500,00	Positivo[a]	53
	Negativo	259
Valido		484
Mancante		71
Totale		555

Dei valori più grandi della variabile o delle variabili dei risultati del test indicano una maggiore prova di uno stato effettivo positivo.

a. Lo stato effettivo positivo è 1.

Table 42: Acute PE diagnosis for Covid-19 negative patients with PERC>0, Wells <= 1

TEP in Covid- PERC >0 e sWells <= 1

D-dimero	diagnosi TEP (0=no, 1=si)	Numero di casi validi (listwise)
< 2000,00	Positivo[a]	15
	Negativo	218
>= 2000,00	Positivo[a]	47
	Negativo	204
Valido		484
Mancante		71
Totale		555

Dei valori più grandi della variabile o delle variabili dei risultati del test indicano una maggiore prova di uno stato effettivo positivo.

a. Lo stato effettivo positivo è 1.

Table 43: Acute PE diagnosis for Covid-19 negative patients with PERC>0, Wells <= 1

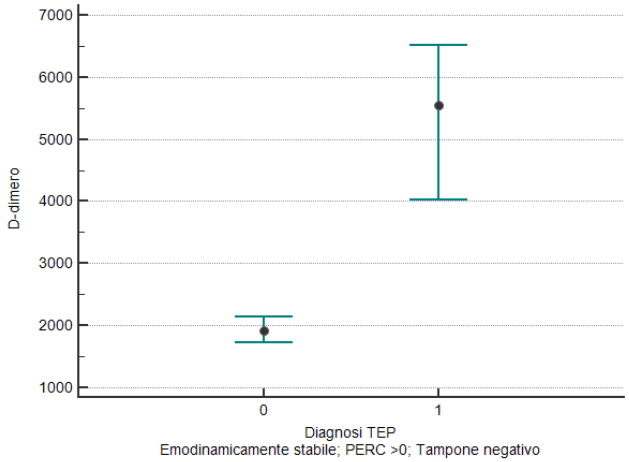

Figure 42: D-dimer concentration distribution for hemodynamically stable patients PERC>0, Covid-19 negative "tampone negativo"

Dati	D_dimero
Codici fattore	diagnosi_TEP__0_no__1_si_
Filtro	AND(Emodinamicamente_instabile = 0; PERC >0; COVID=0)

Dimensione campione	604

Statistiche descrittive

Fattore	n	Minimo	25° percentile	Mediana	75° percentile	Massimo
0	472	0,0000	1103,000	1912,000	3965,000	35000,000
1	132	576,0000	2378,000	5553,500	11285,500	35000,000

Test di Kruskal-Wallis

Statistica test	63,5885
Corretto per valori equivalenti Ht	63,5895
Gradi di libertà (DF)	1
Livello di significatività	P < 0,000001

Fattore	n	Rango medio
(1) 0	472	272,56
(2) 1	132	409,57

Figure 43: Statistical analysis

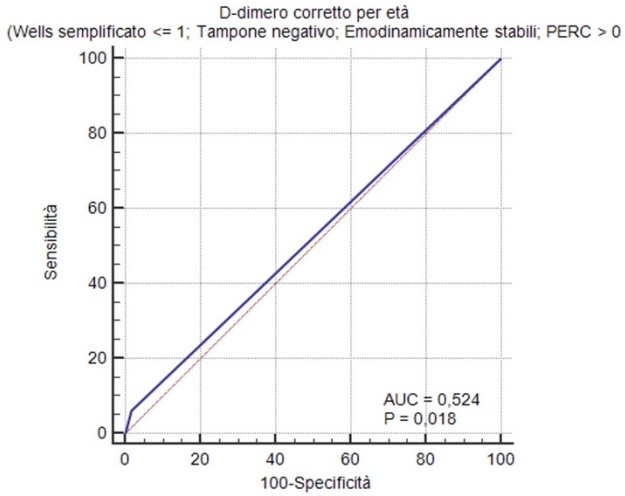

Figure 44: ROC curve sensitivity and specificity, Covid-19 negative hemodynamically stable patients with PERC>0, age-adjusted D-dimer

Variabile	D_dimero_corretto
Variabile di classificazione	diagnosi_TEP__0_no__1_si_
Filtro	AND(Wells_Score_semplificato <= 1; Emodinamicamente_instabile = 0; PERC >0; COVID=0) NOCOVID

Dimensione campione	488
Gruppo positivo [a]	426 (87,30%)
Gruppo negativo [b]	62 (12,70%)

[a] diagnosi_TEP__0_no__1_si_ = 0
[b] diagnosi_TEP__0_no__1_si_ = 1

Prevalenza malattia (%)	sconosciuto

Area sotto la curva ROC (AUC)

Area sotto la curva ROC (AUC)	0,524
Errore standard [a]	0,01000
Intervallo di confidenza del 95% [b]	0,478 a 0,569
Statistica z	2,363
Livello di significatività P (Area=0,5)	0,0181

[a] DeLong et al., 1988
[b] Binomiale esatto

Indice di Youden

Indice di Youden J	0,04725
Criterio associato	≤0
Sensibilità	6,34
Specificità	98,39

Figure 45: Statistical analysis

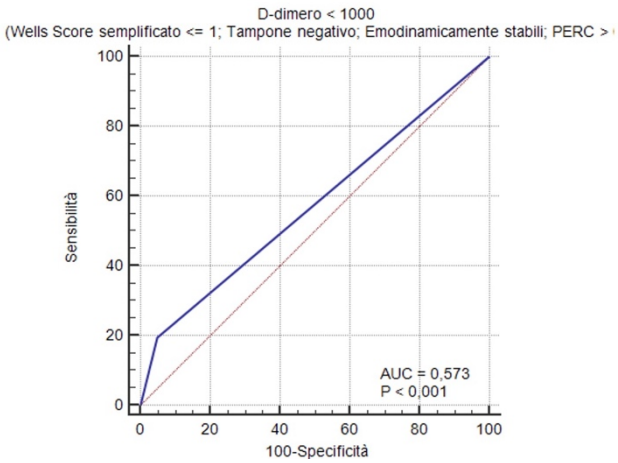

Figure 46: ROC curve sensitivity and specificity, Covid-19 negative hemodynamically stable patients with PERC>0, D-dimer < 1000 ng/ml

Variabile	D_dimero < 1000
Variabile di classificazione	diagnosi_TEP__0_no__1_si_
Filtro	AND(Wells_Score_semplificato <= 1; Emodinamicamente_instabile = 0; PERC >0; COVID=0) NOCOVID

Dimensione campione	484
Gruppo positivo [a]	422 (87,19%)
Gruppo negativo [b]	62 (12,81%)

[a] diagnosi_TEP__0_no__1_si_ = 0
[b] diagnosi_TEP__0_no__1_si_ = 1

Prevalenza malattia (%)	sconosciuto

Area sotto la curva ROC (AUC)

Area sotto la curva ROC (AUC)	0,573
Errore standard [a]	0,0168
Intervallo di confidenza del 95% [b]	0,528 a 0,618
Statistica z	4,347
Livello di significatività P (Area=0,5)	<0,0001

[a] DeLong et al., 1988
[b] Binomiale esatto

Indice di Youden

Indice di Youden J	0,1459
Criterio associato	>0
Sensibilità	19,43
Specificità	95,16

Figure 47: Statistical analysis

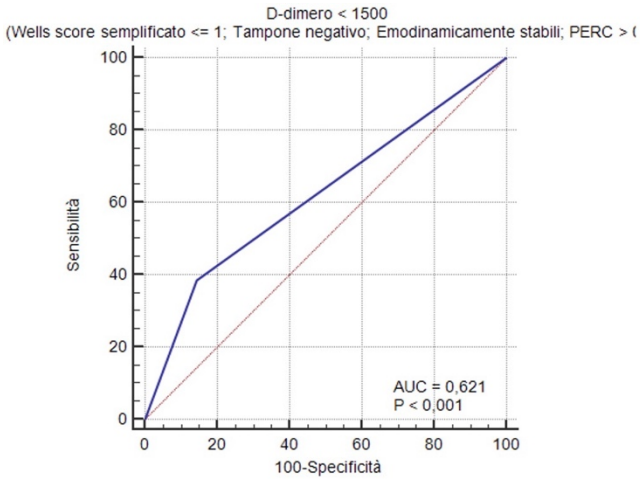

Figure 48: ROC curve sensitivity and specificity, Covid-19 negative hemodynamically stable patients with PERC>0, D-dimer < 1500 ng/ml

Variabile	D_dimero < 1500
Variabile di classificazione	diagnosi_TEP__0_no__1_si_
Filtro	AND(Wells_Score_semplificato <= 1; Emodinamicamente_instabile = 0; PERC >0; COVID=0) NOCOVID

Dimensione campione	484
Gruppo positivo [a]	422 (87,19%)
Gruppo negativo [b]	62 (12,81%)

[a] diagnosi_TEP__0_no__1_si_ = 0
[b] diagnosi_TEP__0_no__1_si_ = 1

Prevalenza malattia (%)	sconosciuto

Area sotto la curva ROC (AUC)

Area sotto la curva ROC (AUC)	0,621
Errore standard [a]	0,0255
Intervallo di confidenza del 95% [b]	0,576 a 0,664
Statistica z	4,731
Livello di significatività P (Area=0,5)	<0,0001

[a] DeLong et al., 1988
[b] Binomiale esatto

Indice di Youden

Indice di Youden J	0,2411
Criterio associato	>0
Sensibilità	38,63
Specificità	85,48

Figure 49: Statistical analysis

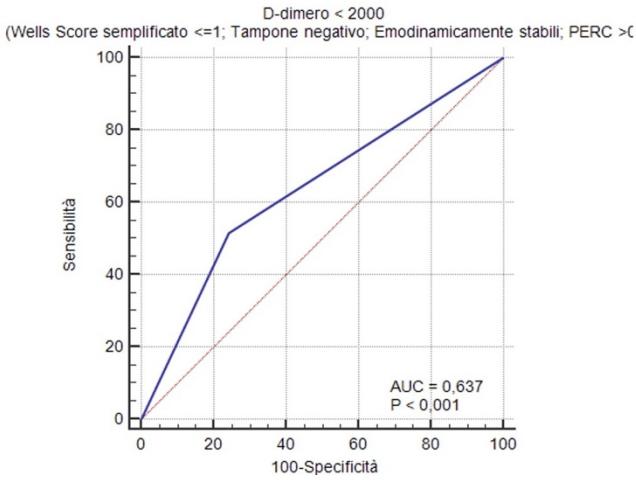

Figure 50: ROC curve sensitivity and specificity, Covid-19 negative hemodynamically stable patients with PERC>0, D-dimer < 2000 ng/m

Variabile	D_dimero < 2000
Variabile di classificazione	diagnosi_TEP__0_no__1_si_
Filtro	AND(Wells_Score_semplificato <= 1; Emodinamicamente_instabile = 0; PERC >0; COVID=0) NOCOVID

Dimensione campione	484
Gruppo positivo [a]	422 (87,19%)
Gruppo negativo [b]	62 (12,81%)

[a] diagnosi_TEP__0_no__1_si_ = 0
[b] diagnosi_TEP__0_no__1_si_ = 1

Prevalenza malattia (%)	sconosciuto

Area sotto la curva ROC (AUC)

Area sotto la curva ROC (AUC)	0,637
Errore standard [a]	0,0300
Intervallo di confidenza del 95% [b]	0,593 a 0,680
Statistica z	4,578
Livello di significatività P (Area=0,5)	<0,0001

[a] DeLong et al., 1988
[b] Binomiale esatto

Indice di Youden

Indice di Youden J	0,2747
Criterio associato	>0
Sensibilità	51,66
Specificità	75,81

Figure 51: Statistical analysis

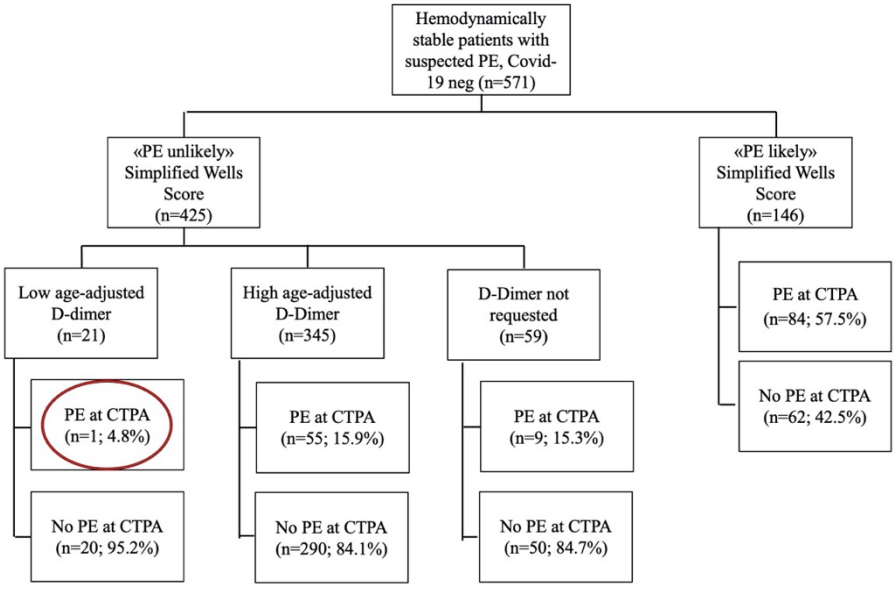

Figure 52: Covid-19 negative hemodynamically stable patients' flowchart with age-adjusted D-dimer

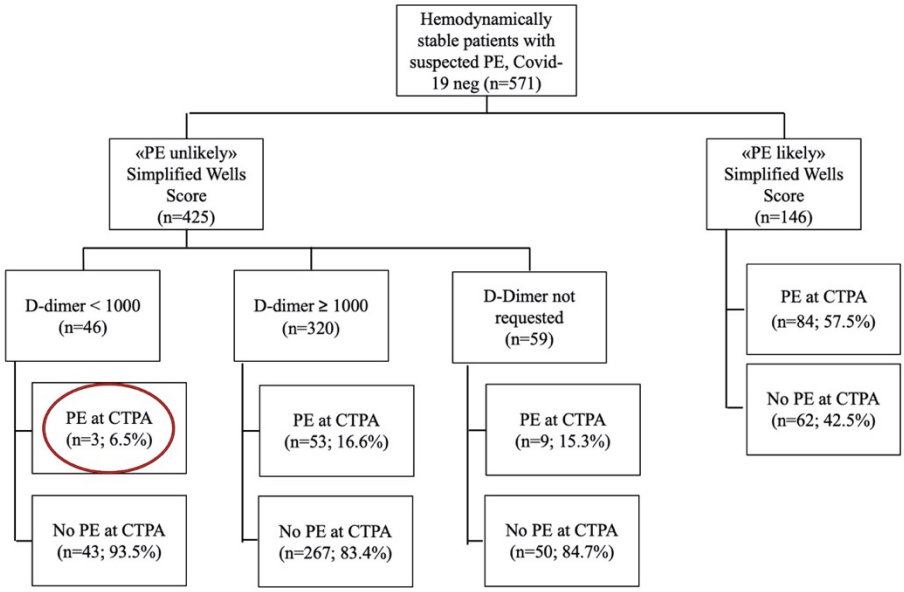

Figure 53: Covid-19 negative hemodynamically stable patients' flowchart with D-dimer < 1000 ng/ml

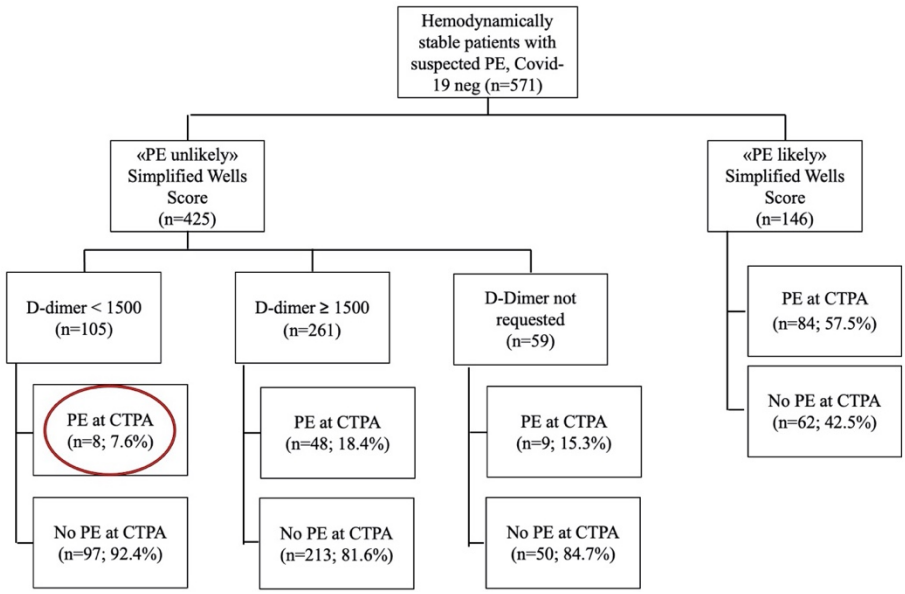

Figure 54: Covid-19 negative hemodynamically stable patients' flowchart with D-dimer < 1500 ng/ml

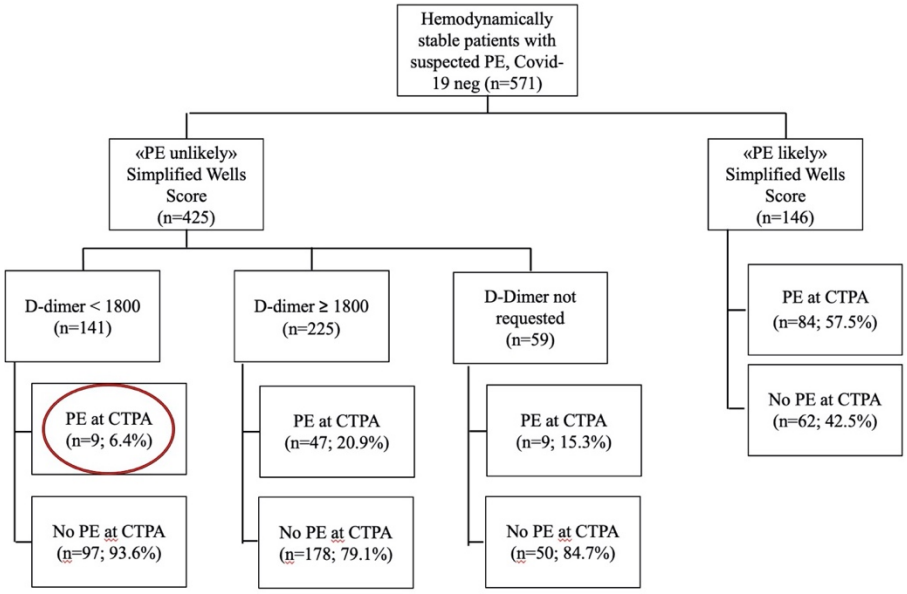

Figure 55: Covid-19 negative hemodynamically stable patients' flowchart with D-dimer < 1800 ng/ml

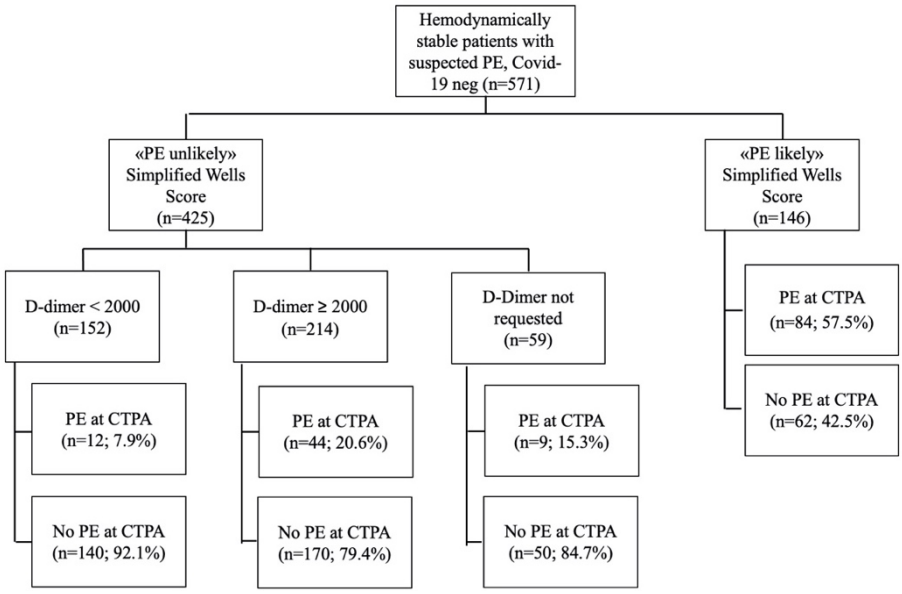

Figure 56: Covid-19 negative hemodynamically stable patients' flowchart with D-dimer < 2000 ng/ml

4.5 "PE unlikely" haemodynamically stable patients with no D-dimer

Analysing the population of haemodynamically stable patients with low risk of acute PE according to Simplified Wells score ("PE unlikely"), it was possible to identify 73 of them for which D-dimer testing was not requested before CTPA.

Color	Number (N)	Frequency (%)
White	0	0
Green	33	45,8
"Low intensity" Yellow	2	2,8
Yellow	37	51,4
Red	0	0

Table 44: Color code priority at admission for patients without D-dimer

	Mean	Standard Deviation
Age	71,	14,2
Systolic BP	140,1	22,4
Diastolic BP	79,2	14,6
HR	86,4	14,6
SpO2	95,9	19,8
P/F	315,4	113,5
Serum lactate	1,3	0,5

Table 45: Vital parameters and ABG results for patients without D-dimer

Out of the 73, only one was positive for Covid-19: for this patient, CTPA was requested both to investigate the extent of the viral pulmonary disease and the possibility of concurrent PE (which was nevertheless excluded at CTPA).

Eventually, acute PE was found in 9 out of these 73 patients (12.3%), as shown in the previous flow charts.

In this group, 22 out of 73 patients received echocardiography:

- 15 patients with negative results, of which 3 then diagnosed with acute PE at CTPA;
- 7 patients with echocardiographic findings compatible with acute PE, of which 1 diagnosed with acute PE at CTPA.

Patients falling into this "PE unlikely, no D-dimer testing" subgroup can be further subdivided into patients with Simplified Wells score = 0 and patients with Simplified Wells score = 1.

The first set (Wells = 0) is composed by 28 patients, 3 of them were diagnosed with acute PE through CTPA.

In the second set (Wells =1), for the remaining 45 patients, each item was investigated to study the correlation to PE at CTPA:

- 2 patients with positivity for "signs of DVT", only 1 with PE at CTPA finally (chief complaint at admission was chest pain and signs of DVT for this patient);

- 5 patients with positivity for the item “PE is the most likely diagnosis” (no alternative diagnosis found), 2 of them with RV dysfunction at echocardiography and positive CUS. All of them consulted the ER in the suspect of PE. Finally, none of them was diagnosed with acute PE through CTPA;
- 3 patients with positivity for the item “immobilization” or “surgery in the last 4 weeks”, all three did not have acute PE at CTPA;
- 15 patients with HR > 100 bpm, 3 of them were diagnosed with acute PE at CTPA;
- 6 patients with previous PE or DVT, 1 diagnosis of acute PE;
- 3 patients with hemoptysis, 0 acute PE at CTPA;
- 11 patients with cancer, 1 diagnosis of acute PE at CTPA.

4.6 Hemodynamically stable population with PERC = 0

In the study, 54 patients were identified with PERC = 0 who nevertheless underwent D-dimer testing and subsequently CTPA.

Color	Number (N)	Frequency (%)
White	0	0
Green	34	63
“Low intensity” Yellow	1	1,9
Yellow	19	35,2
Red	0	0

Table 46: Color code priority at admission for PERC=0 patients

	Mean	Standard Deviation
Age	38,48	10,95
Systolic BP	128,85	18,68
Diastolic BP	79,57	12,16
HR	77,8	10,63
SpO2	98,79	1,2
P/F	390	100,97
Serum lactate	1	0

Table 47: Vital parameters and ABG results for PERC=0 patients

In this group, two patients received bedside echocardiography with findings compatible for signs of acute PE, but finally CTPA excluded this diagnosis for both. 41 patients had high age-adjusted D-dimer levels; of these, 6 were Covid-19 positive.

Five patients had reduced p/f (lower than 300) at ABG.

Overall, only one patient out of the 54 had acute PE at diagnosis.

4.7 Adding ultrasonography to the flowchart of hemodynamically stable patients

Another objective of this study was to integrate the diagnostic algorithm suggested by the guidelines for hemodynamically stable "PE unlikely" patients with the use of ultrasonography (either signs of RV dysfunction at TTE or positive lower or upper extremities at CUS) and, at the same time, the utility of lung ultrasound. In these patients it has mostly been used as differential diagnoses tool, in order to be able to exclude acute PE.

"LUS+" meant the finding of bilateral pleural effusion and bilateral B-lines, indicators of interstitial syndrome often referable to heart failure, or unilateral B-lines, unilateral pleural effusion or pulmonary consolidations, which may instead lead to the suspicion of pneumonia.

At first, an age-adjusted cut off for D-dimer concentration was used, as per the guidelines. Then, higher experimental thresholds for D-dimer were applied.

The following figures represent these results.

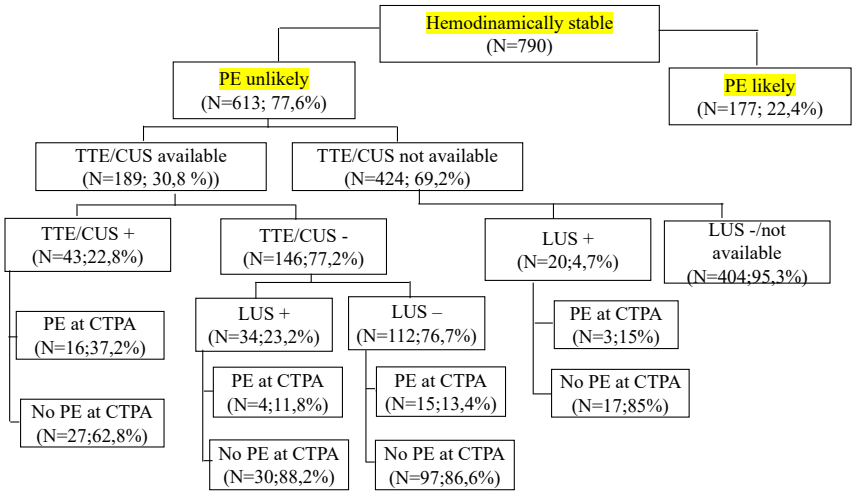

Figure 57: Flowchart of hemodynamically stable patients with unlikely PE analyzed by multi-organ ultrasound

The following flowcharts show the results for patients for which TTE/CUS were not available first *(figures 58 to 61)*, then, those for patients who received TTE/CUS and/or LUS *(figures 62 to 76)*.

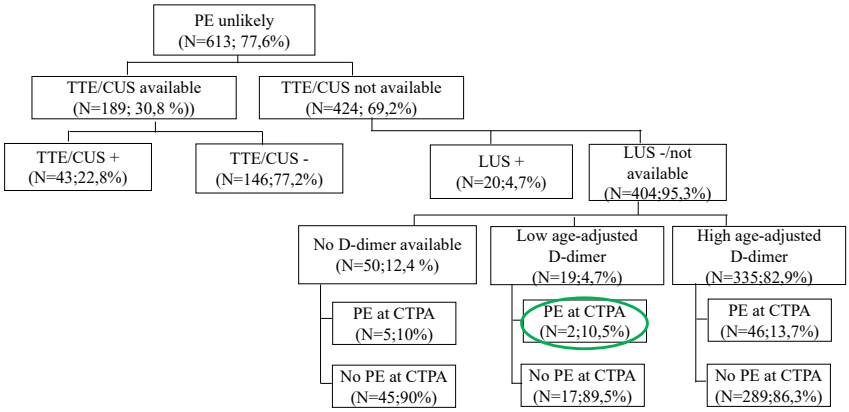

Figure 58: Ultrasound not available, age-adjusted d-dimer

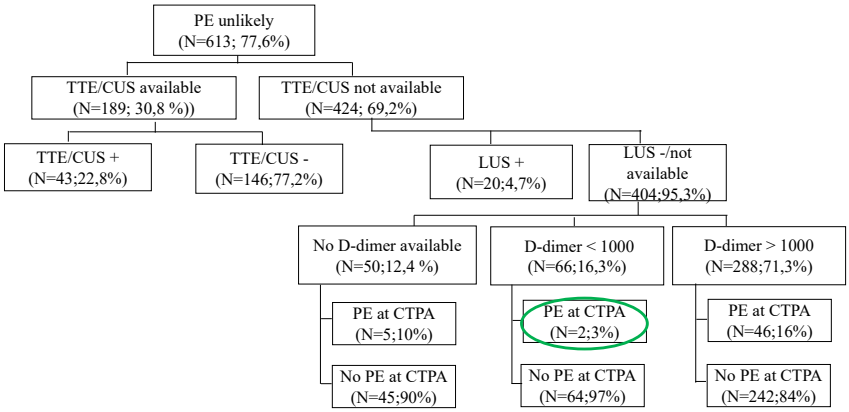

Figure 59: Ultrasonography not available, D-dimer < 1000 ng/ml

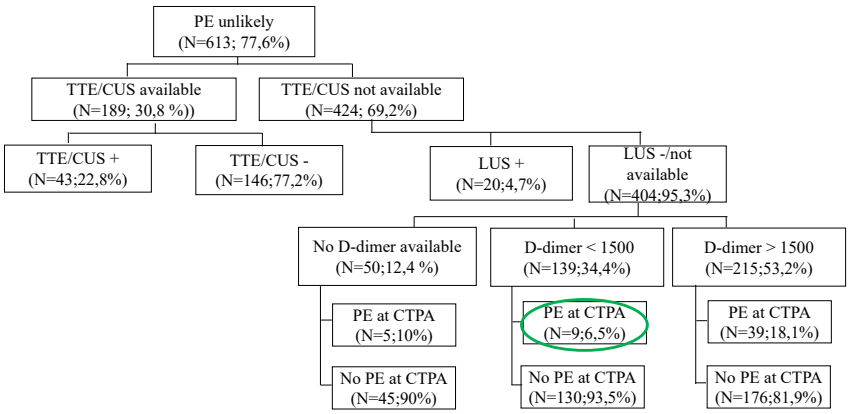

Figure 60: Ultrasonography not available, D-dimer < 1500 ng/ml

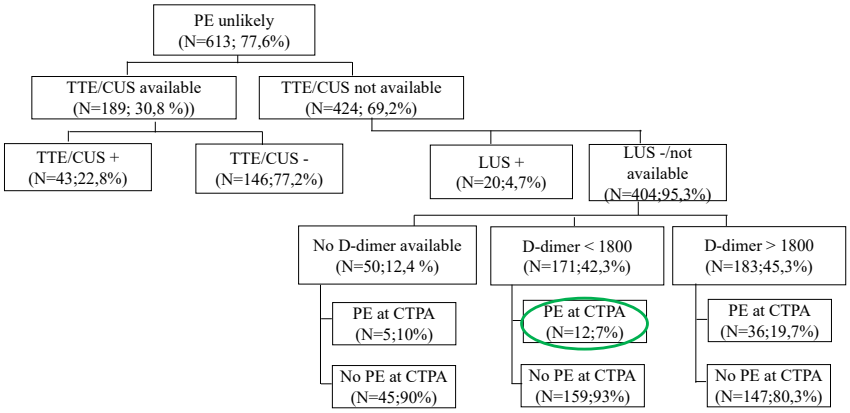

Figure 61: Ultrasonography not available, D-dimer < 1800 ng/ml

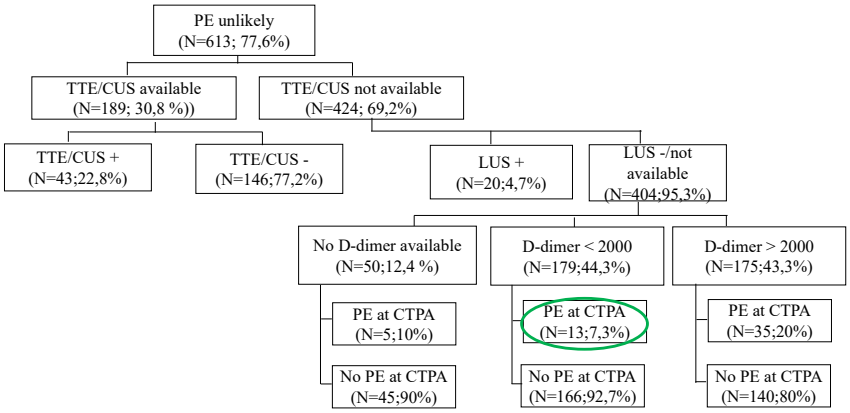

Figure 62: Ultrasonography not available, D-dimer < 2000 ng/ml

US not available	***Low age-adjusted D-dimer***	***D-dimer < 1000***	***D-dimer < 1500***	***D-dimer < 1800***	***D-dimer < 2000***
Number	*19*	*66*	*139*	*171*	*179*
PE at CTPA	*2 (10.5%)*	*2 (3%)*	*9 (6.5%)*	*12 (7%)*	*13 (7.3%)*
NO PE at CTPA	*17 (89.5%)*	*64 (97%)*	*130 (93.5%)*	*159 (93%)*	*166 (92.7%)*

Table 48: Comparison of cut-offs for patients without ultrasound

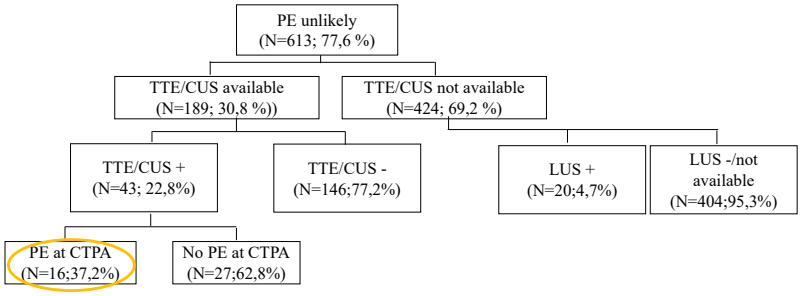

Figure 63: Ultrasonography available

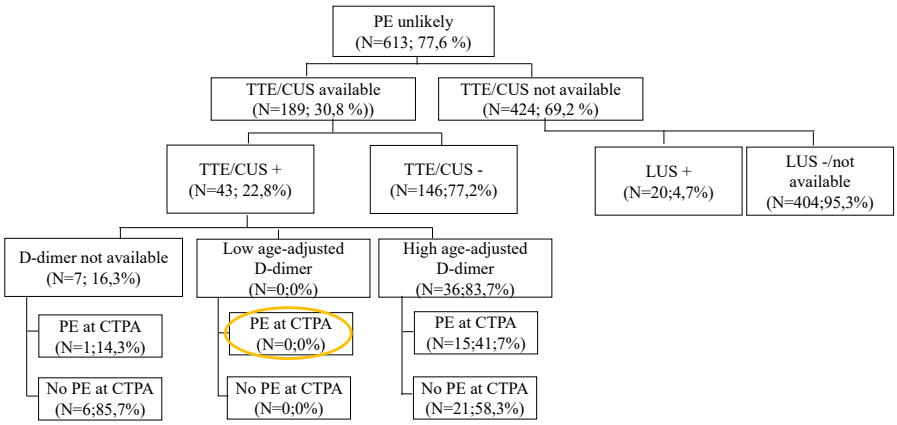

Figure 64: Ultrasonography available age-adjusted D-dimer

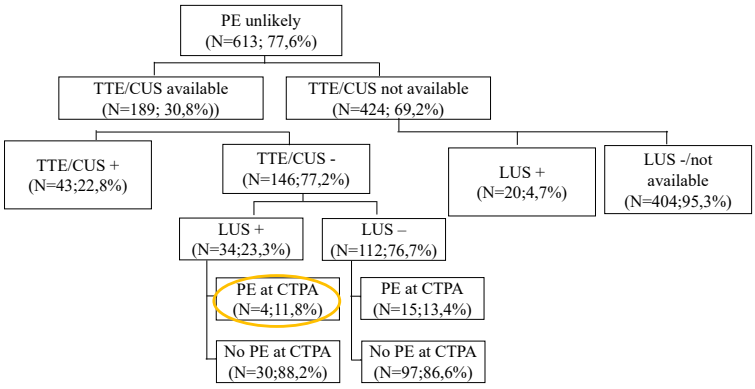

Figure 65: TTE/CUS -, LUS+

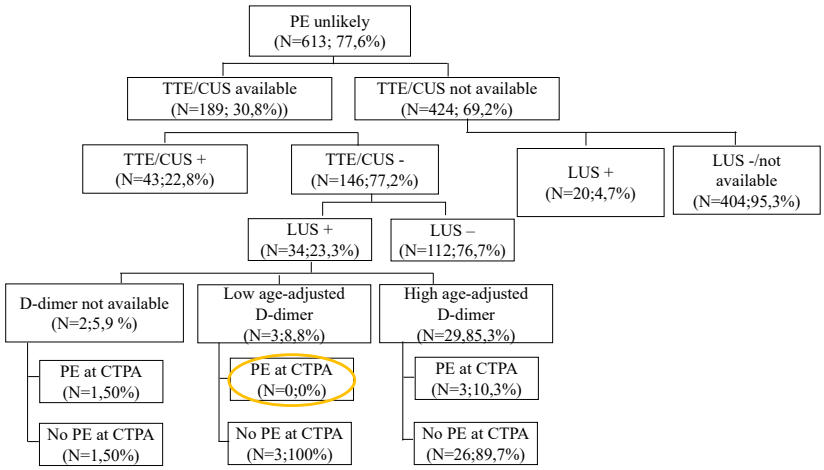

Figure 66: TTE/CUS -, LUS+, age-adjusted D-dimer

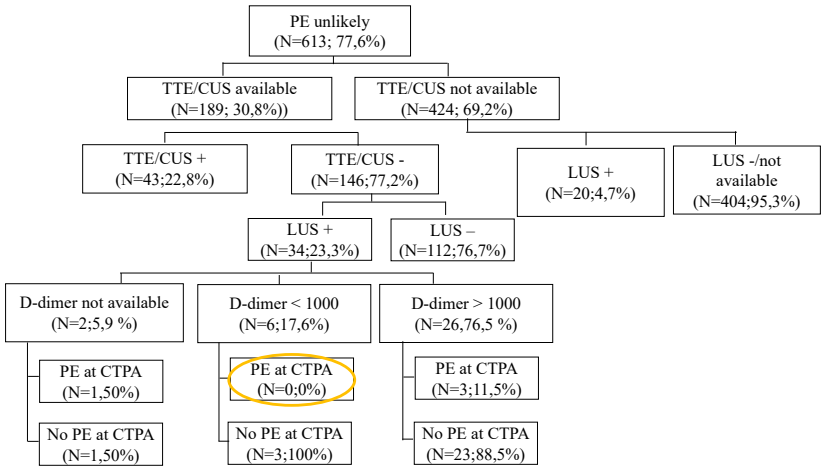

Figure 67: TTE/CUS -, LUS+, D-dimer <1000

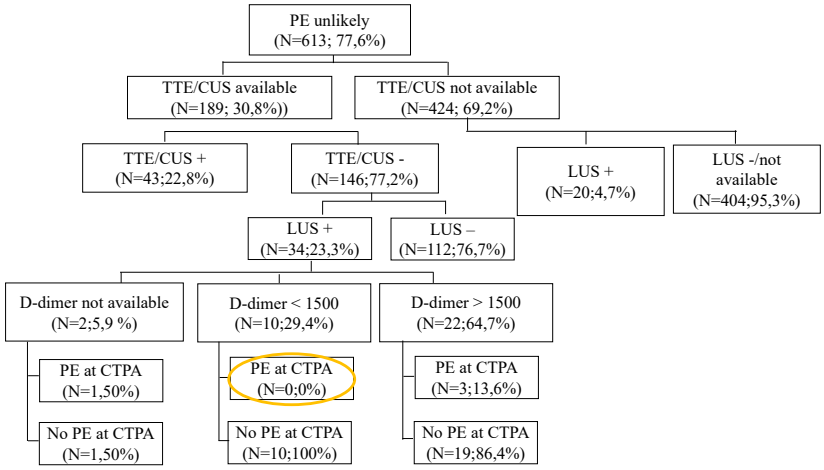

Figure 68: TTE/CUS -, LUS+, D-dimer <1500

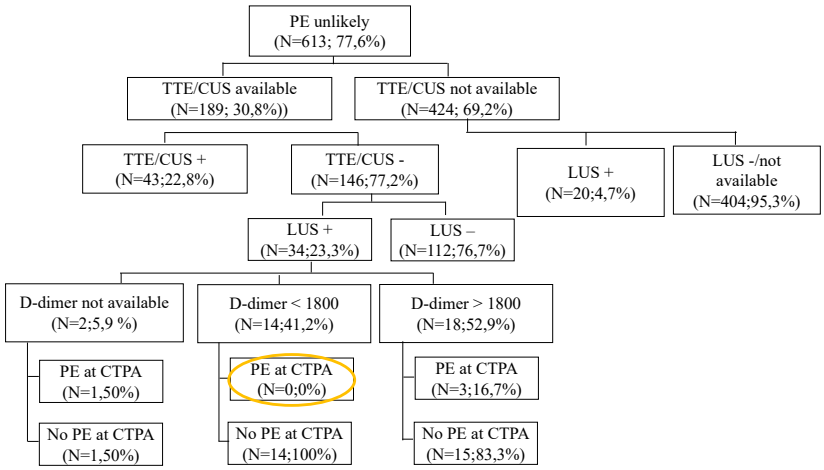

Figure 69: TTE/CUS -, LUS+, D-dimer <1800

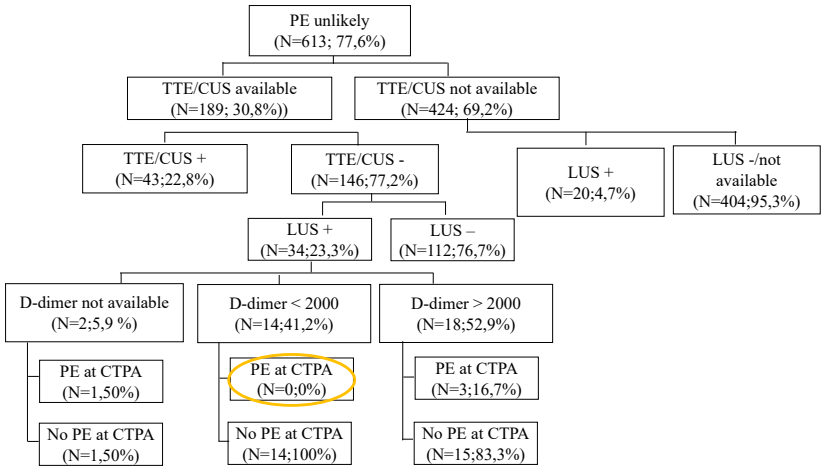

Figure 70: TTE/CUS -, LUS+, D-dimer <2000

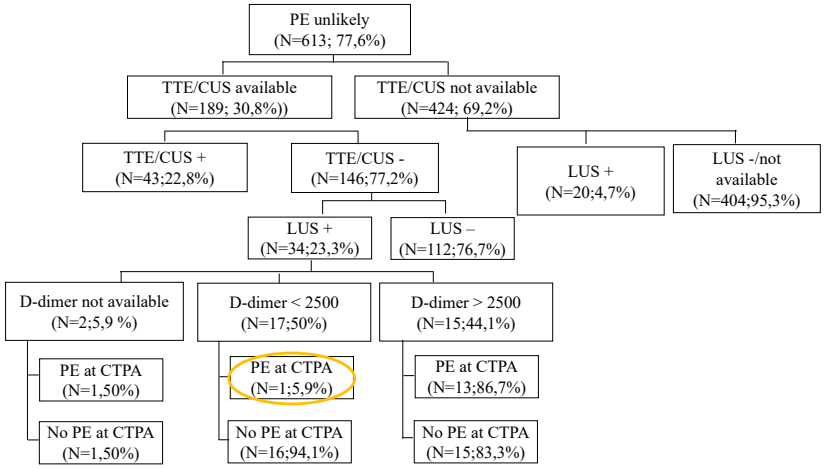

Figure 71: TTE/CUS -, LUS+, D-dimer <2500

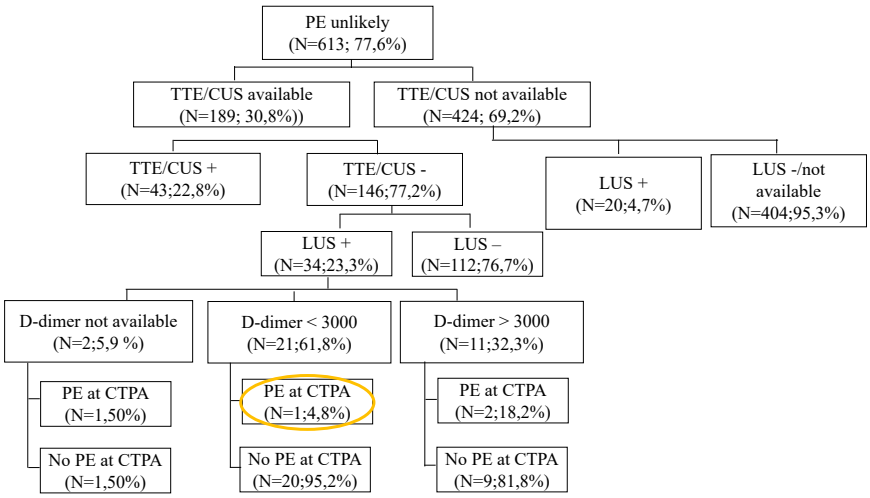

Figure 72: TTE/CUS -, LUS+, D-dimer <3000

LUS + (35)	***Low age-adjusted D-dimer***	***D-dimer < 1000***	***D-dimer < 1500***	***D-dimer < 1800***	***D-dimer < 2000***	***D-dimer < 2500***	***D-dimer < 3000***
Number	*3*	*6*	*10*	*14*	*14*	*17*	*21*
PE at CTPA	*0*	*0*	*0*	*0*	*0*	*1 (5.9%)*	*1 (4.8%)*
No PE at CTPA	*3 (100%)*	*6 (100%)*	*10 (100%)*	*14 (100%)*	*14 (100%)*	*16 (92.7%)*	*20 (95.2%)*

Table 49: Comparison of cut-offs for patients with LUS positive

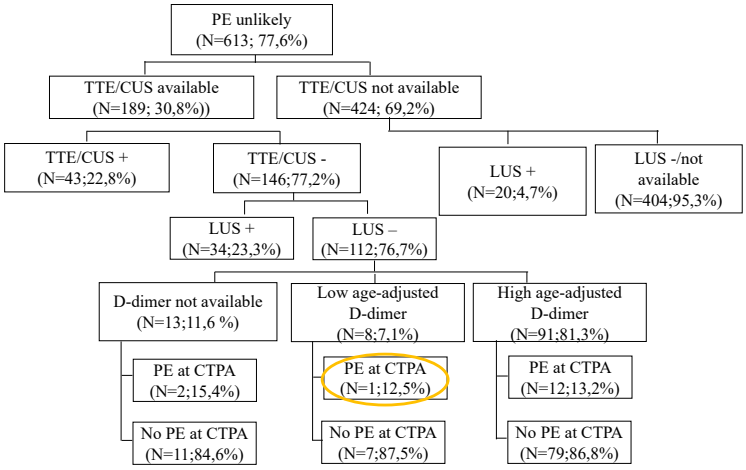

Figure 73: TTE/CUS -, LUS-, age-adjusted D-dimer

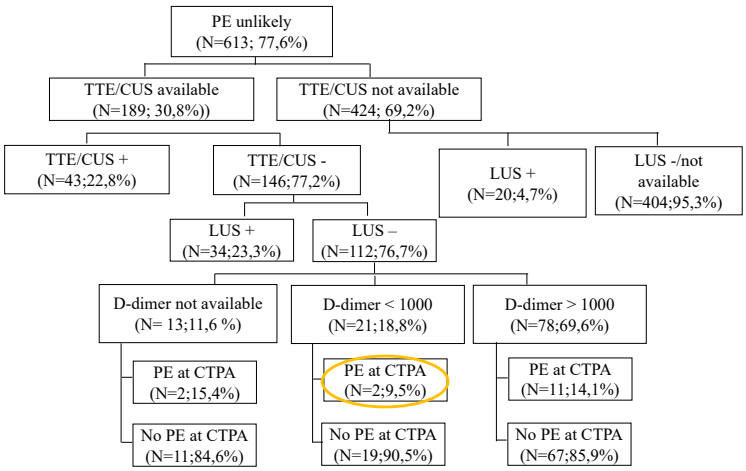

Figure 74: TTE/CUS -, LUS-, D-dimer <1000

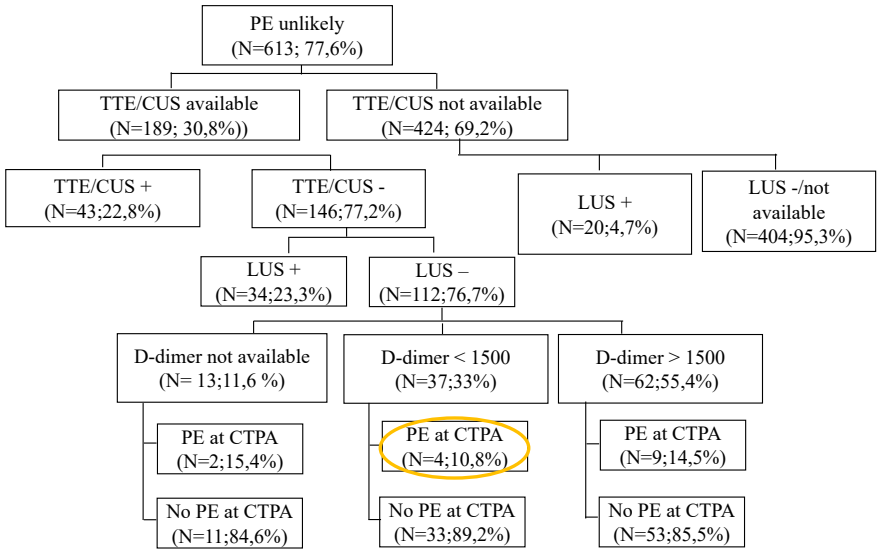

Figure 75: TTE/CUS -, LUS-, D-dimer <1500

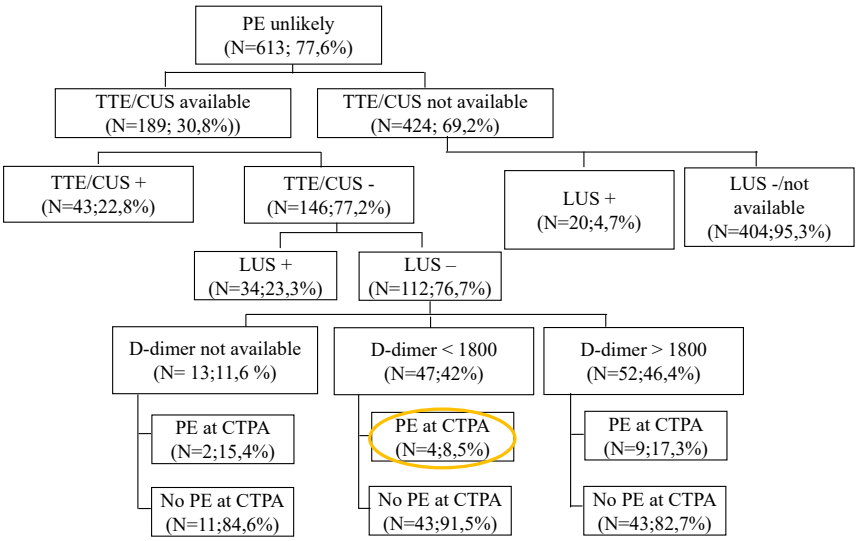

Figure 76: TTE/CUS -, LUS-, D-dimer <1800

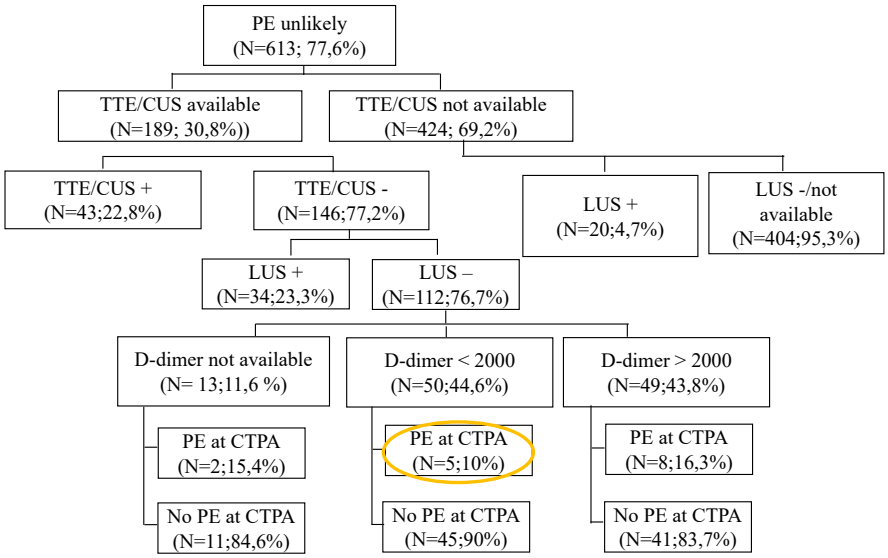

Figure 77: TTE/CUS -, LUS-, D-dimer <2000

LUS - (112)	***Low age-adjusted D-dimer***	***D-dimer < 1000***	***D-dimer < 1500***	***D-dimer < 1800***	***D-dimer < 2000***
Number	*8*	*21*	*37*	*47*	*50*
PE at CTPA	*1 (12,5%)*	*2 (9,5%)*	*4 (10,8%)*	*4 (8,5%)*	*5 (10%)*
NO PE at CTPA	*7 (87,5%)*	*19 (90,5%)*	*33 (89,2%)*	*43 (91,5%)*	*45 (90%)*

Table 50: Comparison of cut-offs for patients with LUS negative

D-dimer	Number	Mean	Standard deviation	p value
TTE+	43	6866,25	7554,41	NS
TTE-	146	4896,94	7430,67	NS

Table 51: Mean and standard deviation of hemodynamically stable patients with PE unlikely compared by TTE/CUS positivity.

The p-value obtained from this analysis is not significant: this means that the two populations do not have a significantly different p-value. It can therefore be deduced that having a positive TTE or CUS has a greater importance than the value of D-dimer, consequently patients with positive TTE or CUS should have CTPA.

The combination of the different D-dimer cut-offs with ultrasounds allow to arrive at the best diagnostic algorithm for the diagnosis of acute PE (figure 59 + figure 70 + figure 76). Indeed, using this new algorithm, 127 CTPAs were saved, with a misdiagnosis of only 6 acute PE, reaching a diagnostic sensitivity of 95.3%.

4.8. Suspected sepsis: algorithm to exclude acute PE in hemodynamically stable patients

Hemodynamically stable patients with unlikely PE were considered in this analysis. We identified a subgroup of patients with high inflammatory indicators (WBC >12 thousand or CRP > 3mg/dL or PCT > 1ng/mL) and high lactates (>2mmol/L) on blood tests. For these patients increasingly higher D-dimer cut-offs were applied, from the one corrected for age up to 4000 ng/ml (*from figure 78 to figure 84*).

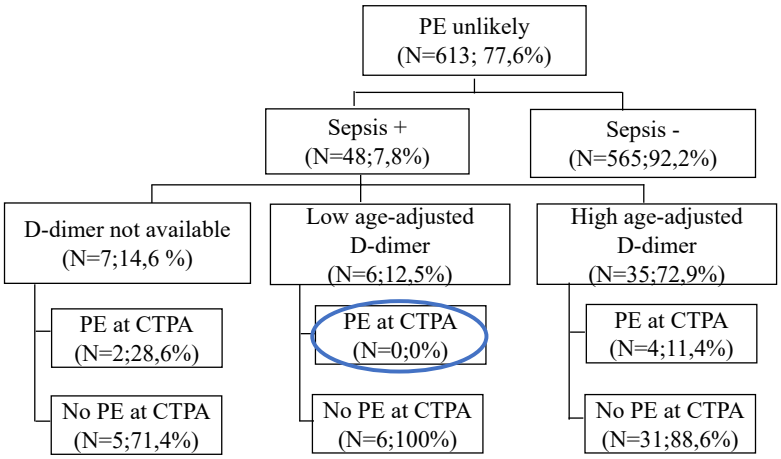

Figure 78: PE unlikely, Suspected sepsis, age-adjusted D-dimer flowchart

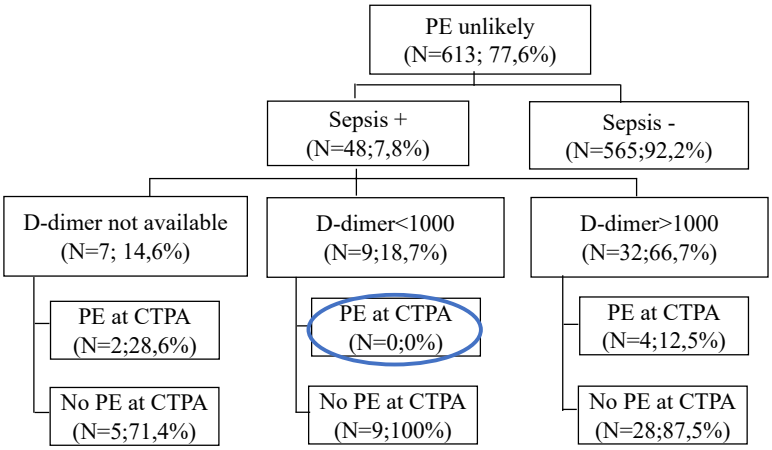

Figure 79: PE unlikely, Suspected sepsis, D-dimer <1000 flowchart

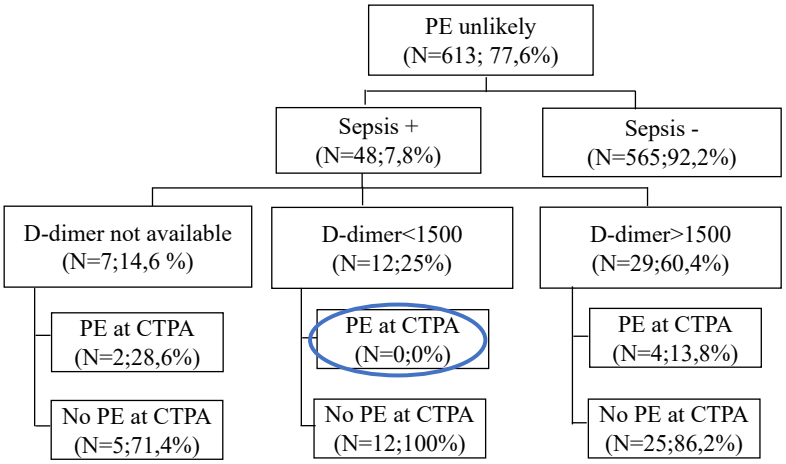

Figure 80: PE unlikely, Suspected sepsis, D-dimer <1500 flowchart

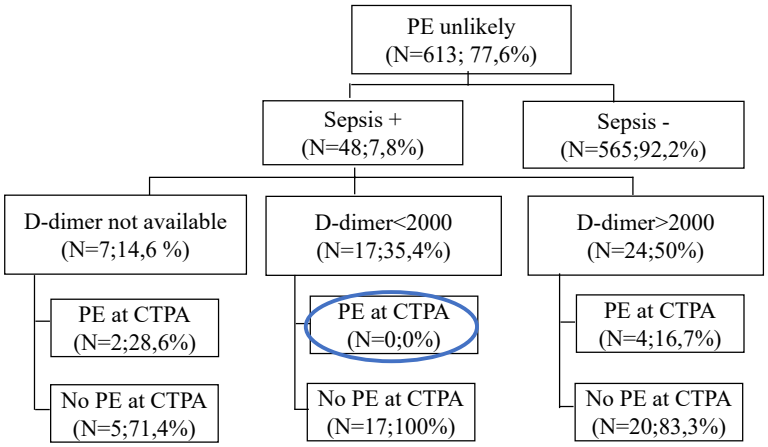

Figure 81: PE unlikely, Suspected sepsis, D-dimer <2000 flowchart

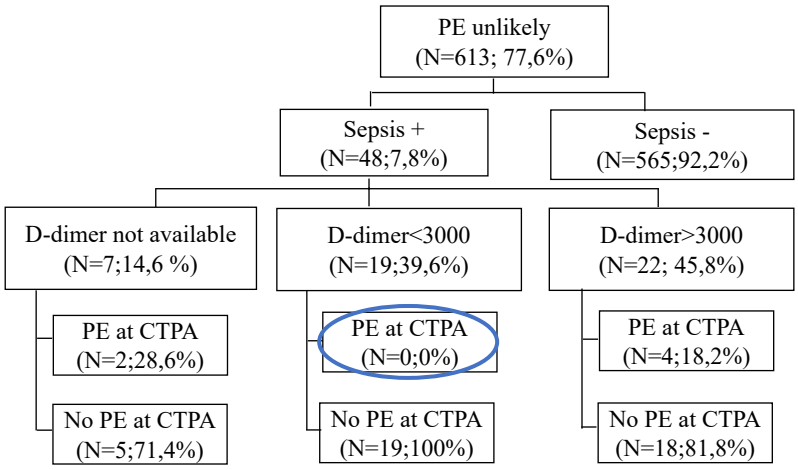

Figure 82: PE unlikely, Suspected sepsis, D-dimer <3000 flowchart

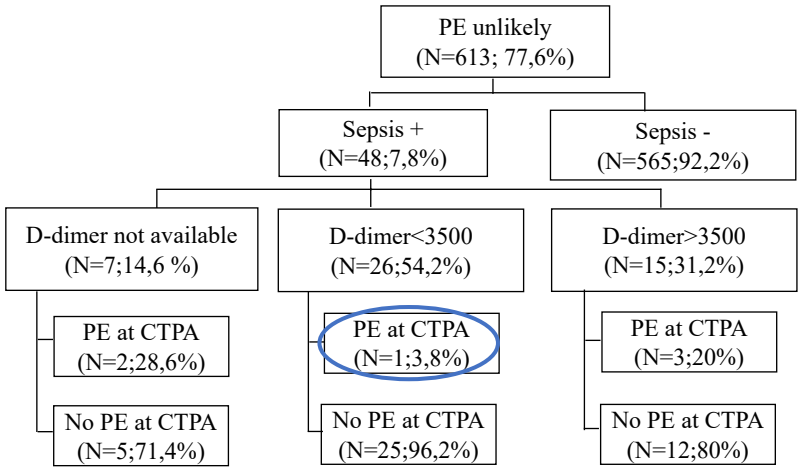

Figure 83: PE unlikely, Suspected sepsis, D-dimer <3500 flowchart

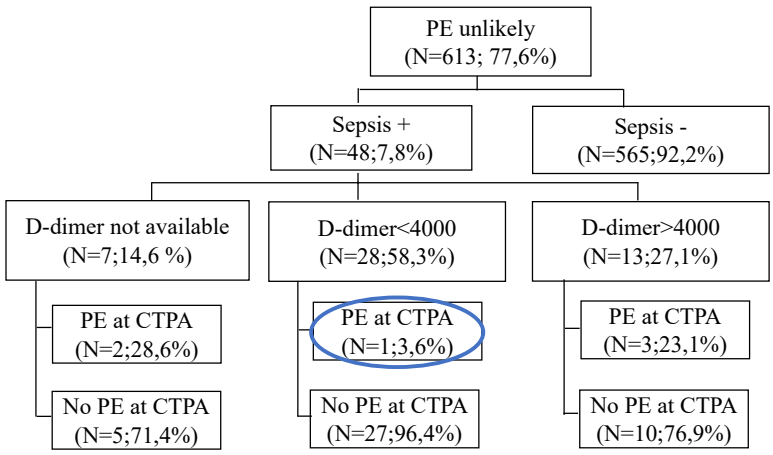

Figure 84: PE unlikely, Suspected sepsis, D-dimer <4000 flowchart

Sepsis (48)	*Low age-adjusted D-dimer*	*D-dimer < 1000*	*D-dimer < 1500*	*D-dimer < 1800*	*D-dimer < 2000*	*D-dimer < 3000*	*D-dimer < 3500*	*D-dimer < 4000*
Number	*6*	*9*	*12*	*16*	*17*	*19*	*26*	*28*
PE at CTPA	*0 (0%)*	*0 (0%)*	*0 (0%)*	*0 (0%)*	*0 (0%)*	*0 (0%)*	*1 (3,8%)*	*1 (3,6%)*
NO PE at CTPA	*6 (100%)*	*9 (100%)*	*12 (100%)*	*16 (100%)*	*17 (100%)*	*19 (100%)*	*25 (96,2%)*	*27 (96,4%)*

Table 52: Comparison of D-dimer cut-offs for patients with suspected sepsis

Considering, instead, patients who do not meet the criteria of suspected sepsis, the following D-dimer cut-offs were applied: corrected for age, 1000, 1500, 1800 and 2000 ng/ml (*from figure 85 to figure 89*)

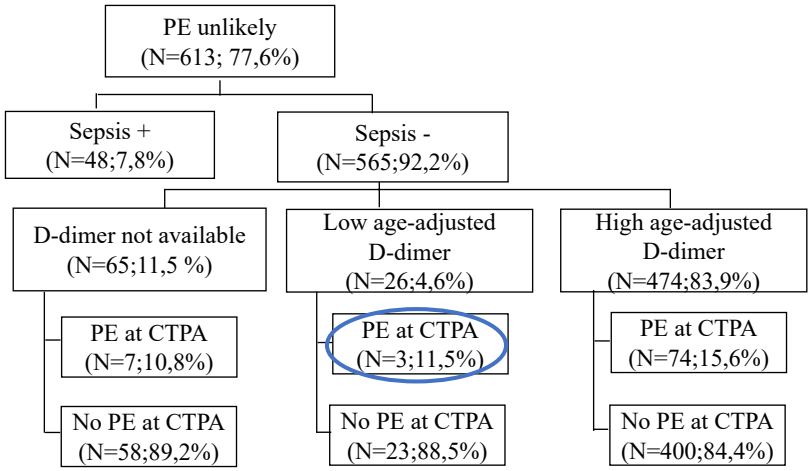

Figure 85: PE unlikely, No Suspected sepsis, age-adjusted D-dimer flowchart

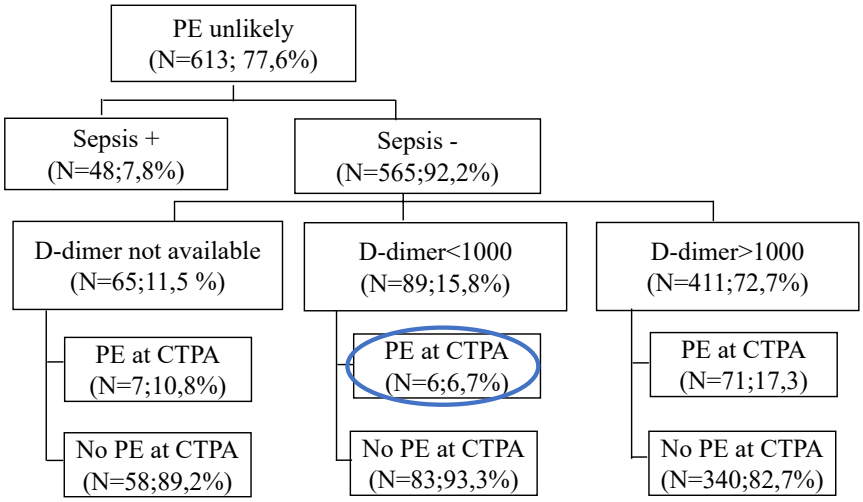

Figure 86: PE unlikely, No Suspected sepsis, D-dimer <1000 flowchart

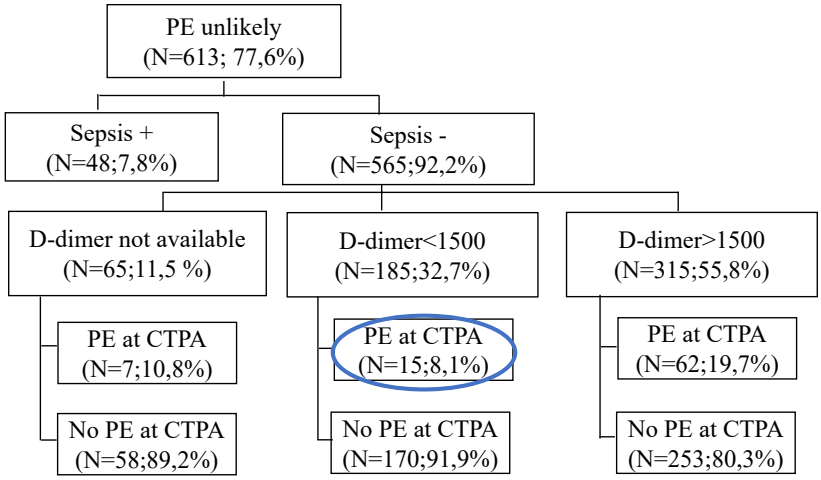

Figure 87: PE unlikely, No Suspected sepsis, D-dimer <1500 flowchart

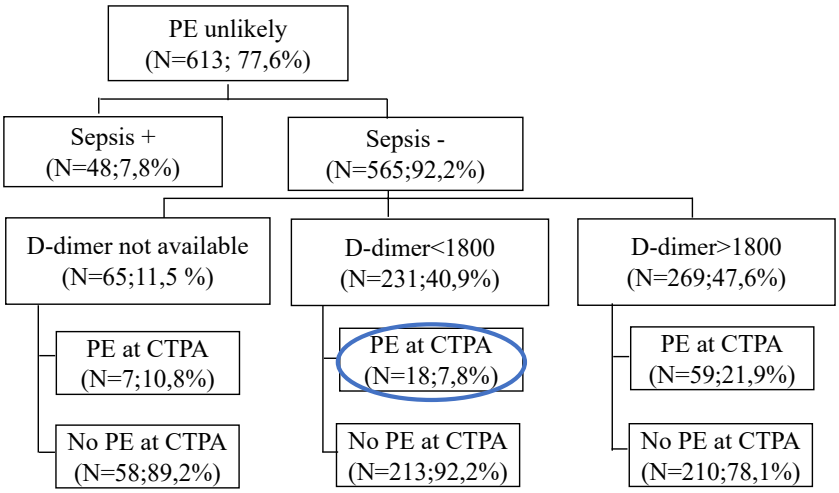

Figure 88: PE unlikely, No Suspected sepsis, D-dimer <1800 flowchart

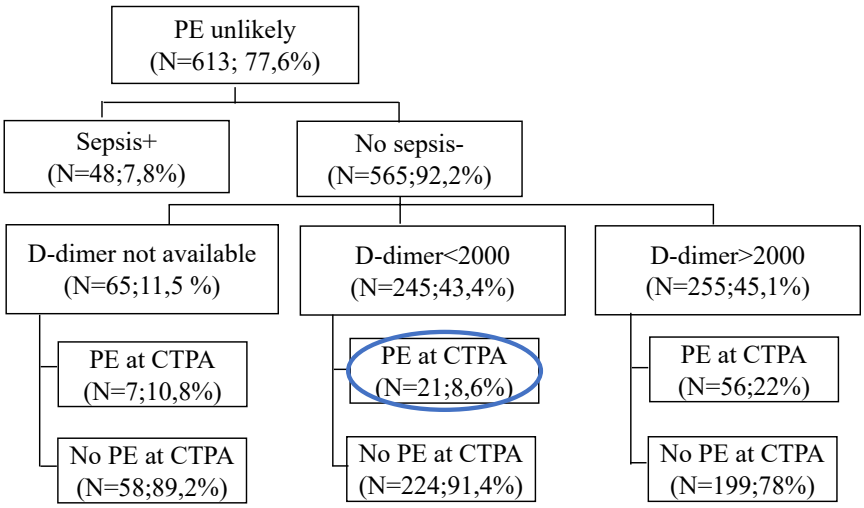

Figure 89: PE unlikely, No Suspected sepsis, D-dimer <2000 flowchart

In this case, the best diagnostic algorithm appears to be composed of a D-dimer cut-off of 3000 ng/ml for patients presenting a suspected sepsis (*figure 82*), and a cut-off of 1000 ng/ml for patients for whom this suspicion had been excluded (*figure 86*)

5. Discussion

5.1 General concepts

This monocentric retrospective study enrolled a consecutive series of patients who consulted the Emergency Department (ED) of the I.R.C.C.S University Hospital Policlinico San Matteo, Pavia, from January 1st 2021 to December 31st 2021. According to the inclusion criteria, enrolled patients all received CTPA in the diagnostic work-up, while in the Emergency Department, to exclude the clinical suspect of Pulmonary Embolism (n=889). Patients who received CTPA in the same window of time but for reasons different to the suspect of acute PE were not enrolled in the study (polytrauma, aortic dissection, pulmonary neoplasm – either primary or secondary, interstitial lung disease).

The objective of this study was to investigate the application of the diagnostic algorithm proposed by the 2019 ESC Guidelines on acute PE. This was done first for hemodynamically unstable patients (n=45) and then for stable ones (n=844), according to the guidelines. For the latter group, pre-test clinical probability was calculated through the Simplified Wells score, Original Wells score and Revised Geneva score.

Subsequently from this analysis, considering hemodynamically stable patients, different D-dimer thresholds from those contained in the guidelines were applied, combined to the same pre-test clinical probability score. Finally, an attempt to include the use of echocardiography in the diagnostic algorithm of hemodynamically stable patients was performed.

Patients for which D-dimer results were not found in the clinical charts were analyzed separately, as well as patients who underwent CTPA notwithstanding a value of PERC equal to zero.

Furthermore, the same analysis and flowcharts elaboration were repeated excluding patients who tested positive for Covid-19 in the ER and patients for which no nasopharyngeal swab for SARS-CoV-2 was obtained during the diagnostic work up. This is because, according to the literature, Covid-19 increases the risk of thrombosis,[112] but such risk would not have been quantified by classical pre-test probability scores. Therefore, considering Covid-19-negative only patients (n=628), a more accurate and homogeneous population was obtained.

5.2 Population analysis

Considering demographic data of the population under study (n=889), a slight majority of patients of female sex were found (56%), versus a male-sex population of 44% *(table 5)*.

The result of epidemiologic analysis is in line with 2019 ESC Guidelines data: mean age of our population was 68,4 ± 17,9, ranging from 16 to 100 years old (according to the inclusion criteria).

For each patient of the 889 included in the study, medical charts were analysed. In *table 6*, it is shown how the majority of patients had cardiovascular events in medical history (59.2%), less frequent but still relevant findings were history of cancer (7.7%) and respiratory diseases (17.1%). This is in line

with 2019 ESC Guidelines, for which cardiovascular diseases and their risk factors, together with cancer are recognized risk factors for acute PE. For what regards patients' chief complaints *(table 8)*, the most common one was by far dyspnea (33.7), which is in line with current literature, followed by chest pain (24.4%) and cough/fever/other infectious diseases signs (16.5%). This latter finding needs to be correlated with the current Covid-19 pandemic, for which, as already said, an increased incidence of thrombotic events is found in affected patients. Therefore, in current times, suspecting PE in a patient that comes with upper respiratory tract infection (URTI) symptoms is not completely incorrect – especially if hypoxia is more severe than what expected in a "classical" URTI or if it is accompanied by other signs, such as hypocapnia, that point toward PE as well. Physical examination was most frequently positive for respiratory abnormalities (40.3%), followed by no abnormalities at all (36.7% - this is not surprising considering that clinically, in many instances, PE is silent), as shown in *table 7*.Similar findings for all categories have been found when the subpopulations of haemodynamically unstable and stable patients were considered separately.

Considering now the analysis on D-dimer testing and clinical probability scores, *figure 21* shows how in patients without acute PE (0 on the y axis), D-dimer does not reach concentration higher than 2000 ng/ml. In fact, D-dimer concentration median for patients without acute PE is 1909 ng/ml for hemodynamically stable patients with PERC>0 and low risk Simplified Wells score and 1913 ng/ml for hemodynamically stable patients at low risk with PERC>0 and negative for Covid-19 *(figures 27 and 42)*. For this reason, considering this median, we analyzed as cut off both 1800 and 2000 ng/ml, other than 1000 and 1500 ng/ml *(paragraphs 5.4 and 5.5)*.
Figures 16 and 17 show how D-dimer testing alone does not allow to accurately predict the diagnosis of acute PE. *Figures 18 and 19* show the ROC curve for D-dimer testing sensitivity and specificity. From this graph, it is possible to conclude that highest specificity and sensitivity would be reached with a cut off of 3460 ng/ml which is, however, clinically unacceptable.
Figures from 8 to 13 represent the percental distribution of acute PE according to progressively higher classes of risk estimated by the three clinical probability scores (Simplified Wells, Original Wells and Revised Geneva). All three scores have shown to be powerful predictors of acute PE in high-risk patients but not so powerful if used alone for low-risk patients. This result is in line with the guidelines which stipulate that low-risk patients assessed with one or more of these scores, should proceed with D-dimer testing to reach adequate specificity.
Figures 14 and 15 shows a comparison of the three scores, from which it is possible to derive that Simplified Wells score has highest sensitivity amongst the three.

5.3 Hemodynamically unstable population analysis

For hemodynamically unstable patients, the diagnostic algorithm suggested by 2019 ESC Guidelines on acute PE was applied retrospectively, first for the overall population under study, then for Covid-

19 negative patients only *(tables 24 and 25)*. It is possible to observe that less than half of these patients (44.4%) underwent ultrasonography before recurring to CTPA, despite indications by guidelines *(figure 1)*. Nevertheless, the importance of bedside ultrasonography is confirmed because in this group, only patients with positive ultrasonographic findings had high probability of being diagnosed with acute PE at CTPA (33% considering all patients and 40% considering Covid-19 negative patients only). However, only a small number of patients (n=45) entered this branch of the study, rendering our findings less statistically significant.

In the relevant paragraph *(4.2 Haemodynamically unstable population analysis)*, the application of Simplified Wells score for patients with negative or not available ultrasonographic examination is reported, even if not suggested by the guidelines. With this regard, it seems that this stratification is not useful to identify hemodynamically unstable patients at high risk. Once more, the limited number of patients in this subgroup makes it difficult to reach statistically significant conclusions.

5.4 Haemodynamically stable population analysis

The diagnostic approach to hemodynamically stable patients with clinically suspected acute PE in the Emergency Department was investigated as well.

Initially, the guidelines' relevant algorithm was applied for this category of patients, according to which, the first step to reach diagnosis should be calculation of clinical probability scores *(table 2)*, provided PERC >0. In this study, all three scores were applied at first but then Simplified Wells score only was considered to build the diagnostic flowcharts, since statistical analysis showed that amongst the three it has highest sensitivity *(figures 14 and 15)*. Therefore, considering the latter scoring system, for each patient it was possible to calculate either a low risk "PE unlikely" or high risk "PE likely" clinical probability of acute PE. According to the guidelines, patient classified with "PE likely" should directly benefit from CTPA. On the contrary, "PE unlikely" patients should undergo further stratification through D-dimer testing, that whenever positive mandates CTPA whilst whenever negative allows PE rule-out. Latest guidelines recommend the application of an age-adjusted D-dimer cut off for patients older than 50 years old, with positivity corresponding to values higher than "age x 10 ng/ml". Even if a lower than threshold D-dimer value would allow PE rule-out without the need of CTPA, in day-to-day clinical practice, in some of these instances CTPA was requested nevertheless, as assessed by the attending physician.

In the study group, all hemodynamically stable patients with available D-dimer concentrations were considered and included in the flowchart *(figure 37).* It appeared that out of 613 "PE unlikely" patients, 31 had a negative age-adjusted D-dimer concentration. These patients underwent CTPA despite what indicated by guidelines and in 3 instances (9.7%) acute PE was diagnosed. It is possible to derive that this age-adjusted threshold is extremely specific but represents at the same time a very low cut off. This is highlighted by the high number of negative CTPA (n=431, 84.6%) belonging to the "PE unlikely but high age-adjusted D-dimer" group (n=509), for which a rule-out is not possible without

recurring to CTPA. With this D-dimer threshold, the number of undiagnosed acute PE would have been 3, 9.7% of the "PE unlikely, low age-adjusted D-dimer".
Considering hemodynamically stable Covid-19 negative patients only *(figure 52)*, even more significant results are obtained: only 1 patient (4.8%) belonging to the "PE unlikely, low age-adjusted D-dimer" would have remained undiagnosed. On the contrary, 84.1% of patients of the "PE unlikely, high age-adjusted D-dimer" obtained a negative result at CTPA.

Subsequently, inspired from a recent study which appeared on NEJM which applied in the same algorithm a D-dimer threshold of 1000 ng/ml,[46] and considering the "YEARS" clinical decision rule which also tries to increase the threshold to 1000 ng/ml for patients without the three chosen items (DVT, haemoptysis, PE as most likely diagnosis),[3] we tried to consider higher D-dimer thresholds to be applied, alternatively to the age-adjusted threshold.
The previously mentioned study published on NEJM found that out of 2017 patients with clinically suspected acute PE, 93% of them with low risk pre-test probability and D-dimer lower than 1000 ng/ml had a negative result at CTPA.
The objective of this study was to investigate whether similar results would be obtained in our population and to expand them further, increasing D-dimer threshold not only to 1000 ng/ml but to 1500, 1800 and 2000 ng/ml too.

- Cut off: 1000 ng/ml *(figures 38-53)*

It appeared that out of 613 "PE unlikely" patients, 97 had a D-dimer concentration lower than 1000 ng/ml, thus allowing a possible PE rule-out. Out of these 97 CTPA that could have been spared, 93.8% would have been negative whilst 6 diagnoses of acute PE would have been missed (6.2%). This result is in line with what has been found by the NEJM study.
Similar results were obtained applying the same flowchart to Covid-19 negative patients only. In this case, in 93.5% of patients "PE unlikely, D-dimer < 1000 ng/ml", CTPA would have been negative for acute PE whilst the number of undiagnosed patients would have been 3 (6.5%).
Excluding both Covid-19 positive and negative patients, this higher D-dimer threshold would have allowed to spare 15% of CTPA (97 out of 613) using the new cut-off compared to only 5% with age-adjusted cut-off (31 out of 613), without an increase in the underdiagnosed cases (9.7% for the age-adjusted threshold and 6.2% for the 1000 ng/ml threshold). These results are in line with findings published on NEJM.

- Cut off: 1500 ng/ml *(figures 39-54)*

It appeared that out of 613 "PE unlikely" patients, 197 had a D-dimer concentration lower than 1500 ng/ml, thus allowing a possible PE rule-out. Out of these 197 CTPA that could have been spared,

92.4% would have been negative (thus in total, it could have been possible to spare 182 CTPAs) whilst 15 diagnoses of acute PE would have been missed (7.6%).
Exactly the same percentages were obtained considering the population of Covid-19 negative only patients (out of 105 patients for which CTPA could have been spared, 7.6% would have been underdiagnosed).

- Cut off 1800 ng/ml *(figures 40-55)*

The same flowchart was repeated using 1800 ng/ml as a cut off to decide whether to proceed with CTPA or not for "PE unlikely" patients. In this case, out of 613 patients in the "PE unlikely" category, 247 would have had a lower than threshold D-dimer concentration, of which 18 (7.3%) with eventually positive CTPA (the underdiagnosed cases) and 229 (92.7%) negative CTPA. Better results were obtained with this cut-off considering Covid-19 negative patients only: out of 141 "PE unlikely" patients with D-dimer < 1800 ng/ml, 9 would have been underdiagnosed (6.4%) but 97 (93.6%) of CTPAs could have been spared.

- Cut off: 2000 ng/ml *(figures 41-56)*

Finally, the last threshold that was investigated is the one corresponding to D-dimer < 2000 ng/ml. This value is also very close to the median value of D-dimer for patients with CTPA negative for acute PE (which is 1800 ng/ml as previously mentioned), even if much higher than what currently suggested by guidelines.
It appeared that out of 613 "PE unlikely" patients, 262 had a D-dimer concentration lower than 2000 ng/ml, thus allowing a possible PE rule-out. Out of these 262 CTPA that could have been spared, 92% would have been negative (thus in total, it could have been possible to spare 241 CTPAs). However, 21 acute PE diagnoses would have been missed (8%). This is not surprisingly the "worst" result, considering that this cut-off is quite high.
In the Covid-19 negative patients subgroup, a minimally better result was obtained: out of a total of 152 patients with a D-dimer < 2000 ng/ml, there would have been 12 missed diagnoses, corresponding to 7.9%, and 140 spared CTPAs, corresponding to 92.1%.
Overall, the results of this evaluation are in accordance with those recently published on the NEJM and suggest as an ideal cut-off 1000 ng/ml.

5.5 Adding ultrasonography to the flowchart of hemodynamically stable patients

The use of ultrasonography, more specifically TTE, is recommended by guidelines to assess hemodynamically unstable patients before recurring to CTPA. Its application for hemodynamically stable patients is not routine yet.

In this study we introduced the use of multi-organ ultrasound, in particular TTE, CUS and LUS not only for the early detection of a possible PE but also for its exclusion if a differential diagnosis could be established in particular through LUS.
In this study, out of 790 hemodynamically stable patients, 613 were identified as low risk of acute PE with Simplified Wells score: 424 did not receive ultrasonography (TTE or CUS) whilst 189 did The latter group was further subdivided into those who had received LUS (20 patients) and those who had not (404 patients) *(figure 57)*.
Initially, patients who did not receive TTE/CUS were considered, differentiating those who received D-dimer testing and those who did not. Then, different D-dimer thresholds were evaluated: the age-adjusted one *(figure 58)*, as suggested by the guidelines, and subsequently higher cut offs such as 1000, 1500, 1800 and 2000 ng/ml (*figures 59 to 62*, for the same reasoning explained in *paragraph 5.2* and applied in *paragraph 5.4*). For this subgroup of patients who did not benefit from TTE or CUS, it appears that the highest sensitivity is obtained with a D-dimer threshold of 1000 ng/ml *(figure 59)*. With this threshold, only 3 acute PE would go undiagnosed (4.4%), but it would be possible to spare 65 negative CTPAs (vs with the age-adjusted D-dimer threshold, 2 acute PE would go undiagnosed but with many more negative CTPAs realized).
Regarding, instead, the group of patients who had received a LUS, no flowcharts were constructed for the different D-dimer cut-offs as it was a small group. Three PE were found in this group: two in Covid+ patients with a D-dimer of 890 and 1500 ng/ml respectively, the other one in Covid- with a D-dimer of 3900 ng/ml.

On the other hand, considering patients who did receive ultrasonography (n=189), different reasonings can be done according to its result:

- With positive TTE/CUS (n=43) the age-corrected D-dimer cut-off was applied; we found 0 values below this threshold (*figure 64*). A positive TTE/CUS increases the level of suspicion for acute PE, so that only a value lower than the cut-off of D-dimer corrected for age can allow, as per the Guidelines, the exclusion of acute PE without having a CTPA. A positive TTE/CUS also predicts an elevated D-dimer concentration and a diagnosis of acute PE on CTPA with a 42% probability. Therefore, no other D-dimer concentration cut-offs were applied in this subgroup.
- Patients with negative TTE/CUS (n=146) were further subdivided according to findings on LUS. Patients presenting a positive LUS (n=34) were analyzed by applying different cut-offs of D-dimer: first the D-dimer corrected for age, then 1000, 1500, 1800, 2000, 2500 and finally 3000 ng/ml (*figure 66-72*). The best cut-off proved to be 2000 ng/ml, as it would save 14 negative CTPA, without missing any diagnosis of acute PE (Table 49). Since our sample is rather small, it cannot be excluded that in the face of higher numbers the cut-off of D-dimer can be raised up to 2500/3000 ng/ml. In the latter cases, in fact, only one PE diagnosis would

be missed (with D-dimer 2200 ng/ml, sPESI=0), with the saving, however, of 21 negative CTPA. Negative TTE/CUS patients with a negative LUS (n=112) were also analyzed by applying different D-dimer cut-offs, as for the previous subgroup, but arriving up to the cut-off of 2000 ng/ml (*figure 73-77*). In this case the best cut-off is 1800 ng/ml. In fact, the relative flowchart shows that in this case the PE diagnoses missed would be 4 (8.5%), with the saving, however, of 43 negative CTPAs (Table 50).

Overall, by combining the flowcharts which performed the best in our analysis (*figures 59, 64, 70 and 76*), it is possible to obtain a single flowchart showing the application of the different cut-offs of D-dimer: 1000 ng/ml for patients without ultrasound exams, 1800 ng/ml for patients negative on ultrasound exams, and 2000 ng/dl for patients negative for TTE/CUS, but positive for LUS; finally age-adjusted D-dimer was the best in patient with TTE/CUS positive.

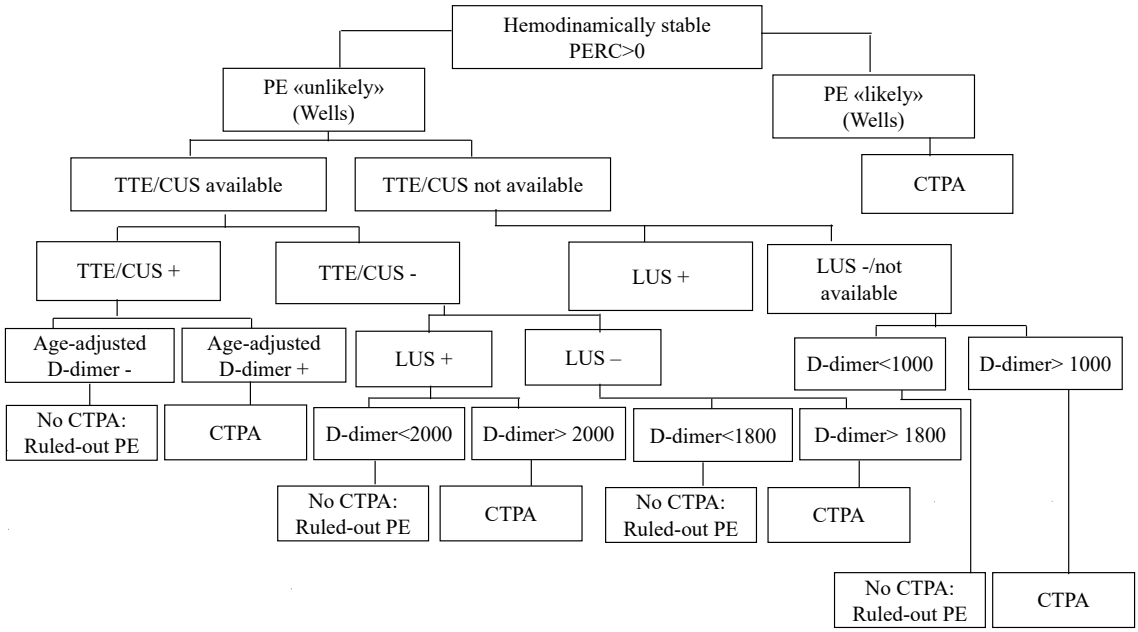

Figure 90: Proposed algorithm for hemodynamically stable PERC>0 patients

The application of the new diagnostic algorithm presented (*figure 90*), could have saved a total of 127 CTPAs, with the loss of only 6 undiagnosed acute PE (4.7%), reaching a sensitivity of 95.3%.
The relative saving is both economic and biological: considering that each CTPA costs 145 euros, the overall saving would have amounted to 18415 euros; moreover, exposure to ionizing radiation, which could cause stochastic damage to the individual, would have been avoided in 127 patients.
The 6 acute PE that would have been missed had the following characteristics:

- 2 acute PE were missed in the group with TTE/CUS not available, with negative LUS and with a D-dimer cut-off equal to 1000 ng/ml. Both had a sPESI=0, therefore a low risk of mortality at 30 days, and negative troponin values; age was 55 and 65 years, respectively; both tested positive for Covid-19 and with sub-segmental PE (one unilateral and one bilateral).

- The other 4 acute PE were missed in the negative TTE/CUS and LUS group, with a D-dimer cut-off equal to 1800 ng/ml. Two with an sPESI=0 (19 and 79 years), the other two with sPESI=1 (93 and 94 years, with elevated troponin levels); all tested negative for Covid-19, and among these 3 were subsegmental PE (1 unilateral and 2 bilateral) and one complete unilateral.

Finally, for patients who did not receive D-dimer testing, it is possible to derive that the probability to have acute PE is higher due to the clinical reasoning of the assessing physician or as a bias of the Wells score retrospective calculation.

5.6 Suspected sepsis: diagnostic algorithm to exclude acute TEP in hemodynamically stable patients

This subgroup includes 613 hemodynamically stable patients with a low Wells score and PERC>0. Among these, 48 patients (7.8%) presented clinical and laboratory signs of sepsis. Different D-dimer cut-offs were applied to the latter group of patients: D-dimer corrected for age, 1000, 1500, 1800, 2000, 3000, 3500, 4000 ng/ml (*figure 78 to 84*). The 4 PE identified in patients with D-dimer dosage show the following values: 3200,22000,35000,35000 ng/ml. This means that patients who had a D-dimer up to a value of 3000 ng/ml might not have CTPA performed. In particular, among the 48 patients with suspected sepsis, 11 presented a positive LUS for mono/bilateral interstitial syndrome and none had acute PE. Among the 11, 6 patients had a D-dimer < 3000 ng/mL. The significance of these evaluations reveals that the laboratory signs which lead to the suspicion of sepsis, together with a thoracic ultrasound which in turn suggests a differential diagnosis, allow us to attribute a good safety threshold to the cut-off of D-dimer equal to 3000 ng/ml. However, among these 6 patients, 2 would present positivity to TTE/CUS, consequently they should have undergone pulmonary CTPA. Below is the proposed diagnostic algorithm.

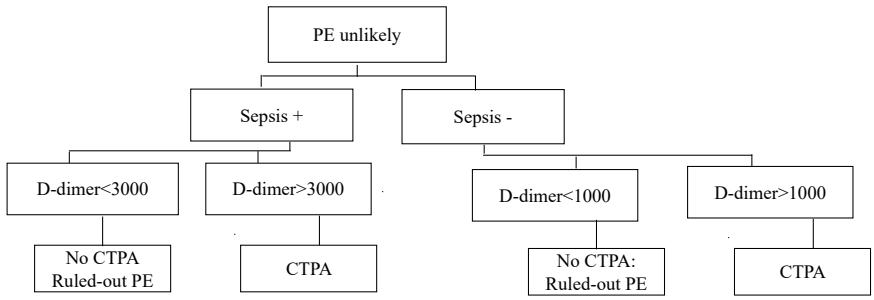

Figure 91: Proposed algorithm for patients with suspected sepsis

5.7 “PE unlikely” hemodynamically stable patients with no D-dimer

According to the guidelines, hemodynamically stable patients with low risk (“PE unlikely”) at pre-test clinical probability scores (for this study: Simplified Wells score) should undergo D-dimer

testing, to distinguish patients for which PE can be reasonably excluded without imaging and patients for which CTPA is needed.

In this study there were 73 patients in the hemodynamically stable group and 59 patients in the hemodynamically stable Covid-19 negative subgroup who did not receive D-dimer testing before recurring to CTPA, despite scoring 0 or 1 at the clinical probability score ("PE unlikely").

This is because they were already stratified as "high risk" through clinical assessment by the attending physician. For this reason, they underwent CTPA straightaway, as if they scored > 1 at Simplified Wells score.

In the paragraph *"4.5 "PE unlikely" haemodynamically stable patients with no D-dimer"*, all items of the score were analysed to investigate which were more predictive of PE in patients with a low-risk score. Overall, it seems that the following were correlated to higher risk of PE in patients with a Simplified Wells score = 1: HR > 100 bpm, signs of DVT and previous PE or DVT.

5.8 Hemodynamically stable patients with PERC = 0

Another scoring system that was considered in the study is "PERC" (Pulmonary Embolism Rule-out Criteria), which can be applied to hemodynamically stable patients with clinically suspected acute PE. This score allows to rule-out PE whenever it is equal to 0, without the need of testing D-dimer levels beforehand. Therefore, it is a precious tool that can assist emergency medicine physicians to decide whether to prescribe D-dimer testing or not.

In this study, 54 patients of the hemodynamically stable group and 21 patients of the Covid-19 negative hemodynamically stable subgroup scored 0 at PERC but underwent CTPA nevertheless. Only one out of the 54 was diagnosed with PE, despite PERC = 0. Considering the medical chart of this patient, it is possible to observe that he was consulting for chest pain and that he underwent CTPA due to a slightly increased D-dimer concentration (670 ng/ml) and recent onset of dyspnea. CTPA was not only able to diagnose PE but also to highlight a pulmonary mass that later was confirmed to be lung cancer. Had cancer been known beforehand, this patient would not have fallen into this group, since he would have scored > 0 at Wells (original and simplified), mandating D-dimer testing.

This result confirms the high sensitivity of these rule-out criteria. If they had been applied correctly, they would have indeed allowed sparing of 52 CTPAs.

5.9 Limitations of the study

The fact that this was a retrospective study implies that clinical probability scores were calculated retrospectively consulting patients' medical charts. Even if maximal efforts were put in trying to reconstruct them trustfully, at times it was impossible to find all information needed to assign a score to each item. For what regards Simplified Wells score, this was mostly the case for the item "PE is the most likely diagnosis", which was sometimes hard to attribute, without having examined the patient

firsthand. On the other hand, the fact that this study was retrospective allowed enrollment of quite a numerous consecutive series of patients.

Another limitation regards the paucity of reports about TTE CUS and/or LUS, both for hemodynamically stable and unstable patients, out of the total number of enrolled patients. The reason behind this, is that not all physicians perform these kinds of imaging in the emergency setting, and in other cases, even if performed, results are not reported on the charts due to forgetfulness or lack of time. Considering the usefulness of TTE, CUS and LUS as demonstrated by this very study, it would be interesting to replicate these results on a bigger scale.

Regarding CTPAs, on the other hand, it is worth mentioning that reports only contained qualitative and not quantitative descriptions, because the application of a score in these terms is not possible in the emergency setting. For this reason, it was not possible to accurately describe the precise extent of acute PE which would have gone undiagnosed with the new D-dimer thresholds, even if for the vast majority they were grossly reported as subsegmental PE.

One last limitation is that not all patients received a SARS-CoV-2 nasopharyngeal swab, rendering the population less homogenic, especially in cases such as the flowchart with ultrasonography, for which exclusion of such patients has not been possible in order not to lose statistical significance.

6. Conclusions

The aim of this study was to investigate the diagnostic approach to patients with clinically suspected acute PE in the Emergency Department. The large sample of 889 patients taken into consideration in the study made it possible to outline the objective.

For what regards hemodynamically unstable patients, TTE has confirmed its sensitivity in identifying patients who will benefit the most from CTPA, as strongly recommended by the 2019 ESC Guidelines on acute PE.

On the contrary, for hemodynamically stable patients, pre-test clinical probability scores have shown their power in identifying the population at high risk for PE, as demonstrated by high percentages of positive CTPA. However, it seems that the age-adjusted D-dimer concentration threshold proposed by the guidelines is too cautionary and limits a faster rule-out in many instances.

The integration of multi-organ ultrasound in the diagnostic algorithm associated with clinical-laboratory evaluations has proven to be particularly useful in order to be able to exclude the diagnosis of acute PE with a god level of confidence, in particular due to the identification of possible differential diagnoses. The diagnostic algorithm outlined in the flowcharts from our study could allow the avoidance of a good number of pulmonary CTPA with the relative advantages. In the future, bigger and prospective studies would be decisive in confirming such results.

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