SEMMELWEIS EGYETEM

DOKTORI ISKOLA

Ph.D. értekezések

3181.

SIMON ANDRÁS

Szív- és érrendszeri betegségek élettana és klinikuma

című program

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ESTIMATION OF ACUTE PULMONARY EMBOLISM PRETEST PROBABILITY USING ELECTROCARDIOGRAPHY AND HIGH SENSITIVITY D-DIMER TEST

PhD thesis

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Budapest

2025

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List of Abbreviations:

adj	adjusted
(-)LR	negative likelihood ratio
(+)LR	positive likelihood ratio
bpm	beats per minute
CI	confidence interval
CO2	carbon dioxide
COVID	coronavirus disease
CT	computed tomography
cv	cutoff value
DD(-)	D-dimer negative
DD(+)	D-dimer positive
ECG	electrocardiography, electrocardiogram
ELFA	enzyme-linked immunofluorescence assay
ELISA	enzyme-linked immunosorbent assay
ESC	European Society of Cardiology
FDA	Food and Drug Administration
FEU	fibrinogen equivalent unit
FN	false negative
FP	false positive
ISTH	International Society for Thrombosis and Haemostasis
LAD	left anterior descendent
LAFB	left anterior fascicular block
LBBB	left bundle branch block
mod.	modified
NICD	nonspecific intraventricular conduction disturbance
NPV	negative predictive value
O2	oxygen
orig.	original
PE(-)dg	pulmonary embolism negative diagnosis
PE(+)dg	pulmonary embolism positive diagnosis

PERC	Pulmonary Embolism Rule-out Criteria
PPV	positive predictive value
RBBB	right bundle branch block
rev.	revised
SaO_2	oxygen saturation
SD	standard deviation
SE	sensitivity
sim.	simplified
SP	specificity
TA	test accuracy

1.Introduction

1.1. Epidemiology of pulmonary embolism

Worldwide, venous thromboembolism is the third most common acute cardiovascular syndrome.(1) The annual incidence of pulmonary embolism per 100,000 population currently ranges from 39 to 115 and is increasing.(2) The incidence is almost eight times higher in people over 80 years of age than in people in their fifties. In aging societies such as Europe and Hungary, the burden of healthcare due to venous thromboembolism is expected to increase. In the United States, pulmonary embolism is responsible for at least 300,000 deaths a year, making it one of the leading causes of cardiovascular death. European figures are similar.(3) Of 454.4 million inhabitants in six European countries, 370,000 were attributed to venous thromboembolism. A third of these patients die suddenly or within hours of the acute event, before treatment is initiated or takes effect, and a high proportion are diagnosed after death.(4) In recent years, the prognosis of pulmonary embolism has improved. Analyses in European, Asian, and North American populations show that the rate of fatal pulmonary embolism is decreasing.(5-7) It is also possible that this improvement in the modern era is due to the overdiagnosis of sub-segmental or even non-existent pulmonary embolism cases to the total number of pulmonary embolism cases.(8) But probably mainly as a consequence of improved use of therapeutic options and stricter application of guidelines. Over the past forty years, the proportion of investigations confirming a working diagnosis of pulmonary embolism has fallen to one-tenth, from 50% to 5%, partly because investigators are more likely to think of venous thromboembolic disease and partly because non-invasive imaging tests are more widely available.(9)

1.2. Current diagnostic management of acute pulmonary embolism

Pulmonary embolism can occur as an incidental finding. However, in the vast majority of cases, it is most often suspected based on non-specific clinical signs (e.g. hypoxia, hypocapnia, tachycardia) and non-specific symptoms that initiate an

investigation. The classic symptoms of pulmonary embolism are dyspnea, hemoptysis, chest pain, which is sharp and stabbing in case of pleural involvement and rather compressive in central or extensive pulmonary embolism, presyncope, syncope; the latter may also indicate a visceral perfusion defect or hemodynamic instability. From the point of view of differential diagnosis, a broad spectrum of cardiac and pulmonary diseases and possible causes of pulseless electrical activity can be considered. A detailed investigation for pulmonary embolism in all such cases would be expensive, with potential adverse complications. Partly to avoid overuse of diagnostic tests when pulmonary embolism is suspected, the guideline recommends that the likelihood of it should be determined by considering predisposing factors, symptoms, and clinical findings before choosing a diagnostic strategy to confirm or exclude it. The pretest probability assessment can either be done by empiric clinical judgment, which may use electrocardiography (ECG), but has not been standardized to date or by validated prediction rules, which are standardized but do not take ECG into account. (10) Using currently accepted pretest probability determination methods, patients suspected of having pulmonary embolism can be categorized so that the resulting groups correspond well to the prevalence of proven pulmonary embolism. When applying a two-tier classification, the resulting pulmonary embolism likely/unlikely groups have a proportion of patients with proven pulmonary embolism of 30% and 12%, respectively. If a three-tier classification is followed, the proportion of patients with proven pulmonary embolism in the low, medium and high probability categories is 10-30-65%.(11)

The imaging tests used to diagnose pulmonary embolism differ in many ways. They differ in whether they are available at each center, their cost, and whether they have potentially harmful consequences, for example, whether they are invasive or involve radiation or contrast agent exposure. They also differ in their accuracy and the proportion of inconclusive results.

Pulmonary angiography, which used to be the gold standard, is costly, involves the highest radiation exposure, and is rarely performed because of the risk of invasiveness and the need for specialist equipment and facilities unavailable in all centers. In most cases, CT angiography is used, which is available in most centers, and can be performed relatively quickly. However, one should be aware of its limitations. It is inconclusive in 3-5% and false positive in 2%, especially in cases of low pretest probability. The

widespread use of CT angiography has led to a drastic increase in the incidence of pulmonary embolism with only a small decrease in mortality. This may be due to overdiagnosis derived from false positive cases. (8) Finally, pulmonary scintigraphy is considered in hemodynamically stable patients where contrast or irradiation is not appropriate.

Estimation of pretest probability is crucial in the diagnosis of acute pulmonary embolism because it affects the diagnostic strategy and the post-test probability as well, therefore, the clinical value of the result of an imaging modality or D-dimer test. Furthermore, it determines the initial therapeutic steps while the diagnostic workup is ongoing. It is essential that tests should be available to exclude the possibility of pulmonary embolism safely but with a specificity that ensures that, if positive, an indication for anticoagulation can be established.

1.2.1. Pretest probability estimation methods

In the past, until the end of the 1980s, it was mainly done based on physicians' clinical expertise, which nonspecific examinations, such as blood gas, X-ray, or electrocardiography, might have helped. However, the need for a tool of an objective and reproducible judgment has been recognized.

Several prediction rules have been created for this purpose. These take into account clinical symptoms and signs and also the presence of predisposing factors for venous thromboembolism. The European Society of Cardiology (ESC) guideline(3) encourages applying the use of the modified Wells Score(12) or the Revised Geneva Score(13) for the above objectives and the Pulmonary Embolism Rule-out Criteria (PERC)(14) to identify minimal-risk cases in which the likelihood of pulmonary embolism is so low that diagnostic testing is not even needed to be initiated.

1.2.1.1. Wells score

Originally, Wells et al. had developed an algorithm for the clinical model to determine the pretest probability of pulmonary embolism and categorize patients based on that.(15) The Wells score is calculated from a few weighted parameters of clinical symptoms, signs and risk factors. Specifically, clinical signs and symptoms of deep

venous thrombosis, pulmonary embolism is the most likely diagnosis, tachycardia (>100/min), immobilization or post-surgery state, hemoptysis, malignancy, history of pulmonary embolism or deep venous thrombosis and, notably, included a subjective element: “an alternative diagnosis less likely than pulmonary embolism". The Wells score was developed based on data from outpatients and inpatients.

In 2000, with the emergence of D-dimer assays after the revision of the rule, simplified versions were introduced. In the original version, there are ”low”, “moderate”, and “high” categories with scores (<2, 2-6, >6, out of 12.5, respectively), whereas the modified version uses only “likely”(>4) or “unlikely” (≤4/12.5) categories. In the simplified version(16), the weighting of the parameters is different and uses only a two-tier classification with a cut-off value of <2/7 in differentiating pulmonary embolism unlikely patients. The various scores have been validated in many settings and populations.

1.2.1.2. Geneva score

A working group from Geneva built a scoring system to standardize the assessment by avoiding including a subjective variable, such as the physician’s opinion. It was developed based on data from patients presenting at the emergency department. It consists of 8 parameters: older age, history of recent surgery, history of thromboembolism, partial pressure of CO2 in arterial blood, partial pressure of O2 in arterial blood, tachycardia and chest X-ray findings (platelike atelectasis/ elevation of hemidiaphragm). Points have been given to each variable. A cutoff of <5/16 is suggested for use to find patients with a low probability of pulmonary embolism. 5-8/16 points indicate a moderate probability, and >8/16 points indicate a high probability of pulmonary embolism.

A few years later, the score was revised (Revised Geneva score)(13) for easier practical implementation as the use of arterial blood gas analysis became less frequent. According to the results of the logistic regression analysis, the following parameters were included in the weighted scoring system: age above 65 years, prior deep venous thrombosis or pulmonary embolism, recent surgery or lower limb fracture, active malignancy, hemoptysis, heart rate (2 categories: 75-94/min or >95/min), lower limb pain on one side and concurrence of pain on lower-limb palpation and unilateral oedema. The score has been externally validated except for inpatients. Patients are divided into low-

(<4), intermediate- (4-10) and high-probability (>10) categories. A simplified version (Simplified Geneva score**)** has been validated to avoid miscalculations due to the different weighting of each parameter.(17) According to this version, patients with a score below 3/9 are considered unlikely to have a current pulmonary embolism.

1.2.1.3. PERC

The Pulmonary Embolism Rule-out Criteria (PERC) rule(14) has been created to exclude acute pulmonary embolism in the emergency room. It is applied to those with a very low probability. In the case of a patient <50 years of age, with a pulse <100/min, SaO_2 ≥95%, without hemoptysis, without estrogen use, no history of recent surgery or trauma, no prior thromboembolism or present signs of deep venous thrombosis, no further diagnostics are needed, acute pulmonary embolism can be ruled out. With a poor specificity of 27% in low-risk patients and 15% in very-low-risk patients, the rule was validated in two studies, which supported the possible exclusion of pulmonary embolism in patients who also met all the criteria.(18) (19) However, as the overall prevalence of pulmonary embolism in these studies was low, the results cannot be generalized.

1.2.2. The role of electrocardiography in the diagnosis of acute PE

ECG is one of the first tests to be performed in case of symptoms such as chest pain, dyspnea, presyncope or syncope, which are also the non-specific symptoms of acute pulmonary embolism. As it is painless, non-invasive, non-hazardous, relatively quick and inexpensive, it is widely available in healthcare institutions where the other diagnostic procedures for pulmonary embolism suggested by the guideline may not be.(20)

The current ESC guideline provides extensive details on the value and prognostic power of the information provided by imaging modalities (computed tomographic pulmonary angiography, lung scintigraphy, pulmonary angiography, magnetic resonance angiography, echocardiography, compression ultrasonography, computed tomography venography) and laboratory tests (D-dimer, B-type natriuretic peptide, N-terminal pro-B-type natriuretic peptide, troponin, heart-type fatty acid binding protein) in the diagnostic

arsenal for pulmonary embolism. In contrast, ECG is only briefly mentioned as a possible tool to assist non-standardized empirical clinical judgment.

As highlighted in a 2015 consensus recommendation, ECG as a prognostic clinical tool was conspicuously absent and has not been included in the ESC guideline since.(21) In the 2018 guidelines for management of venous thromboembolism: diagnosis of venous thromboembolism of the American Society of Hematology electrocardiography is not mentioned.(22) The Scientific Statement From the American Heart Association on Management of Massive and Submassive Pulmonary Embolism, Iliofemoral Deep Vein Thrombosis, and Chronic Thromboembolic Pulmonary Hypertension includes a short subsection with an unstructured list of specific ECG abnormalities that could help identify patients at risk of adverse outcomes and correlate with worse short-term prognosis in acute pulmonary embolism. (23)

1.2.2.1. The Daniel ECG score

There was an effort to determine the prognosis of patients with pulmonary embolism, for which several scoring systems have been developed. However, none used ECG abnormalities other than the tachycardia, which, strictly considered, is not actually an ECG abnormality. Historically, the study by Daniel et al(24) in 2001 is regarded as a landmark, as no previous study had compared the frequency of ECG abnormalities observed in pulmonary embolism between patients with and without confirmed pulmonary embolism. They developed an ECG scoring system to distinguish patients with massive pulmonary embolism from those with milder pulmonary embolism and those without pulmonary embolism. (Table 1) The scoring system was validated in a group of 85 patients, of whom 34 had pulmonary embolism ruled out, 51 had confirmed acute pulmonary embolism, of which 25 were fatal. They found that a score of 10 or higher out of a total of 21 identified severe pulmonary hypertension (systolic pulmonary artery pressure >50 mmHg) with 23.5% sensitivity and 97.7% specificity. The severity of pulmonary hypertension is associated with the presence of right ventricular dysfunction in pulmonary embolism.(25) When examined in patients without pulmonary embolism, there was no gradual increase in the Daniel ECG score by the degree of systolic pulmonary hypertension.

Table 1 The Daniel-ECG-score components and their scoring weightings

Characteristics	Score
Tachycardia (>100 bpm)	2
Incomplete right bundle branch block	2
Complete right bundle branch block	3
T wave inversions in leads V1-V4	4
T wave inversion in lead V1 (mm)	
<1	0
1-2	1
>2	2
T wave inversion in lead V2 (mm)	
<1	1
1-2	2
>2	3
T wave inversion in lead V3 (mm)	
<1	1
1-2	2
>2	3
S wave in lead I	0
Q wave in lead III	1
Inverted T wave in lead III	1
If all of S1Q3T3 are present	2

Since then, several studies have been conducted on the applicability of the Daniel ECG score.(26-29) Overall, it appears that the Daniel score may be suitable for predicting right ventricular dysfunction in acute pulmonary embolism. However, there is conflicting evidence that it is indeed capable of predicting complicated in-hospital courses, in-hospital or 12-month mortality or clot burden score, a parameter which can be objectified by CT angiography. In order to improve clinical applicability, various cut-off values of the Daniel ECG score were combined with other parameters. For example, in combination with arterial blood gas results and shock index, it has been shown to be useful in predicting right ventricular dysfunction or severe cases of pulmonary embolism.(30) In combination with pulse oximetry-measured hypoxemia and serum troponin levels, it has been shown to be equivalent to echocardiography in predicting poor outcomes in normotensive pulmonary embolism cases. (31)

1.2.2.2. The TwiST score

Another ECG score, the TwiST score(32), has been developed, which is faster and easier to use than the Daniel score. Its advantage may be identifying patients who developed right heart strain and are consequently at risk of short-term (<5 days) adverse clinical events, with a slightly higher sensitivity and specificity than the Daniel score. In its development, three ECG abnormalities were included in the scoring system, all independently associated with right heart strain. T-wave inversion in V1 through V3 is worth 5 points, S-wave in I leads is worth 2 points, and tachycardia (>100/min) is worth 3 points. A score of 5 indicates patients who should be monitored closely and screened further with imaging (e.g. echocardiography) for risk stratification, and a score of 2 or below indicates unlikely right heart strain.

1.2.2.3. Current controversies

Later, many studies investigated the association of other ECG signs and those included in the Daniel score with pulmonary embolism's short- and long-term prognosis.(33, 34) The meta-analyses of these studies suggest that several ECG components can be identified to predict clinical deterioration, circulatory shock in patients with pulmonary embolism and in-hospital mortality. A revised scoring system would have to be developed to predict the outcome and severity of acute pulmonary embolism. Moreover, the potential role of ECG in determining pretest probability and ruling out pulmonary embolism needs to be clarified. According to the European Society of Cardiology's current guidelines, ECG is not recommended for the diagnosis of acute pulmonary embolism. Nevertheless, in our clinical experience, we have found the ECG helpful in diagnosing pulmonary embolism.

1.2.3. The diagnostic role of D-dimer in acute pulmonary embolism

D-dimer is a protein fragment, one of the fibrin degradation products that is cleaved by plasmin during fibrinolysis, the breakdown of blood clots. It consists of two D-domains that are cross-linked by covalent binding mediated by factor XIII during clot formation. It works as a unique epitope to which antibodies bind during laboratory tests to detect whether the blood clotting system produces thrombin, i.e. whether thrombosis

can be detected. These laboratory tests follow different methods, use different units of measurement and are not standardized, so they are not considered equivalent.(35) The most commonly used procedures today are enzyme-linked immunosorbent assays (ELISA), enzyme-linked immunofluorescence assays (ELFA), latex-enhanced immunoturbidimetric assays, and whole-blood point-of-care assays. They differ in whether they require a trained specialist, how automated they are, whether they need a central laboratory or can be performed at the bedside, and whether they give qualitative or quantitative results.(36) A not insignificant consideration in their everyday use is their different cost aspects, and the time it takes to perform the test, ranging from a few minutes to 4 hours.(37) Systematic reviews and meta-analyses of studies that have evaluated D-dimer assays in the diagnosis of venous thromboembolic diseases report a relatively wide range of values, with sensitivity ranging from 69-97% and specificity from 43-99%. Generally, tests with high sensitivity only have moderate specificity, and tests with higher specificity have lower sensitivity.(38) Therefore, the results of a study using one method cannot automatically apply to another method.

At low concentrations, D-dimer can be measured under physiological conditions. Levels increase with age, even in healthy individuals.(39) In everyday practice, beyond venous thromboembolic diseases and disseminated intravascular coagulation, increased D-dimer level is expected in all other processes involving fibrin overproduction and degradation; for example, in other cardiovascular diseases such as coronary artery disease, ischemic conditions, aortic dissection, abdominal aortic aneurysm, and if there is an atrial thrombus in atrial fibrillation. Elevated D-dimer levels are also observed in malignant diseases, infectious diseases, liver diseases, injuries, bleeding, recent surgery, pregnancy, inflammatory diseases, renal failure and many other conditions.(36) D-dimer levels are nearly always elevated in acute venous thromboembolism. Higher concentrations may be detected in the presence of more extensive thrombus or embolic masses(40) and in cases of shorter-standing symptoms or complaints.(41) Levels decrease with longer-standing clinical symptoms or fall significantly with the initiation of anticoagulant therapy.(42)

1.2.3.1. D-dimer for ruling out venous thromboembolism

The primary purpose of the D-dimer test would be to rule out venous thromboembolism without further imaging. The level above which the result of a particular assay is considered positive, i.e. abnormal, or negative, i.e. normal, is determined by the manufacturer of the particular D-dimer assay. The basic principle in setting the cut-off value is to maximize the test's sensitivity to ensure that all thromboembolisms are detected ideally.(43) Nevertheless, as mentioned earlier, D-dimer levels can be elevated in many cases without venous thromboembolism and also increase with age, so the use of a fixed universal cut-off value reduces the clinical applicability of the test. The high sensitivity chosen is associated with a lower specificity, resulting in more false-positive cases, i.e. more cases will still require further imaging. To overcome this problem, efforts have been made to define different cut-off values in various clinical settings with different prevalence of venous thromboembolism. It was proposed to adjust the threshold for age by multiplying the age by 10 μg/L for patients over 50 years of age and leaving the threshold for patients under 50 at 500 μg/L.(44) To adapt various D-dimer levels for different pretest-probability, in a prospective trial (YEARS), they combined three elements of the Wells score (deep venous thrombosis, hemoptysis and if pulmonary embolism is the most likely diagnosis). If none were present, the D-dimer level cut-off value was set to <1000 μg/L. This method is validated for both inpatients and outpatients, though not for those already on anticoagulant treatment or showing hemodynamic instability. It also has a pregnancy-adapted version. Its weakness is including a subjective component, like the Wells score. The results of studies using different age-adjusted and pretest probability-adapted cut-off values showed that the proportion of patients referred for imaging could be reduced while preserving safety.(45-47)

According to the current guidelines, a high-sensitivity D-dimer assay is recommended for outpatient and emergency care. The test should be performed only in non-high pretest probability or pulmonary embolism-unlikely patient groups. At the same time, the use of cut-off values adjusted for age and adapted for pretest probability should be considered, though standing at a lower recommendation level.(3) In patient groups with a high pretest probability (e.g. patients with malignant disease, post-surgery, immobilized patients), many factors are present that can cause an increase in D-dimer levels per se, so it is unlikely that they will have negative results. And if positive, imaging

is needed anyway. To date, it is still uncertain whether a negative D-dimer test can safely exclude venous thromboembolism in this subgroup, as most studies have focused on patients with low to moderate pretest probability. The present guideline does not recommend D-dimer testing in high pretest probability- or pulmonary embolism-likely patient groups.

1.2.3.2. The role of D-dimer in the diagnosis of venous thromboembolism beyond the exclusion

D-dimer testing is most commonly performed to rule out venous thromboembolism. However, there have also been attempts to establish the positive predictive value of elevated D-dimer levels in diagnosing pulmonary embolism. Smaller case-control studies found that a 1.5-fold increase above normal value was suggestive of pulmonary embolism in inpatients and patients in emergency departments. There is also evidence that CT angiography should be considered for patients with significantly elevated D-dimer levels (i.e. more than four times the normal level), even in cases with a low pretest-probability for pulmonary embolism.(48) However, at present, elevated D-dimer level is not recommended to set the diagnosis of pulmonary embolism per se, but its prognostic significance in predicting venous thromboembolism recurrence is recognized. In acute thrombosis, the D-dimer level increases and then falls spontaneously over time, but more markedly with initiation of anticoagulant treatment. In patients in whom, without an obvious provoking factor, D-dimer levels do not normalize after 3 months but remain elevated, the risk of recurrence of venous thromboembolism is doubled if anticoagulation treatment is withdrawn. For those D-dimer is included as a factor in prediction rules developed for this purpose to assess the risk of recurrence of a new event but is not recommended as a stand-alone test.(49, 50)

2. Objectives

2.1. Objective 1

To develop an ECG score as a tool in the diagnostic process of acute pulmonary embolism, assess its performance in determining the pretest probability of pulmonary embolism and compare it with the most widely used prediction rules.

2.2. Objective 2

To assess whether a high-sensitivity D-dimer test can be used as a stand-alone test to exclude acute pulmonary embolism, independent of the pretest probability of acute pulmonary embolism as determined by clinical prediction rules.

3. Methods:

Three studies were carried out.

3.1. Retrospective pilot study

First, we performed a retrospective analysis. ECGs were collected from 136 patients treated at the 3rd Department of Internal Medicine of Semmelweis University and the Department of Cardiology, Saint Imre University Teaching Hospital for confirmed pulmonary embolism between 2012 and 2017. Paper-based 12-lead ECGs were recorded as part of the routine clinical assessment at a paper speed of 25 mm/s and 10 mm/mV amplification. By analyzing the ECGs of these patients, we developed a new ECG score for the diagnosis of acute pulmonary embolism.

The rationale for selecting the ECG signs to be tested is explained in detail in the discussion section. In brief, the development of the score was guided by the aim to select and assort previously known morphological ECG signs that best represent the cardiac effects of the main pillars of the pathogenesis of acute pulmonary embolism. Namely, right ventricular dilatation from acute pulmonary arterial hypertension and consequent right ventricular ischemia and right-sided intraventricular conduction disturbances. Another main guiding concept was followed in developing the ECG scoring system, which was extended from a previous observation. Kosuge et al. pointed out that concomitant acute anteroseptal and inferior T inversions are not indicative of acute coronary syndrome but rather of acute pulmonary embolism. (51) By reviewing the literature, we found it plausible that this observation could be extended to suggest that other ischemic abnormalities and conduction disturbances occurring simultaneously in leads representing the right ventricle also indicate acute pulmonary embolism. Each ECG characteristic was considered to count for 1 point based on approximately equal importance(52), with similar sensitivity, specificity, positive predictive value and positive likelihood ratio.(53) Considering the extent of the underlying pathology, the ECG score was weighted to give more points if an ECG abnormality was observed in more than one typical lead and/or if more than one ECG abnormality was observed simultaneously in the lead.

The following ECG signs were included in the score:

- Primary ST elevation in aVR, in any of leads V1-3, in any of the inferior (II, III, aVF) leads, (Figures 2-4)
- T wave inversion (i.e. negative T) in any of leads V1-3, in any of the inferior leads, (Figures 3-4)
- QR or qR in V1,
- R/S> 1 in V1, (Figure 1)
- Q wave in any of the inferior leads, (Figures 1-3)
- novel incomplete or complete right bundle branch block, (Figure 3)
- r' wave terminally in aVR, (Figures 1-2 and 4)
- S1S2S3 syndrome, (Figure 4)
- S wave in I, or in aVL, or in any of leads V5-6, (Figures 2-3)
- slurring in the terminal part of the QRS or fragmented QRS in aVR, in any of leads V1-3 or in any of the inferior leads.(Figures 1-3)

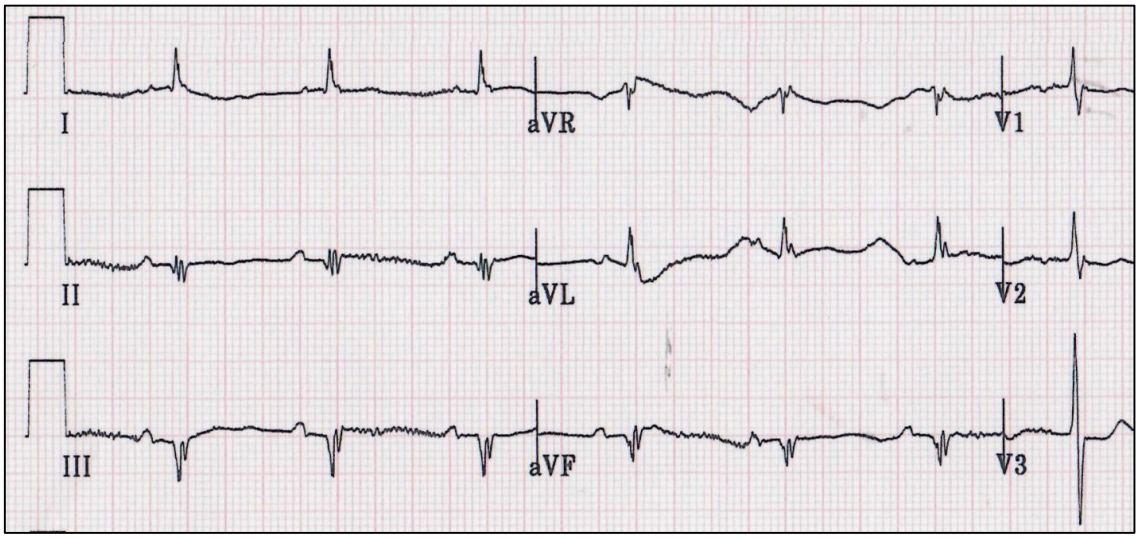

Figure 1 ECG showing Q and fragmented QRS in the inferior leads and aVR, r' wave terminally in aVR and R/S> in V1

The isoelectric line was defined at the TP level and was compared to the ST segments evaluated 80 ms after the J-point. Intraventricular conduction disturbances have been defined following the recommendations of the 2009 American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology, the American College of Cardiology Foundation, and the Heart Rhythm Society guidelines.(54) Fragmentation was determined following the definition of Macfarlane et al.(55), and slurring, according to Das et al.(56)

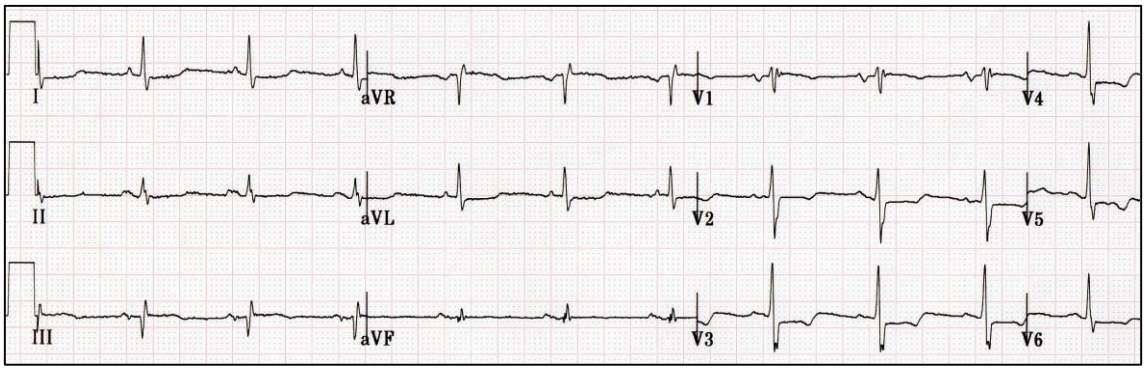

Figure 2 ECG showing S wave in I and in leads V4-6, Q and ST elevation in lead III, ST elevation and r' wave terminally in aVR, fragmentation in V1, slurring in the terminal part of the QRS in leads II and in V2-3

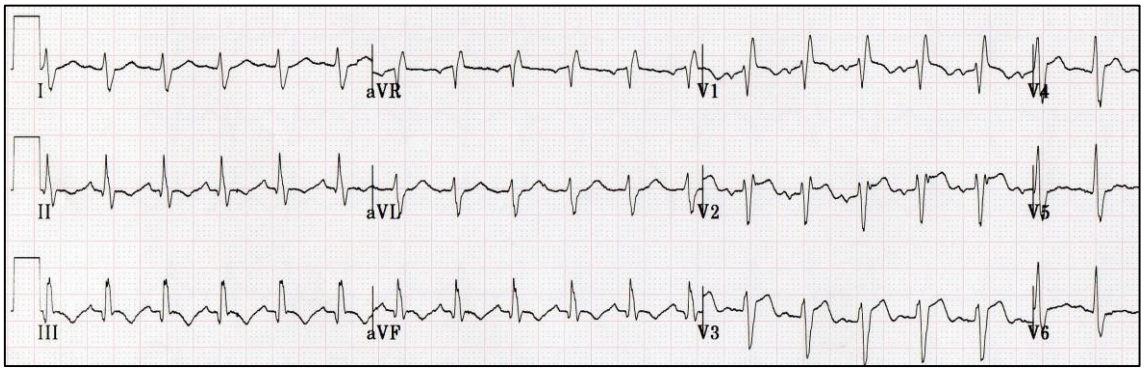

Figure 3 ECG showing right bundle branch block, Q and T-inversion in the inferior leads, ST elevation in leads V1-3, slurring in the terminal part of the QRS in aVF and V3

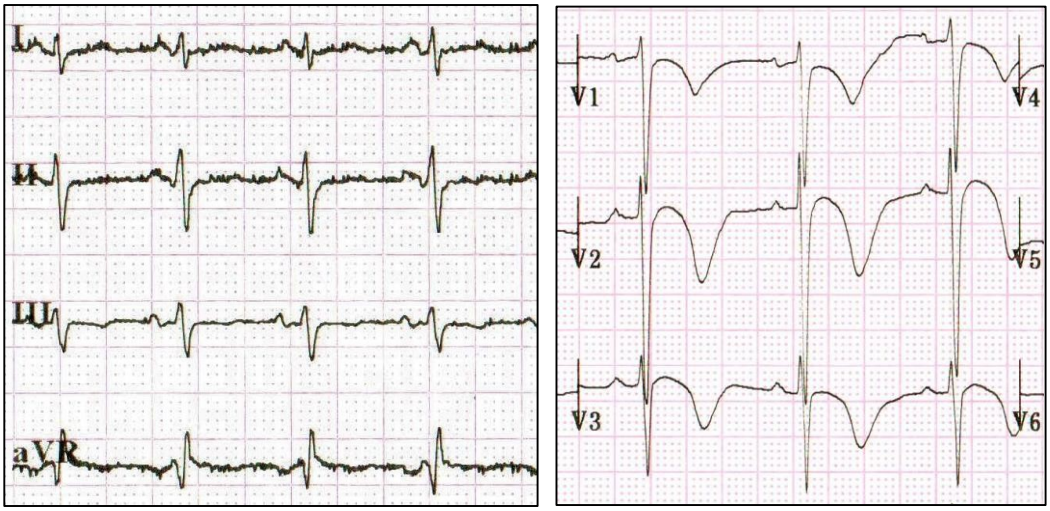

Figure 4 The first ECG panel showing S1S2S3 syndrome and r' terminally in aVR. The second ECG panel showing T inversion in leads V1-3 and ST elevation in leads V2-3

A separate scoring was created for patients with right bundle branch block, where T wave inversion in precordial leads is secondary to intraventricular conduction disturbance and is not a primary abnormality.

From the individual ECG alterations, we constructed a four-step ECG score, and with the help of that, we evaluated the ECGs of the retrospective pilot study cohort. A diagnosis of *acute pulmonary embolism-unlikely* was intuitively established with a score of less than 3, and an *acute pulmonary embolism-likely* was a score of 3 or more.

3.2. Prospective cohort

Despite the very good test accuracy results obtained in the retrospective pilot study cohort with the developed four-step ECG score, with the expectation that it can further improve the positive predictive value and specificity of the method, we added a fifth criterion, in which the presence of ST elevation or QS, QR morphologies in the right-sided chest leads (RV4-6) (Figure 5) was worth a further 1 point. This way, the maximum ECG score was 9 for patients with right bundle branch block and 10 for all others. *Acute pulmonary embolism-likely* diagnosis was established intuitively at ≥4. The developed new five-step ECG score is shown in Table 2; for patients with right bundle branch block, it is shown in Table 3.

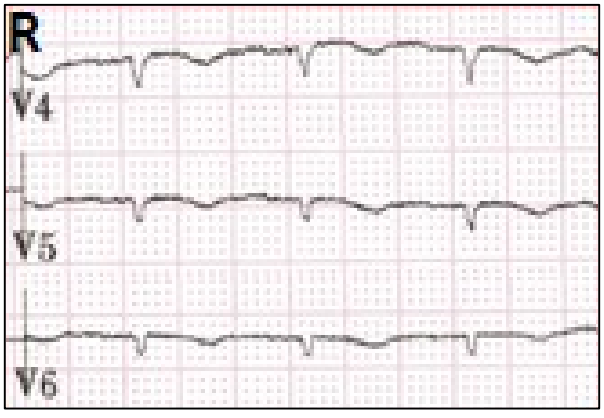

Figure 5 ECG showing QS in leads RV4-6

Table 2 Five-step ECG scoring sheet for patients without right bundle branch block (57)

	ECG signs		**points**
1	S1QinferiorTinferior or S1+T wave inversion in leads V1-3	If any two are present simultaneously	1
		If three are present simultaneously	2
2	Primary ST-segment elevation in the inferior leads and/or lead aVR and/or leads V1-3 or T wave inversion in the inferior leads and/or leads V1-3	Either ST elevation or T wave inversion in one of the locations	1
		Either ST elevation or T wave inversion in 2 or more of the locations OR both ST elevation and T wave inversion in one location	2
		ST elevation in 2 or more of the locations and T wave inversion in one location OR ST elevation in one location and T wave inversion in 2 or more of the locations	3
		Both ST elevation and T inversion in 2 or more locations	4
3	QR or qR complexes or R/S>1 in lead V1	If any present	1
4	Terminal r' wave in lead aVR and/ or S1S2S3 syndrome and/or S wave in leads aVL, V4-6 and /or fragmented or slurred QRS complexes in lead aVR and/or in leads V1-3 and/or inferior leads	If only terminal r' wave in lead aVR and/ or S1S2S3 syndrome and/or S wave in leads aVL, V4-6 OR only fragmented or slurred QRS complexes in lead aVR and/or in leads V1-3 and/or inferior leads	1
		If terminal r' wave in lead aVR and/ or S1S2S3 syndrome and/or S wave in leads aVL, V4-6 AND fragmented or slurred QRS complexes in lead aVR and/or in leads V1-3 and/or inferior leads	2
5	Primary ST-segment elevation and/or QS or QR complexes in leads RV4-6	If present	1

Table 3 Five-step ECG scoring sheet for patients with right bundle branch block (57)

	ECG signs		**points**
1	Qinferior or primary Tinferior	If either present	1
		If both are present simultaneously	2
2	Primary ST-segment elevation in the inferior leads and/or lead aVR and/or leads V1-3 or T wave inversion in the inferior leads	Either ST elevation or T wave inversion in one of the locations	1
		ST elevation and T wave inversion in the inferior leads OR ST elevation in 2 or more of the locations	2
		ST elevation in 2 or more locations and T inversion	3
3	QR or qR complexes in lead V1	If any present	1
4	Proven new RBBB and/or fragmented or slurred QRS complexes in lead aVR and/or in leads V1-3 and/or inferior leads	If only new RBBB OR only fragmented or slurred QRS complexes in lead aVR, leads V1-3 and/or inferior leads	1
		If new RBBB AND fragmented or slurred QRS complexes in lead aVR and/or in leads V1-3 and/or inferior leads	2
5	Primary ST-segment elevation and/or QS or QR complexes in leads RV4-6	If present	1

RBBB, right bundle branch block

In our second, prospective study, we assessed the diagnostic accuracy of the ECG score developed in the first study. We included 149 consecutive patients over a one-year period (from November 2017 to October 2018) at the 3rd Department of Medicine of Semmelweis University and the Saint Imre University Teaching Hospital, presenting with characteristic symptoms of acute pulmonary embolism: chest pain, dyspnea, collapse or syncope, and hemoptysis, who had an electrocardiogram with right-sided leads within 7 days of symptom onset. Patients who did not have an ECG with right chest leads in the emergency department had them done on admission. Data on the variables of the Wells and Geneva scores and imaging and relevant laboratory test results were extracted from the electronic medical records of each patient. Acute pulmonary embolism was considered confirmed or excluded based on one or more of the following: pulmonary CT

angiography, lung scintigraphy and high-sensitivity ELISA D-dimer test. The D-dimer was also evaluated with a fixed cut-off (<500 μg/L) and an age-adjusted cut-off (<500 μg/L in subjects younger than 50 and age multiplied by 10 μg/L above 50). A 3-month follow-up was performed via telephone interviews for patients with excluded acute pulmonary embolisms based on the D-dimer test. Exclusion criteria were: the presence of a left bundle branch block on the ECG, persistent right ventricular pacemaker drive, and the underlying cause of the symptoms not identifiable. The ECGs of two patients could not be included in the ECG analysis, one due to the absence of evaluable right-sided leads and the other due to an atypical left bundle branch block. Thus, ECG scores were finally evaluated in 147 patients using our previously developed ECG score (Table 2, Table 3) and the Daniel score (Table 1) analyzed by two experts with extensive experience in ECG analysis, blinded to the diagnosis of pulmonary embolism. If the diagnoses made by the two specialists using each ECG score differed (22 cases with the new ECG score and 5 cases with the Daniel ECG score), the cases were re-evaluated. Discrepancies were resolved by consensus. Subsequently, we assessed the diagnostic value of the two types of ECG scores, the various Wells and Geneva scores, and the D-dimer test in the available cases to estimate the pretest probability of acute pulmonary embolism.

3.3. Retrospective study of pretest probability evaluation with our modified ECG score and high sensitivity D-dimer test

3.3.1. Setting and participants

Third, we conducted a retrospective study of 1270 consecutive patients with no current anticoagulation treatment undergoing CT angiography at the Emergency Department of the Saint Imre University Teaching Hospital between March 2020 and July 2021 for suspected acute pulmonary embolism presented with its characteristic symptoms and complaints. The medical records of all patients were reviewed, and the CT scan results, the parameters corresponding to each criterion of the Wells scores and Geneva scores, the D-dimer results and their electrocardiograms, if available, taken within 7 days of the onset of symptoms, were individually extracted. Patients with a negative D-dimer

test result were followed up for 3 months for possible venous thromboembolic events. Those rehospitalized during this time by reviewing their patient records and the others by telephone interview.

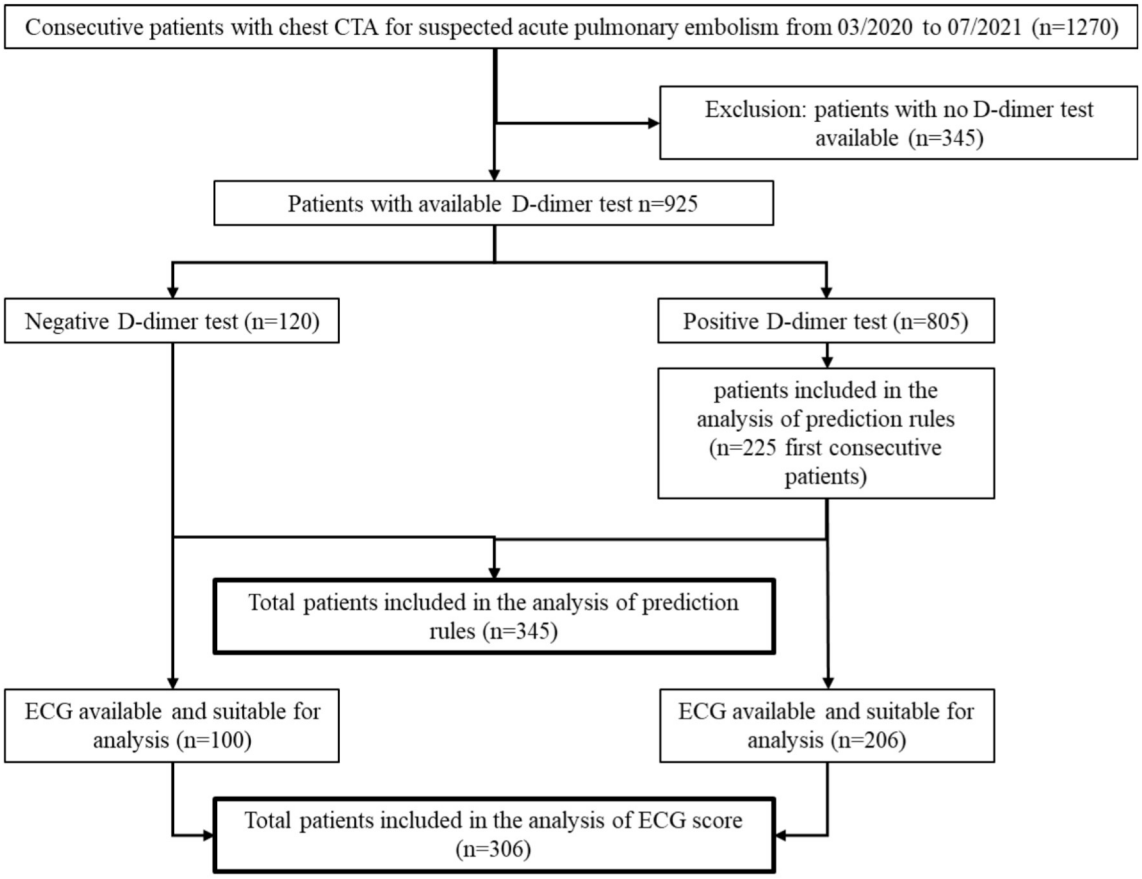

Figure 6 Design of the third study

3.3.2. Imaging and laboratory tests

CT angiography was performed with a 256 Slice GE Revolution CT scanner. D-dimer tests were performed by latex-enhanced immunoturbidimetric assay (D-dimer FS test, DiaSys Diagnostic Systems GmbH, Holzheim Germany) with a sensitivity (provided by the manufacturer) of 93% (89-95). According to the manufacturer's recommendation, test results were negative if they were below <500 µgFEU/L in subjects younger than 50 and below the age-adjusted D-dimer cut-off value (age multiplied by 10 in µgFEU/L) in all other subjects. Of the 1270 patients, 925 patients had a D-dimer test available.

3.3.3. Evaluating the pretest probability of acute pulmonary embolism

The 120 patients with negative D-dimer test results and the first consecutive 225 D-dimer positive patients were evaluated to determine the pretest probability of acute pulmonary embolism by different Wells scores and Geneva scores. According to the two-tiered approach, *acute pulmonary embolism-likely* was defined by an original Wells score ≥5 and a revised Geneva score ≥6. According to the three-tiered classification, the low, medium, and high pretest probability of acute pulmonary embolism was determined at the values of <2, 2-6, ≥7, and <4, 4-10, ≥11 for the original Wells score and the revised Geneva score, respectively. We also determined the pretest probability of acute pulmonary embolism using a modified version of the new ECG score we developed previously in our first study. Since, in most cases, ECGs of patients with right-sided chest leads were not available in this retrospective study, we had to omit criterion 5 from our original ECG score. Compensating for this, to preserve the diagnostic accuracy of our ECG score, we have included two additional, previously not used ECG signs in criterion 3 instead, which also reflect well the effects of acute pulmonary embolism. One of the two new signs included was low voltage, defined as the maximum peak-to-peak QRS amplitude not exceeding 0.5 mV in either limb lead. The other was an R/S ratio <1 in the V5 lead (Figure 7). Further modifications were made as follows: if T negativity was present in the inferior or V1-3 leads with an S wave in lead I, or if inferior T wave negativity was associated with an inferior Q wave, it was only considered in criterion 1 but not in step 2 (Table 4). ECGs were recorded and analyzed using the same methods and definitions as in the former study. We have also created a separate modified scoring system for patients with right bundle branch block. (Table 5)

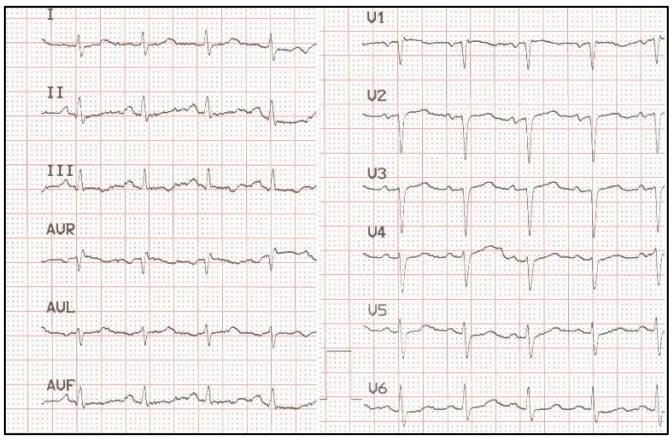

Figure 7 ECG showing low voltage and R/S ratio <1 in lead V5

Table 4 The modified ECG score for patients without right bundle branch block (58)

	ECG signs		**points**
1	S1QinferiorTinferior or S1+T wave inversion in leads V1-3	If any two are present simultaneously	1
		If three are present simultaneously	2
		If four are present simultaneously	3
2	Primary ST-segment elevation in the inferior leads and/or lead aVR and/or leads V1-3 or T wave inversion in the inferior leads and/or leads V1-3	Either ST elevation or T wave inversion in one of the locations	1
		Either ST elevation or T wave inversion in 2 or more of the locations OR both ST elevation and T wave inversion in one location	2
		ST elevation in 2 or more of the locations and T wave inversion in one location OR ST elevation in one location and T wave inversion in 2 or more of the locations	3
		Both ST elevation and T inversion in 2 or more locations	4
3	QR or qR complexes or R/S>1 in lead V1 and/or horal rotation in precordial leads and /or low voltage in frontal leads	If any present	1
		If two are present	2
		If all three are present	3
4	Terminal r' wave in lead aVR and/ or S1S2S3 syndrome and/or S wave in leads aVL, V4-6 and /or fragmented or slurred QRS complexes in lead aVR and/or in leads V1-3 and/or inferior leads	If only terminal r' wave in lead aVR and/or S1S2S3 syndrome and/or S wave in leads aVL, V4-6 OR only fragmented or slurred QRS complexes in lead aVR andr/or in leads V1-3 and/or inferior leads	1
		If terminal r' wave in lead aVR and/ or S1S2S3 syndrome and/or S wave in leads aVL, V4-6 AND fragmented or slurred QRS complexes in lead aVR and/or in leads V1-3 and/or inferior leads are present simultaneously	2

Table 5 The modified ECG score for patients with right bundle branch block (58)

	ECG signs		**points**
1	Qinferior or primary Tinferior	If either present	1
		If both are present simultaneously	2
2	Primary ST-segment elevation in the inferior leads and/or lead aVR and/or leads V1-3	ST elevation present in one of the locations	1
		ST elevation present in 2 or more of the locations	2
3	QR or qR complexes in lead V1 and/or horal rotation in precordial leads and /or low voltage in frontal leads	If any present	1
		If two are present	2
		If all three are present	3
4	Proven new RBBB and /or fragmented or slurred QRS complexes in lead aVR and/or in leads V1-3 and/or inferior leads	If only new RBBB OR only fragmented or slurred QRS complexes in lead aVR and/or in leads V1-3 and/or inferior leads	1
		If new RBBB AND fragmented or slurred QRS complexes in lead aVR and/or in leads V1-3 and/or inferior leads	2

RBBB, right bundle branch block

The maximum ECG score was 9 for patients with right bundle branch block and 10 for all others. Acute pulmonary embolism was diagnosed at ≥5/9 for patients with right bundle branch block and ≥6/10 for all others.

Exclusion criteria included left bundle branch block and right ventricular pacemaker rhythm. Out of 345 patients, 100 D-dimer negative and 206 D-dimer positive, a total of 306 patients had ECG tracings of adequate quality available for analysis. (4 D-dimer negative and 9 D-dimer positive patients had left bundle branch block, and 1 D-dimer negative and 3 D-dimer positive patients had pacemaker rhythm on their ECG.) The patients' ECGs were analyzed using our modified ECG score by the same two experts, with extensive experience in ECG analysis as those who performed the ECG analysis in the previous study, blinded to the diagnosis of pulmonary embolism. The diagnosis of the two specialists by the modified ECG score differed in 8% (25 cases). These cases were re-evaluated. Discrepancies were resolved by consensus.

3.4. Statistical methods

A $p<0.05$ value was considered statistically significant. GraphPadPrism version 6 for Windows (GraphPad Software Inc., La Jolla, CA, USA) was used to calculate and compare sensitivity, specificity and predictive values. N-1 $\chi 2$ test was applied without adjustment for multiple comparisons. Patient characteristics were compared with Fisher's exact test. In case of +LR and -LR, statistical significance was concluded if 95% confidence intervals did not overlap.

IBM SPSS Statistics 25 for Windows software package (IBM Corp. Armonk, NY, USA) was used for measuring interobserver variability by kappa statistics. The overall interobserver agreement was categorized as follows: as near complete if $\kappa > 0.8$, good if $\kappa = 0.61$ to 0.8, moderate if $\kappa = 0.41$ to 0.6, fair if $\kappa = 0.21$ to 0.4 and poor if $\kappa < 0.2$.

3.5. Declarations

The studies were conducted in accordance with the principles of the Declaration of Helsinki and were approved by the Scientific and Research Ethics Committee of the National Medical Research Council and the Regional and Institutional Ethical Committee of the South Buda Central Hospital, Saint Imre University Teaching Hospital.

4. Results

4.1. Retrospective pilot study cohort

Of the 136 patients, 27 had massive, 46 submassive and 63 peripheral pulmonary embolism. The score gave a correct diagnosis in all 27 cases of massive pulmonary embolism, 40 of 46 cases of submassive pulmonary embolism (87%) and 52 of 63 cases of peripheral pulmonary embolism (82.5%). We have found a test accuracy of 87.5% (119 correct diagnoses/ 136 total cases) in the retrospective pilot study cohort.

4.2. Prospective cohort

Out of the 149 patients, acute pulmonary embolism was excluded in 73 and confirmed in 76. Pulmonary embolism was considered confirmed or excluded in 125 [85%] based on pulmonary CT angiography and in 3 patients [2%] based on lung scintigraphy, and in 130 patients with a high sensitivity D-dimer test result, of whom 25 patients (25/130 [19%]) had a negative D-dimer test to exclude pulmonary embolism.

According to telephone interviews, none of the patients with excluded acute pulmonary embolisms based on the D-dimer test had venous thromboembolic events during 3 months of follow-up.

The two patients whose ECG could not be included in the analysis, one due to the absence of evaluable right-sided leads and the other due to an atypical left bundle branch block, were from the pulmonary embolism-negative group.

Table 6 shows the true and false positive and negative diagnoses with the investigated methods in the prospective cohort. Our ECG score had a significantly lower rate of false negative diagnoses: 1/50 cases (2%) than the other tested scores: Daniel ECG score 61/125 (49%), original Wells score 36/98 (35%), modified Wells score 34/95 (36%) simplified Wells score 30/88 (34%), revised Geneva score 25/66 (38%), revised, simplified Geneva score 27/71 (38%) ($p<0.001$ for each), whereas there was no significant difference in false positive diagnoses.

Table 6 True and false positive and negative diagnoses with the investigated methods in the prospective cohort (57)

Methods	n	TP	FP	TN	FN
novel ECG score	147	75	22	49	1
Daniel ECG score	147	15	7	64	61
Wells score orig.	149	40	11	62	36
Wells score mod.	149	42	12	61	34
Wells score sim.	149	46	15	58	30
Geneva score rev.	149	51	33	40	25
Geneva score rev., sim.	149	49	29	44	27
D-dimer 500 µg/L cv.	129	61	53	15	0
D-dimer age-adj. cv.	129	60	44	25	0

TP true positive, FP false positive, TN true negative, FN false negative, orig. original, mod. modified, sim. simplified, rev. revised, cv cut-off value, age-adj. age-adjusted.

Our ECG score had a sensitivity of 98.7% and a specificity of 69%. Its negative predictive value was 98%, and its positive predictive value was 77.3%. It had a negative likelihood ratio value of 0.019. Interobserver agreement was lower with our ECG score (κ: 0.701) than with the Daniel score (κ: 0.934). Its overall performance was better when compared to the other scores or D-dimer testing, with a test accuracy of 84.4%

Our ECG score was found to be superior in regards of sensitivity, negative predictive value and negative likelihood ratio to all other scores and in level with the D-dimer. It was significantly superior to the Geneva scores and the D-dimer test but not the Daniel or Wells scores regarding the positive predictive value. The positive likelihood ratio did not differ significantly between the scores. The specificity of our ECG score was lower than the Daniel score's and Wells scores, similar to the revised, simplified Geneva score's, but higher than the revised Geneva score's and the D-dimer test's. In overall, Wells scores performed better than Geneva scores, although their sensitivity was lower. The sensitivity and the negative predictive value of the D-dimer test alone was 100% and the negative likelihood ratio was 0 with both cut-off values. It had a low specificity and positive predictive value. The comparisons of the performance of the different scores are shown in Table 7.

Table 7 The sensitivity, specificity, test accuracy, predictive values and likelihood ratios of the tested methods (57)

Methods (n)	SE % (95% CI)	SP % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	TA, % (95% CI)	-LR (95% CI)	+LR (95% CI)
novel ECG score (147)	98.7 (92.9-100)	69 (56.9-79.5)	77.3 (67.7-85.2)	98.0 (89.4-99.9)	84.4 (78.5-90.2)	0.02 (0.003-0.13)	3.19 (2.25-4.51)
Daniel ECG score (147)	19.7 (11.5-30.5) ***, ‡‡‡,♠♠♠	90.1 (80.7-95.9) ***	68.2 (45.1-86.1)	51.2 (42.1-60.2) ***	53.7 (45.7-61.8) ***,♠♠	0.89 (0.78-1.02)	2.00 (0.87-4.62)
Wells score orig. (149)	52.6 (40.8-64.2) ***,†,♦,‡‡‡, ♠♠♠,###	84.9 (74.6-92.2) **,†††,♦♦♦, ♠♠♠,‡‡‡	78.4 (64.7-88.7) †††, ♠♠,#	63.3 (52.9-72.8) ***,♠♠♠,‡‡‡,#	68.5 (61-75.9) **,##	0.558 (0.43-0.72)	3.49 (1.95-6.27)
Wells score mod. (149)	55.3 (43.4-66.7) ***,†,###,‡‡‡, ♠♠♠	83.6 (73.0-91.2) **,†††,♦♦♦, ♠♠♠,‡‡‡	77.8 (64.4-88.0) ††,♦♦,‡‡‡, ♠♠♠	64.2 (53.7-73.8) ***,♠♠♠,‡‡‡,#	69.1 (61.7-76.5) **,##	0.54 (0.40-0.70)	3.36 (1.93-5.86)
Wells score sim. (149)	60.5 (48.6-71.6) ***,###,‡‡‡, ♠♠♠	79.5 (68.4-88.0) *,†††,♦♦♦, ♠♠♠,‡‡‡,#	75.4 (62.7-85.5) ††,♦,♠♠,‡‡‡	65,9 (56-75.8) ***,♠♠♠,‡‡‡,#	69.8 (62.4-77.2) **,##	0.5 (0.37-0.67)	2.95 (1.81-4.79)
Geneva score rev. (149)	67.1 (55.4-77.5) ***,###,‡‡‡, ♠♠♠	54,8 (42.7-66.5) *,###	60.7 (49.5-71.2) **	61.5 (48.6-73.3) ***,♠♠♠,‡‡‡	61.1 (53.2-68.9) ***	0.6 (0.41-0.88)	1.48 (1.10-2.00)
Geneva score rev. sim. (149)	64,5 (52.7-75.1) ***,###,‡‡‡, ♠♠♠	60.3 (48.1-71.5) ###	62,8 (51.1-73.5) **	62 (49.7-73.2) ***,♠♠♠,‡‡‡	62.4 (54.6-70.2) ***	0,59 (0.41-0.84)	1.62 (1.17-2.25)
D-dimer 500 µg/L cv. (129)	100 (94.1-100)	22.1 (12.9-33.8) ***	53,5 (43.9-62.9) ***	100 (78.2-100)	58.9 (50.4-67.4) ***	0 (0-0)	1.28 (1.13-1.46)
D-dimer age-adj. cv. (129)	100 (94-100)	36.2 (25-48.7) ***	57.7 (47.6-67.3) ***	100 (86.3-100)	65.9 (57.7-74.1) ***	0 (0-0)	1.57 (1.31-1.87)

CI confidence intervals, mod. modified, sim. simplified, rev. revised, adj adjusted, cv cutoff value, NPV negative predictive value, orig. original, SE sensitivity, SP specificity, PPV positive predictive value, TA test accuracy, -LR negative likelihood ratio, +LR positive likelihood ratio,

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ versus novel ECG score, # $p < 0.05$, ## $p < 0.01$, ### $p < 0.001$ versus Daniel ECG score, † $p < 0.05$, †† $p < 0.01$, ††† $p < 0.001$ versus Geneva score revised, ♦ $p < 0.05$, ♦♦ $p < 0.01$, ♦♦♦ $p < 0.001$ versus Geneva score revised, simplified, ‡ $p < 0.05$, ‡‡ $p < 0.01$, ‡‡‡ $p < 0.001$ versus D-dimer 500 µg/L cutoff value, ♠ $p < 0.05$, ♠♠ $p < 0.01$, ♠♠♠ $p < 0.001$ versus D-dimer age-adjusted cutoff value.

Among the scores, a negative diagnosis based on our ECG score indicated the false positive D-dimer test cases the best. Also, a positive diagnosis based on our ECG score indicated the true positivity of the D-dimer test, similar to the Wells score and superior to the Geneva scores and Daniel score (Table 8).

Table 8 The sensitivity, specificity, test accuracy and predictive values of the different investigated methods when they were applied together with a positive D-dimer test in the prospective cohort (n=104) (57)

∗p < 0.05, ∗∗p < 0.01, ∗∗∗ p < 0.001 versus our ECG score, # p < 0.05, ## p < 0.01, ### p < 0.001 versus Daniel ECG score,† p < 0.05, †† p < 0.01, ††† p < 0.001 versus Geneva score revised, ‡ p < 0.05, ‡‡ p < 0.01, ‡‡‡ p < 0.001 versus Geneva score revised, simplified, ♠ p < 0.05, ♠♠p < 0.01, ♠♠♠p < 0.001 versus Wells score simplified. NPV negative predictive value, PPV positive predictive value, TA test accuracy.

Methods	Sensitivity	Specificity	PPV	NPV	TA
positive D-dimer test (age-adjusted cut-off value)					
+ Our ECG score	98.3%	72.7%	83.1%	97%	87.5%
+Daniel ECG score	20%***	88.6%*	70.6%*	44.8%***	49%***
+ Wells score original	53.3%***,###	79.5%†††,‡‡‡	78%‡,††	55.6%***	64.4%***,#
+ Wells score modified	51.7%***,###	86.4%*,♠,†††,‡‡‡	83.8%#,‡‡,†††	56.7%***	66.3%***,#
+ Wells score simplified	56.8%***,###	71.8%‡‡,†††,##	69.4%†	59.6%***	63.9%***,#
+ Geneva score revised	63.3%***,###	45.5%***	61.3%***	47.6%***	55.8%***
+ Geneva score revised, simplified	61.7%***,###	52.3%**	63.8%**	50%***	57.7%***

4.3. Retrospective study of pretest probability evaluation with our modified ECG score and high sensitivity D-dimer test

4.3.1. Participants

In total, 345 outpatients with a D-dimer measurement were included in the analysis. Their mean age was 58.5 years (SD 18.1), and 53.9% of them were male. ECG score could be calculated in 306 of these cases. In the D-dimer negative group, more cases of ECGs were unsuitable or unavailable for analysis.

There was no significant difference between the D-dimer negative (DD(-)) and D-dimer positive (DD(+)) groups in other patient characteristics, as shown in Table 9. The ratio of patients getting hospitalized seemed to be higher in the DD(+) group (69% vs 50% in the DD(-)), though it did not show statistical significance.

Table 9 Patient characteristics (58)

	All patients n = 345	**DD(−) patients n = 120**	**DD(+) patients n = 225**
Age, mean (SD), years	58.5 (18.1)	58.3 (17)	58.7 (18.7)
Sex, male, n(%)	186 (53.9)	63 (52.5)	123 (54.7)
Chronic heart failure, n(%)	42 (12.2)	16 (13.3)	26 (11.6)
Chronic lung disease, n(%)	56 (16.2)	22 (18.3)	34 (15.1)
Active malignancy, n(%)	18 (5.2)	7 (5.8)	11 (4.9)
Immobilization ≥3 days or surgery in the previous 4 weeks, n(%)	14 (4.1)	2 (1.7)	12 (5.3)
ECG characteristics	**n = 306**	**n = 100**	**n = 206**
Intraventricular conduction disturbances			
RBBB, n(%)	30 (9.8)	10 (10)	20 (8.9)
RBBB + LAFB, n(%)	8 (2.6)	4 (4)	4 (1.9)
LBBB, n(%)	13 (4.2)	4 (4)	9 (4.3)
NICD + LAFB, n(%)	1 (0.3)	0 (0)	1 (0.4)
Reasons why ECG analysis was not feasible			
ECG was unavailable	21 (6.9)	15 (15)	6 (2.9)***
Poor quality ECG strip	1 (0.3)	0 (0)	1 (0.4)
LBBB, n(%)	13 (4.2)	4 (4)	9 (4.3)
Pacemaker rhythm, n(%)	4 (1.3)	1 (1)	3 (1.4)

DD(+) D-dimer positive, DD(-) D-dimer negative, SD standard deviation, RBBB right bundle branch block, LAFB left anterior fascicle block, LBBB left bundle branch block, NICD nonspecific intraventricular conduction disturbance

4.3.2. Pretest probability of acute pulmonary embolism in the D-dimer negative and D-dimer positive groups

When applying the ECG score, we found a good interobserver agreement (κ = 0.748).

Of the 100 patients in the D-dimer negative group with available ECG, one had an acute pulmonary embolism diagnosis (1%). With the ECG score, 2-tiered Wells and Geneva scores, there were 2/100 (2%), 9/120 (7.5%) and 28/120 (23%) *acute pulmonary embolism likely* diagnoses, respectively. In 7 cases, both the Wells and the Geneva scores stated that acute pulmonary embolism was likely. Using the 3-tiered scores, 7 cases were sorted into the high probability acute pulmonary embolism category by both.

CT angiography confirmed an acute pulmonary embolism diagnosis in 27% (55/206) of cases in the D-dimer positive group with analyzable ECG and 24.9% of (56/225) cases in total. In this group, 29/206 (14%) patients were labelled as *acute pulmonary embolism likely* with the ECG score, 27/225 (12%) with the Wells score and 76/225 (34%) with the Geneva score. With the 3-tiered versions of Wells and Geneva scores, a high probability acute pulmonary embolism diagnosis was set up in 15/225(6.7%) and 8/225 (3.5%) patients, respectively. True positive and negative cases according to the different pretest probability tests in the groups based on D dimer results are shown in Table 10.

Table 10 True and false positive and negative cases in the D dimer negative and positive groups and in the total analysed cohort

D-dimer negative						
	total n	PE likely diagnosis, n (%)	TP	FP	TN	FN
ECG score	100	1 (1%)	0	1	98	1
Wells score	120	10 (8.3%)	1	9	110	0
Geneva score	120	29 (24.2%)	1	28	91	0
D-dimer positive						
ECG score	206	29 (14.1%)	20	9	142	35
Wells score	225	27 (12%)	13	14	156	42
Geneva score	225	76 (33.8%)	29	47	117	32
Total						
ECG score	306	30 (9.8%)	20	10	240	36
Wells score	345	37 (10.7%)	14	23	266	42
Geneva score	345	105 (30.4%)	30	75	208	32

PE pulmonary embolism, FN false negative, FP false positive, TN true negative, TP true positive

The overall diagnostic performance of the modified ECG score could be described as follows: specificity: 96.0%, sensitivity: 35.7%, positive predictive value: 66.7%, negative predictive value: 87.0%, test accuracy: 85.0%, as shown in Table 11. The modified ECG score was significantly better than both the other scores in respect of specificity and PPV. The Geneva score showed significantly higher sensitivity than the other scores. The positive likelihood ratio of the ECG score was higher than that of the Geneva score and did not differ significantly from the Wells score. There was no difference in regard of the negative likelihood ratio and the NPV between the scores, all NPV-s were higher than 86%. The test accuracy of the ECG score was significantly higher than that of the Geneva score, but not than that of the Wells score.

Table 11 Measures of diagnostic performance of each score in the whole group

	TP	FP	TN	FN	SE% (95% CI)	SP% (95% CI)	PPV% (95% CI)	NPV% (95% CI)	+LRatio (95% CI)	-LRatio (95% CI)	TA% (95% CI)
ECG score n=306	20	10	240	36	35.7** 23.2-48.3	96.0* 93.6-98.4	66.7*** 49.8-83.5	87.0 83.0-90.9	8.93 4.43-18.0	0.67 0.55-0.82	85.0 81.0-89.0
Wells score n=345	14	23	266	42	25.0¤¤¤ 13.7-36.3	92.0¤¤¤ 88.9-95.2	37.8¤¤ 22.2-53.5	86.4 82.5-90.2	3.14 1.73-5.72	0.82 0.7-0.95	81.2¤¤¤ 77.0-85.3
Geneva score n=345	30	75	208	32	48.4# 35.9-60-8	73.5# 68.4-78.6	28.6# 19.9-37.2	86.7 82.4-91.0	1.83## 1.32-2.52	0.70 0.55-0.90	69.0# 64.1-73.9

FN false negative, FP false positive, TN true negative, TP true positive, CI confidence intervals, NPV negative predictive value, SE sensitivity, SP specificity, PPV positive predictive value, TA test accuracy, -LR negative likelihood ratio, +LR positive likelihood ratio,
ECG vs Wells: *p<0.05, **p<0.01, ***p<0.001; Wells vs Geneva: ¤¤ p<0.01, ¤¤¤ p<0.001; # ECG vs. Geneva p<0.001, ## significant by not overlapping confidence intervals;

4.3.3. Comparison of the performance of each score in D-dimer negative patients

We have found 1 case of acute pulmonary embolism out of 120 D-dimer negative patients (incidence 0.8%). Regarding test accuracy, the ECG score and the Wells score had similar values, both being significantly higher than the Geneva score's (98% and 92.5%, respectively, vs 76.7%, p<0.001 for both). Zero true positive cases were identified with the ECG score; therefore, the sensitivity, positive predictive value and positive likelihood ratio were all 0. Its specificity was 99%, and the negative predictive value was 98.7%. Among the sensitivity (SE), specificity (SP), positive predictive value (PPV), negative predictive value (NPV), and positive and negative likelihood ratios [(+)LR, (−)LR] only the SP and NPV of the different methods used to estimate the pretest probability of acute pulmonary embolism were comparable by statistical analysis. The reason for this was that the SE, PPV and (+)LR of the ECG score were 0 due to the 0 true positive acute pulmonary embolism diagnosis established by the ECG score, and the (−)LRs of the Wells and Geneva scores were 0 due to their 0 false negative acute pulmonary embolism diagnosis and consequently their SEs and NPVs were 100 %.

The specificity of the Wells score and the Geneva score were both lower (92.4% and 76.5%, p< 0.05), with a significant difference between the two also (p<0.001). The Wells score had a higher positive likelihood ratio than the Geneva score. (Table 12) Thromboembolic events did not occur in any of the patients during the 3-month follow-up.

Table 12 The sensitivity, specificity, test accuracy, predictive values and likelihood ratios of the tested methods in the D-dimer negative patients (58)

Methods (n)	**SE %** (95 % CI)	**SP %** (95% CI)	**PPV %** (95 % CI)	**NPV %** (95 % CI)	**TA %** (95% CI)	**(−)LR** (95 % CI)	**(+)LR** (95% CI)
modified ECG score (n=100)	0 % (NA)	99 % ### (94.5-100)	0 % (NA)	99 % (94.5-100)	98 % ### (95.3–100)	1.01 (0.99–1.03)	0 (NA)
Wells score orig. (n=120)	100 (NA)	92.4 % *, ### (86.1–96.5)	10 % # (0.3–44.5)	100 % (96.7-100)	92.5 % ### (87.8–97.2)	0 (NA)	13.22 (7.1–24.8)
Geneva score rev. (n=120)	100 % (NA)	76.5 % *** (67.8–83.8)	3.4 % (0.9–17.8)	100 % (96-100)	76.7 % *** (69.1–84.2)	0 (NA)	4.25 (3.1–5.9)

*p < 0.05, **p < 0.01, ***p < 0.001 vs. novel ECG score, #p < 0.05, ##p < 0.01, ###p < 0.001 vs. Geneva score. 95%CI 95 % confidence interval, SE sensitivity, SP Specificity PPV positive predictive value, NPV negative predictive value, TA test accuracy, (−)LR negative likelihood ratio, (+)LR positive likelihood ratio, orig. original, rev. revised. NA not applicable.

4.3.4. Comparison of the performance of each score in D-dimer positive patients

In the group of D-dimer positive patients, the ECG and the Wells scores had higher test accuracy than the Geneva score (78.6 % and 75.1% vs 64.9%, p<0.01 and p<0.05, respectively). The ECG score had a higher positive predictive value than both other scores (69% vs 48.1% and 38.2%, p<0.001 for both). Its sensitivity was higher compared to the Wells score but lower than the Geneva score (36.4%, 23.6% and 47.5%, p<0.01 and p<0.05, respectively). The specificity of the ECG score and the Wells score were higher than the Geneva score's (94%, 91.48% and 71.3%, p<0.001 for both). In the positive likelihood ratio, there was a significant difference between the ECG and Geneva score. The negative predictive value and negative likelihood ratio were similar with all the scores. (Table 13)

Table 13 The sensitivity, specificity, test accuracy, predictive values and likelihood ratios of the tested methods in the D-dimer positive patients.(58)

Methods (n)	SE % (95 % CI)	SP % (95 % CI)	PPV % (95 % CI)	NPV % (95 % CI)	TA % (95% CI)	(−)LR (95 % CI)	(+)LR (95% CI)
modified ECG score (n=206)	36.4 % # (23.8–50.4)	94 % ### (89–97.2)	69 % ### (49.2–84.7)	80.2 % (73.6–85.8)	78.6 % ## (73–84.2)	0.677 (0.552–0.83)	6.101 (2.96–12.58)
Wells score orig. (n=225)	23.6 % **, ### (13.2–37)	91.8 % ### (86.6–95.4)	48.1 % ***, # (28.7–68.1)	78.8 % (72.4–84.3)	75.1 % # (69.5–80.8)	0.832 (0.714–0.97)	2.87 (1.44–5.73)
Geneva score rev. (n=225)	47.5 % * (34.6–60.7	71.3 % *** (63.8–78.1)	38.2 % *** (27.2–50)	78.5 % (71.9–84.8)	64.9 ** (58.7–71.1)	0.735 (0.568–0.952)	1.66 (1.16–2.37)

*p < 0.05, **p < 0.01, ***p < 0.001 vs. novel ECG score, #p < 0.05, ##p < 0.01, ###p < 0.001 vs. Geneva score. 95%CI 95 % confidence interval, SE sensitivity, SP Specificity PPV positive predictive value, NPV negative predictive value, TA test accuracy, (−)LR negative likelihood ratio, (+)LR positive likelihood ratio, orig. original, rev. revised.

5. Discussion

5.1. ECG for the diagnosis of acute pulmonary embolism

The present guideline on pulmonary embolism provides separate dedicated subsections detailing the testing modalities for pulmonary embolism but does not include electrocardiography as a recommended diagnostic test. It is mentioned tangentially, but only because of its possible role in differential diagnosis, and a few specific signs are listed (e.g. T-wave inversion in V1-V4, QR in V1, S1Q3T3, complete or incomplete right bundle branch block) which, if present, may help to identify more severe cases. The assumed reason for this is partly that although several ECG abnormalities are known to occur more frequently in patients with verified acute pulmonary embolism than in those in whom symptoms and complaints raise the suspicion of pulmonary embolism but eventually it is ruled out, none of these ECG abnormalities is sufficiently sensitive or specific on its own to be used with certainty in the diagnosis of pulmonary embolism. Using the individual ECG signs to create a carefully composed score system seemed reasonable. We have kept in mind that this comes at the cost of complexity, which may make it more time-consuming to apply and, therefore, more challenging to use at the bedside at first. This issue could be solved using calculators supported by computer applications, which are now part of everyday life. Presumably, the interobserver variability compared to the Daniel score was higher in our second study because our ECG score consists of more criteria and is, therefore, more complex. Daniel et al. derived their scoring by analyzing the ECGs of 239 patients with massive or submassive pulmonary embolism from four previous studies to rank the prevalence of seven ECG abnormalities associated with massive pulmonary embolism. Three of these, P-pulmonale, right and left axis deviation, were later excluded because the observers involved in their validation study had difficulty interpreting their criteria, although the authors aimed to develop a scoring system that could be rapidly performed with acceptable precision by primary care physicians.(24)

Based on our results, more and particularly well-chosen ECG components result in excellent diagnostic accuracy. Navigating between Scylla and Charybdis, we may have

needed to sacrifice near-perfect interobserver agreement. However, our scoring system remained at a good level in this respect.

By analyzing the ECGs of the patients in the pilot study cohort, we constructed an ECG score that resulted in very good test accuracy. However, we were concerned that a non-negligible proportion of a pulmonary embolism-negative control group would have had a false positive result. To avoid this, to increase the diagnostic power of our test, we added a fifth criterion and raised the cut-off value to 4.

The results of the prospective study showed that our ECG score's diagnostic accuracy was superior to the other most widely used acute pulmonary embolism prediction scores and the Daniel ECG score. This is mainly due to the superiority of our ECG score in terms of sensitivity, negative predictive value, test accuracy and negative likelihood ratio. Only its specificity was below the Wells and Daniel scores.

A negative diagnostic test is considered good if it has a negative likelihood ratio of <0.1. Among the methods tested in our study, only our ECG score and the D-dimer test met this criterion. Neither method met a positive likelihood ratio value of >10, which is a criterion for a good positive diagnostic test.

Although all suitable patients were consecutively included in the prospective study cohort after the inclusion and exclusion criteria had been taken into account, we were confronted with the finding that the cohort did not reflect the generally observed rate of a much higher proportion of patients in whom acute pulmonary embolism is eventually excluded than in whom it is confirmed among those in whom it is suspected and investigated. This unintentional selection bias might be because patients who tested negative for D-dimer and/or did not eventually require hospitalization and could be discharged from the emergency department were lost to the cardiologists and internists involved in the study. Another issue to be considered is that in everyday practice, right-sided chest leads are not widely used for the differential diagnosis of pulmonary embolism. With these aspects in mind, we conducted our third study, in part to optimize and fine-tune our methodology to fit the population for which we intend to use our ECG score. By integrating other ECG signs into our modified ECG score instead of the right-sided leads in our third study, we also had promising results.

5.1.1. The rationale for deriving our ECG score.

5.1.1.1. The issue of subjectivity and standardisability

Previously, scoring systems assessing pretest probability have been introduced for standardizability and reproducibility, but their specificity and positive predictive value are suboptimal, which may question their usefulness on their own. Several studies have compared the diagnostic accuracy of the most widely validated prediction scores. A meta-analysis showed that the Wells score is more effective than the revised Geneva score.(59) Our results are in line with this. The objective parameters of the Wells score are very similar to the items of the revised Geneva score. The Wells score is suggested to be superior because it includes a subjective variable: "alternative diagnosis less likely than pulmonary embolism."(60) A study also confirmed that the Geneva score becomes more accurate when supplemented with the possibility of empiric clinical judgment.(61) So, on the one hand, there is a definite need for standardisation, as there can be considerable variability in the empirical judgement of physicians with different experiences in the effectiveness of pretest probability assessment. On the other hand, the strength of the objective components of the scores developed for this purpose is not convincing. Hence, it still needed to be strengthened by adding clinician empirical judgement.(60) In fact, there is growing evidence that empirical clinical judgement alone outperforms scoring systems. It should be recognized that scoring systems based on predisposing factors, symptoms, and clinical findings for venous thromboembolism cannot be sophisticated enough to be extensively applied in all clinical situations. If such a detailed system were attempted, it would undoubtedly be challenging to memorize and would limit its applicability in everyday practice. For example, consider a situation where someone has no lower limbs because of amputations or no chronotropic competence due to drug effects. In such cases, the subjective component obviously should override the pretest probability categorized by the scoring system.

By developing our ECG score, we have met the need to eliminate the subjective component. We have established a consistent and standardizable decision support method for assessing the pretest probability of pulmonary embolism.

5.1.1.2. Our concept, a pathophysiological approach

The derivation cohort of the Daniel score included cases only with massive and submassive pulmonary embolism, not cases with less severe pulmonary embolism. Their score was created by ranking each ECG abnormality's incidence and prognostic significance to distinguish cases of massive pulmonary embolism from mild cases or those without pulmonary embolism. Together with the TwiST score, they were both created for prognostic purposes: to help identify patients with high-risk pulmonary embolisms who should, therefore, be treated according to a different care protocol. Optimally, scores should be able to accurately reflect risk in both low and high-risk patient categories and not only aim to identify high-risk patients. The correct classification of patients into a low-risk category allows the allocation of appropriate diagnostic resources to all patients undergoing the screening process.

Cases of pulmonary embolism of varying severity, including 63% peripheral pulmonary embolisms and not only severe cases, were involved in our pilot study cohort, as our primary aim was to develop an ECG score not for prognostics but for pretest probability determination and diagnostics, which would be suitable for identifying patients with low probability of pulmonary embolism and patients without pulmonary embolism. We have been successful in this respect. Our method's overall very good results in assessing the pretest probability of acute pulmonary embolism can be attributed to the different rationale of the score generation. We have tried to select and combine ECG signs that best reflect the main pathophysiological steps of acute pulmonary embolism.

Incidental pulmonary embolism is rare, and some of these cases are due to false positive CT findings. Of note, there is no robust, clear evidence on the clinical significance of small, isolated, sub-segmental contrast deficits and the therapeutic consequences of incidental pulmonary embolism. Previous results from the era of pulmonary angiography have shown that even very small obstruction of the pulmonary arterial bed up to 13% leads to systemic hypoxia, from which the authors concluded that even the smallest emboli detected by pulmonary angiography, the historical gold standard, result in systemic hypoxemia in almost all (95%) cases.(62) In pulmonary embolisms that result in a complaint or symptom, cardiac consequences and subsequent ECG changes can be expected. It has been observed that in acute pulmonary embolism, a

decrease of less than 25% in the total diameter of the pulmonary atrial bed is sufficient to cause a significant increase in pulmonary pressure.(63) Several studies have found a discrepancy between the hemodynamic consequences of acute pulmonary embolism and the degree of mechanical obstruction caused by embolism.(64) This has drawn attention to another contributing factor, pulmonary vasoconstriction, as in addition to the mechanical obstruction caused by the embolus, there is a more significant acute reduction in the total diameter of the pulmonary vascular bed. Pulmonary embolism-induced acute pulmonary vasoconstriction is mediated by the release of humoral platelet-derived factors, thromboxane A2(65) and serotonin, which acts as a vasodilator in the systemic circulation but has the strongest vasoconstrictor effect on the pulmonary circulation.(66) Vasoconstriction and hypoxia exacerbated by intrapulmonary arterio-venous shunting consequently result in a significant increase in pulmonary vascular resistance during the initial phase of pulmonary embolism. The acute increase in right ventricular pressure following an increase in resistance can be compensated for by the right ventricle up to about 40 mmHg in the unconditioned right heart, after which it dilates(62), tricuspid regurgitation develops or worsens. Wall tension is increased, leading to excessive neurohormonal activation, which tends to improve pulmonary blood flow and stabilize low systemic blood pressure by increasing inotropy and chronotropy. The discrepancy between supply and demand sometimes results in ischemia progressing to infarction. Right ventricular ischemia and high right ventricular pressure lead to conduction disturbances, further prolonging right ventricular contraction time and worsening interventricular dyssynchrony. In early diastole, the prolonged right ventricular contraction inhibits left ventricular filling, compresses the left ventricle, worsens left ventricular preload and cardiac output, and thus, in a vicious circle, hypotension until collapsing circulation.(67) In developing the new pulmonary embolism ECG score, we searched for 12-lead ECG signs highly indicative of the key components of its cardiac pathophysiologic effects, such as right ventricular ischemia, right ventricular dilatation due to acute pulmonary pressure increase, and disturbances of the right intraventricular conduction due to the previous two, as well as right ventricular wall strain.

The ECG signs of severe right ventricular ischemia associated with pulmonary embolism progressing to definitive necrosis are observed in the relevant leads. In the conventional 12-lead system, the inferior leads (of which most likely lead III) represent

the inferior wall of the right ventricle, the aVR the outflow tract and the anterior wall of the right ventricle, and leads V1-3 the outflow tract, the anterior and paraseptal parts of the right ventricle. Of the right-sided chest leads, RV4 best represents the free wall of the right ventricle.(68) Dilatation of the right ventricle upon an acute increase in pulmonary pressure may be so extensive that, in addition to the above, ECG signs may be observed in the chest leads as far as V5 or RV6, and sometimes in the limb leads as far as aVF or even in lead II. In the study design, we tried to take into account the observation that many ECG signs in pulmonary embolism are transient. The literature suggests that some ECG signs may regress a few days or hours after the pulmonary embolic event. Therefore, it is advisable to analyze ECGs taken as soon as possible after the onset of the clinical symptoms. Finally, patients whose symptoms were still present within 7 days before the ECG was obtained were analyzed in our studies. ST elevations are usually transient and last for a shorter time compared to ST elevations in left ventricular infarction.(69, 70) The time of persistence of ST elevation may also be related to the extent of right ventricular necrosis. T inversions (i.e. negative T-waves) are observed to develop later but are expected to persist longer. In the absence of prior ST elevation, severe ischemia alone can affect and reverse the direction of repolarization, leading to T-wave inversion, or it may correspond to the reperfusion or subacute phase following an ST elevation in the ischemia process.(68, 71, 72) Nevertheless, hypoxemia, catecholamines released during neurohormonal activation and serotonin may also play a role in the development of negative T waves.(73) Negative T waves in the anterior leads are observed in proximal left anterior descending (LAD) artery disease too, but whereas in pulmonary embolism, negative T amplitudes show a gradual decrease from V1 to V5; in acute coronary syndrome caused by LAD disease, the largest T wave amplitudes are observed in V3-4.(51) The more leads in which ST elevation or T-inversion is seen, the greater the extent of transmural ischemia. If the ischemia eventually progresses to definitive necrosis, it is reasonable to speculate that pathological Q waves, analogous to those in left ventricular infarcts, may develop in the right ventricular leads. This may be a realistic scenario for right-sided chest leads: QR and QS may also form in right ventricular infarction, but this is not the case for other leads.(69) In these, the cause of the shift of the initial vector of the QRS away from the electrode, i.e. the development of a Q wave in pulmonary embolism, is predominantly different. Physiologically, the initial vector of ventricular

depolarization points left to right, posterior to anterior and up to down, producing a small r wave in V1. This vector disappears as a result of right ventricular dilatation due to an acute rise in pulmonary pressure and the horizontal rotation of the heart.(74) The qR, Qr or QR seen in V1 may be due to the flattening of the interventricular septum (the echocardiographic D-sign) or the consequence of the right ventricle pushing backwards and compressing the left ventricle. (68, 75-77) There is also a clockwise rotation along the longitudinal axis of the heart, which is manifested on the electrocardiogram as a shift to the left of the thoracic transition further than V4 in the precordial leads or a terminal S wave in I-aVL and a terminal r' wave in aVR. (74, 78) Changes in QRS morphology and axis are not only caused by the changes mentioned above in the electrical position of the heart but also by dilatation, wall strain and significant right ventricular ischemia due to an acute increase in pulmonary pressure, which can directly impair, sometimes temporarily, the right intraventricular conduction structures and thus alter the activation sequence.(69) With the prolongation of right ventricular contraction and the lesion of the right ventricular conduction structures, the enlarged right ventricle is increasingly responsible for the formation of QRS terminal vectors, which may first appear as slurring or fragmentation in the leads representing the right ventricle, with progressive impairment of the conduction before evolving to incomplete and complete right bundle branch block.(79) S1S2S3 syndrome refers to a posterior dislocation of the apex of the right ventricle. In S1S2S3 syndrome, the QRS may be slightly widened. There is a delay in the inflow tract of the right ventricle and a marked delay concerning the basal parts, outflow tract, and supraventricular crest. These terminal vectors are no longer counterbalanced by the left ventricular electric forces and point upwards and to the right.(80, 81) The R/S ratio in the chest leads usually increases from right to left. Early and frequent serial ECG studies of patients with acute pulmonary embolism show that a decrease in the R/S ratio is also an early and sensitive, but potentially reversible, transient sign.(73, 82) The decrease in the QRS potential observed in the frontal plane can be explained by right ventricular dilatation and systemic fluid-engorged tissues following pulmonary embolism.(83-86) However, there is also the possibility of an additive role of right ventricular endocardial potential reduction caused by right ventricular myocardial stress. (71, 87)

It should be remembered that ECG signs may not appear simultaneously; some may appear earlier and some later. Individual differences may be due to, for example, the anatomy of the cardiac conduction system or previous disease involvement. The score system also attempts to correct for variability due to individual and temporal factors. As described previously, the score was weighted to give more points if an ECG abnormality was observed in more than one typical location [1) the inferior leads, 2) leads V1-3, 3) aVR] because the simultaneous appearance of ECG abnormalities in these leads is suggestive of right ventricular involvement as opposed to when they appear separately, which may be more indicative of left ventricular involvement. The ECG score was also weighted to give more points if more than one ECG abnormality was observed concurrently in one location. The strong performance of the S1Q3T3 alteration, also known as the McGinn-White sign(88), can also be explained by the fact that it indicates the three main effects of pulmonary embolism on the heart at the same time, namely: S1 indicates a change in the activation sequence due to intraventricular conduction disturbance, Q3 indicates a vectorial change in the initial activation due to positional causes of right ventricular dilatation, and T3 indicates right ventricular ischemia.

We have validated the score and tested its performance in a different cohort of outpatients and have found it better than the previously existing clinical prediction rules in regards of sensitivity, negative predictive value, test accuracy, and negative likelihood ratio. When we modified the score for easier implementation, we found similarly good performance when testing it in a larger cohort of patients, better reflecting the real-world prevalence of pulmonary embolism in the emergency room.

5.1.2. Positioning the value of our study

After reviewing the literature, we found that only one other ECG score for the diagnosis of pulmonary embolism has been published since the development of our ECG score. Following the completion of our third study, a Chinese research team reported results that were very similar to ours.(89) They compared the diagnostic value of a method they developed based on ECG signs with the Daniel score and the Wells and Geneva scores in assessing the pretest probability of acute pulmonary embolism. Similar to our results, their method, the Sichuan Provincial People's Hospital-ECG model, also showed superiority over other prediction scores due to its higher sensitivity, negative predictive

value and test accuracy. However, its specificity and positive predictive value were lower than the results of the other three. Their model was developed using a different methodology. They measured the frequency of 27 ECG abnormalities in the confirmed pulmonary embolism cases. Then, they built a multivariate model using those factors - 13 in total - that showed a significant statistical association with pulmonary embolism in the univariate models. The article does not discuss how the 27 ECG signs were selected initially, but they point out that they included ECG abnormalities not just seen in severe pulmonary embolism. Their results are similar to ours, though their inclusion and exclusion criteria were more stringent. Their study included patients who had an ECG within 48 hours of the onset of complaints, as opposed to our study, which selected patients who had an ECG within 7 days of the onset of complaints. Considering that ECG signs are often transient, we assume that we could have found even stronger correlations if we had also set a 48-hour time limit. They did not include patients with a history of heart or lung disease, whereas our score was implemented irrespective of pre-existing cardiorespiratory disease; there were chronic heart failure, chronic pulmonary disease patients and patients with coronavirus disease (COVID) infection in our study population.

A growing body of evidence supports the clinical experience that electrocardiography can reasonably claim a role in diagnosing pulmonary embolism, not only in identifying high-risk patients but also in assessing pretest probability, and it may be valuable in ruling out pulmonary embolism.

5.2. Expansion of the role of D-dimer in ruling out pulmonary embolism

Analyzing the data from the prospective study conducted to validate our new ECG score, we observed that no patient with a negative D-dimer had pulmonary embolism, which was also confirmed at 3 months follow-up. Our retrospective study reaffirmed this finding with a larger number of patients, with a total of 1 false negative case.

In 2017, the International Society for Thrombosis and Haemostasis (ISTH) proposed the reduction of the traditionally accepted diagnostic safety threshold of 2.7% based on their systematic review and meta-analysis(90): they recommended a

proportionately varying maximum acceptable failure rate of <2% for future studies of suspected pulmonary embolism or new diagnostic algorithms in different healthcare settings depending on the prevalence of pulmonary embolism in the population under investigation. In detail, in self-referral emergency care, where the prevalence of acute pulmonary embolism is 7.5%, 0.71-1.86%; in primary healthcare, where the prevalence of acute pulmonary embolism is 8.9%, 0.72-1. 87%, in referred secondary care, where the prevalence of acute pulmonary embolism is 20.2%, the value 0.78-1.92% and finally, for inpatients and nursing home care, where the prevalence of acute pulmonary embolism is 24%, the value 0.8-1.95% was suggested.

In 2018, Fronas et al.(91) published a single-center prospective outcome study which concluded that the high sensitivity D-dimer with a fixed cut-off value of <500 μg/L as a stand-alone test can safely and effectively exclude deep venous thrombosis independently of the pretest probability established by the Wells score, after 298 (33%) of 913 patients tested negative for D-dimer, of which only 1 (0.3%) proved to be false negative.

Similar results were obtained for pulmonary embolism. In a prospective study published in 1999 involving a total of 918 consecutive emergency department patients with clinical suspicion of venous thromboembolism, a 99.3% negative predictive value was achieved using a fixed cut-off value (<500 μg/L) of a standard rapid ELISA D-dimer test as only 2 of 286 patients (0.7%) had a normal D-dimer value, thus proving false negative.(92) Another prospective study published in 2002 found a 1% false negative rate of rapid ELISA D-dimer test among consecutive inpatients and outpatients with suspected pulmonary embolism.(93) In 2004, Righini et al. published their study in which they retrospectively analyzed data from two prospective management trials of a total of 1409 patients with suspected venous thromboembolism or pulmonary embolism alone.(94) Of the 439 (31%) negative cases with high-sensitivity rapid quantitative ELISA tests at 3-month follow-up, none was found to be false negative regardless of pretest probability, as determined by either implicit evaluation, original Geneva score, or implicit evaluation overriding the original Geneva score. Finally, in 2016, Bates et al.(95) published the results of a management study of a prospective cohort with 15% of inpatients conducted between 2003 and 2007. 420 (52%) of 808 patients with suspected pulmonary embolism were negative for D-dimer using the MDA D-dimer rapid quantitative latex agglutination

assay. The normal value for this assay is usually below 500 μg FEU/L. However, in their study, they increased this value to 750 μg FEU/L to reduce the false positive D-dimer results. The overall negative predictive value of the D-dimer test was 99.8%, and it was concluded that with the increased cut-off value the test was safe to exclude pulmonary embolism. However, they questioned the extendibility of this finding to cases of high pretest probability because they considered the proportion of patients with high pretest probability in their study relatively low. Nevertheless, a later study showed that a stand-alone D-dimer test with a threshold universally increased to a higher specific (750 μg/L) value has not fulfilled the expectations and is unsafe in excluding pulmonary embolism.(96)

In our study, we have also investigated the possibility of using a high-sensitivity D-dimer as a stand-alone test in both cohorts. In our third study cohort, the prevalence of acute pulmonary embolism was 16.5%. The proportion of patients with a high pretest probability was similar to the 10-30% seen in the literature in emergency departments. We found that false negative diagnoses of acute pulmonary embolism occurred in <1% of cases. Thus, in all the studies listed above and in ours, without exception, the failure rate remained below the threshold value of 2% recommended by the ISTH. These numbers are comparable with the results of the most widely accepted tests for confirming or excluding pulmonary embolism today, pulmonary CT angiography and the historical gold standard, pulmonary angiography. The rate of venous thromboembolic events occurring within 3 months of a negative CT angiography finding was 1.2%, with a rate of 2% in cases with high pretest probability categorized as *pulmonary embolism likely* by the Wells score.(97) Moreover, after negative pulmonary angiography, the three-month incidence of venous thromboembolism was 1.7%.(98)

All this supports that a negative D-dimer test with high sensitivity, regardless of pretest probability, is suitable to rule out acute pulmonary embolism in patients presenting at the emergency department with suspected pulmonary embolism. However, the recommended practice in the current guideline is different because it states that only in cases of low to medium pretest probability should negative D-dimer be used for this purpose. Presumably, cost-effectiveness considerations are also involved. It is not only about how much each D-dimer assay costs but also considering that in patients with high pretest probability, it is unlikely that they will have negative results. About 10 D-dimer

tests may be needed in that group to avoid 1 CT angiography scan.(99) Another aspect might be that, as Wells et al. found, the prevalence of confirmed pulmonary embolism increased proportionally among D-dimer-negative patients according to the pretest probability set by the original Wells score.(100) However, it should be pointed out that in their study, they used a SimpliRED D-dimer assay with a sensitivity below the sensitivity of the procedures recommended by the ESC guideline. SimpliRED has a sensitivity of 83%, compared to methods such as ELISA, ELFA and latex-enhanced immunoturbidimetric assays, as detailed in the introduction, which have a 93-96% sensitivity.(37) The guideline does not provide a thorough description of the reasons behind the recommendation of not considering a high-sensitivity D-dimer assay safe in high pretest probability patients. The two references behind the recommendation are reviews of carefully selected prospective trials from almost 20 years ago that investigated the role of D-dimer in ruling out pulmonary embolism or deep vein thrombosis. Their conclusions include that some high-sensitivity D-dimer assays - those recommended by the guideline itself and already available at that time - considering their negative likelihood ratio, are just as useful as the imaging tests recommended.(38, 101) Undoubtedly, there are diverse types of D-dimer testing procedures in various healthcare settings, which may prevent a general conclusion from being drawn. Therefore, there is a strong need for standardization of D-dimer assays.(43, 102) A study published in 2021 also draws attention to the lack of standardization of D-dimer assays, obtained by post hoc analysis of data from the YEARS study between 2013 and 2015. A comparison analysis of four different D-dimer assays found that among higher-risk patients, there was a false negative rate of only 0.9% (3/331) at a D-dimer cut-off value of 500 μg/L. The negative predictive value of the different assays varied between 97-100%.(103)

Theoretically, standardization and drawing a general conclusion might require a prospective comparative study in which all types of D-dimer assays are performed in all patients or a random assignment of each assay to each patient. Also, the presence of pulmonary embolism should be assessed by imaging all patients with any pretest-probability and then reassessing the possibility of venous thromboembolism after 3 months. Such an investigation is unlikely to be carried out. If we wanted to test these associations solely in patients with high pretest probability, we would need an even more

enormous number of cases, probably beyond the scope of a single study. A meta-analysis of several studies could lead to a goal, a statistically confirmed robust conclusion.

However, from observational studies like ours, valuable real-world data from everyday healthcare can be extracted and structurally analyzed to provide real-world evidence to support claims of safety and effectiveness. Increasingly, the results of observational studies are being recognized, particularly for evaluating biomarkers or data on the accuracy of diagnostic tests or when randomized clinical trials cannot be performed.(104) Some of the data in our studies were obtained by practices that differ from the diagnostic management algorithm recommended by the current guidelines. For example, from cases where D-dimer testing was performed despite a high probability of a pretest for acute pulmonary embolism. In addition, from cases where CTA was performed in patients with low pretest probability and D-dimer levels within normal limits. The former may be because in overcrowded emergency departments, extended laboratory tests, including D-dimer tests, are often ordered before a proper history is taken and a physical examination is carried out to save time. The latter may be due to the overriding empirical clinical judgement of emergency department health care providers. Namely, they nevertheless considered the risk of pulmonary embolism high. The probable explanation for that is our third study being conducted during the COVID pandemic. At that time, there was a lack of experience and recommendations to determine the impact of COVID infection on the risk of thromboembolism. Therefore, for patients undergoing CT scanning to rule out COVID pneumonia, physicians also obtained simultaneous CT angiography at the Emergency Department.

Most commercially available D-dimer assays are not approved by the Food and Drug Administration (FDA) for excluding venous thromboembolism. In 2016, only 8 central laboratory D-dimer assays had FDA approval to rule out pulmonary embolism and deep vein thrombosis without additional imaging.(36) For a D-dimer assay to obtain FDA approval for ruling out venous thromboembolism in low to moderate pretest probability cases, the manufacturer must perform a management study with at least three sites. The negative predictive value should reach 97% and the sensitivity 95%. To achieve this, the sample size should be high enough to include about 300-300 patients with pulmonary embolism and deep vein thrombosis separately. And for those with a negative D-dimer

test, a further confirmation of no venous thromboembolic event after a 3-month follow-up is required. The United Kingdom has even stricter regulations. (43)

Most studies conducted to analyze D-dimer's role in excluding pulmonary embolism focused only on patients with low to moderate pretest probabilities. A recent survey intended to fill this gap. Out of 12,300 patients in 3 large European studies, those with a high pretest probability of pulmonary embolism with the Wells or Geneva score and D-dimer testing were examined in a post hoc analysis. Among them, the prevalence of pulmonary embolism was 31.3%. (105) In total, 70 of 651 patients with a high pretest probability had age-adjusted D-dimer levels within the normal range. No thromboembolic events were confirmed, which was also true during the 3-month follow-up. Thus, showing an actual failure rate of 0% (with the probability of the defined strategy exceeding a failure rate over 2% less than 10^{-5}).

Our conclusions are also supported by the results of a recently published Canadian prospective multicenter implementation study.(106) 16,155 emergency department patients were screened for suspected pulmonary embolism. Pulmonary embolism was considered excluded without further imaging, regardless of pretest probability, if the D-dimer was below 500 μg/L. Of 2578 such cases, none were diagnosed with pulmonary embolism within 30 days. Thus, the D-dimer-guided approach without assessment of pretest probability was found to be safe.

5.3. Combining prediction rules and D-dimer test and moving towards standardizability

In everyday practice, applying pretest scores with suboptimal specificity and positive predictive value in groups with low and medium pretest probability has only shown promising results when combined with D-dimer testing.(107, 108) The combined methods, however, have been broadly validated. Current trends are moving towards integrating the most useful criteria of the prediction rules and the D-dimer test into a single score rather than the current three-step practice of performing a D-dimer test and/or

imaging after determining the risk by a prediction rule. Also, emphasis is placed on removing the subjective component to allow standardization. For example, the LEGEND score(109) has omitted criteria from the Wells score, the revised Geneva score and the PERC score that appear not to affect performance. Thus, age, heart rate above 100 bpm, hemoptysis, ongoing hormonal therapy, and oxygen saturation have been removed. Active malignancy, signs or symptoms of deep venous thrombosis, previous history of venous thromboembolism, and surgery, trauma, or immobilization within 1 month remained. Combining these remaining criteria with a D-dimer test with a cutoff value of 1000 μg/L yielded better diagnostic results than the Wells score, the revised Geneva score or the YEARS algorithms combined with the pretest-probability adapted-D-dimer values. Basically, it has simplified the score as it has fewer criteria to consider, improving its applicability at the bedside, which can lead to better compliance among clinicians. However, the reduced number of criteria may result in empirical clinical judgement overriding the diagnostic pathway determined by the pretest probability score in special clinical situations.

Another recently published new diagnostic management approach shows excellent results in accurately assessing individual risk by including the quantitative D-dimer as a continuous variable and not a dichotomized value in the model.(110) Data from a total of 28,305 patients from 16 studies worldwide were processed in a meta-analysis, with patients from various healthcare settings with different prevalences of pulmonary embolism. The final design comprised nine objective variables, emphasizing the exclusion of subjective assessment. This model also included previous venous thromboembolism, symptoms of deep vein thrombosis, recent surgery or immobilization, and cancer. It contains age and hemoptysis, which the LEGEND score omitted, and also sex and inpatient status. The method's limitations might be its complexity, as a computer application is needed to calculate the probability of pulmonary embolism and the fact that it requires every patient to have a D-dimer test. It should also be noted that once the precise probability is determined, there will still be a subjective decision, made by the physician with or without the patient, whether or not to perform imaging depending on the prevalence of pulmonary embolism in the actual clinical setting.

When validating our ECG score, we have found that combined with a negative D-dimer test, it was more useful in ruling out acute pulmonary embolism than the other

scores combined with the D-dimer. (57) Also, our score more reliably indicates the false positivity of a D-dimer test. Furthermore, in D-dimer positive patients, a positive ECG score supported the acute pulmonary embolism positive diagnosis better than the other scores, providing a more solid indication for imaging tests. In our later study, we have also seen that a positive D-dimer and a positive ECG score together increased the likelihood of acute pulmonary embolism compared to the other scores.(58) As the D-dimer test alone was safe to rule out acute pulmonary embolism, the possible added value of the ECG could not be assessed. Based on these results, in line with the recent trends of performing D-dimer tests in every suspected case of acute pulmonary embolism, the ECG score may be useful for further discrimination.

According to Bayes' theorem, the failure rate of a test used in diagnosing pulmonary embolism also depends on the prevalence of pulmonary embolism in the cohort being studied. (58) If only studies with sufficient statistical power of high pretest probability patients are accepted to state that high-sensitivity D-dimer testing is suitable for excluding D-dimer, then a robust sample size would be required. Such studies are not yet available, only those representing everyday practice. The results of our observational study are in line with the results of previous and recent prospective management studies that a high-sensitivity D-dimer test can be used as a stand-alone test to exclude acute pulmonary embolism among patients presenting with signs and symptoms of acute pulmonary embolism at the emergency room, independent of the pretest probability of acute pulmonary embolism as determined by clinical prediction rules. The guideline recommends using a high-sensitivity D-dimer in the three-step assessment process for the diagnostic management of acute pulmonary embolism, but the D-dimer test should only be performed in patients with a non-high pretest probability. This is partly because it is considered unlikely to be negative in these cases. However, based on the literature and our studies, everyone could be given the chance to avoid unnecessary exposure to radiation and contrast agents in case of a negative D-dimer test. Safety is defined by the failure rate, and high-sensitivity D-dimer testing produces failure rates similar to the failure rates of imaging studies. Prediction scores may help doctors with less clinical experience to reduce the number of time-consuming imaging procedures with potential side effects and health costs. Nevertheless, recent trends towards standardization are integrating the D-dimer score into the probability assessment for everyone, without

exception. No algorithm can be perfect because the scores developed cannot cover all clinical situations. For simple and easy-to-memorize scores, leaving the possibility of subjective override seems appropriate. If we want to have a standardized method (i.e. machines that can apply the rules accurately and consistently), systems that consider all relevant patient clinical data are on the horizon.(111, 112) As machine learning and artificial intelligence-aided technologies permeate all areas of medicine with the supervision of professionals and support their work, they will also play an important role in the diagnostic management of pulmonary embolism. (113, 114) Providing relevant, high-quality big data is the responsibility and task of specialists.

5.4. Future perspectives acknowledging the limitations of our research series

In general, scores are handy, objective, and consistent tools for risk assessment. Due to potential mistakes in data entry, the more criteria included, the more the error potential and the higher the interobserver variability. As is the case with any score development, we faced the limitations of our studies in developing our score. Recognizing these can help us further in fine-tuning, which is a routine step in creating a scoring system, aiming to make it as easy to use, widely accepted, and valuable as a decision-support tool. This is also how the Wells and Geneva scores were created, and their variations further developed. A key step in score development is to assess the diagnostic performance of the method in different patient populations and scenarios to optimize implementation. As mentioned earlier, in the data analysis of our prospective study, we were confronted with the non-intended bias that the proportion of patients who are ultimately not confirmed to have pulmonary embolism was much higher than observed usually at an emergency department. It was also found that the cohort had a higher than-usual representation of patients with high pretest probability. In contrast, in our third study, the prevalence of pulmonary embolism and the proportion of patients with high pretest probability were at the generally expected level. We used widely accepted statistical metrics with their well-known inherent limitations. The differences in the results of our studies were determined mainly by the two cohorts' different characteristics and the imposed change in the composition of the score. The fine-tuning of the ECG score

we developed may be taken further (e.g. to see how the score performs in a real-life population by back-integrating the right-sided chest leads or by adding new ECG signs (e.g. the difference between QTc measured in V1 and V6(115)). The comparability of our ECG score with the Daniel score is not straightforward because the Daniel score was developed for the prediction of severe right heart strain due to pulmonary embolism and not for exclusion or pretest assessment. A further limitation of our study series is that sometimes the individual scores were calculated retrospectively when their value was not registered in the emergency department patient records, in which case the subjective component of the Wells score was not assessed in all instances during the physician-patient encounter. Therefore, the comparison with the Wells score must be evaluated with this factor in mind. Another limitation of our studies is the relatively low number of cases, not only in terms of patients but also in terms of certain ECG signs.

However, our ECG score's value and uniqueness are that it can be fitted to both approaches: it does not represent a complexity that cannot be managed at the bedside and can, therefore, be used in healthcare settings where not all modern equipment is available. But in our increasingly digital world, it can also be integrated into computer-aided decision support systems.

For now, it has a role in supporting the suspicion or ruling out acute pulmonary embolism in patients with symptoms and complaints. However, it may be used to identify cases of hemodynamic compromise high-risk pulmonary embolism when imaging is not available for immediate initiation of therapy for high-time factor disease. Moreover, its potential diagnostic power in special groups such as pregnant women needs to be clarified.

Inexpensive, easily accessible and safe, electrocardiography is one of the most commonly performed tests in patients with acute pulmonary embolism symptoms. The information it provides can also be used for differential diagnosis. It can be concluded that, so far undeservedly neglected, it justifiably claims a place in the diagnosis of pulmonary embolism. It can now be standardized in score form for validation in a larger patient population.

6. Conclusions

Based on the results of our studies, the following conclusions can be drawn:

1. Through careful selection and combination of ECG abnormalities that best reflect the main cardiac pathophysiological components of acute pulmonary embolism, a bedside usable score system has been developed that is free of subjectivity and thus standardizable, making electrocardiography an established tool in the diagnostic process of acute pulmonary embolism not only in identifying severe cases but also in assessing pretest probability and exclusion.
2. Due to the superiority in sensitivity, negative predictive value, test accuracy and negative likelihood ratio, the diagnostic accuracy of our ECG score is superior to the Daniel ECG score and prediction rules endorsed by the current ESC guidelines for determining the pretest probability of acute pulmonary embolism.
3. In our population sample, a high-sensitivity D-dimer test could be safely used as a stand-alone test to exclude acute pulmonary embolism among symptomatic emergency department patients, not on anticoagulant treatment independent of the pretest probability of acute pulmonary embolism as determined by clinical prediction rules.

7. Summary

In the current ESC guideline, electrocardiography is mentioned as a test that may assist empirical clinical judgement in some cases but is not listed as a recommended diagnostic procedure in the diagnostics of acute pulmonary embolism. Our clinical experience has shown that it is a valuable method, so in our studies, we developed an ECG score for the assessment of the pretest probability of acute pulmonary embolism. The rationale of constructing our ECG score was to select ECG abnormalities that reflect well the pathomechanism and cardiac effects of acute pulmonary embolism and are highly indicative of right ventricular ischemia, strain, dilatation and conduction disturbances that are due to acute pulmonary embolism. We have developed a standardizable, bedside available technique for all healthcare settings that is superior to a previous pulmonary embolism ECG score, the Daniel score and the ESC guideline-endorsed pretest-probability prediction scores like Wells scores and Geneva scores in sensitivity, negative predictive value, test accuracy and negative likelihood ratio. Therefore, the ECG can legitimately claim a place in diagnosing acute pulmonary embolisms, not only in identifying severe cases but also in assessing pretest probability and exclusion.

Stating that a normal result does not exclude pulmonary embolism with safety in cases of high clinical probability, the ESC guideline recommends against D-dimer testing. In our study population, patients with symptoms of acute pulmonary embolism in the emergency department, a negative result of the high-sensitivity D-dimer test with a false-negative rate of <1%, regardless of pretest probability, safely excluded acute pulmonary embolism. This result further supports the accumulating evidence that a negative result of a D-dimer test with sufficiently high sensitivity should be acceptable as a stand-alone diagnostic test for the exclusion of pulmonary embolism, independent of pretest probability.

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10. Acknowledgements

I am grateful to many people for their continuous support, without whom the present thesis could not have been written. First, I would like to thank my scientific supervisor, Professor András Vereckei, for his continued support. I express my sincere gratitude to Professor Zoltán Járai, who provided the background to my research, continuously supported me, and always led me in the right direction. I thank all my co-authors, especially Viktória Baracsi-Botos and Bertalan Szőke, for their invaluable support in the scientific field and clinical practice. I also thank all former and current colleagues of the Department of Cardiology at Saint Imre University Teaching Hospital. Finally, words cannot express my gratitude to my wife and family for their lifelong support, patience and love.