Usefulness of a Novel Electrocardiographic Score to Estimate the Pre-Test Probability of Acute Pulmonary Embolism

András Vereckei, MD, PhD[a,1,*], András Simon, MD[b,1], Gábor Szénási, MS, PhD[c], Gábor Katona, MD[a], László Hankó, MD[a], Mónika Krix, MD[a], Vince Bertalan Szőke, MD[b], Viktória Baracsi Botos, MD[b], Zoltán Járai, MD, PhD[b,1], and Tamás Masszi, MD, PhD[a,1]

According to our experience the 12-lead electrocardiogram (ECG) may be used to estimate the pretest probability of acute pulmonary embolism (acPE). To this end, we devised a novel ECG score (nECGs) composed of 5 known ECG criteria, best characterizing the key pathogenetic steps of acPE. A retrospective derivation cohort including 136 patients with acPE and a prospective validation cohort including 149 consecutive patients were used to devise and validate the nECGs. The latter cohort consisted of 76 patients with acPE and 73 controls presenting with characteristic symptoms of acPE, in whom the work-up ruled out acPE. We compared the diagnostic value of our nECGs with those of another ECG score (Daniel-ECG-score) and of the best prediction rules (3 Wells score and 2 Geneva score variants). The sensitivity (98.7%), negative predictive value (98%), test accuracy (84.4%) and the negative likelihood ratio (LR) (0.019) of the nECGs were superior to those of all other investigated methods. There was no between-groups difference in the positive LR. The specificity (69%) of the nECGs was inferior to those of the Daniel-ECG-score and Wells scores and did not differ or was superior to those of the Geneva score variants. The positive predictive value (77.3%) of the nECGs was superior to those of the 2 Geneva scores and did not differ from those of the other methods. In conclusion, the nECGs due to its superior sensitivity, negative predictive value, test accuracy, and negative LR estimated the pretest probability of acPE better than the Daniel-ECG-score and the prediction rules. **© 2020 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license. (http://creativecommons.org/licenses/by/4.0/)** **(Am J Cardiol 2020;130:143−151)**

Our clinical experience, in contrast to the current ESC acute pulmonary embolism (acPE) guideline,[1] suggests, that the 12-lead electrocardiogram (ECG) can be applied to estimate the pretest probability of acPE, which can be assessed by empiric clinical judgment, that can use the ECG, but lacks standardization, or by standardized prediction rules, such as the Wells and Geneva scores, that do not include the ECG.[1] Most studies evaluated the application of the prediction rules together with the D-dimer test, there are only limited, indecisive data on their stand-alone diagnostic value in the diagnosis of acPE.[2−4] An optimal sensitivity ELISA D-dimer test in randomized studies could rule out acPE or deep venous thrombosis irrespective of clinical probability[5−7] and the specificity and positive predictive value of the prediction rules are suboptimal,[4] not strongly supporting the use of the prediction rules. Our aim was to devise an ECG score with a better diagnostic value than the best prediction rules in the determination of pretest acPE probability. To this end, we devised an ECG score from 5 known ECG criteria, which best reflect the key pathogenetic steps of acPE.

Methods

We conducted a retrospective study to devise the novel ECG score (nECGs) in a group of patients (derivation cohort) and then tested the established nECGs prospectively in a different set of patients (validation cohort) at the 3rd Department of Medicine, Semmelweis University and the Department of Cardiology, Saint Imre University Teaching Hospital.

In the retrospective study we collected 12-lead ECGs from 136 patients with verified acPE (derivation cohort) between 2012 and 2017 after applying the same inclusion and exclusion criteria as in the prospective study.

In the prospective study, which was conducted for 1 year and was finished recently, we enrolled 149 consecutive patients (validation cohort) admitted with characteristic symptoms of acPE, such as chest pain, dyspnea, collapse or loss of consciousness, hemoptysis, in whom a 12-lead ECG with complementary right-sided chest leads was recorded within 7 days from the onset of symptoms. Among the 149 patients 76 were verified to have acPE and 73 were control

[a]3rd Department of Medicine, Semmelweis University, Budapest, Hungary; [b]Department of Cardiology, Saint Imre University Teaching Hospital, Budapest, Hungary; and [c]Institute of Translational Medicine, Semmelweis University, Budapest, Hungary. Manuscript received April 18, 2020; revised manuscript received and accepted May 27, 2020.

[1]The first two authors contributed equally and the last two authors contributed equally as well to this work.See page 151 for disclosure information.

*Corresponding author: Tel.: 36-1-266-0926.

E-mail address: vereckei.andras@med.semmelweis-univ.hu (A. Vereckei).

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patients having cardiopulmonary disease associated with symptoms characteristic to acPE, in whom acPE was ruled out. The exclusion criteria were: the presence of 1) left bundle branch block, 2) persistent ventricular pacemaker rhythm; 3) if work-up failed to elucidate the underlying cause of the admission symptoms. Two patients were excluded from ECG analysis (1 due to the lack of chest leads, the other proved to have an atypical left bundle branch block), therefore the ECG scores were applied in 147 patients. The acPE diagnosis was verified or ruled out by chest CT angiography (125 of 149[85%] patients), lung scintigraphy (3 of 149[2%] patients) and negative high sensitivity ELISA D-dimer test (25 of 130[19%] patients). None of the patients with a negative D-dimer test experienced venous thromboembolism event during a 3-month follow-up. The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Scientific and Research Ethics Committee of the National Medical Research Council.

The rationale of the nECGs was the following

I. ECG criteria, which best reflected important components of the pathomechanism of acPE described below, were selected for the nECGs.

1) *transmural right ventricular ischemia*

In the acute stage ST segment elevation in the inferior leads, leads aVR, $V_{1\text{-}3}$, and right-sided $V_{4\text{-}6}$ leads ($R_{V4\text{-}6}$), and in the subacute stage T wave inversion in the inferior leads and $V_{1\text{-}3}$ are the characteristic alterations.

2) *right ventricular dilation, acute pulmonary arterial hypertension*

QR or qR complexes in lead V_1, QS, or QR complexes in leads $R_{V4\text{-}6}$ and Q wave in the inferior leads from the $S_1Q_{inferior}T_{inferior}$ criterion (explained by the posterior displacement of the initial depolarization vector, giving rise normally to the r wave in lead V_1 and the q wave in the anterolateral leads, directed left to right and anteriorly, which is rotated away from lead V_1, because the dilated right ventricle pushes backward and compress the left ventricle).[8–10]

3) *Right-sided intraventricular conduction disturbances (due to right ventricular ischemia, dilation and increased right ventricular wall tension)*

New incomplete or complete right bundle branch block, terminal r' wave in lead aVR, $S_1S_2S_3$ syndrome, S wave in leads I, aVL, $V_{4\text{-}6}$, slurring at the terminal part of the QRS, or fragmented QRS complexes in leads aVR and $V_{1\text{-}3}$ and inferior leads.

II. The other important guiding principle described by Kosuge et al[11,12] in the compilation of the nECGs was that simultaneous acute inferior and anteroseptal ischemic ECG alterations (T wave inversions) suggest acPE and not acute coronary syndrome.

Since inferior leads reflect the right ventricular inferior wall and leads aVR and V_1 ($V_{1\text{-}3}$) reflect the right ventricular outflow tract and anterior wall electrical activity, we expanded the observation of Kosuge et al[11,12] and assumed that the simultaneous presence of other alterations than T wave inversions (e.g., ST elevation, intraventricular conduction disturbance) in the above mentioned leads, suggest also acPE.

Greater nECGs value was given when more than 1 characteristic ECG alterations were simultaneously present in the typical leads (such as simultaneous ST elevation and T wave inversion) and/or when 1 characteristic ECG alteration was present in more than 1 typical lead simultaneously. The presence of each criterion of the nECGs resulted in 1 ECG score point, because their relative weight is approximately equal, due to their similar sensitivity, specificity, positive predictive and positive likelihood ratio values.[13,14]

Figure 1 shows the nECGs and Figure 2 shows a modified version of the nECGs, which was used in patients with right bundle branch block pattern.

The maximum value of the nECGs was 10 or 9 in patients without or with right bundle branch block pattern, respectively. If the nECGs value was ≥4, acPE diagnosis was established, and a <4 nECGs value suggested an acPE negative diagnosis.

In the derivation cohort we used a similar ECG score, but without the fifth criterion and the ECGs were analyzed by 1 investigator (AV). An acPE diagnosis was established if the ECG score was ≥3, a <3 score value suggested an acPE negative diagnosis.

Intraventricular conduction disturbances were defined according to the 2009 AHA/ACCF/HRS recommendations[15] with some modifications concerning the definition of left bundle branch block proposed by Strauss et al[16]. QRS fragmentation and slurring were defined according to Das et al[17] and Macfarlane et al[18] respectively.

We compared the diagnostic value of our nECGs with that of the Daniel-ECG-score[19] (Figure 3), the Wells (original, modified, simplified) and Geneva (revised, revised and simplified) scores and the D-dimer test in the estimation of pretest probability of acPE. Figure 4 demonstrates the practical application of the nECGs in 2 representative cases.

In the prospective study 2 investigators (AV and AS) blinded to the final clinical diagnosis analyzed all ECGs, by applying the nECGs and the Daniel-ECG-score. The 2 investigators disagreed in the diagnosis of 22 ECGs using the nECGs and of 5 ECGs using the Daniel-ECG-score, but after re-evaluation of these cases they could resolve the disagreement by consensus. Data based on the consensus of the 2 investigators are presented.

Sensitivity, specificity and predictive values were calculated by GraphPadPrism version 6 for Windows (GraphPad Software Inc., La Jolla, CA, USA) and compared using a modified chi-square test without adjustment for multiple comparisons. A $p < 0.05$ value was considered statistically significant. Significantly different likelihood ratios were indicated by disjoint (non-overlapping) 95% confidence intervals. The kappa statistic was performed to quantify overall interobserver agreement using the IBM SPSS Statistics 25 for Windows software

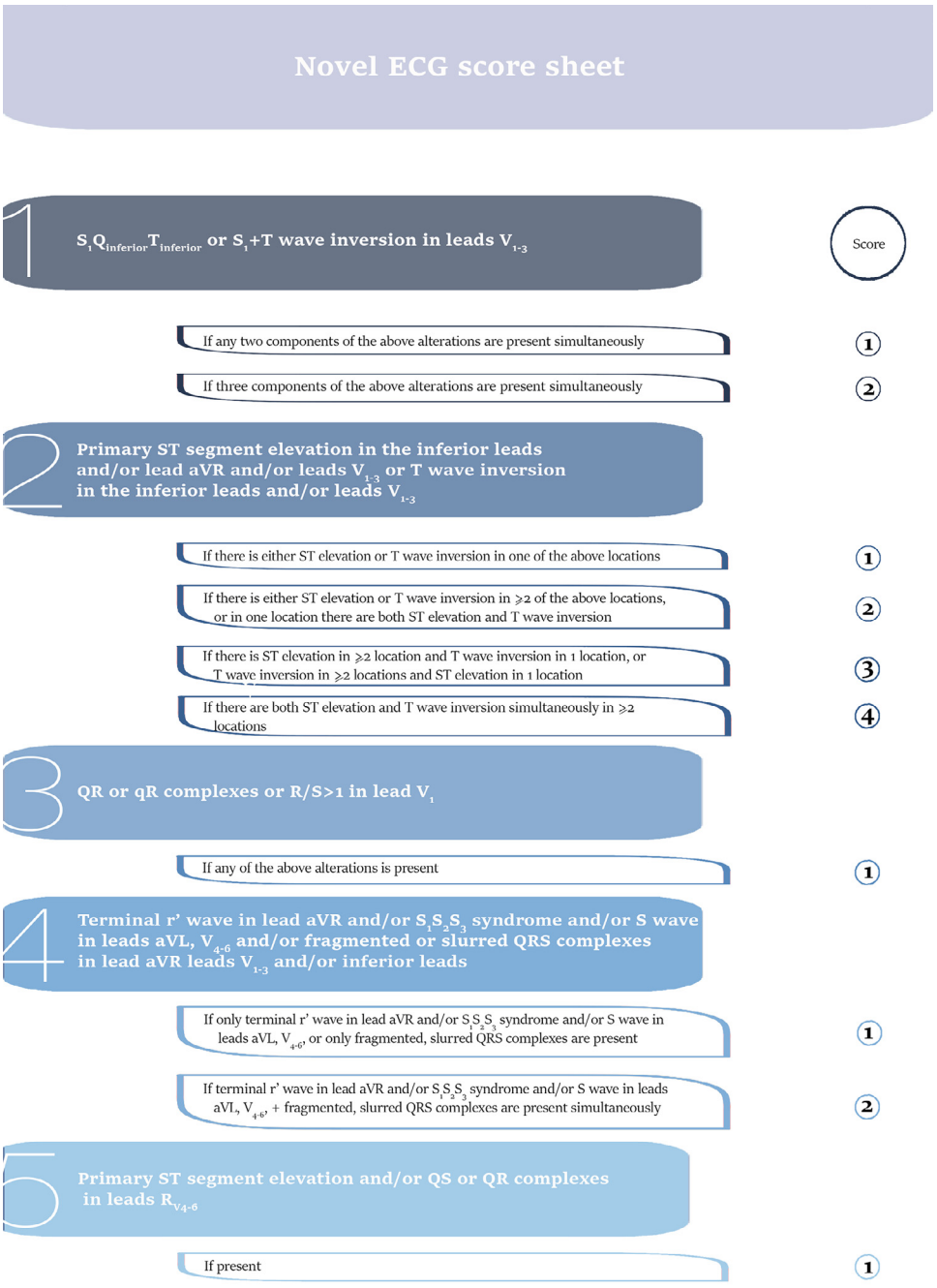

Figure 1. Novel ECG score sheet for patients without right bundle branch block (RBBB) pattern.

package (IBM Corp. Armonk, NY, USA). Overall inter-observer agreement was defined 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 $\kappa < 0.2$.[20]

Results

In the derivation cohort the nECGs established 119 of 136(87.5%) correct and 17 of 136(12.5%) false diagnoses indicating a very good test accuracy. However, in the retrospective study only ECGs from patients with acPE were analyzed, and we had the impression (without doing a systematic analysis) that the first version of the nECGs might give false positive results in a nonnegligible portion of control patients. Thus, to increase the positive predictive value and specificity, in the prospective study we included the fifth criterion in the final version of the nECGs and set a higher (≥4) nECGs value for acPE diagnosis.

In the validation cohort the nECGs established far less (1 of 50[2%]) ($p < 0.001$ for all) false negative acPE(-) diagnoses and a similar number of false positive acPE(+) diagnoses compared with those of other scores (Table 1), which is

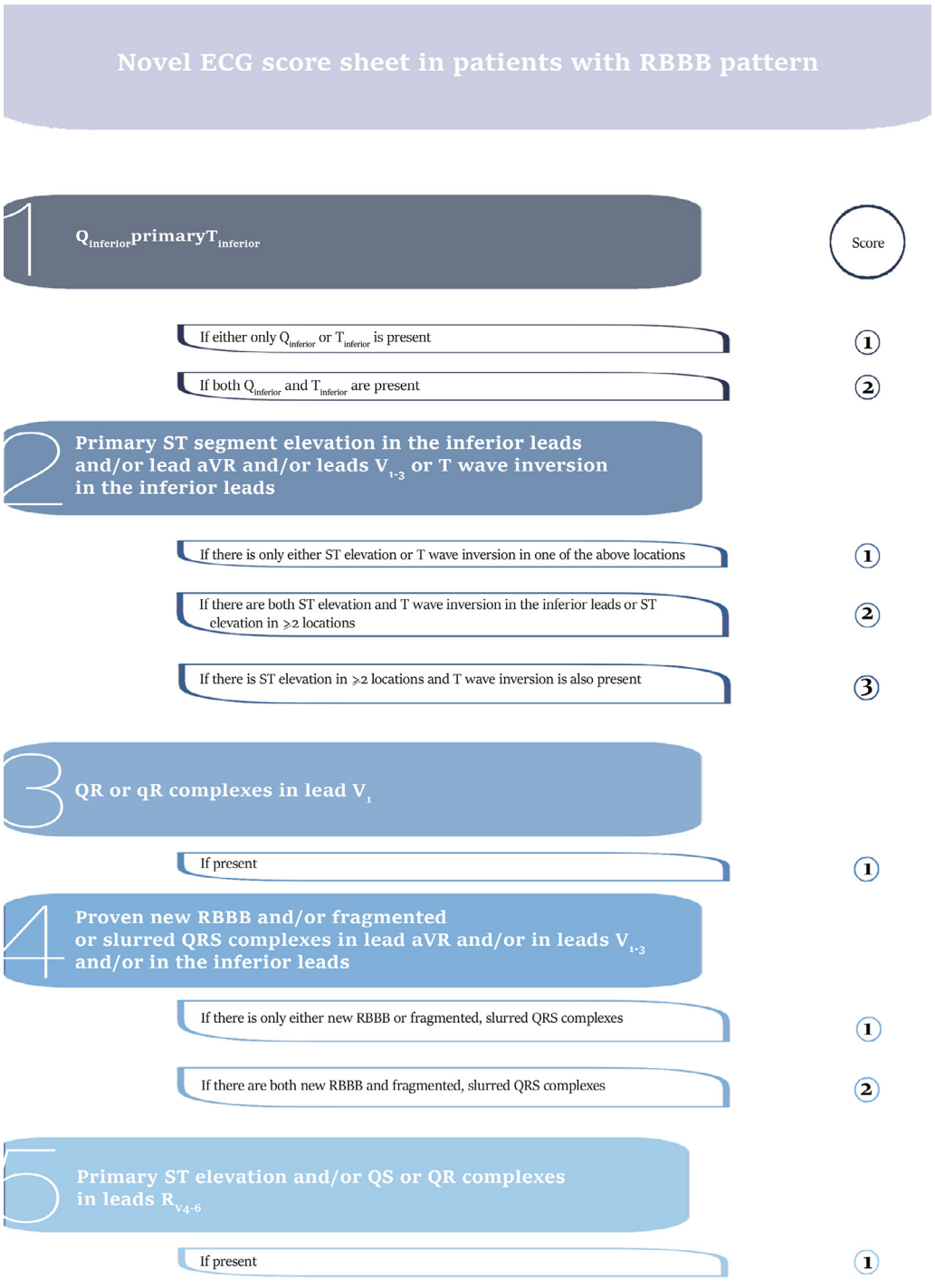

Figure 2. Novel ECG score sheet for patients with right bundle branch block (RBBB) pattern.

the basis of its better overall diagnostic performance. The very low percentage (2%) of false negative diagnoses by using the nECGs is close to the value (<1 to 2%) required from a reliable, stand-alone diagnostic test to safely rule out acPE, such as a CT or pulmonary angiography.[4,21]

The test accuracy of the nECGs (84.4%) was superior to those of the D-dimer test and all other investigated scores (Table 2). The ELISA D-dimer test had 100% sensitivity and negative predictive value and 0 negative likelihood ratio when either absolute cut-off (<500 μg/L) or age-adjusted cut-off values (age X 10 μg/L above 50 years) were used, because the negative D-dimer test safely ruled out acPE, but its specificity and positive predictive value were quite poor. The sensitivity and negative predictive value of the nECGs (98.7% and 98% respectively) were as high as those of D-dimer test and were superior to those of

Daniel-ECG-score

Characteristic		Score
Tachycardia (>100 beats/min)?		2
Incomplete right bundle branch block?		2
Complete right bundle branch block?		3
T wave inversion in all leads V_1 through V_4?		4
T wave inversion in lead V_1?	<1 mm	0
	1-2 mm	1
	>2 mm	2
T wave inversion in lead V_2?	<1 mm	1
	1-2 mm	2
	>2 mm	3
T wave inversion in lead V_3?	<1 mm	1
	1-2 mm	2
	>2 mm	3
S wave in lead I?		0
Q wave in lead III?		1
Inverted T wave in lead III?		1
If all of $S_IQ_{III}T_{III}$ is present, add		2

Figure 3. The Daniel-ECG-score sheet. Based on Figure 1 of Ref. 20 with minor modification. The maximum value of the Daniel ECG score is 21. If the score was ≥10, acPE(+) diagnosis, if it was <10, acPE(-) diagnosis was established.

all other scores. The positive predictive value (77.3%) of the nECGs was superior to those of the D-dimer test and both Geneva scores and tended to be superior to that of the Daniel-ECG-score ($p = 0.083$) and did not differ from those of the 3 Wells scores. The nECGs had similar negative likelihood ratio value (0.019) to that of D-dimer test and significantly lower than those of other scores. A good negative diagnostic test is characterized by a <0.1 negative likelihood ratio value and among all investigated methods only the nECGs and the D-dimer test fulfilled this requirement. There was no between-groups difference in the positive likelihood ratio. None of the methods reached the requirement of >10 positive likelihood ratio for a good positive diagnostic test. The nECGs had inferior specificity (69%) to those of the Daniel-ECG-score and all Wells scores, which did not differ from that of the revised, simplified Geneva score and was superior to those of the revised Geneva score and D-dimer test. The Wells scores performed better or similar to the Geneva scores with the exception of sensitivity.

In the case of a positive D-dimer test an acPE(-) diagnosis set up by the nECGs shows better the false positivity of the D-dimer test than any other method (Table 3). Furthermore, the acPE(+) diagnosis by the nECGs predicted at least as well the true positivity of the D-dimer test as the Wells scores and better than the Geneva scores and the Daniel-ECG-score.

After the initial evaluation, the interobserver agreement was near complete (κ: 0.934) using the Daniel-ECG-score and good (κ: 0.701) using the nECGs.

The severity of acPE was classified according to Stein et al[22] as massive, submassive and peripheral PE based on CT angiography results. The nECGs established a correct diagnosis in 59 of 59 (100%) patients with massive, 15 of 16(94%) patients with submassive, and -1 of 1(100%) patient with peripheral PE.

Discussion

The superior overall diagnostic accuracy of the nECGs to predict the pretest probability of acPE is based on its superior sensitivity, negative predictive value, test accuracy and negative likelihood ratio to those of all other investigated scores. Only the specificity of the nECGs was inferior to those of the Wells scores and the Daniel-ECG-score.

Wells et al[2] reported that the prevalence of verified acPE increased proportionally in patients with negative D-dimer test with the pretest probability of acPE determined by the original Wells score. However, the authors used SimpliRED D-dimer test of suboptimal sensitivity (approx.

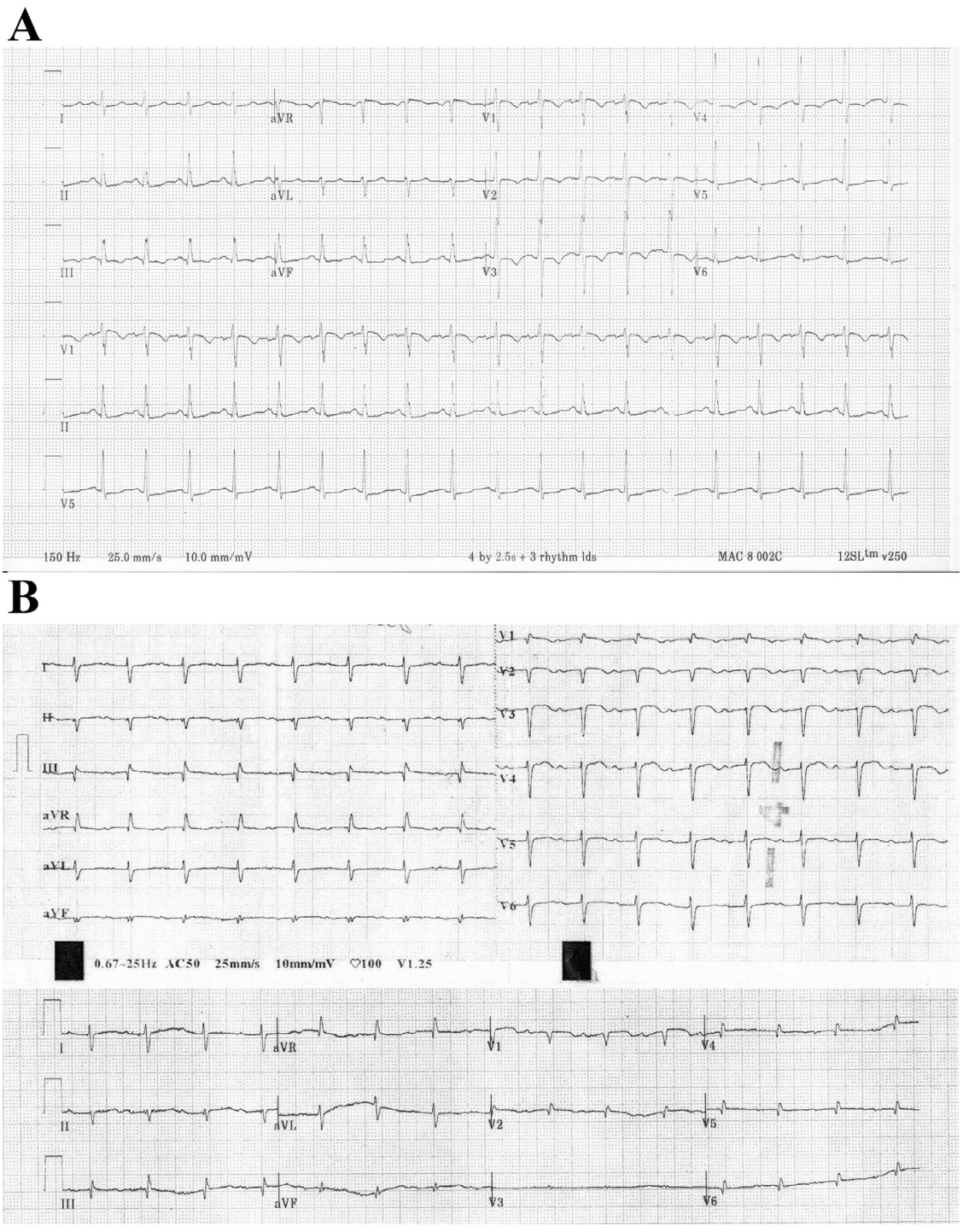

Figure 4. Practical application of the novel ECG score. **Panel A:** 12-lead ECG tracing recorded in a patient with acPE. 1st criterion: S_I and T_{III} and T wave inversions in leads V_{1-4} are present: 2 points, 2nd criterion: T wave inversions in leads III and V_{1-4} and mild ST segment elevations in leads aVR and V_1 are seen: 4 points, 3rd criterion: 0 point, 4th criterion: fragmented QRS complexes in all inferior leads, leads aVR and V_1 + terminal r' wave in lead aVR and S waves in leads aVL, V_{4-5} are present: 2 points, fifth criterion: 0 point (the right chest leads are not shown). Altogether 8/10 points, consistent with acPE diagnosis. **Panel B:** ECG tracings recorded in another patient diagnosed with acPE. The upper tracing shows the 12-lead ECG, the chest leads of the lower tracing are right sided chest leads of the same patient. Upper 12-lead ECG: 1st criterion: S_I,Q_{III},Q_{aVF} and T wave inversions in leads V_{1-3} are present: 2 points, 2nd criterion: T wave inversions in leads V_{1-3} and mild ST segment elevations in leads II, V_{1-4} are present: 3 points, 3rd criterion: QR complex is seen in lead V_1: 1 point, 4th criterion: fragmented QRS complexes in leads III and aVF + terminal R' wave in lead aVR and S waves in leads aVL and V_{4-6} are present: 2 points. Lower ECG tracing: fifth criterion: QR complexes are present in leads R_{V4-6}: 1 point. Lead R_{V3} cannot be analyzed due to electrode contact failure. Altogether 9/10 points, establishing the diagnosis of acPE.

Table 1
Percentage of false negative and false positive diagnoses with the investigated methods in the validation cohort

	FN/PE(-) dg	FP/PE(+) dg
Novel ECG score (n = 147)	1/50(2%)	22/97(23%)
Daniel ECG score (n = 147)	61/125(49%)***	7/22(32%)
Wells score original (n = 149)	36/98(35%)***	11/51(21.6%)
Wells score modified (n = 149)	34/95(36%)***	12/54(22%)
Wells score simplified (n = 149)	30/88(34%)***	15/61(24.6%)
Geneva score revised (n = 149)	25/66(38%)***	33/83(40%)
Geneva score revised, simplified (n = 149)	27/71(38%)***	29/78(37%)

*** $p < 0.001$ versus novel ECG score, FN = false negative, FP = false positive.

83%) instead of an ELISA D-dimer test of optimal sensitivity (96% to 97%).[23] When ELISA D-dimer tests with optimal sensitivity were used alone to rule out acPE, the venous thromboembolism rate was <1 to 2%, as low as after a normal pulmonary angiography in patients left without anticoagulant treatment during a 3-month follow-up.[21] Considering the ≤1% false negative results with the ELISA D-dimer tests, they could safely rule out acPE or deep venous thrombosis in 3 randomized studies irrespective of the clinical probability.[5-7] Thus, despite the recommendations in the literature and acPE guideline,[1,21,24] the high sensitivity ELISA D-dimer test in itself may be sufficient to rule out acPE irrespective of the pretest probability of acPE. The nECGs seems much more appropriate to confirm the diagnosis of a negative D-dimer test, due to its very

Table 2
The sensitivity, specificity, test accuracy, predictive values and likelihood ratios of the tested methods in the validation cohort

Methods **(n)**	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	TA % (95% CI)	-LR (95% CI)	+LR (95% CI)
novel ECG score	**98.7%**	**69%**	**77.3%**	**98%**	**84.4%**	**0.019**	**3.185**
(n = 147)	(96.1-101.2)	(58.3-79.8)	(69-85.7)	(94.1-101.9)	(78.5-90.2)	(0.003-0.134)	(2.249-4.511)
Daniel ECG score	**19.7%**$^{***,\ddagger\ddagger\ddagger,\spadesuit\spadesuit\spadesuit}$	**90.1%*****	**68.2%**	**51.2%*****	**53.7%**$^{***,\spadesuit\spadesuit}$	**0.89**	**2.002**
(n = 147)	(10.8-28.7)	(83.2-97.1)	(48.7-87.6)	(42.4-60)	(45.7-61.8)	(0.778-1.02)	(0.867-4.622)
Wells score orig.	**52.6%**$^{***,\dagger,\blacklozenge,\ddagger\ddagger\ddagger,\spadesuit\spadesuit\spadesuit,\#\#\#}$	**84.9%**$^{**,\dagger\dagger\dagger,\blacklozenge\blacklozenge\blacklozenge,\spadesuit\spadesuit\spadesuit,\ddagger\ddagger\ddagger}$	**78.4%**$^{\dagger\dagger\dagger,\spadesuit\spadesuit,\#}$	**63.3%**$^{***,\spadesuit\spadesuit\spadesuit,\ddagger\ddagger\ddagger,\#}$	**68.5%**$^{**,\#\#}$	**0.558**	**3.493**
(n = 149)	(41.4-63.9)	(76.7-93.1)	(67.1-89.7)	(53.7-72.8)	(61-75.9)	(0.432-0.72)	(1.946-6.269)
Wells score mod.	**55.3%**$^{***,\dagger,\#\#\#,\ddagger\ddagger\ddagger,\spadesuit\spadesuit\spadesuit}$	**83.6%**$^{**,\dagger\dagger\dagger,\blacklozenge\blacklozenge\blacklozenge,\spadesuit\spadesuit\spadesuit,\ddagger\ddagger\ddagger}$	**77.8%**$^{\dagger\dagger,\blacklozenge\blacklozenge,\ddagger\ddagger\ddagger,\spadesuit\spadesuit\spadesuit}$	**64.2%**$^{***,\spadesuit\spadesuit\spadesuit,\ddagger\ddagger\ddagger,\#}$	**69.1%**$^{**,\#\#}$	**0.535**	**3.362**
(n = 149)	(44.1-66,4)	(75.1-92.1)	(66.7-88.9)	(54.6-73.9)	(61.7-76.5)	(0.409-0,701)	(1.929-5.858)
Wells score sim.	**60.5%**$^{***,\#\#\#,\ddagger\ddagger\ddagger,\spadesuit\spadesuit\spadesuit}$	**79.5%**$^{*,\dagger\dagger\dagger,\blacklozenge\blacklozenge\blacklozenge,\spadesuit\spadesuit\spadesuit,\ddagger\ddagger\ddagger,\#}$	**75.4%**$^{\dagger\dagger,\blacklozenge,\spadesuit\spadesuit\spadesuit,\ddagger\ddagger\ddagger}$	**65.9%**$^{***,\spadesuit\spadesuit\spadesuit,\ddagger\ddagger\ddagger,\#}$	**69.8%**$^{**,\#\#}$	**0.497**	**2.946**
(n = 149)	(49.5-71.5)	(70.2-88.7)	(64.6-86.2)	(56-75.8)	(62.4-77.2)	(0.367-0.672)	(1.811-4.79)
Geneva score rev.	**67.1%**$^{***,\#\#\#,\ddagger\ddagger\ddagger,\spadesuit\spadesuit\spadesuit}$	**54.8%**$^{*,\#\#\#}$	**60.7%****	**61.5%**$^{***,\spadesuit\spadesuit\spadesuit,\ddagger\ddagger\ddagger}$	**61.1%*****	**0.6**	**1.484**
(n = 149)	(56.5-77.7)	(43.4-66.2)	(50.3-71.2)	(49.7-73.4)	(53.2-68.9)	(0.409-0.88)	(1.102-1.999)
Geneva score rev., sim.	**64.5%**$^{***,\#\#\#,\ddagger\ddagger\ddagger,\spadesuit\spadesuit\spadesuit}$	**60.3%**$^{\#\#\#}$	**62.8%****	**62%**$^{***,\spadesuit\spadesuit\spadesuit,\ddagger\ddagger\ddagger}$	**62.4%*****	**0.589**	**1.623**
(n = 149)	(53.7-75.2)	(49-71.5)	(52.1-73.5)	(50.7-73.3)	(54.6-70.2)	(0.413-0.841)	(1.169-2.253)
D-dimer 500 ng/ml cv.	**100%**	**22.1%*****	**53.5%*****	**100%**	**58.9%*****	**0**	**1.283**
(n = 129)	(100-100)	(12.2-31.9)	(44.4-62.7)	(100-100)	(50.4-67.4)	(0-0)	(1.131-1.456)
D-dimer age-adj. cv.	**100%**	**36.2%*****	**57.7%*****	**100%**	**65.9%*****	**0**	**1.568**
(n = 129)	(100-100)	(24.9-47.6)	(48.2-67.2)	(100-100)	(57.7-74.1)	(0-0)	(1.313-1.873)

Statistical comparison was performed only between the sensitivity, specificity, predictive values and test accuracy of the novel ECG score, Daniel ECG score, Wells and Geneva score variants and D-dimer test. Significant between-groups difference in the likelihood ratios is indicated by disjoint (non-overlapping) 95% confidence intervals.

* $p < 0.05$,
** $p < 0.01$,
*** $p < 0.001$ 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,
$^{\blacklozenge}$ $p < 0.05$,
$^{\blacklozenge\blacklozenge}$ $p < 0.01$,
$^{\blacklozenge\blacklozenge\blacklozenge}$ $p < 0.001$ versus Geneva score revised, simplified,
‡ $p < 0.05$,
‡‡ $p < 0.01$,
‡‡‡ $p < 0.001$ versus D-dimer 500 μg/L cutoff value,
$^{\spadesuit}$ $p < 0.05$,
$^{\spadesuit\spadesuit}$ $p < 0.01$,
$^{\spadesuit\spadesuit\spadesuit}$ $p < 0.001$ versus D-dimer age-adjusted cutoff value. Red colored numbers indicate those parameters of the novel ECG score, which were superior to those of the Daniel ECG score and all Wells and Geneva score variants. 95% CI = 95% confidence intervals, adj = adjusted, cv =c utoff value,-LR = negative likelihood ratio, +LR = positive likelihood ratio, mod. = modified, NPV = negative predictive value, orig. = original, PPV = positive predictive value, rev. = revised, sim. = simplified, TA = test accuracy.

Table 3
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 validation cohort

Methods D-dimer test age-adjusted cut-off value PE(+) dg. (n = 104)	Sensitivity	Specificity	PPV	NPV	TA
+novel 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%***

* $p < 0.05$,
** $p < 0.01$,
*** $p < 0.001$ 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 Wells score simplified. NPV= negative predictive value, PPV = positive predictive value, TA = test accuracy.

high sensitivity and negative predictive value and very low negative likelihood ratio, than any prediction rule variant indicating low or intermediate pretest probability. Due to its very low negative likelihood ratio value (0.019), the nECGs can rule out as well or better acPE than a normal ventilation/perfusion lung scan (negative LR: 0.1).[23] Furthermore, the acPE(-) nECGs diagnosis predicts the false positivity of the D-dimer test with a high probability and better than the prediction rules indicating a low pretest acPE probability.

Many individual ECG alterations were described in patients with acPE, which are difficult to memorize and all have a low sensitivity and specificity.[9,22,25] Therefore, the combination of several ECG criteria seems to be a better approach, as shown in the case of sudden cardiac death, where an ECG score consisting of 5 ECG criteria significantly improved risk prediction compared with single ECG parameters.[26] The Daniel-ECG-score,[19] the only ECG score devised so far for the diagnosis of acPE, did not produce convincing results. The very good overall diagnostic value of our nECGs in the estimation of acPE pretest probability can be due to the carefully selected ECG criteria, which best reflect the most important pathogenetic components of acPE. The same reason explains the good performance of the classic $S_1Q_3T_3$ criterion, because its 3 criteria reflect 3 different pathogenetic steps of acPE: S_1 reflects right-sided intraventricular conduction disturbance, Q_3 reflects the posterior displacement of the initial QRS vector due to right ventricular dilation and T_3 reflects subacute transmural right ventricular ischemia.

Our study has several limitations. Larger multicenter studies are needed to confirm the diagnostic value of our nECGs, as we enrolled relatively small number of patients in our study. The greater number of acPE than control patients despite the enrollment of all suitable patients consecutively in the study, without any selection after considering the inclusion and exclusion criteria, represents an unintended selection bias and an important limitation of our study. The explanation for this is that cardiologists and/or internists performed this study and some control patients who had negative D-dimer test at the emergency department and/or their further hospitalization was not necessary at the cardiology or internal medicine departments were lost for the study. The inadequacy of the nECGs for application in patients with left bundle branch block and persistent pacemaker rhythm, and the underrepresentation of patients with peripheral PE in our study are also important limitations.

In conclusion, based on our results ECG claims a role in the rule out diagnostic work-up of acPE. Due to its very high sensitivity, negative predictive value, and very low negative likelihood ratio value the nECGs can be used alone or together with a negative D-dimer test to rule out acPE more reliably than the low or intermediate pretest acPE probability determined by the prediction rules. The nECGs can more reliably indicate the false positivity of the D-dimer test than the Daniel-ECG-score and the low pretest probability by the prediction rules. The acPE(+) diagnosis by the nECGs may further increase the likelihood of acPE when the D-dimer test is positive and there is a high pretest probability of acPE by the prediction rules. Due to its sufficiently high positive predictive value, the acPE(+) diagnosis established by the nECGs in patients with a positive D-dimer test justifies the performance of a chest CT angiography, even without the application of a prediction rule. Thus, without questioning the extensively validated diagnostic value of the clinical prediction rules in the estimation of pretest probability of acPE, we state that the nECGs is superior to them in this aspect. We recommend to record also

right-sided chest leads in all patients admitted with acute cardiopulmonary symptoms, which, in addition to the verification or exclusion of right ventricular myocardial infarction, renders possible the application of the nECGs for the estimation of the pretest probability of acPE.

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Disclosures

The authors have no conflicts of interest to disclose.

Author Contributions

A. V. devised the nECGs, A. V. and A. S. analyzed the ECGs, A. V., A. S., G. S., Z. J., and T. M. had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis and contributed substantially to the study design, data interpretation, and the writing of the manuscript. G. K., L. H., M. K., V. B. S., and V. B. B. contributed significantly to the enrollment of patients, collection of data, data interpretation and critical revision of the manuscript.

Declaration of Interests

The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this paper.

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