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PROGRESSIVE CLINICAL PRACTICE

# Findings From 12-lead Electrocardiography That Predict Circulatory Shock From Pulmonary Embolism: Systematic Review and Meta-analysis

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## Abstract

***Objectives:*** Treatment guidelines for acute pulmonary embolism (PE) recommend risk stratifying patients to assess PE severity, as those at higher risk should be considered for therapy in addition to standard anticoagulation to prevent right ventricular (RV) failure, which can cause hemodynamic collapse. The hypothesis was that 12-lead electrocardiography (ECG) can aid in this determination. The objective of this study was to measure the prognostic value of specific ECG findings (the Daniel score, which includes heart rate > 100 beats/min, presence of the S1Q3T3 pattern, incomplete and complete right bundle branch block [RBBB], and T-wave inversion in leads V1–V4, plus ST elevation in lead aVR and atrial fibrillation suggestive of RV strain from acute pulmonary hypertension), in patients with acute PE.

***Methods:*** Studies were identified by a structured search of MEDLINE, PubMed, EMBASE, the Cochrane library, Google Scholar, Scopus, and bibliographies in October 2014. Case reports, non-English papers, and those that lacked either patient outcomes or ECG findings were excluded. Papers with evidence of a predefined reference standard for PE and the results of 12-lead ECG, stratified by outcome (hemodynamic collapse, defined as circulatory shock requiring vasopressors or mechanical ventilation, or in hospital or death within 30 days) were included. Papers were assessed for selection and publication bias. The authors also assessed heterogeneity ($I^2$) and calculated the odds ratios (OR) for each ECG sign from the random effects model if $I^2 > 24\%$ and fixed effects if $I^2 < 25\%$. Funnel plots were used to examine for publication bias.

***Results:*** Forty-five full-length studies of 8,209 patients were analyzed. The most frequent ECG signs found in patients with acute PE were tachycardia (38%), T-wave inversion in lead V1 (38%), and ST elevation in lead aVR (36%). Ten studies with 3,007 patients were included for full analysis. Six ECG findings (heart rate > 100 beats/min, S1Q3T3, complete RBBB, inverted T waves in V1–V4, ST elevation in aVR, and atrial fibrillation) had likelihood and ORs with lower-limit 95% confidence intervals above unity, suggesting them to be significant predictors of hemodynamic collapse and 30-day mortality. OR data showed no evidence of publication bias, but the proportions of patients with hemodynamic collapse or death and S1Q3T3 and RBBB tended to be higher in smaller studies. Patients who were outcome-negative had a significantly lower mean ± SD Daniel score (2.6 ± 1.5) than patients with hemodynamic collapse (5.9 ± 3.9; $p = 0.039$, ANOVA with Dunnett's post hoc), but not patients with all-cause 30-day mortality (4.9 ± 3.3; $p = 0.12$).

***Conclusions:*** This systematic review and meta-analysis revealed 10 studies, including 3,007 patients with acute PE, that demonstrate that six findings of RV strain on 12-lead ECG (heart rate > 100 beats/min, S1Q3T3, complete RBBB, inverted T waves in V1–V4, ST elevation in aVR, and atrial fibrillation) are associated with increased risk of circulatory shock and death.

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Treatment guidelines recommend that clinicians employ a clinical strategy that includes the risk stratification of patients with pulmonary embolism (PE) to estimate the probability of circulatory shock and 30-day all-cause mortality.[1,2] Experts generally agree that patients with PE and right ventricular (RV) failure have an elevated risk of hemodynamic collapse and should be considered for additional treatment beyond standard anticoagulation, including fibrinolytic therapy.[1–3] Patients with low-risk PE might be considered for immediate treatment at home.[4–6] Well-recognized methods for risk stratification include scoring systems, blood biomarkers (troponins I and T, brain natriuretic peptides), echocardiographic findings of RV strain, and findings of a dilated RV on computed tomography (CT) scanning.[3,7,8] The 12-lead electrocardiogram (ECG) also provides information about severity of PE. A scoring system was developed by Daniel et al.[9] in 2001 that assigns points (0 to 21) to ECG components that predicted increased pulmonary arterial pressure (Figure 1). The Daniel score was found to correspond to the degree of perfusion defect on ventilation-perfusion lung scanning, and a score > 8 predicted worsened clinical outcomes, including death, shock, or respiratory failure.[10] However, the weights given to the Daniel score components were derived implicitly, and many clinicians believe that other findings, such as ST elevation in the aVR lead and atrial arrhythmias, predict worse outcome from PE.

The purpose of this study was to measure the prognostic value of ECG findings indicative of RV strain from acute pulmonary hypertension in patients with acute PE. To accomplish this, we conducted a systematic literature review and meta-analysis to quantify the value of each component of the Daniel score, plus ST elevation in aVR and atrial fibrillation, for the prediction of hemodynamic collapse or death within 30 days in acute PE.

## METHODS

### Study Design

This was a systematic review and meta-analysis. Methods for paper selection and reporting followed the

| Characteristic | | Present | Absent | Score |
|---|---|---|---|---|
| Tachycardia (>100 beats/min)? | | ☐ | ☐ | 2 |
| Incomplete Right Bundle Branch Block? | | ☐ | ☐ | 2 |
| Complete Right Bundle Branch Block? | | ☐ | ☐ | 3 |
| T wave inversion in all leads V1 through V4? | | ☐ | ☐ | 4 |
| T wave inversion in lead V1?: *If Present Check Maximum only. If absent, leave blank.* | < 1 mm | ☐ | ☐ | 0 |
| | 1 – 2 mm | ☐ | ☐ | 1 |
| | > 2 mm | ☐ | ☐ | 2 |
| T wave inversion in lead V2?: *If Present Check Maximum only. If absent, leave blank.* | < 1 mm | ☐ | ☐ | 1 |
| | 1 – 2 mm | ☐ | ☐ | 2 |
| | > 2 mm | ☐ | ☐ | 3 |
| T wave inversion in lead V3?: *If Present Check Maximum only. If absent, leave blank.* | < 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 SI QIII TIII is present, add | | | | 2 |
| | | | | Max = 21 |

**Figure 1.** Daniel score for prediction of cardiac stress associated with acute pulmonary embolism. (Reproduced, with permission, Chest 2001;120:474–81).

guidelines set forth by the PRISMA statement and those recommended by the MOOSE standardized reporting guidelines.[11,12] This study was registered at http://www.crd.york.ac.uk/PROSPERO/ on December 16, 2014 (CRD42014015502).

### Study Setting and Population

This study included a population of patients with acute PE, proven by diagnostic testing, with available 12-lead ECG. Patients presented in multiple settings and were not limited to those diagnosed in the emergency department (ED). Full inclusion and exclusion criteria are described in further detail below.

### Study Protocol

***Literature Search.*** In October 2014, we performed a systematic search of MEDLINE, PubMed (for non-MEDLINE records), EMBASE, the Cochrane library, Google Scholar, and Scopus for studies that examined the value of ECG findings for predicting outcome in patients with PE. We also searched the proceedings of the annual scientific meetings of the American College of Cardiology, American College of Chest Physicians, and the American College of Emergency Physicians for the past 3 years. A supplemental PubMed search was performed in April 2015. Databases were searched from inception, and no additional year limits were applied. Search strategies combined database-specific subject headings and keyword variants for three main concepts—PE, ECG, and prognosis/predictive value. For the ECG concept, specific abnormalities usually diagnosed by ECG were also included in the searches (e.g., bundle branch block, arrhythmias, PR, QRS, QT intervals). Results were limited to the English language, and single case reports were excluded. Detailed search strategies are provided in Data Supplement S1 (available as supporting information in the online version of this paper). A master's-level medical librarian (TWE) conducted the database searches. We also searched the bibliographies of meta-analyses and book chapters on topics relevant to PE diagnosis and prognosis: clinical prediction rules,[7,13,14] clinical pathways and guidelines,[1,3,15–18] and other diagnostic methods.[19–21]

***Selection Process.*** Two authors (JDS, LKS) reviewed the results of the search for relevance and independently read the titles and abstracts of all retrieved citations. The same two authors then independently read the retained full-length articles that passed the initial relevance screen for inclusion in the final analysis. We assessed interobserver reliability with Cohen's kappa. Discordances were resolved by consensus with a third author (JAK) as arbiter.

***Inclusion and Exclusion Criteria.*** The initial inclusion criteria were studies of symptomatic patients who underwent objective diagnostic testing proving PE, which included data on risk factors for VTE. Diagnosis of PE required pulmonary vascular imaging demonstrating a filling defect on a contrast-enhanced study, unmatched perfusion defects on scintillation lung scan, or autopsy. Retained full-length articles were then read for the following criteria: evidence of a prospective or retrospective selection algorithm with a predefined reference standard for PE that included at least either pulmonary vascular imaging or mixed-objective testing plus clinical outcomes assessed until at least hospital discharge and the results of 12-lead ECG, stratified by outcome. The minimum ECG criteria required to include a study was the presence of heart rate, S1Q3T3 (a large S wave in lead I, a Q wave in lead III, and an inverted T wave in lead III), and right bundle branch block (RBBB) data. Exclusion criteria included the written statement that hemodynamically unstable patients were excluded, studies without adequate ECG criteria, and those studies that clearly indicated the data were nonadditive (i.e., redundant with previously published data), including secondary analyses of other published data. Hemodynamic collapse was defined as systolic blood pressure < 90 mm Hg requiring or associated with the use of vasopressors, need for endotracheal intubation, catheter or surgical thrombectomy, any use of thrombolytics, cardiopulmonary resuscitation, or extracorporal perfusion. Hemodynamic collapse was assessed up until day of discharge but not beyond; death was reported as all-cause and up to 30 days after PE diagnosis. Patients alive at 30 days without hemodynamic collapse were deemed "outcome-negative." The primary data for analysis are the total number of patients with PE and the number with each outcome. When necessary, we e-mailed the corresponding authors for additional data up to three times.

***Quality Assessment.*** We graded study quality using the Quality Assessment of Diagnostic Accuracy Studies tool (QUADAS-2), using a standard form.[22] Each study was graded as "low risk," "high risk," or "unclear risk" for bias in terms of selection of patients and reference standard. For patient selection, we considered a study low risk if it enrolled patients under conditions similar to what a physician is likely to experience in evaluating a patient with diagnosed PE in the absence of other influences. We considered patient selection bias at high risk if the paper or personal communication with the author indicated that patients were preselected or excluded for either more or less severity in terms of presentation (e.g., positive biomarker such as troponin or echocardiography). We considered the reference standard at low risk of bias if all patients included had positive pulmonary vascular imaging and had outcomes followed until hospital discharge. Studies without these criteria had a high-risk reference standard. Studies lacking sufficient criteria to understand patient selection or reference standard had an unclear risk.

### Outcomes

The main question of this work was to determine the quantitative value of each component in Figure 1 (heart rate over 100 beats/min, presences of the S1Q3T3 pattern, unspecified RBBB, incomplete and complete RBBB, and T wave inversion in leads V1–V4), plus ST elevation in aVR and atrial fibrillation, for the prediction of either death within 30 days of diagnosis or the development of hemodynamic collapse (defined below). This 30-day outcome includes papers that only reported in-hospital mortality, which usually occurs in the first week

after diagnosis. Findings of T-wave inversions in leads V1–V4 were simplified to a binary input (either present or absent), and RBBB was classified as incomplete, complete, or unspecified (incomplete, complete, or not stated). The primary unit of measurement was the prevalence of each finding in patients with and without the outcome, because these proportions form the basis of the likelihood and odds ratios (ORs).

### Data Analysis

We generated a table that included total number of PE+ patients, the number of PE+ patients that had each outcome, and the pooled true-positive and false-positive rates for each ECG finding. We assessed for heterogeneity between studies using the inconsistency indexes ($I^2$ and $I^2_v$), where $I^2$ represents the percentage of the total variability in a set of effect sizes due to true heterogeneity owing to between-studies variability; $I^2_v$ includes a random-effects correction term to account for variability in different populations sampled.[23] We calculated the likelihood ratios (LRs) and their 95% confidence intervals (CIs) directly from the pooled true-positive and false-positive proportions. We calculated the ORs for each variable from the random-effects model and the fixed-effects OR only if heterogeneity was low ($I^2 < 25\%$).[24] Unless otherwise stated, all CIs are from the random-effects model, otherwise they were calculated from the Clopper-Wilson exact binomial formula. The authors prepared a database in Microsoft Excel detailing the calculations for the pooled true-positive and false-positive rates and the random-effects calculations using the method of Neyeloff et al.;[23] a copy of the spreadsheet is available from the corresponding author. A funnel plot was used to examine for publication bias using Egger's test of asymmetry, with $p > 0.1$ considered absence of publication bias.[25] We also performed a post hoc sensitivity analysis to exclude one study with risk of bias. We calculated the mean Daniel score for patients based on outcome (negative, hemodynamic collapse, or all-cause death) and compared means (after normality testing with the Shapiro-Wilk test) with one-way analysis of variance with Dunnett's post hoc test to compare patients with death or hemodynamic collapse to patients who were outcome-negative as controls with $p < 0.05$ considered significant (StatsDirect, version 4.0).

## RESULTS

### Article Selection

The search revealed 3,680 unique titles and abstracts that were screened for relevance by two independent reviewers, with 45 selected for full-length review yielding a good combined interobserver reliability for retained studies ($\kappa = 0.94$; 95% CI = 0.89 to 1.0). Figure 2 shows the selection process, and Data Supplement S2 (available as supporting information in the online version of this paper) shows the characteristics of each study retained for full-length review, including elements of QUADAS-2. Additionally, Data Supplement S3 (available as supporting information in the online version of this paper) shows which ECG components were reported for each of the 45 papers reviewed in full, including the prevalence of each component. To provide context about what type of ECG data authors included, Table 1 shows the numbers of patients with each ECG finding that were reported, and the percentage of PE patients who manifested the ECG finding of all studies included in Data Supplement S2. The ECG features that were most frequently found in patients with PE were tachycardia (HR > 100 beats/min) and T-wave inversion in lead V1 (38% each) and ST elevation in the aVR lead (36%). The overall 30-day mortality across all patients

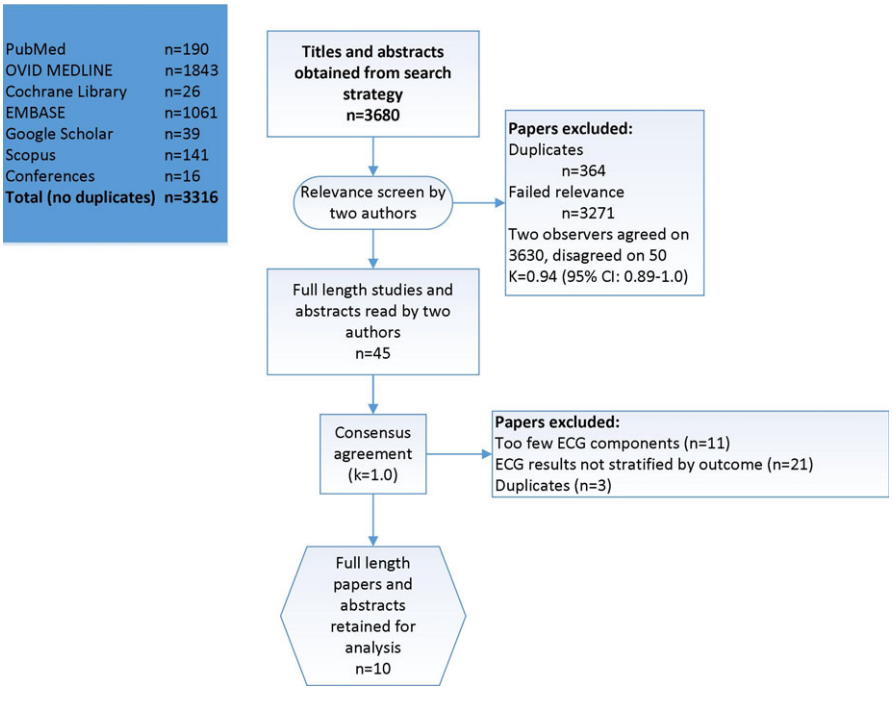


**Figure 2.** PRISMA diagram of the selection process for papers. ECG = electrocardiogram.

Table 1
Summary of Outcomes and ECG Findings of Patients With Pulmonary Embolism (All Studies in Data Supplement S2).

| Feature | Total No. of Patients With Finding | Total No. of Patients With Available Data | Prevalence, % | 95% CI |
|---|---|---|---|---|
| ECG findings | | | | |
| HR > 100 beats/min | 1,865 | 4,936 | 38 | 36.7–39.4 |
| S1 | 427 | 1,284 | 33 | 30.4–35.6 |
| Q3 | 296 | 919 | 32 | 29.0–35.0 |
| iT3 | 291 | 959 | 30 | 27.1–32.9 |
| S1Q3T3 | 1,273 | 5,382 | 24 | 22.9–25.1 |
| RBBB | | | | |
| Unspecified | 931 | 7,751 | 12 | 11.3–12.7 |
| Incomplete | 273 | 2,242 | 12 | 10.7–13.4 |
| Complete | 247 | 2,435 | 10 | 8.8–11.2 |
| T-wave inversion | | | | |
| V1–V4 | 1,314 | 4,463 | 29 | 27.7–30.3 |
| V1 | 277 | 736 | 38 | 34.5–41.5 |
| V2 | 169 | 714 | 24 | 20.9–27.1 |
| V3 | 125 | 583 | 21 | 17.7–24.3 |
| ST elevation in aVR | 749 | 2,054 | 36 | 33.9–38.1 |
| Afib | 449 | 2,995 | 15 | 13.7–16.3 |
| Outcomes | | | | |
| Hemodynamic collapse | 581 | 3,342 | 17 | 15.7–18.3 |
| Death | 541 | 5,368 | 10 | 9.2–10.8 |

Afib = atrial fibrillation; ECG = electrocardiogram; HR = heart rate; RBBB = right bundle branch block.

with acute PE reported in the initial 45 papers selected for full-length review was 10%.

Two readers had perfect agreement on their choices of 10 retained full-length papers included in the outcome analysis (Table 2; Kucher 2003,[26] Geibel 2005,[27] Toosi 2007,[28] Kostrubiec 2009,[29] Marchick 2009,[30] Kukla 2011,[31] Janata 2012,[32] Kukla 2014,[33] Agrawal 2014,[34] and Kukla 2015[35]). We also included data observed from a poster presentation (Hoechtl et al., 2009[36]) to supplement Janata et al.[32] All studies had adequate reference standards, ECG timing, ECG components, and ECG results reported by outcomes. Table 3 shows the clinical features of the 3,007 patients contained in these 10 studies. The mean age was approximately 60 years, and 57% of patients were female. The mortality ranged from 5% to 23% in those study populations included in the outcome analysis.

### Prognostic Value of ECG findings

Table 4 shows the main results, namely, the pooled true-positive rate and false-positive rate for each ECG finding stratified by outcome. These pooled data showed a wide range of heterogeneity, with $I^2$ and $I^2_V$ ranging from 0% to 96%. The LR data in Table 4 were calculated with outcome-negative patients considered disease-free and either hemodynamic collapse or death considered disease-positive. The LR values were calculated from the sensitivity and specificity values from the random-effects model and included patients with either hemodynamic collapse or death as disease-positive. These LR data suggest that six ECG findings can significantly alter prognosis of patients with PE (heart rate > 100 beats/min, S1Q3T3, complete RBBB, inverted T waves in V1–V4, ST elevation in aVR, and atrial fibrillation), assuming that ECG findings with both a negative LR (LR–) value with upper limit 95% CI below unity and a positive LR (LR+) value with a lower limit 95% CI above unity modify the probability of hemodynamic collapse or death. Table 5 shows the ORs from the random effects model and corroborates the LR data regarding which ECG findings are significant predictors of hemodynamic collapse or death.

We then calculated the numeric Daniel score for patients, stratified by outcome. For this calculation, we included an additional study by Kline et al.[37] that directly reported the Daniel score but not the results of the individual ECG components. The Shapiro-Wilk test showed no evidence of nonnormality ($p = 0.68$). Table 6 shows these data and associated p-values, indicating that patients who had hemodynamic collapse had significantly higher (mean ± SD = 5.9 ± 3.9) scores than patients who were outcome-negative (2.6 ± 1.5; $p = 0.039$, Dunnett's post hoc), but patients' all-cause mortality did not have a significantly elevated Daniel score (4.9 ± 3.3; $p = 0.12$).

### Publication Bias

For the OR data, the p values from Egger's tests indicated no evidence of publication bias for any of the three minimum required ECG criteria (heart rate > 100 beats/min, $p = 0.401$; S1Q3T3, $p = 0.826$; or RBBB, $p = 0.616$), and funnel plots were symmetric. Figure 3 shows the funnel plot for RBBB. However, we also produced funnel plots using the proportions of patients that were used to calculate the LR data in Table 4 (as opposed to the OR) with each of the ECG criteria in Table 4, and these suggested possible publication bias for S1Q3T3 ($p = 0.007$) and RBBB ($p < 0.001$). In both cases, the shapes of the funnel plots suggested that smaller studies tended to have higher proportions of patients with hemodynamic collapse or death with these two ECG findings.

Table 2
Ten Publications Included in the Outcome Analysis

| Citation | *N* | Age (yr), Mean ± SD | % Female | Design | Criterion Standard | Study Purpose and Relationship to ECG | ECG Timing Stated? | Minimal ECG Data Present? | ECG Results Stratified by Outcome? | Risk of Bias | Included in Main Analysis? |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Kucher 2003[26] | 75 | — | — | Prospective | CTA | ECG data related to troponin, RVSD, therapy, mortality | Yes | Yes | Yes | Low | Yes |
| Geibel 2005[27] | 508 | 63 ± 15 | 58 | Prospective | PA, high-probability V/Q scan or Doppler U/S | Comparison of ECG sings in survivors vs. nonsurvivors (30-day mortality) | No | Yes | Yes | High–no ECG timing | Yes |
| Toosi 2007[28] | 159 | 59 ± 18 | 55 | Retrospective | High-probability V/Q scan or CT | Comparison of ECG scores based on hospital course, mortality, and RV contraction | Yes | Yes | Yes | Low | Yes |
| Kostrubiec 2009[29] | 56 | 64 ± 17 | 61 | Retrospective | CT | Comparison of ECG scores based on complicated vs. uncomplicated course | Yes | Yes | Yes | Low | Yes |
| Marchick 2009[30] | 384 | 58 ± 18 | 55 | Prospective | CTA or V/Q | ECG performed at diagnosis | Yes | Yes | Yes | Low | Yes |
| Kukla 2011[31] | 292 | 65 ± 16 | 63 | Retrospective | CT, V/Q, ECHO, Doppler U/S, or autopsy | Comparison of ECG signs in patients w/death, survival + complications, and no complications | Yes | Yes | Yes | Low | Yes |
| Janata 2012[32] | 396 | 60 ± 19 | 52 | Retrospective | High probability V/Q scan or CTA | Comparison of ECG signs and mortality in intermediate and high risk groups | Yes | Yes | Yes | Low | Yes |
| Kukla 2014[33] | 500 | 65 ± 16 | 63 | Retrospective | CT, V/Q, ECHO, or autopsy | Comparison of ECG signs in patients +/– CS, then survival vs. death | Yes | Yes | Yes | Low | Yes |
| Agrawal 2014[34] | 200 | 44 | 39 | Prospective | CTPA or ECHO | Comparison of ECG signs in patients based on mortality and complications | Yes | Yes | Yes | Low | Yes |
| Kukla 2015[35] | 437 | 67 ± 15 | 61 | Retrospective | CTA, ECHO, or autopsy | ECG findings in +/– cardiogenic shock | Yes | Yes | Yes | Low | Yes |

CS = Cardiogenic shock; CTA = computed tomographic angiography; CTPA = CT pulmonary angiography; ECHO = echocardiography; ECG = electrocardiogram; PA = pulmonary angiography; RV = right ventricle; RVSD = right ventricular systolic dysfunction; U/S = ultrasound; V/Q = ventilation-perfusion.

Table 3
Clinical Information From the 10 Included Studies

| Study | *N* | Age (yr), Mean ± SD | % Female | Hemodynamic Collapse % (95% CI) | Death % (95% CI) |
|---|---|---|---|---|---|
| Kostrubiec 2009[26] | 56 | 64 ± 17 | 61 | 14 (4.9–23.1) | 7 (0.3–13.7) |
| Toosi 2007[28] | 159 | 59 ± 18 | 55 | 13 (7.8–18.2) | 7 (3.0–11.0) |
| Kukla 2014[33] | 500 | 65 ± 16 | 63 | 18 (14.6–21.4) | 10 (7.4–12.6) |
| Agrawal 2014[34] | 200 | 44 | 39 | 20 (14.5–25.5) | 18 (12.7–23.3) |
| Kukla 2011[31] | 292 | 65 ± 16 | 63 | 25 (20.0–30.0) | 11 (7.4–14.6) |
| Kucher 2003[26] | 75 | — | — | 27 (17.0–37.1) | 7 (1.2–12.8) |
| Janata 2012[32] | 396 | 60 ± 19 | 52 | — | 7 (4.5–9.5) |
| Geibel 2005[27] | 508 | 63 ± 15 | 58 | — | 23 (19.3–26.7) |
| Marchick 2009[30] | 384 | 58 ± 18 | 55 | 1 (0.0–2.0) | 5 (2.8–7.2) |
| Kukla 2015[35] | 437 | 67 ± 15 | 61 | 21 (17.2–24.8) | 9 (6.3–11.7) |
| Total | 3007 | — | 57 | 17 (15.7–18.3) | 10 (8.9–11.1) |

### Sensitivity Analysis

We recalculated the LR and OR data (using proportions calculated using the random effects model) after excluding one large study (Geibel et al.[27]). This study had a high risk of bias because it did not report ECG timing relative to death, did not report hemodynamic collapse, and only reported heart rate, S1Q3T3, and RBBB. For the recalculated heart rate > 100 beats/min, the LR+ was 2.24 (95% CI = 1.88 to 2.58), the LR– was 0.33 (95% CI = 0.22 to 0.50), and the OR was 6.58 (95% CI = 3.69 to 12.31); for S1Q3T3 the LR+ was 1.55 (95% CI = 1.26 to 1.88), the LR– was 0.84 (95% CI = 0.76 to 0.92), and the OR was 1.84 (95% CI = 1.35 to 2.49); for unspecified RBBB, the LR+ was 1.73 (95% CI = 1.33 to 2.23), LR– was 0.91 (95% CI = 0.85 to 0.96), and the OR was 1.90 (95% CI = 1.37 to 2.61); and for complete RBBB, the LR+ was 1.55 (95% CI = 0.90 to 2.61), the LR– was 0.95 (95% CI = 0.87 to 1.01), and the OR was 1.62 (95% CI = 0.81 to 3.04). Thus, exclusion of Geibel et al.[27] reduced the significance of the LR and OR data for complete RBBB.

## DISCUSSION

This systematic review and meta-analysis of 3,007 patients found six ECG findings (heart rate, S1Q3T3, cRBBB, inverted T waves in V1–V4, ST elevation in aVR, and atrial fibrillation) to predict hemodynamic collapse and death within 30 days after acute PE. These six findings had significant LR values and ORs from the random-effects model. Furthermore, calculation of the Daniel score, a previously derived 21-point ECG scoring system for severity of pulmonary hypertension from PE, was not significantly elevated in patients who died, but was significantly higher in patients who suffered hemodynamic collapse, than in those who were outcome-negative. These findings were not surprising, given that the majority of patients who die within 30 days after PE diagnosis succumb to other illness (e.g., cancer), whereas most patients who suffer hemodynamic collapse (or circulatory shock) have RV failure. Although we cannot determine the exact timing of the hemodynamic collapse for all studies, prior registries found that 90% of patients who develop circulatory shock do so within 24 hours of diagnosis, and most in-hospital deaths directly attributed to PE occur within 48 hours of diagnosis.[38–42] Thus, we believe these ECG findings have relevance to decision-making for patients with PE in the ED setting. Taken together, these results suggest the validity of the individual components of the Daniel score and generally support the use of ECG in the risk stratification of patients with acute PE.

The major strengths of this work include the pragmatic nature of the ECG and the large number of patients, confirming that several ECG components risk stratify patients with PE. Indeed, several of the ECG components (particularly heart rate, inverted T waves in leads V2 and V3, and ST elevation in aVR) had ORs higher than echocardiography findings of RV strain, an RV/LV ratio > 0.9 on CT scanning, or an elevated troponin I concentration.[1] The value of this review for the practicing clinician comes from the fact that the ECG is woven into the standard workflow of evaluating patients with symptoms of PE, is inexpensive and noninvasive, and can diagnose alternative disease processes. Recent meta-analyses of clinical trials of fibrinolysis for intermediate-risk PE have emphasized the need for careful patient selection both in terms of bleeding risk and risk of hemodynamic decompensation.[43–45] Normotensive patients with non-high bleeding risk and high risk of hemodynamic decompensation from RV failure may benefit from either systemic or catheter-directed fibrinolysis. We submit that the six ECG findings provide a composite biomarker of RV failure and thus provide specific bedside evidence of the need for intensive care services and therapies known to reduce pulmonary arterial pressure, including systemic or catheter-based fibrinolysis or possibly pulmonary selective vasodilation.[3,46] Moreover, the pooled data suggest that a Daniel score should be used in the decision to evaluate a patient with PE for possible home treatment.[6,47,48] Our data suggest that a patient with PE and a Daniel ECG score > 5, or ST elevation in aVR or atrial fibrillation, should be considered to have a risk of hemodynamic collapse that is too high to safely allow home treatment, even if the patient is low risk by other criteria.[7]

## LIMITATIONS

Limitations include the possibility that authors tended to be more likely to publish smaller papers that overrepresented the importance of an abnormal ECG in predicting a bad outcome from PE. However, neither the Egger's test nor the funnel plots for the OR data for

Table 4
Prevalence and Predictive Value of Findings From 12-lead ECG

| | Outcome negative* | | | | | Hemodynamic collapse* | | | | | Death | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ECG finding | *n* | % | %† | 95% CI† | $I^2/I^2_v$ | *n* | % | %† | 95% CI† | $I^2/I^2_v$ | *n* | % | %† | 95% CI† | $I^2/I^2_v$ | LR–† LR+† | 95% CI |
| HR ≥ 100 | | | | | | | | | | | | | | | | | |
| Y | 507 | 46.3 | 39.1 | 20.5–57.7 | 96 | 36 | 69.2 | 67.2 | ‡45.6–90.4 | 0 | 147 | 75.4 | 74.8 | 68.6–80.6 | 0 | 0.48 | 0.39–0.60 |
| N | 589 | | | | 22 | 16 | | | | 0 | 48 | | | | 32 | 1.60 | 1.45–1.76 |
| S1 | | | | | | | | | | | | | | | | | |
| Y | 175 | 30.1 | 36.4 | 23.3–49.5 | 80 | 30 | 57.7 | 52.8 | 29.8–75.9 | 20 | 18 | 43.9 | 36.8 | 29.7–44.0 | 0 | 0.69 | 0.55–0.84 |
| N | 406 | | | | 17 | 22 | | | | -0 | 23 | | | | 0 | 1.71 | 1.34–2.13 |
| Q3 | | | | | | | | | | | | | | | | | |
| Y | 145 | 27.3 | 30.1 | 20.3–39.9 | 64 | 12 | 37.5 | 47.9 | ‡18.3–66.6 | 0 | 9 | 25.0 | 19.8 | 4.5–35.0 | 4 | 0.95 | 0.78–1.10 |
| N | 386 | | | | 0 | 20 | | | | 1550 | 27 | | | | 0 | 1.13 | 0.76–1.61 |
| T3 | | | | | | | | | | | | | | | | | |
| Y | 133 | 25.0 | 25.9 | 8.8–42.9 | 93 | 13 | 40.6 | 41.4 | 25.5–58.3 | 0 | 11 | 30.6 | 28.2 | ‡12.2–48.1 | 0 | 0.86 | 0.70–1.01 |
| N | 398 | | | | 32 | 19 | | | | 73 | 25 | | | | 836 | 1.41 | 0.97–1.96 |
| S1Q3T3 | | | | | | | | | | | | | | | | | |
| Y | 504 | 22.1 | 21.9 | 14.2–29.6 | 95 | 147 | 49.8 | 51.6 | ‡41.8–58.0 | 0 | 106 | 31.0 | 33.7 | 20.0–49.3 | 78 | 0.77 | 0.72–0.83 |
| N | 1775 | | | | 43 | 148 | | | | 0 | 236 | | | | 19 | 1.80 | 1.59–2.03 |
| uRBBB | | | | | | | | | | | | | | | | | |
| Y | 427 | 11.8 | 12.5 | 8.7–16.3 | 92 | 75 | 22.1 | 20.9 | 11.5–30.2 | 69 | 104 | 19.1 | 17.0 | 10.5–23.4 | 62 | 0.90 | 0.87–0.94 |
| N | 3191 | | | | 32 | 264 | | | | 0 | 441 | | | | 9 | 1.72 | 1.46–2.01 |
| iRBBB | | | | | | | | | | | | | | | | | |
| Y | 193 | 14.4 | 13.4 | 7.0–19.8 | 90 | 12 | 27.3 | 25.2 | -0.2–50.7 | 56 | 25 | 10.5 | 9.6 | ‡5.7–13.7 | 0 | 1.02 | 0.96–1.06 |
| N | 1146 | | | | -18 | 32 | | | | 0 | 214 | | | | 0 | 0.91 | 0.65–1.25 |
| cRBBB | | | | | | | | | | | | | | | | | |
| Y | 121 | 9.4 | 10.5 | 4.9–16.1 | 91 | 4 | 12.5 | 13.2 | 0.5–53.1 | NA | 47 | 23.7 | 16.4 | 4.5–28.2 | 69 | 0.86 | 0.79–0.91 |
| N | 1168 | | | | 22 | 28 | | | | NA | 151 | | | | 0 | 2.36 | 1.75–3.16 |
| iT wave V1–V4 | | | | | | | | | | | | | | | | | |
| Y | 325 | 27.1 | 27.6 | 13.6–41.5 | 96 | 98 | 49.7 | 38.7 | 21.4–56.0 | 66 | 63 | 43.8 | 38.3 | 24.5–52.2 | 4 | 0.72 | 0.65–0.80 |
| N | 874 | | | | 42 | 99 | | | | 0 | 81 | | | | 0 | 1.74 | 1.50–2.00 |
| iT wave V1 | | | | | | | | | | | | | | | | | |
| Y | 185 | 34.8 | 48.6 | -0.5–97.8 | 99 | 20 | 62.5 | 58.5 | 27.8–89.2 | 12 | 18 | 50.0 | 45.5 | 29.8–61.1 | 0 | 0.68 | 0.50–0.87 |
| N | 346 | | | | 0 | 12 | | | | 0 | 18 | | | | 0 | 1.60 | 1.23–2.00 |
| iT wave V2 | | | | | | | | | | | | | | | | | |
| Y | 90 | 15.5 | 24.3 | 8.5–40.1 | 94 | 30 | 57.7 | 53.8 | 29.3–78.3 | 24 | 18 | 43.9 | 33.4 | 31.2–35.7 | 0 | 0.57 | 0.45–0.69 |
| N | 491 | | | | 81 | 22 | | | | 0 | 23 | | | | 0 | 3.33 | 2.51–4.34 |
| iT wave V3 | | | | | | | | | | | | | | | | | |
| Y | 70 | 13.2 | 29.8 | 7.4–52.2 | 97 | 16 | 50.0 | 43.7 | 10.3–77.1 | 41 | 13 | 36.1 | 31.4 | 9.4–53.3 | 17 | 0.66 | 0.52–0.79 |
| N | 461 | | | | 83 | 16 | | | | 18 | 23 | | | | 8 | 3.24 | 2.24–4.53 |
| STEaVR | | | | | | | | | | | | | | | | | |
| Y | 250 | 28.9 | 28.6 | 25.6–31.6 | 0 | 181 | 68.8 | 67.9 | 63.4–72.4 | 0 | 60 | 28.8 | 44.6 | 1.9–87.4 | 93 | 0.69 | 0.62–0.76 |
| N | 615 | | | | 7 | 82 | | | | 29 | 148 | | | | 0 | 1.77 | 1.54–2.03 |
| Afib | | | | | | | | | | | | | | | | | |
| Y | 158 | 18.3 | 18.1 | 15.4–20.8 | 0 | 71 | 27.0 | 25.9 | 21.8–29.9 | 0 | 22 | 30.6 | 28.0 | ‡17.6–43.1 | 0 | 0.88 | 0.82–0.95 |
| N | 707 | | | | 0 | 192 | | | | 1 | 50 | | | | 0 | 1.52 | 1.21–1.89 |

*See text for definitions.
†Calculated from random-effects model.
‡CI from fixed-effects model
Afib = atrial fibrillation; ECG = electrocardiogram; iT wave = inverted T wave; LR– = negative likelihood ratio; LR+ likelihood ratio; R = heart rate, beats/min; uRBBB, iRBBB, cRBBB = unspecified, incomplete, and complete right bundle branch block; STE = ST elevation.

Table 5
Odds Ratios for the ECG Components for the Risk of Hemodynamic Collapse or Death

| ECG Finding | OR (95% CI) |
|---|---|
| HR > 100 beats/min | 4.46 (1.68–11.84) |
| S1 | 1.76 (1.09–2.85) |
| Q3 | 0.98 (0.5–1.93) |
| T3 | 1.68 (0.44–6.52) |
| S1Q3T3 | 2.06 (1.23–3.45) |
| RBBB | |
| Unspecified | 1.89 (1.27–2.81) |
| Incomplete | 1.05 (0.46–2.42) |
| Complete | 2.67 (1.81–3.95) |
| iT wave | |
| V1–V4 | 1.69 (0.83–3.43) |
| V1 | 2.63 (1.47–4.73) |
| V2 | 6.94 (2.41–19.96) |
| V3 | 7.07 (1.13–44.22) |
| STEaVR | 5.24 (3.98–6.91) |
| Atrial fibrillation | 1.75 (1.15–2.66) |

Afib = atrial fibrillation; ECG = electrocardiography; HR = heart rate; PE = pulmonary embolism; RBBB = right bundle branch block, STE = ST elevation.

Table 6
Mean Daniel ECG Score From 12 Studies*

| Outcome | Mean | SD | p-value† |
|---|---|---|---|
| Negative | 2.6 | 1.5 | – |
| Hemodynamic collapse | 5.9 | 3.9 | 0.039 |
| Death | 4.9 | 3.3 | 0.12 |

*Calculated by assigning point values from Figure 1 to each specific ECG finding reported per outcome for Kostrubiec 2009,[29] Toosi 2007,[28] Kukla 2014,[33] Agrawal 2014,[34] Kukla 2011,[31] Kucher 2003,[26] Janata 2012,[32] Geibel 2005,[27] Marchick 2009,[30] Kukla 2015,[35] Hoechtl 2009,[36] and Kline 2006.[37]
†One-way analysis of variance with Dunnett's post hoc.

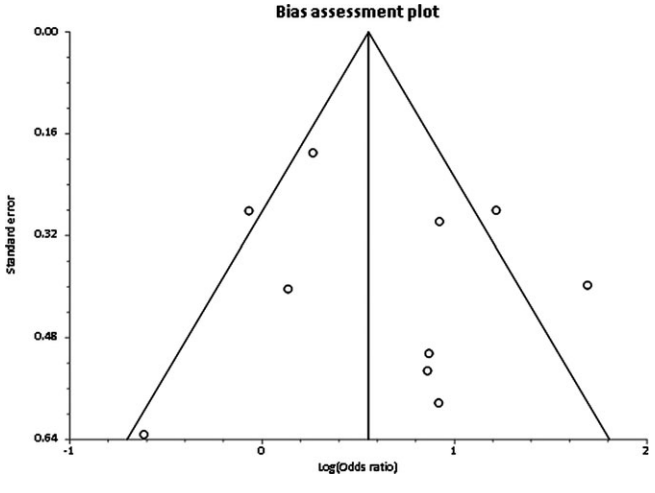


**Figure 3.** Funnel plots for the odds ratio for right bundle branch block (Egger's test p = 0.616).

heart rate, S1Q3T3, and RBBB demonstrated evidence of publication bias. Another possible limitation of this study was the inconsistent reporting of all ECG criteria across the 45 papers selected for full-length review. Although all included papers were required to contain data on heart rate, S1Q3T3, and RBBB, variable reporting led to variable sample sizes of the other ECG findings of pulmonary hypertension. Other limitations include the definition and classification of specific ECG findings. First, most papers allowed no differentiation of the degree of T-wave inversion in leads V1 to V4. We therefore had to simplify all findings of T-wave inversion in leads V1 to V4 to a binary input of either present or absent. Studies were also inconsistent in the classification of RBBB. While some of the included studies categorized RBBB as either incomplete or complete, this was not always the case. We therefore created an "unspecified" group to include all RBBB findings (incomplete, complete, and not stated). It is also possible that we could have missed relevant data or additional studies in our systematic search to include in this analysis. We attempted to minimize this risk by using broad search terms and e-mailing corresponding authors for additional data when necessary. It should also be noted that, given the nature of this review, we were unable to make any statement on the value of a completely normal ECG. We are unable to make any assessment about changes or timing of ECG. We were also unable to calculate a summary receiver operating characteristic curve for the Daniel score. Further, we graded study quality using the QUADAS-2 rather than QUIPs, which has also been used as a quality assessment instrument in prognostic systematic reviews.[49] Finally, we wish to emphasize that while atrial fibrillation with PE worsens prognosis, this should not be taken to indicate that most patients with atrial fibrillation should have diagnostic testing for PE.[50]

## CONCLUSIONS

This systematic review and meta-analysis demonstrates that six findings on 12-lead electrocardiogram that suggest right ventricle strain from acute pulmonary hypertension (sinus tachycardia, the S1Q3T3 pattern, right bundle branch block, T-wave inversions in V2 and V3, ST elevation in the aVR lead, and atrial fibrillation) are associated with significantly increased probability of circulatory shock and death from pulmonary embolism. A Daniel electrocardiogram score > 5 increases the probability of hemodynamic collapse. The 12-lead electrocardiogram should be used to risk-stratify patients with acute pulmonary embolism to make decisions about the need for advanced therapy or home treatment.

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## Supporting Information

The following supporting information is available in the online version of this paper:

**Data Supplement S1.** Detailed search strategies.

**Data Supplement S2.** Study description and risk of bias in all 45 studies.

**Data Supplement S3.** Outcomes and prevalence of electrocardiographic findings for all 45 papers reviewed in full length.