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Prognostic value of electrocardiography in elderly patients with acute pulmonary embolism

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Conflict of interest

The authors declare that they have no conflict of interest.

Author Contributions

All authors participated in the research and preparation of the manuscript.

Study concept and design: D. Aujesky; Data acquisition: D. Aujesky; Data analysis and interpretation: L. Bolt, S. Lauber, D. Samim, A. Löwe, T. Tritschler, C. Baumgartner, D. Aujesky; Drafting the manuscript: L. Bolt, C. Baumgartner, D. Aujesky; Critical revision of the manuscript: L. Bolt, S. Lauber, A. Limacher, D. Samim, A. Löwe, T. Tritschler, C. Baumgartner, D. Aujesky; Statistical analyses: A. Limacher; Study supervision: D. Aujesky

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ABSTRACT

Background: Electrocardiographic (ECG) signs of right ventricular strain could be used as a simple tool to risk-stratify patients with acute pulmonary embolism.

Methods: We studied consecutive patients aged ≥65 years with acute pulmonary embolism in a prospective multicenter cohort study. Two readers independently analyzed 12 predefined ECG signs of right ventricular strain in all patients. The outcome was the occurrence of an adverse clinical event, defined as death from any cause within 90 days or a complicated in-hospital course. We determined the interrater reliability for each ECG sign and examined the association between right ventricular strain signs and adverse events using logistic regression, adjusting for the Pulmonary Embolism Severity Index and cardiac troponin.

Results: Overall, 320/390 patients (82%) showed at least one ECG sign of right ventricular strain. The interrater reliability for individual ECG signs was highly variable (κ 0.40-0.95). Patients with ≥1 of the three classic signs of right ventricular strain (S1Q3T3, right bundle branch block, or T wave inversions in V1-V4) had a higher incidence of adverse events than those without (13% vs. 6%; p=0.026). After adjustment, the presence of ≥1 of the three classic signs of right ventricular strain (OR 2.11, 95%-CI 1.00-4.46) and the number of right ventricular strain signs present were significantly associated with adverse events (OR 1.35 per sign, 95%-CI 1.08-1.69).

Conclusions: ECG signs of right ventricular strain are common in elderly patients with acute pulmonary embolism. Although such signs may have prognostic value, their variable reliability and the rather modest prognostic effect size may limit their usefulness in the risk stratification of pulmonary embolism.

INTRODUCTION

The clinical presentation and prognosis of pulmonary embolism varies widely from mild manifestations to cardiogenic shock and sudden death.[1] For this reason, an early risk assessment is crucial for therapeutic management strategies.[1]

When a patient presents with symptoms or signs of pulmonary embolism, an electrocardiogram (ECG) is one of the first tests performed in the emergency setting. Multiple ECG findings have been associated with right ventricular dysfunction in the context of pulmonary embolism, including right bundle branch block,[2-4] S1Q3T3,[3-5] and T wave inversions.[2-5] Right ventricular dysfunction is associated with an increased clot burden[6] and is a significant prognostic factor in pulmonary embolism.[7-9] The presence of several of these ECG signs has been related to an increase in short-term mortality and clinical deterioration among patients with pulmonary embolism in prospective[2, 3, 10-13] and retrospective studies.[4, 14] As such, ECG might serve as an easily available prognostic tool to help guide management of patients with acute pulmonary embolism.

Although elderly patients have an increased risk for pulmonary embolism[15-17] and pulmonary embolism-related adverse outcomes[7] compared to younger individuals, the prognostic value of specific ECG findings has not been examined in the elderly. Ischemic heart disease,[18] arterial hypertension,[19] and pulmonary diseases[20] show an increased prevalence with age and are commonly associated with ECG signs, including abnormal Q waves,[21] right axis deviation,[22] T wave inversions,[23] and right bundle branch block.[24] Thus, ECG signs indicating right ventricular strain may be less specific and prognostically less useful in the elderly with acute pulmonary embolism. We therefore evaluated the prognostic value of ECG

signs in a multicenter prospective cohort of elderly patients with acute symptomatic pulmonary embolism.

METHODS

Study design and cohort sample

This study was conducted as part of a prospective multicenter cohort to evaluate long-term medical outcomes and quality of life in elderly patients with objectively diagnosed, symptomatic acute venous thromboembolism in nine Swiss university and non-university hospitals (09/2009-12/2013).[25] Consecutive patients aged ≥65 years with objectively diagnosed deep vein thrombosis or pulmonary embolism were enrolled in the inpatient and outpatient services of participating study sites. Exclusion criteria were the inability to provide informed consent (i.e., severe dementia), conditions incompatible with follow up (i.e., terminal illness), insufficient German or French speaking ability, catheter-related thrombosis, or previous enrollment in the cohort. The study was approved by the Ethics Committee at each participating center. The study methods have been described previously.[25]

For this analysis, we considered patients with objectively confirmed symptomatic pulmonary embolism, who had an ECG performed within 24 hours before or after the diagnosis of pulmonary embolism. We defined symptomatic pulmonary embolism as a positive spiral computed tomography or pulmonary angiography, a high-probability ventilation-perfusion scan, or a proximal deep vein thrombosis confirmed by compression ultrasonography or contrast venography in patients with acute chest pain, new/worsening dyspnea, hemoptysis, or syncope.[25]

Baseline data collection

At each study site trained study nurses prospectively collected baseline demographic information (age and sex), data on comorbid conditions (active cancer, chronic or acute heart failure, chronic lung disease), vital signs (heart rate, blood pressure, respiratory rate, temperature, mental status), laboratory findings (high-

sensitive cardiac troponin T [hs-cTnT]), and the initial treatment (systemic or catheter-based thrombolysis, thromboembolectomy) using standardized data collection forms. Within the first days of enrolment, all patients underwent transthoracic echocardiography according to a standardized protocol to determine the presence of right ventricular dysfunction, defined as a right ventricular (RV)/left ventricular (LV) end-diastolic diameter ratio >0.9 in the apical four chamber view in echocardiography.[26] Venous blood samples were collected at the time of pulmonary embolism diagnosis. They were immediately centrifuged, frozen, and stored at -80°C. Measurement of hs-cTnT plasma concentrations was done using electrochemiluminescence methods on Cobas e601 analyzers (Elecsys™, Roche, Rotkreuz, Switzerland) at a central laboratory. Elevated troponin was defined as a plasma concentration of hs-cTnT >14 ng/L.[27]

Electrocardiography

We obtained 12-lead ECGs that were performed within 24 hours before or after the diagnosis of pulmonary embolism in all patients. If several ECGs were available, we used the tracing that was temporally most closely related to the time of pulmonary embolism diagnosis. Two trained readers who were unaware of patients' baseline and outcome data independently analyzed the ECGs. In case of disagreement, the ECG was examined by a third independent reader.

The presence of the following 12 ECG signs was considered suggestive of right ventricular strain: tachycardia (heart rate >100/min),[4, 12, 28] atrial fibrillation or flutter,[29] incomplete and complete right bundle branch block,[2-4, 12, 30] clockwise rotation (transition zone at V4 or further leftward),[12, 28] right axis deviation (QRS axis between +90° and +180°),[28, 29] S1Q3T3 sign (S wave in lead I >1.5mm, Q in lead III >1.5mm associated with negative T wave in lead III),[3, 4, 29, 30] Qr in V1 (presence of a

prominent Q wave of ≥0.2mV and a ventricular depolarization <120ms),[2, 12] T wave inversions in V1 to V4,[2-4, 29, 30] ST depression in V4 to V6 (≥0.05mV),[14, 28, 29] ST elevation in V1, aVR or III (≥1mV),[12, 14] low voltage (QRS <5mm in the limb leads),[31] and ≥3 leads with inverted T waves (discordant T waves in limb leads and negative T waves in precordial leads).[13, 14] As our primary definition of right ventricular strain, we used the presence of at least one of the following three classic signs: S1Q3T3, complete or incomplete right bundle branch block, or T wave inversions in V1-V4.[3, 30] We chose these signs because they are the most frequently used in clinical practice.[3] Figure 1 demonstrates an ECG example with four signs of right ventricular strain (S1Q3T3, Qr in V1, T wave inversions in V1-V4, and clockwise rotation) in a 72-year-old patient with pulmonary embolism.

Study outcome

Our study outcome was the occurrence of an adverse event, defined as the composite of death from any cause within 90 days or a complicated in-hospital course (need for vasopressors, systemic or catheter-based thrombolysis, thromboembolectomy, or cardiopulmonary resuscitation).[4] These adverse events were assessed through hospital chart review or patient or proxy interviews.[25] A committee of three blinded, independent clinical experts adjudicated all outcomes and classified the cause of all deaths as definitely due to pulmonary embolism, possibly due to pulmonary embolism, due to major bleeding, or due to other cause.[25] Final classifications were made on the basis of the committee's full consensus.[25]

Statistical analysis

We determined the prevalence of each of the 12 predefined ECG signs and the interrater reliability for each ECG sign using the unweighted kappa coefficient

(κ).[32] We classified interrater reliability based on the magnitude of the κ coefficients as follows: 0.0 to 0.19, poor; 0.20 to 0.39, fair; 0.40 to 0.59, moderate; 0.60 to 0.79, substantial; and 0.80 to 1.0, almost perfect.[33] We compared baseline characteristics and treatments between patients with and without right ventricular strain using the chi-squared or Fisher's exact test, or the non-parametric Wilcoxon rank-sum tests, as appropriate.

We calculated the incidence of an adverse event and the Wilson 95% confidence interval (CI) by the number of ECG signs present (0, 1, 2, 3 or ≥4 signs) and used Kaplan-Meier analysis to determine the cumulative 90-day incidence of an adverse event based on the presence of right ventricular strain on ECG and right ventricular dysfunction on echocardiography.

We used logistic regression to examine the association between right ventricular strain and an adverse event, adjusting for the baseline Pulmonary Embolism Severity Index (PESI) and elevated hs-cTnT values. We also explored the association between the presence of at least one of the 12 predefined ECG signs, the number of ECG signs present, and the occurrence of an adverse event in secondary analyses.

We used multiple imputation by chained equations to impute missing values of PESI items and hs-cTnT. The imputation models were based on all other variables as well as an indicator variable for death, complicated in-hospital course, and hospital site. Fifty imputed data sets were generated and analyzed as described, using Rubin's rules to combine results across data sets.[34] All analyses were made using Stata 15 (Stata Corporation, College Station, Texas).

RESULTS

Study sample

Of the 1003 patients with venous thromboembolism enrolled in the SWITCO65+ cohort, 695 patients had a diagnosis of pulmonary embolism. Of these, 305 patients were excluded from analysis because they did not have an ECG performed within 24 hours before or after diagnosis of pulmonary embolism (n=297), did not allow the use of their data (n=7), or withdrew consent early (n=1). The final study sample comprised 390 patients with acute pulmonary embolism. There were no significant differences between analyzed and excluded patients concerning baseline characteristics (data not shown).

Prevalence of ECG signs and interrater reliability

Overall, ECG of 320 (82%) of patients showed at least one of the 12 predefined ECG signs of right ventricular strain. Overall, 32% of patients had right ventricular strain (S1Q3T3, complete or incomplete right bundle branch block, or T wave inversions in V1-V4) based on our primary definition. The most common ECG signs of right ventricular strain were inverted T waves in ≥3 leads (49%), clockwise rotation (46%), and tachycardia (26%). S1Q3T3 and right bundle branch block was each present in 15% of patients and T wave inversions in V1-V4 in 13% (Table 1). The κ coefficients for individual ECG signs varied widely from 0.40 for ST depression to 0.95 for tachycardia (Table 1). The interrater reliability was substantial for S1Q3T3 (κ 0.67) and right bundle branch block (κ 0.68) and almost perfect for T wave inversions in V1-V4 (κ 0.92).

Baseline characteristics

The baseline patient characteristics stratified by right ventricular strain are shown in Table 2. Overall, the median age was 74 years and 54% of patients were men. Patients with right ventricular strain based on our primary definition were significantly more likely to have a respiratory rate ≥30/min (8% vs 2%, p=0.008) and right ventricular dysfunction on echocardiography (34% vs 21%, p=0.003).

Association between RVS and an adverse event

Death from any cause within 90 days or a complicated in-hospital course occurred in 32 patients (8%) (Table 3). Patients with right ventricular strain had a significantly higher incidence of an adverse event than those without (13% vs 6%, p=0.026), primarily due to a higher incidence of a complicated in-hospital course (11% vs 3%, p=0.001). Patients with or without right ventricular strain did not differ in terms of all-cause mortality (3% vs 4%, p=1.000), pulmonary embolism-related mortality (2% vs 1%, p=0.334), and bleeding-related mortality (0% vs 0.4%, p=1.000) at 90 days (Table 3).

With increasing numbers of right ventricular strain signs on ECG, there was a significant trend towards an increase in the incidence of death within 90 days or complicated in-hospital course (Figure 2; p for trend <0.001). The cumulative incidence of death within 90 days or a complicated in-hospital course was lowest in the group of patients with neither right ventricular strain nor right ventricular dysfunction (5%), while it was highest in the group with both right ventricular strain and right ventricular dysfunction (18%) (Figure 3).

In unadjusted analyses, the presence of right ventricular strain (odds ratio [OR] 2.25, 95%-CI 1.09-4.67) and the number of right ventricular strain signs present (OR 1.45 per sign, 95%-CI 1.17-1.79) were statistically significantly associated with the composite of death within 90 days or complicated in-hospital course (Table 4). After

adjustment for the PESI and hs-cTnT, both the presence of right ventricular strain (OR 2.11, 95%-CI 1.00-4.46) and the number of right ventricular strain signs present remained statistically significantly associated with adverse events (OR 1.35 per sign, 95%-CI 1.08-1.69). The presence of at least one of the 12 predefined ECG signs was not predictive of adverse outcomes.

DISCUSSION

Our study demonstrates that electrocardiographic signs of right ventricular strain are common in the elderly with acute pulmonary embolism but that the reliability of these signs is highly variable (κ 0.40-0.95). Patients who had at least one of three classic signs of right ventricular strain, i.e., S1Q3T3, right bundle branch block, or T wave inversions in V1-V4, were more likely to have echocardiographic right ventricular dysfunction than patients without right ventricular strain and had a higher risk of a complicated in-hospital course. When adjusted for the PESI and hs-cTnT, the presence of at least one of the three classic ECG signs of right ventricular strain doubled the odds of an adverse event.

The majority of patients (82%) presented at least one of the 12 prespecified signs and about one third had at least one of the three classic ECG signs of right ventricular strain in our study. As studies on the prognostic value of ECG in pulmonary embolism vary widely in terms of patient selection criteria (e.g., exclusion of patients with non-major pulmonary embolism,[11] massive pulmonary embolism,[3, 10, 35] or cardiorespiratory diseases[3, 13, 35]) and the number/type of ECG signs examined, the prevalence of ECG signs of right ventricular strain is difficult to compare across studies.

Patients with right ventricular strain were significantly more likely to have a RV/LV diameter ratio >0.9 on echocardiography. This is not astonishing as both ECG signs of right ventricular strain[2, 36] and an elevated RV/LV diameter ratio[37] measure right ventricular dysfunction. The relationship between ECG signs indicating right ventricular strain, echocardiographic right ventricular dysfunction, and pulmonary artery pressure is well known.[2, 3, 13, 38] In contrast to prior studies enrolling healthier and hemodynamically stable patients with pulmonary embolism,[2, 3] the prevalence of

myocardial injury (i.e., elevated hs-TnT) did not differ among patients with and without right ventricular strain in our sample of elderly patients.

We found a significant trend towards a higher incidence of adverse events with increasing numbers of right ventricular strain signs present. Patients with classic ECG signs of right ventricular strain (S1Q3T3, right bundle branch block, or T wave inversions in V1-V4), especially those with concomitant echocardiographic right ventricular dysfunction, had also a higher incidence of adverse events compared to those without the relevant ECG signs. Importantly, patients with or without right ventricular strain did not differ in terms of overall or pulmonary embolism-related mortality, the increased incidence of adverse events in patients with right ventricular strain was driven by the greater risk of a complicated in-hospital course. After adjustment for the PESI and hs-cTnT, both the dichotomized, simpler definition of right ventricular strain (presence of any of the three classic signs of right ventricular strain) and the number of ECG signs present was significantly associated with adverse events. This finding is consistent with the results of prior studies that found a significant correlation between the number of ECG signs of right ventricular strain and pulmonary artery pressure in patients with pulmonary embolism.[39, 40] In a prospective study of 386 younger, healthier, hemodynamically stable patients with pulmonary embolism, the presence of any of the three classic signs of right ventricular strain was significantly associated with clinical deterioration or in-hospital death (hazard ratio 2.6).[3] Among the 12 ECG signs of right ventricular strain examined in our study, the three classic ECG signs of right ventricular strain appear to be prognostically the most useful, given their relatively good reproducibility and independent association with adverse events.

The results of studies on the prognostic value of ECG in pulmonary embolism are highly inconsistent due to differences in patient selection (severe vs.

hemodynamically stable pulmonary embolism), the number and types of ECG signs examined, and the outcomes used (overall/pulmonary embolism-specific mortality, complicated in-hospital course, and/or escalation of therapy). Several studies found that individual ECG signs, including tachycardia,[10] atrial arrhythmias,[10] number of leads with negative T waves,[13, 14] ST elevation in V1 or aVR,[14] right bundle branch block,[14] and Qr in V1[2, 12] were associated with adverse outcome, but others did not.[11] While two studies showed that the presence of at least one out of several prespecified ECG signs of right ventricular strain independently predicted adverse outcomes in patients with acute pulmonary embolism,[3, 11] others did not confirm these findings.[2, 10] A complex 21-item ECG score correlated well with clot burden and hemodynamic parameters in patients with pulmonary embolism, but its ability to predict clinical outcomes was less impressive.[4, 35, 36, 40, 41] Two studies demonstrated that ECG signs of right ventricular strain were particularly or exclusively prognostically useful in patients who had concomitant right ventricular dysfunction based on other imaging modalities, such as echocardiography or computed tomography.[3, 30] Overall, the lack of consistent evidence regarding their prognostic value and the variable interrater reliability limit the prognostic usefulness of many ECG signs in patients with acute pulmonary embolism.

Although our study is based on a sample of elderly patients with a broad disease severity spectrum, prospectively collected data, and a blinded ECG reading and adjudication process, our work has potential limitations. First, we excluded 44% of patients from our analysis, mostly, because ECG was not done within 24 hours of pulmonary embolism diagnosis. However, as excluded and analyzed patients did not differ in terms of baseline characteristics, the risk of a selection bias is low. Second, the managing physicians were aware of the ECG results, which might have influenced treatment choice, such as the administration of thrombolysis[42] and patient

outcomes. Finally, we did not have antecedent or follow-up ECG tracings of our study patients. Therefore, we do not know if ECG signs of right ventricular strain were preexisting or if they resolved after treatment.

In conclusion, ECG signs of right ventricular strain are common in elderly patients with pulmonary embolism and the presence of any of the three classic ECG signs of right ventricular strain as well as the number of ECG signs present are associated with adverse events. Overall, the three classic ECG signs of right ventricular strain appear to be prognostically the most useful. Although ECG is inexpensive and readily available at the time of pulmonary embolism diagnosis, the variable interrater reliability of many individual ECGs signs and their rather modest prognostic effect size may limit the value of many ECG signs in the risk stratification for pulmonary embolism, at least as a stand-alone test. Whether combinations of ECG signs of right ventricular strain with cardiac biomarkers or imaging modalities are prognostically useful should be further examined.

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References

1. Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *European Heart Journal.* 2014;35:3033-3069.

2. Casazza F, Pacchetti I, Rulli E, et al. Prognostic significance of electrocardiogram at presentation in patients with pulmonary embolism of different severity. *Thrombosis Research.* 2018;163:123-127.

3. Vanni S, Polidori G, Vergara R, et al. Prognostic value of ECG among patients with acute pulmonary embolism and normal blood pressure. *The American Journal of Medicine.* 2009;122:257-264.

4. Toosi MS, Merlino JD, Leeper KV. Electrocardiographic score and short-term outcomes of acute pulmonary embolism. *The American Journal of Cardiology.* 2007;100:1172-1176.

5. Punukollu G, Gowda RM, Vasavada BC, Khan IA. Role of electrocardiography in identifying right ventricular dysfunction in acute pulmonary embolism. *The American Journal of Cardiology.* 2005;96:450-452.

6. Wong LF, Akram AR, McGurk S, Van Beek EJR, Reid JH, Murchison JT. Thrombus load and acute right ventricular failure in pulmonary embolism: correlation and demonstration of a "tipping point" on CT pulmonary angiography. *The British Journal of Radiology.* 2012;85:1471-1476.

7. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet (London, England).* 1999;353:1386-1389.

8. Kasper W, Konstantinides S, Geibel A, Tiede N, Krause T, Just H. Prognostic significance of right ventricular afterload stress detected by echocardiography

in patients with clinically suspected pulmonary embolism. *Heart.* 1997;77:346-349.

9. Lee K, Kwon O, Lee E-J, et al. Prognostic value of echocardiographic parameters for right ventricular function in patients with acute non-massive pulmonary embolism. *Heart and Vessels.* 2019.

10. Escobar C, Jimenez D, Marti D, et al. [Prognostic value of electrocardiographic findings in hemodynamically stable patients with acute symptomatic pulmonary embolism]. *Revista Espanola de Cardiologia.* 2008;61:244-250.

11. Geibel A, Zehender M, Kasper W, Olschewski M, Klima C, Konstantinides SV. Prognostic value of the ECG on admission in patients with acute major pulmonary embolism. *The European Respiratory Journal.* 2005;25:843-848.

12. Kucher N, Walpoth N, Wustmann K, Noveanu M, Gertsch M. QR in V1--an ECG sign associated with right ventricular strain and adverse clinical outcome in pulmonary embolism. *European Heart Journal.* 2003;24:1113-1119.

13. Kosuge M, Kimura K, Ishikawa T, et al. Prognostic significance of inverted T waves in patients with acute pulmonary embolism. *Circulation Journal: Official Journal of the Japanese Circulation Society.* 2006;70:750-755.

14. Kukla P, Dlugopolski R, Krupa E, et al. Electrocardiography and prognosis of patients with acute pulmonary embolism. *Cardiology Journal.* 2011;18:648-653.

15. Kniffin WD, Jr., Baron JA, Barrett J, Birkmeyer JD, Anderson FA, Jr. The epidemiology of diagnosed pulmonary embolism and deep venous thrombosis in the elderly. *Archives of Internal Medicine.* 1994;154:861-866.

16. Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrom J. Incidence and mortality of venous thrombosis: a population-based study. *Journal of Thrombosis and Haemostasis: JTH.* 2007;5:692-699.

17. Oger E. Incidence of venous thromboembolism: a community-based study in Western France. EPI-GETBP Study Group. Groupe d'Etude de la Thrombose de Bretagne Occidentale. *Thrombosis and Haemostasis.* 2000;83:657-660.

18. Leening MJG, Ferket BS, Steyerberg EW, et al. Sex differences in lifetime risk and first manifestation of cardiovascular disease: prospective population based cohort study. *BMJ: British Medical Journal.* 2014;349:g5992.

19. Fryar CD, Ostchega Y, Hales CM, Zhang G, Kruszon-Moran D. Hypertension Prevalence and Control Among Adults: United States, 2015-2016. *NCHS Data Brief.* 2017:1-8.

20. Thannickal VJ, Murthy M, Balch WE, et al. Blue journal conference. Aging and susceptibility to lung disease. *American Journal of Respiratory and Critical Care Medicine.* 2015;191:261-269.

21. Lazaro VL. 2014 PHA Clinical Practice Guidelines for the Diagnosis and Management of Patients with Coronary Heart Disease. *ASEAN Heart Journal: Official Journal of the ASEAN Federation of Cardiology.* 2016;24:3.

22. Kilcoyne MM, Davis AL, Ferrer MI. A Dynamic Electrocardiographic Concept Useful in the Diagnosis of Cor Pulmonale. *Circulation.* 1970;42:903-924.

23. Ostrander LD, Jr., Brandt RL, Kjelsberg MO, Epstein FH. Electrocardiographic Findings Among the Adult Population of a Total Natural Community, Tecumseh, Michigan. *Circulation.* 1965;31:888-898.

24. Holtzman D, Aronow WS, Mellana WM, et al. Electrocardiographic Abnormalities in Patients with Severe versus Mild or Moderate Chronic Obstructive Pulmonary Disease Followed in an Academic Outpatient Pulmonary Clinic. *Annals of Noninvasive Electrocardiology.* 2011;16:30-32.

25. Mean M, Righini M, Jaeger K, et al. The Swiss cohort of elderly patients with venous thromboembolism (SWITCO65+): rationale and methodology. *Journal of Thrombosis and Thrombolysis.* 2013;36:475-483.

26. Jaff MR, McMurtry MS, Archer SL, et al. Management of Massive and Submassive Pulmonary Embolism, Iliofemoral Deep Vein Thrombosis, and Chronic Thromboembolic Pulmonary Hypertension. *Circulation.* 2011;123:1788-1830.

27. Vuilleumier N, Simona A, Mean M, et al. Comparison of Cardiac and Non-Cardiac Biomarkers for Risk Stratification in Elderly Patients with Non-Massive Pulmonary Embolism. *PloS one.* 2016;11:e0155973.

28. Stein PD, Matta F, Sabra MJ, et al. Relation of electrocardiographic changes in pulmonary embolism to right ventricular enlargement. *The American Journal of Cardiology.* 2013;112:1958-1961.

29. Kukla P, Kosior DA, Tomaszewski A, et al. Correlations between electrocardiogram and biomarkers in acute pulmonary embolism: Analysis of ZATPOL-2 Registry. *Annals of Noninvasive Electrocardiology.* 2017;22:e12439.

30. Carroll BJ, Heidinger BH, Dabreo DC, et al. Multimodality Assessment of Right Ventricular Strain in Patients With Acute Pulmonary Embolism. *The American Journal of Cardiology.* 2018;122:175-181.

31. Kukla P, McIntyre WF, Fijorek K, et al. Electrocardiographic abnormalities in patients with acute pulmonary embolism complicated by cardiogenic shock. *The American Journal of Emergency Medicine.* 2014;32:507-510.

32. Cohen J. A coefficient of agreement for nominal scales. *Educational and Psychological Measurement.* 1960;20:37-46.

33. Landis JR, Koch GG. The Measurement of Observer Agreement for Categorical Data. *Biometrics.* 1977;33:159-174.

34. Rubin D. *Multiple Imputation for Nonresponse in Surveys*. New York: J. Wiley & Sons; 1987.

35. Golpe R, Castro-Anon O, Perez-de-Llano LA, et al. Electrocardiogram score predicts severity of pulmonary embolism in hemodynamically stable patients. *Journal of Hospital Medicine.* 2011;6:285-289.

36. Ryu HM, Lee JH, Kwon YS, et al. Electrocardiography Patterns and the Role of the Electrocardiography Score for Risk Stratification in Acute Pulmonary Embolism. *Korean Circulation Journal* 2010;40:499-506.

37. Frémont B, Pacouret G, Jacobi D, Puglisi R, Charbonnier B, de Labriolle A. Prognostic Value of Echocardiographic Right/Left Ventricular End-Diastolic Diameter Ratio in Patients With Acute Pulmonary Embolism: Results From a Monocenter Registry of 1,416 Patients. *Chest.* 2008;133:358-362.

38. Keller K, Geyer M, Coldewey M, Beule J, Balzer JO, Dippold W. Elevated systolic pulmonary artery pressure for prediction of myocardial necrosis and right ventricular dysfunction in acute pulmonary embolism. *Cor et Vasa.* 2016;58:e403-e410.

39. Yoshinaga T, Ikeda S, Shikuwa M, Miyahara Y, Kohno S. Relationship Between ECG Findings and Pulmonary Artery Pressure in Patients With Acute Massive Pulmonary Thromboembolism. *Circulation Journal.* 2003;67:229-232.

40. Daniel KR, Courtney DM, Kline JA. Assessment of cardiac stress from massive pulmonary embolism with 12-lead ECG. *Chest.* 2001;120:474-481.

41. Iles S, Heron CJL, Davies G, Turner JG, Beckert LEL. ECG Score Predicts Those With the Greatest Percentage of Perfusion Defects Due to Acute Pulmonary Thromboembolic Disease. *Chest.* 2004;125:1651-1656.

42. Konstantinides S, Geibel A, Heusel G, Heinrich F, Kasper W. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. *The New England Journal of Medicine.* 2002;347:1143-1150.

Figure Legends

Figure 1.

Electrocardiogram showing four signs of right ventricular strain (i.e., S1Q3T3, Qr in V1, T wave inversions in V1-V4, clockwise rotation) in a 72-year-old patient diagnosed with pulmonary embolism.

Figure 2.

The bars represent the incidence of all-cause death within 90 days or a complicated in-hospital course by the number of electrocardiography (ECG) signs present (0, 1, 2, 3, and ≥4), the whiskers indicate the 95% Wilson confidence interval. The incidence of all-cause death within 90 days or a complicated in-hospital course was 5.7% for the presence of 0 ECG signs, 2.1% for 1 ECG sign, 6.7% for 2 ECG signs, 10.3% for 3 ECG signs, and 18.6% for ≥4 ECG signs (p-value for trend =0.001).

Abbreviation: RVS= right ventricular strain

Figure 3.

Kaplan-Meier curves showing the cumulative incidence of all-cause death at 90 days or a complicated in-hospital course by right ventricular strain on electrocardiography and echocardiographic right ventricular dysfunction. The cumulative incidence of all-cause death within 90 days or a complicated in-hospital course was 5.1% for the

presence of neither right ventricular strain nor right ventricular dysfunction, 8.9% for right ventricular strain but no right ventricular dysfunction, 8.7% for no right ventricular strain but right ventricular dysfunction, and 18.2% for right ventricular strain and right ventricular dysfunction (p=0.047).

Abbreviations: RVS= right ventricular strain, RVD= right ventricular dysfunction

Prognostic value of electrocardiography in elderly patients with acute pulmonary embolism

Clinical Significance

Word count: 58

- Electrocardiographic signs of right ventricular strain are common in elderly patients with acute pulmonary embolism
- The number of electrocardiographic signs of right ventricular strain present is associated with adverse events.
- The variable interrater reliability of individual electrocardiographic signs and their modest prognostic effect size, however, limits their usefulness in the risk stratification for pulmonary embolism in older patients.

Table 1. Prevalence and interrater reliability of ECG signs in 390 patients

ECG sign	Prevalence n (%)	Unweighted κ coefficient
Tachycardia	101 (26)	0.95
Atrial fibrillation or flutter	31 (8)	0.80
RBBB (complete or incomplete)	60 (15)	0.68
Clockwise rotation	179 (46)	0.71
Right axis deviation	12 (3)	0.83
S1Q3T3	57 (15)	0.67
Qr in V1	22 (6)	0.54
T wave inversions in V1-V4	52 (13)	0.92
ST depression	25 (6)	0.40
ST elevation	58 (15)	0.56
Low voltage	18 (5)	0.68
≥3 leads with inverted T waves	191 (49)	0.58

Abbreviations: ECG= electrocardiography, RBBB= right bundle branch block.

Table 2. Baseline patient characteristics by presence of right ventricular strain

Characteristic	All* (n=390)	RVS† (n=126)	No RVS (n=264)	p-value
	n (%) or median (interquartile range)			
Age, years	74.0 (69.0; 81.0)	74 (69.0; 81.3)	74 (69.0; 80.0)	0.89
Male sex	209 (54)	68 (54)	141 (53)	0.92
Active cancer‡	58 (15)	13 (10)	45 (17)	0.08
Acute or chronic heart failure§	46 (12)	14 (11)	32 (12)	0.77
Chronic lung disease¶	50 (13)	21 (17)	29 (11)	0.12
Heart rate ≥110 beats/min.	52 (13)	11 (9)	41 (16)	0.07
Systolic BP <100 mm Hg	14 (4)	6 (5)	8 (3)	0.39
Respiratory rate ≥30/min.	15 (4)	10 (8)	5 (2)	0.008
Temperature <36°C	23 (6)	11 (9)	12 (5)	0.10
Altered mental status**	15 (4)	7 (6)	8 (3)	0.26
Arterial oxygen saturation <90%	58 (15)	21 (17)	37 (14)	0.46
PESI, points	95.0 (80.0; 113.0)	95.5 (79.0; 115.0)	94 (80.0; 111.0)	0.57
Elevated hs-cTnT††	180 (46)	64 (51)	116 (44)	0.20
Echocardiographic RVD‡‡	98 (25)	43 (34)	55 (21)	0.003

Abbreviations: RVS= right ventricular strain, BP= blood pressure, PESI= Pulmonary Embolism Severity Index, hs-cTnT= high-sensitive cardiac troponin T, RVD= right ventricular dysfunction.

* Data on respiratory rate was missing in 18% of patients, temperature in 1%, arterial oxygen saturation in 4%, hs-cTnT in 12%, and right ventricular dysfunction in 18%.

†Defined as the presence of at least one of the following ECG signs: S1Q3T3, (in)complete RBBB, or T wave inversions in V1-V4.

‡Solid or hematologic cancer requiring chemotherapy, radiotherapy, surgery, or palliative care during the last 3 months.

§Heart failure, mechanical heart valve, or coronary heart disease.

¶Known chronic lung disease, such as chronic obstructive pulmonary disease, active asthma, lung fibrosis, cystic fibrosis, or bronchiectasis.

**Confusion, disorientation, or somnolence.

††Defined as a plasma concentration of >14 ng/L

‡‡Right ventricular/left ventricular end-diastolic diameter ratio >0.9 in the apical four chamber view on echocardiography.

Table 3. Adverse outcome by presence of right ventricular strain

Outcome	All (n=390)	RVS* (n=126)	No RVS (n=264)	p-value
	n (%)			
All-cause death within 90 days or complicated in-hospital course	32 (8)	16 (13)	16 (6)	0.026
All-cause death within 90 days	14 (4)	4 (3)	10 (4)	1.00
PE-related death	5 (1)	3 (2)	2 (1)	0.33
Bleeding-related death	1 (0)	0 (0)	1 (0)	1.00
Complicated in-hospital course	21 (5)	14 (11)	7 (3)	0.001
Need for vasopressors	7 (2)	4 (3)	3 (1)	0.22
Thrombolysis†	15 (4)	11 (9)	4 (2)	0.001
Thromboembolectomy	1 (0)	0 (0)	1 (0)	1.00
Cardiopulmonary resuscitation	4 (1)	3 (2)	1 (0)	0.10

Abbreviations: RVS= right ventricular strain, PE= pulmonary embolism, RBBB= right bundle branch block.

*Defined as the presence of at least one of the following ECG signs: S1Q3T3, RBBB, or T wave inversions in V1-V4.

†Systemic or catheter-based.

Table 4. Association between right ventricular strain and adverse outcome

Predictor	Unadjusted OR (95%-CI)	Adjusted OR* (95%-CI)
RVS†	2.25 (1.09 - 4.67)	2.11 (1.00 - 4.46)
Any ECG sign present‡	1.58 (0.54 - 4.66)	1.17 (0.38 - 3.60)
Number of ECG signs, per sign§	1.45 (1.17 - 1.79)	1.35 (1.08 - 1.69)

Abbreviations: OR= odds ratio, CI= confidence interval, RVS= right ventricular strain, ECG= electrocardiography, RBBB= right bundle branch block, hs-cTnT= high-sensitive cardiac troponin T.

*Adjusted for the Pulmonary Embolism Severity Index and elevated hs-cTnT.

†Presence of at least one of the following ECG signs: S1Q3T3, RBBB, or T wave inversions in V1-V4.

‡Presence of at least one of the 12 predefined ECG signs.

§Number of the 12 predefined ECG signs present.

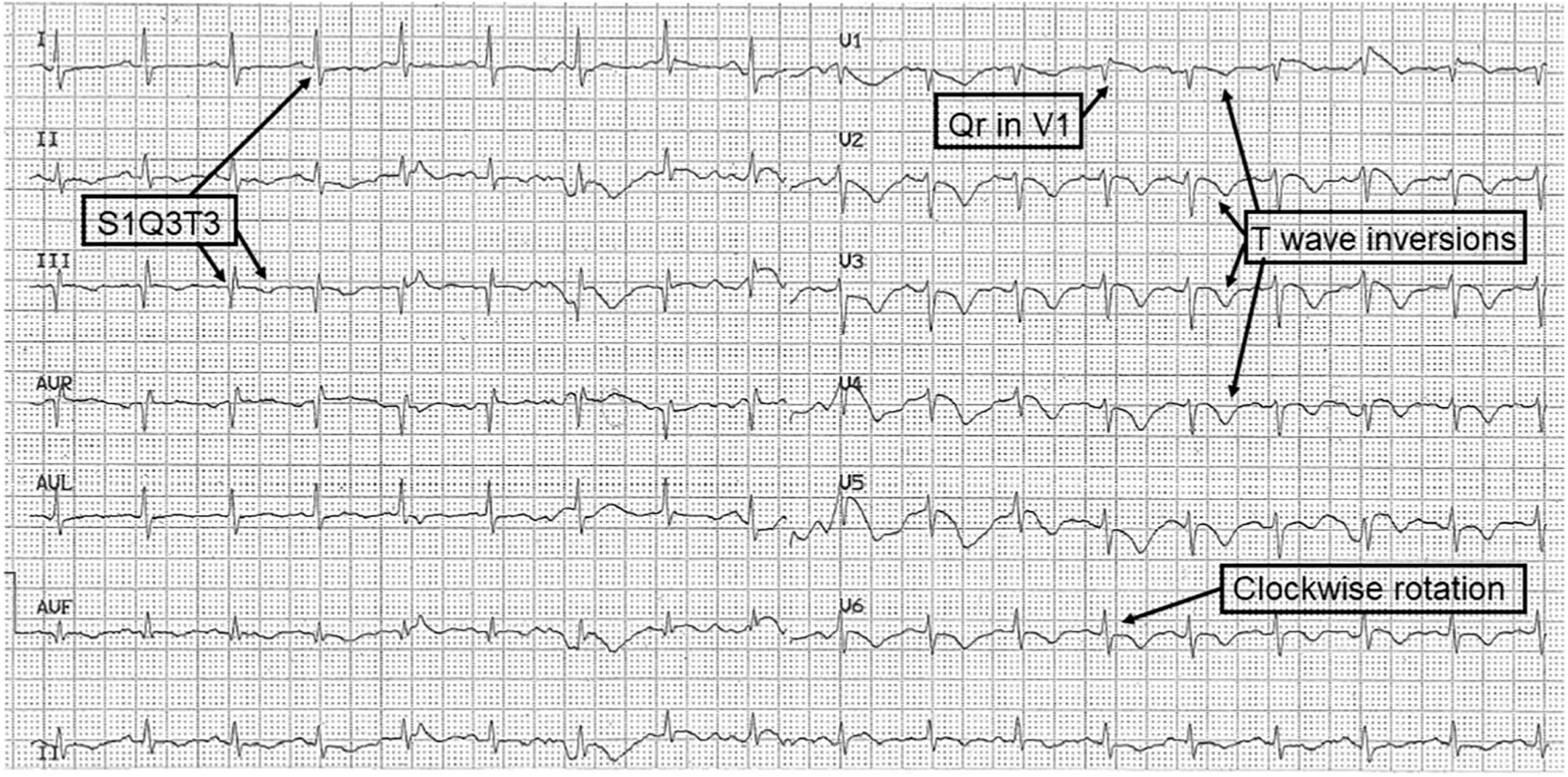
I
II
III
AUR
AUL
AUF
II
V1
V2
V3
V4
V5
V6
S1Q3T3
Qr in V1
T wave inversions
Clockwise rotation

Figure 1

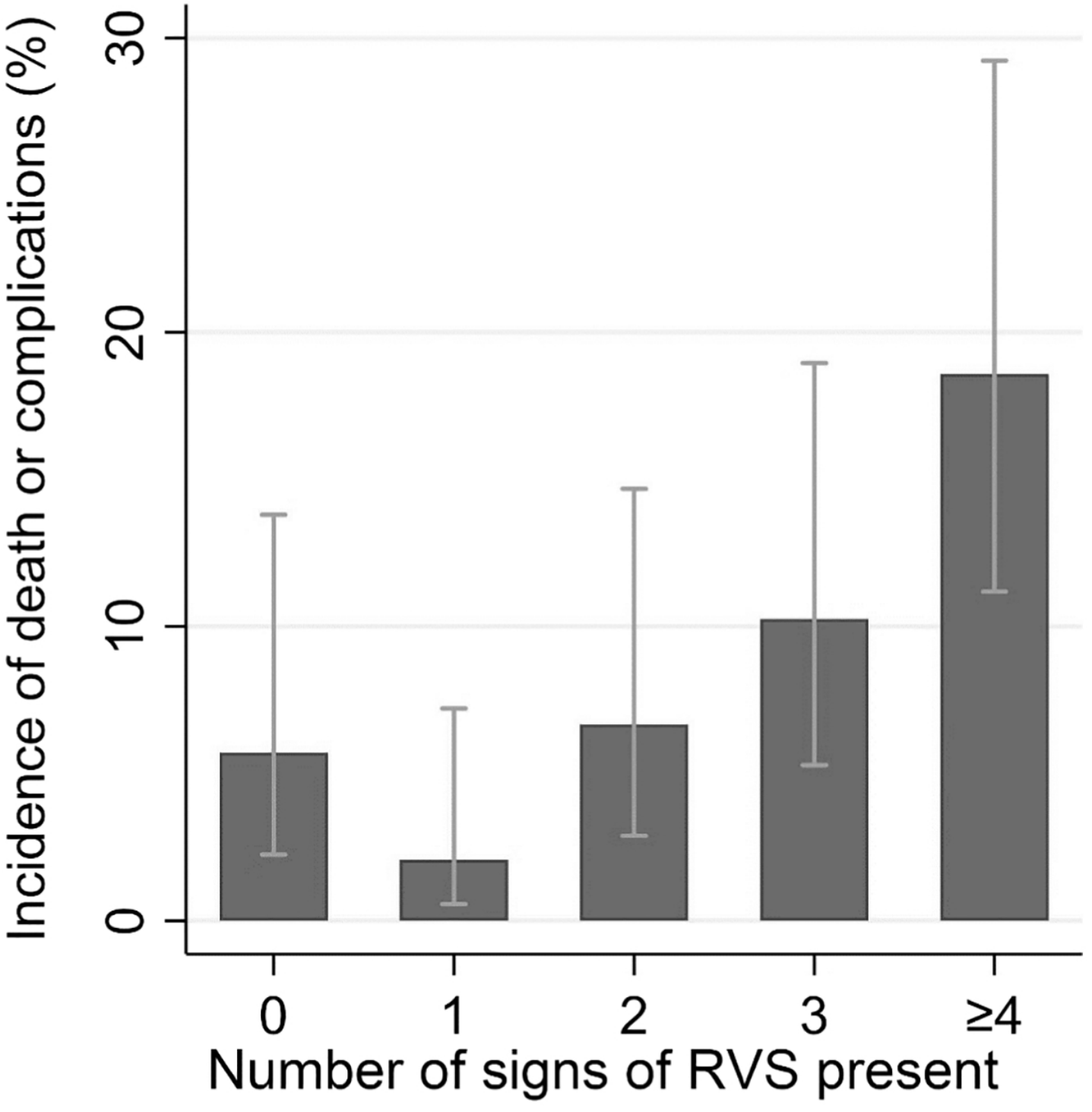
Incidence of death or complications (%)
0
10
20
30
0
1
2
3
≥4
Number of signs of RVS present

Figure 2

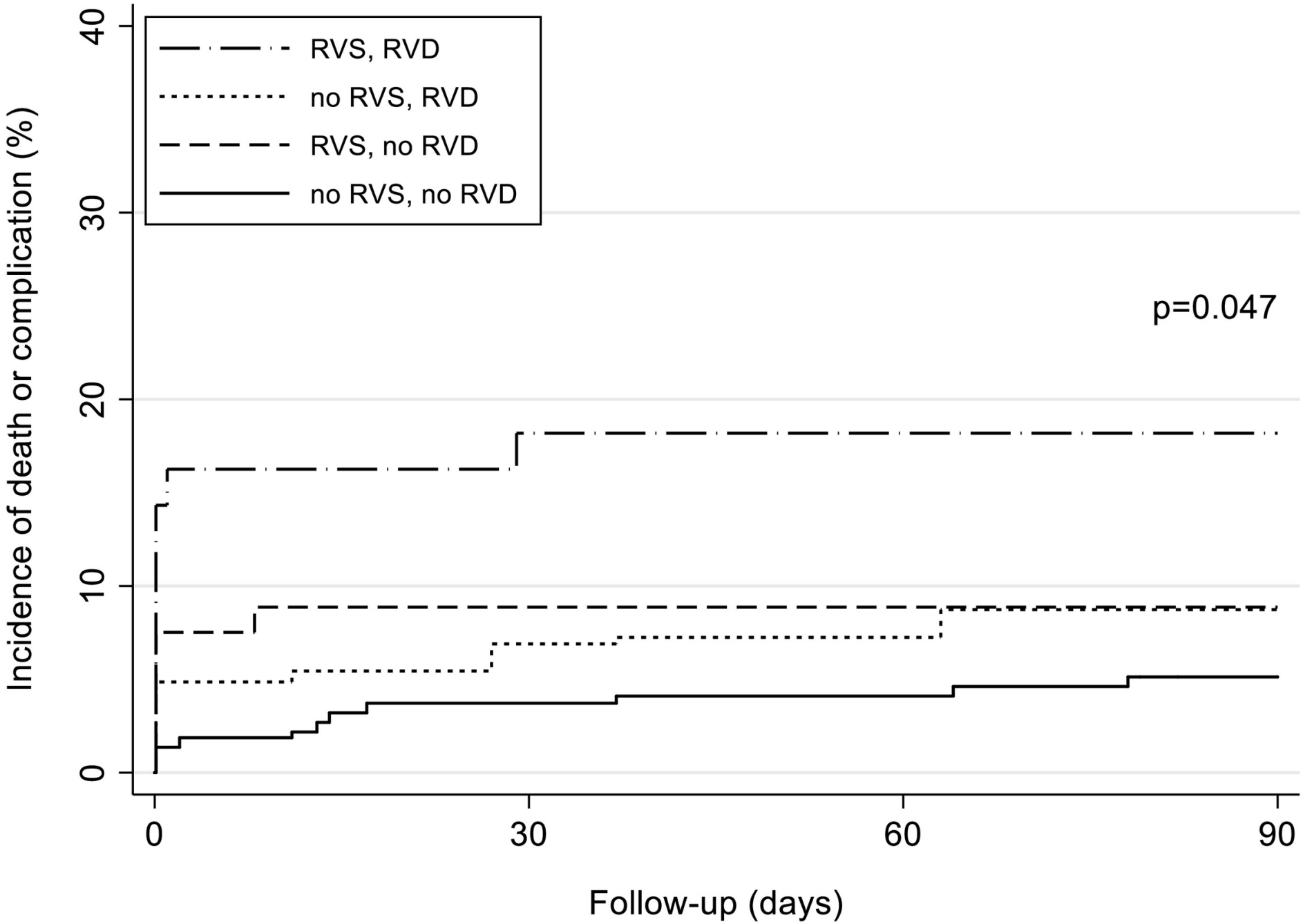
RVS, RVD
no RVS, RVD
RVS, no RVD
no RVS, no RVD
p=0.047
Incidence of death or complication (%)
0
10
20
30
40
0
30
60
90
Follow-up (days)

Figure 3