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External validation of a simple non-invasive algorithm to rule out chronic thromboembolic pulmonary hypertension after acute pulmonary embolism

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ABSTRACT

Purpose: International guidelines do not provide strong recommendations on the duration and intensity of follow-up after acute pulmonary embolism (PE), nor on screening-programs for chronic thromboembolic pulmonary hypertension (CTEPH). We aimed to address this gab by performing an external validation of the easy "CTEPH rule-out-criteria" based on a normal NT-proBNP level and the absence of 3 ECG characteristics.
Methods: 134 patients underwent clinical follow-up 6 months after PE. Predefined transthoracic echocardiographic (TTE) criteria were used to categorize patients as "PH unlikely" or "PH possible/likely". The latter patients underwent further (invasive) diagnostic procedures to confirm and classify the diagnosis of pulmonary hypertension. NT-proBNP and ECGs, both assessed at the day of echocardiography, were evaluated post-hoc.
Results: Sixty-three patients (47%) scored none of the "CTEPH rule-out criteria" positive, of whom 61 had normal TTE (97%). Twenty-five patients (19%) were categorized by TTE as "PH possible/likely"; of those, 6 were diagnosed with CTEPH. The sensitivity of rule-out criteria for CTEPH was 100% (95%CI 56-100%; 6/6 patients identified), and for "PH possible/likely" on TTE 92% (95%CI 74-99%; 23/25 patients identified): 2 asymptomatic patients with estimated systolic pulmonary arterial pressure of 36 mmHg and 38 mmHg, respectively, who remained stable during further 2-year follow-up, were not identified. Inter-observer agreement for the adjudication of the ECG characteristics was excellent (kappa-statistic 0.97).
Conclusions: In this external validation cohort, we confirmed the diagnostic accuracy and reproducibility of the "CTEPH rule-out criteria". These results provide a solid ground for future outcome trials applying this algorithm.

Introduction

The long-term course of acute pulmonary embolism (PE) can be complicated by several adverse events, including the development of chronic thromboembolic pulmonary hypertension (CTEPH) [1,2]. CTEPH is considered to result from incomplete resolution of thrombi and pathological remodelling of the small distal pulmonary arteries [2,3]. The resulting increased pulmonary vascular resistance ultimately leads, if left untreated, to progressive pulmonary hypertension and death [2,3]. The exact prevalence of CTEPH in patients who have suffered acute PE is debated: most studies report cumulative rates of 0.57% to 4.0% within the first 2 years after PE diagnosis, depending on patient selection and diagnostic criteria [4–8].

Screening programs for CTEPH after an episode of acute PE are still at a preliminary stage, and their cost effectiveness remains a subject of debate. Identification of patients at risk and the optimal diagnostic tools for screening are unclear, and effective CTEPH-prevention measures are unknown. Due to these uncertainties, current international guidelines are characterised by a lack of clear recommendations on the frequency and duration of follow-up after acute PE, and they hardly evoke specific screening programs for CTEPH [9,10]. Since delay in the initiation of treatment for CTEPH may result in worse prognosis, early establishment of the diagnosis is considered essential [2,3]. On the other hand, subjecting all patients who survived acute PE to transthoracic echocardiography (TTE), may have a low diagnostic yield [7,11]. Additionally, since the optimal time point for screening is unclear, recommending (repetitive) TTE examinations for all survivors of acute PE would impose a substantial financial burden on health systems.

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Consequently, there is great need for a simple, non-invasive diagnostic 'exclusion' test for identification of patients whose probability of developing CTEPH is low enough to render further diagnostic work-up unnecessary. It has been previously suggested that the combination of normal N-terminal pro-brain natriuretic peptide (NT-proBNP) plasma concentrations and the absence of three specific electrocardiographic (ECG) characteristics of right ventricular (RV) overload, the so-called "CTEPH rule-out criteria", accurately excludes the presence of CTEPH in patients with persistent dyspnoea after acute PE [12,13].

In the present study, we externally validated these "CTEPH rule-out criteria" in a prospective cohort of patients with acute PE who underwent TTE during follow-up. Furthermore, we evaluated modified "CTEPH rule-out criteria" in which high-sensitive troponin T (hsTnT) is used instead of NT-proBNP levels in combination with ECG parameters.

Materials and Methods

Patient Cohort

Consecutive patients aged 18 years or older who were diagnosed with acute PE at the University hospital of Göttingen, Germany, between October 2005 and August 2008 (cohort A), and between May 2011 and June 2013 (cohort B), were included in a prospective cohort study (Pulmonary Embolism Registry of Göttingen [PERGO]) and invited for a 6-month follow-up visit at the outpatient clinic of the Department of Cardiology and Pulmonology of the University of Göttingen as part of standard medical care at this institution. Patients included in PERGO between August 2008 and May 2011 were not subjected to standardized long term follow-up, and hence were excluded from this analysis.

Study Protocol: Inclusion Criteria and Baseline Proceedings

The study protocol has been described in detail previously [14,15]. Briefly, for inclusion in PERGO, patients had to fulfil the following criteria: (i) high clinical probability of PE as documented by the Wells score, or low/intermediate probability and a positive (≥0.5 mg/L) D-dimer test and (ii) confirmation of PE by an imaging procedure (contrast-enhanced computed tomography, ventilation-perfusion lung scan, pulmonary angiography, or TTE showing mobile thrombi in the right atrium or ventricle, or in the proximal portions of the pulmonary artery) based on the diagnostic algorithms proposed by recent guidelines [9,10]. At baseline, complete data on clinical, hemodynamic, and laboratory parameters were obtained using a standardized Case Report Form.

Treatment decisions were made by the physicians caring for the patient according to current guidelines [9,10] and not dictated by the study protocol. Hemodynamically stable patients were initially treated with intravenous unfractionated heparin (UFH), subcutaneous low molecular weight heparin (LMWH) or fondaparinux, respectively, followed by vitamin-K antagonists (VKA; target INR 2.0-3.0) or the factor-Xa-inhibitor rivaroxaban for a minimum period of three months. In hemodynamic unstable patients reperfusion therapy including administration of thrombolytic drugs was performed unless contraindicated. The study protocol was approved by the Ethics Committee of the University of Göttingen, and all patients provided written informed consent.

Study Protocol: Follow-up Visit

At least 6 months had to have passed since the acute PE event for the follow-up visit to take place, but a delay of up to 2 months was acceptable if the logistics of the outpatient service or the patient's preference made this necessary. At this follow-up visit, that was part of routine clinical care, venous blood samples were drawn and stored at –80 °C. Conventional 12-lead ECGs were recorded with the patient in supine position for a 10-second period using the standard 12-lead electrode configuration at a speed of 50 mm/s and sensitivity of 1 mV/10 mm. In addition, standard 6-month follow-up care after PE strongly recommends a TTE at this institution, regardless of the patient's physical condition or reported symptoms. TTE examinations were performed by experienced echocardiographers according to a predefined standardized protocol. We predefined the following echocardiographic criteria for suspected pulmonary hypertension (PH) according to the guidelines of the European Society of Cardiology (ESC): 1) tricuspid regurgitation velocity >2.8 m/s; 2) estimated systolic pulmonary artery pressure >36 mmHg (maximal pressure gradient across the tricuspid valve calculated by the modified Bernoulli equation plus the estimated right atrium pressure), and 3) any additional echocardiographic variables suggestive of PH e.g. systolic septal flattening, RV hypertrophy, or W-pattern in the RV outflow curve [7,11,12]. The presence of PH was considered *unlikely* in the absence of all of these criteria [11]. *Possible* PH was defined as tricuspid regurgitation velocity 2.9–3.4 m/s, estimated systolic pulmonary artery pressure 37–50 mmHg, or additional echocardiographic variables suggestive of PH [11]. In case of tricuspid regurgitation velocity >3.4 m/s or estimated systolic pulmonary artery pressure >50 mmHg, the presence of PH was considered *likely*.

For patients diagnosed with either *possible* or *likely* PH, the study protocol recommended further testing including ventilation-perfusion lung scan and right heart catheterization for invasive assessment of the pulmonary artery hemodynamics. Diagnostic criteria for CTEPH were: 1) mean pulmonary arterial pressure ≥25 mmHg with a pulmonary capillary wedge pressure ≤15 mmHg as assessed with right heart catheterisation and 2) signs of thromboembolic occlusion of the pulmonary artery tree on ventilation-perfusion lung scan and either conventional or CT pulmonary angiography, after a minimum period of 3 months with adequate anticoagulation. Treatment decisions including further diagnostic testing were made by the physicians caring for the patient and not dictated by the study protocol.

Post-hoc Study Procedures

ECGs were evaluated for the presence of one or more of the following three criteria indicative of RV overload by two independent researchers (F.A.K. and M.L.) who were unaware of the patients' clinical condition and results of the TTE: 1) rSR' or rSr' pattern in lead V1, 2) R:S >1 in lead V1 with R >0.5 mV and 3) QRS axis >90° [12,16]. NT-proBNP plasma concentrations were measured in batches after a single thaw by the use of a quantitative immunoassay (Elecsys® 2010, Roche Diagnostics, Mannheim, Germany). An abnormal NT-proBNP level was defined as a level over the age and sex dependent threshold [17]. Additionally, hsTnT plasma concentrations were assessed from the same material (Elecsys® 2010, Roche Diagnostics, Mannheim, Germany). Abnormal hsTnT level was defined as levels ≥14 pg/ml.

Statistical Analysis

Descriptive statistics for relevant baseline characteristics are provided with corresponding frequency, mean or median with standard deviation or interquartile range, dependent on Gaussian or skewed distribution. Continuous variables found not to follow a normal-distribution were compared using the unpaired Mann-Whitney U test and categorical variables were compared using Fisher's exact test or Chi^2 test, as appropriate. To investigate the incidence rate of CTEPH, the number of patient years (py) was calculated from the date of the PE diagnosis until the date of follow-up. For assessment of ECG characteristics of RV overload, inter-observer agreement was calculated based on the proportion of agreement as expressed by the kappa-statistic. The point estimates of the sensitivity and negative predictive value of the "CTEPH rule-out criteria" were calculated and reported with corresponding 95% confidence intervals. On forehand, we planned a sensitivity analysis that was restricted to patients with dyspnoea only. Finally, we substituted hsTnT for NT-proBNP results, and calculated the