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Full Length Article

Assessment of coexisting deep vein thrombosis for risk stratification of acute pulmonary embolism

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ABSTRACT

Background: In patients with acute pulmonary embolism (**PE**), studies have shown an association between coexisting deep vein thrombosis (**DVT**) and short-term prognosis. It is not known whether complete compression ultrasound testing (**CCUS**) improves the risk stratification of their disease beyond the recommended prognostic models.

Methods: We included patients with normotensive acute symptomatic PE and prognosticated them with the European Society of Cardiology (**ESC**) risk model for PE. Subsequently, we determined the prognostic significance of coexisting DVT in patients with various ESC risk categories. The primary endpoint was a *complicated course* after the diagnosis of PE, defined as death from any cause, haemodynamic collapse, or adjudicated recurrent PE.

Results: According to the ESC model, 37% of patients were low-risk, 56% were intermediate-low risk, and 6.7% were intermediate-high risk. CCUS demonstrated coexisting DVT in 375 (44%) patients. Among the 313 patients with low-risk PE, coexisting DVT (46%) did not show a significant increased risk of complicated course (2.8%; 95% confidence interval [**CI**], 0.8%–7.0%), compared with those without DVT (0.6%; 95% CI, 0%–3.2%), ($P = 0.18$). Of the 478 patients with intermediate-low risk PE, a complicated course was 14% and 6.8% for those with and without DVT, respectively ($P = 0.01$). Of the 57 patients that had intermediate-high risk PE, a complicated course occurred in 17% and 18% for those with and without DVT, respectively ($P = 1.0$).

Conclusions: In normotensive patients with PE, testing for coexisting DVT might improve risk stratification of patients at intermediate-low risk for short-term complications.

1. Introduction

Pulmonary embolism (**PE**) is a common cardiovascular condition with high morbidity and mortality [1]. Since the mortality of acute PE varies by clinical presentation, the presence of comorbid disease, and other underlying factors [2], risk stratification tools may help with decision-making regarding appropriate management of patients with acute PE [3]. Based on predictors of early mortality risk, the European Society of Cardiology (**ESC**) has proposed a risk classification schema that uses a validated clinical prediction score [4,5], along with hemodynamic status, imaging assessment of right ventricle (**RV**) dysfunction, and cardiac laboratory biomarkers to predict the risk [6].

Prior studies have shown an association between lower limb complete compression ultrasound (**CCUS**)-detected coexisting deep vein thrombosis (**DVT**) in patients with acute PE and short-term outcomes, such as all-cause mortality and PE-related complications [7,8]. However, imaging of the lower limbs to detect DVT after confirmation of PE diagnosis is not routinely performed, and would require some change in practice and additional resources. Therefore, it is important to assess whether performing CCUS to detect coexisting DVT might have additive prognostic discrimination to each subgroup of patients already stratified by guideline-recommended models.

The PROgnosTic valuE of CT scan in hemodynamically stable patients with acute symptomatic pulmonary embolism (**PROTECT**) study

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was designed to prospectively assess the prognostic significance of multidetector computed tomography (**MDCT**) findings and other cardiovascular prognostic factors in hemodynamically stable patients with acute symptomatic PE [9]. The purpose of the present study was to evaluate the role of CCUS in combination with the ESC prognostic model for risk stratification of normotensive patients with acute symptomatic PE.

2. Methods

2.1. Study design

This substudy used prospectively collected data from patients enrolled in the PROTECT study [9]. All patients provided written consent for participation in the study in accordance with local ethics committee requirements.

2.2. Setting

Patients underwent recruitment from the Emergency Departments of 5 academic and 7 general urban hospitals in Spain between January 1, 2009, and May 31, 2011.

2.3. Study eligibility and patients

The study screened consecutive patients with objectively confirmed diagnosis of acute symptomatic PE for study participation. Study eligibility required confirmation of the diagnosis of PE with a positive MDCT. The study also required that patients to have technically adequate MDCT and transthoracic echocardiography **(TTE)** studies [9]. Exclusion criteria were hemodynamic instability at presentation (defined as cardiogenic shock, systolic blood pressure < 90 mm Hg, or use of inotropic support), treatment with thrombolytics at the time of PE diagnosis, life expectancy < 3 months as determined by the investigator, pregnancy, geographic inaccessibility that precluded follow-up, and age younger than 18 years.

2.4. ESC prognostic model

The central coordinating center prospectively determined the simplified Pulmonary Embolism Severity Index (**sPESI**), as previously described [5]. The study defined echocardiographic right ventricular (**RV**) dysfunction as the presence of at least two of the following: dilatation of the RV (end-diastolic diameter > 30 mm from the parasternal view or the RV appearing larger than the left ventricle from the subcostal or apical view), hypokinesis of the RV free wall (any view), and estimated systolic pulmonary artery pressure over 30 mm Hg [10]. PROTECT defined cTnI concentrations of > 0.05 ng/mL as indicative of myocardial injury (cTnI positive) [11].

For this substudy, according to the ESC prognostic model, a sPESI score of 0 identified low-risk patients; intermediate-low risk patients if the sPESI was ≥1 and either echocardiographic RV dysfunction or elevated troponin levels (or none) were present; and intermediate-high risk patients if the sPESI was ≥1 and both echocardiographic RV dysfunction and elevated troponin levels were present [6].

2.5. Lower limb ultrasound testing

Patients underwent bilateral proximal and distal lower extremity CCUS of the veins within 48 h after the diagnosis of PE. Trained and certified vascular surgeons who were unaware of patients' clinical details, used a standardized CCUS protocol to evaluate for DVT [12]. Vein incompressibility was the sole diagnostic criterion for DVT.

2.6. Study endpoints and outcome measures

This substudy used a *complicated course* after the diagnosis of PE as the primary endpoint, defined as death from any cause, haemodynamic collapse (systolic blood pressure < 90 mm Hg for at least 15 min, catecholamine administration because of persistent arterial hypotension or shock, need for thrombolysis, need for endotracheal intubation, or need cardiopulmonary resuscitation), or adjudicated recurrent PE. We used all-cause mortality and PE-related death as secondary endpoints. Study outcomes were assessed for the first 30-days of follow-up after the diagnosis of PE. The Adjudication Committee, whose members were blinded to initial prognostic test results, adjudicated all serious adverse events.

2.7. Statistical analyses

For reporting of continuous data, we used standard descriptive statistics. For non-normally distributed continuous data as determined by Kolmogorov-Smirnov test, we reported the median and 25th and 75th percentiles. For categorical data, we described baseline characteristics with counts and proportions.

To estimate the outcomes of time to complicated course, Kaplan-Meier probabilities were computed, and differences between the groups were assessed with the log-rank test. Within each of the ESC risk categories (i.e., low-risk, intermediate-low risk, and intermediate-high risk), we calculated study outcomes according to the presence or absence of ultrasound-detected coexisting DVT. To assess the test and performance characteristics of the six prognostic groups, we estimated sensitivity, specificity, and positive and negative predictive values and likelihood ratios for predicting a complicated course. Ninety-five percent CIs were computed from the binomial distribution by using Statistical Package for Social Sciences (**SPSS**) Statistics 20.0 (IBM, Chicago, IL, USA), and we used Stata, version 11.2 (StataCorp, College Station, Texas) for Windows, for all other analyses.

3. Results

3.1. Study sample

Between January 1, 2009, and May 31, 2011, the PROTECT study screened 999 normotensive patients with acute PE from 5 academic and 7 general urban hospitals in Spain. The final study cohort consisted of 848 patients (416 men and 432 women) who had a diagnosis of hemodynamically stable acute PE at the time of presentation to the Emergency Department. Twenty-eight patients did not have complete baseline CCUS data required for analyses (3.3%; 95% CI, 2.2% to 4.7%). No statistically significant difference was observed between patients with and without CCUS testing regarding demographics, medical history, and clinical presentation.

The patients' clinical symptoms, predisposing conditions, and relevant findings at presentation are described in detail elsewhere and summarized in Table 1 [9]. In our study, we found that 313 patients (37% of the entire study population) had a sPESI of 0 points (*low-risk ESC group*), 478 (56%) patients with a sPESI ≥1 point(s) had echocardiographic RV dysfunction or elevated troponin level or none (*intermediate-low risk ESC group*), and 57 (6.7%; 95% CI, 5.1–8.6%) patients with a sPESI ≥1 point(s) had echocardiographic RV dysfunction and elevated troponin level (*intermediate-high risk ESC group*). Of the 848 enrolled patients, 375 (44%) had coexisting (all proximal) DVT (DVT-positive group) and the remaining 473 patients did not (DVT-negative group). DVT was confirmed in 182 of the 263 (69%) patients who had symptoms or clinical signs of DVT, and 51% (193/375) of the patients with proven DVT were asymptomatic. One hundred and seventy patients (20%) were low risk according to the PESI, and did not have coexisting DVT. Eighteen (2.1%) were intermediate-high risk according to the ESC, and had coexisting DVT.