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Early View

Research letter

# ROLE OF A CLINICAL PREDICTION SCORE IN A CTEPH RULE-OUT STRATEGY

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**ROLE OF A CLINICAL PREDICTION SCORE IN A CTEPH RULE-OUT STRATEGY**

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Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare and serious complication after pulmonary embolism (PE). Its incidence in the general population is around 3-30 cases per million. The incidence of CTEPH after acute PE ranges between 0.1 and 8.8%[1,2,3,4,5]. In a meta-analysis including 4,047 PE patients, the incidence of CTEPH was 2.8% (95% CI 1.5-4.1) in “PE survivors”

without major comorbilities[6]. In studies not using objective diagnostic criteria to diagnose CTEPH, the pooled incidence was 6.3% (95% CI 4.1-8.4)[6].

To diagnose CTEPH, a number of tests are required. Transthoracic echocardiography (TTE) should always be performed when CTEPH is suspected, but is not enough to support a treatment decision. It is mandatory to demonstrate the combination of precapillary pulmonary hypertension (defined by mean pulmonary arterial pressure [PAP] levels ≥25 mmHg at rest) on right heart catheterization (RHC) and mismatched perfusion defects on lung scan. All patients also need a multidetector CT angiography, MR imaging or conventional pulmonary angiography to look for specific signs such as ring-like stenosis, webs/slits and/or chronic total occlusions (pouch lesions or tapered lesions)[7]. The prognosis of patients with CTEPH without treatment is poor,[8] but early detection and pulmonary endarterectomy (PEA) may improve outcomes considerably. In fact, the time elapsed between the last PE episode and PEA influences the mortality rate[9]. However, a significant number of patients, presumably 40%, develop CTEPH in the absence of prior acute PE[10 11].

TTE is considered the first test in the diagnostic algorithm for CTEPH, but routine TTE in all patients with PE is not cost-effective, given its low diagnostic yield for CTEPH, around 25%, between 6-12 months after an acute episode of PE[12,13]. Consequently, current guidelines from the ESC/ERS recommend to only consider CTEPH in patients with exercise/persistent dyspnea several weeks after PE[14]. The most common symptom of CTEPH initially is progressive dyspnea on exercise, although some patients with PE may transiently experience some improvement in symptoms. Therefore, early identification of CTEPH soon after the PE is difficult.

A simple and non-invasive tool that could be used as a routine assessment in patients with acute PE might help to discriminate those patients that could safely avoid further diagnostic tests. Recently, a clinical prediction score for CTEPH was derived from three large prospective cohorts including 772 patients with acute PE [15]. The authors built a clinical prediction score assigning points to six clinical variables: unprovoked PE, known hypothyroidism, symptom onset >2 weeks before PE diagnosis, right ventricular dysfunction on computed tomography or TTE, known diabetes mellitus and thrombolytic therapy or embolectomy. They considered the diagnosis very unlikely in patients with scoring ≤ 6 points. The sensitivity of the score obtained with this threshold was 91% (95% CI 70–98%).

We tried to externally validate this score in a CTEPH rule-out strategy in 2256 patients with acute PE included in RIETE registry. Patients with history of heart failure or chronic pulmonary disease were not considered for the study. All patients underwent TTE between 6 to 12 months after the PE episode. Since RIETE has no information available on CTEPH diagnosis, we considered patients not to have CTEPH when a low probability of pulmonary hypertension was found on TTE, according to current guidelines recommendations[7,16]: systolic PAP levels ≤36 mmHg or peak tricuspid regurgitation velocity ≤2.8 m/sg (or not measurable), and no additional TTE signs suggesting pulmonary hypertension (right ventricle/left ventricle basal diameter ratio>1, diastolic right ventricle

diameter>35mm, right ventricle hypokinesia, left ventricular eccentricity index >1.0 in systole and/or diastole and/or tricuspid annulus plane systolic excursion (TAPSE) <17 mm).

The flow-chart of patients appears in Figure 1. From 25,695 PE patients included in the RIETE registry, we selected 2,807 in whom a TTE was performed 6 to 12 months after acute PE. Finally, 2,256 patients were analyzed. CTEPH was ruled out by TTE in 1670 patients (74%), of whom 1295 were classified as "low-risk" by the clinical prediction score (≤ 6 points). Among the remaining 586 patients with "likely" CTEPH on TTE, only 160 were classified as "high-risk" according to the score. In a « rule-out » strategy, using the score would help to avoid 1295 (57%) unnecessary TTEs, but the proportion of false negatives was of 72.7% (95% CI: 68.9–76.1%). In other words, the score would mistakenly suggest that TTE could be avoided in 426/2,256 (19%) of patients.

The sensitivity of the score was 27.3% (95% CI: 23.7–30.9%) and the negative predictive value 75.2% (95% CI: 73.2–77.3%). Others parameters, like specificity and positive predictive value are not relevant in this approach since the aim of this study was to validate the score in a rule-out-strategy. Even if a higher threshold of ≤8 points were applied this strategy would not be associated with a better sensitivity: 12.1% (95% CI: 9.4–14.7%).

Early diagnosis of CTEPH still remains challenging, with a considerable delay between symptoms onset and CTEPH diagnosis. The reported median time is around 14 months, even in experienced centers[17]. CTEPH is characterized by the classical "honeymoon": since patients may worsen after an initial improvement. Then, an easily available score early after PE diagnosis may help clinicians to decide what patients would benefit from a more thorough screening for CTEPH.

The potential benefit of CTEPH screening at the time of PE diagnosis is controversial, but some authors suggested the possibility to identify patients at high risk. In 2015 Klok et al [18] built a CTEPH rule-out-criteria based on a normal NT-proBNP level and the absence of 3 electrocardiographic characteristics in a prospective cohort of patients with PE undergoing TTE during follow-up. The presence of pulmonary hypertension was unlikely in 81% based on TTE criteria, with a sensitivity of 100% (95% CI: 56-100%). The main limitations were that the validation was only possible in 134 patients, and at 6 months. Interestingly however, no clinical variables were included in the rule out criteria, so some cases of "new onset" CTEPH could be previous to the acute PE episode.

Our findings do not confirm the sensitivity, and negative predictive value of the score obtained during the derivation study[18]. The score may help us to avoid until 57% unnecessary TTEs, but with the risk of an important amount of false negative patients. One of the advantages of our approach is that it has been tested in a large sample of "real world" patients who underwent routine follow-up visits and one TTE between 6 to 12 months after PE.

Our approach has a number of limitations. First, even though TTE is still recommended as the initial noninvasive tool in the screening of PH, it may frequently be inaccurate in estimating systolic PAP levels[19]. Second, the RIETE registry was not initially designed to identify PE patients at risk for CTEPH, and there is no information on a final confirmation of CTEPH in most of these patients. Besides, one of the variables in the model (symptom onset >2 weeks before PE diagnosis) is not available in RIETE. Thus, we replaced it by `isolated dyspnea´ at baseline. Hence, we slightly modified the original score. Our main strengths are the large number of PE patients in the registry (n=2,256), and that the TTE criteria used for defining very unlikely CTEPH were based on current guidelines recommendations[7] .

Our results suggest that a predictive score based on data obtained during the index PE is not enough sensitive in a CTEPH rule-out strategy. With the aim to improve the diagnostic accuracy, other strategies should be evaluated, such as a combination of a predictive score based on the index PE and more specific biomarkers, for example NT-proBNP, during follow-up[18].

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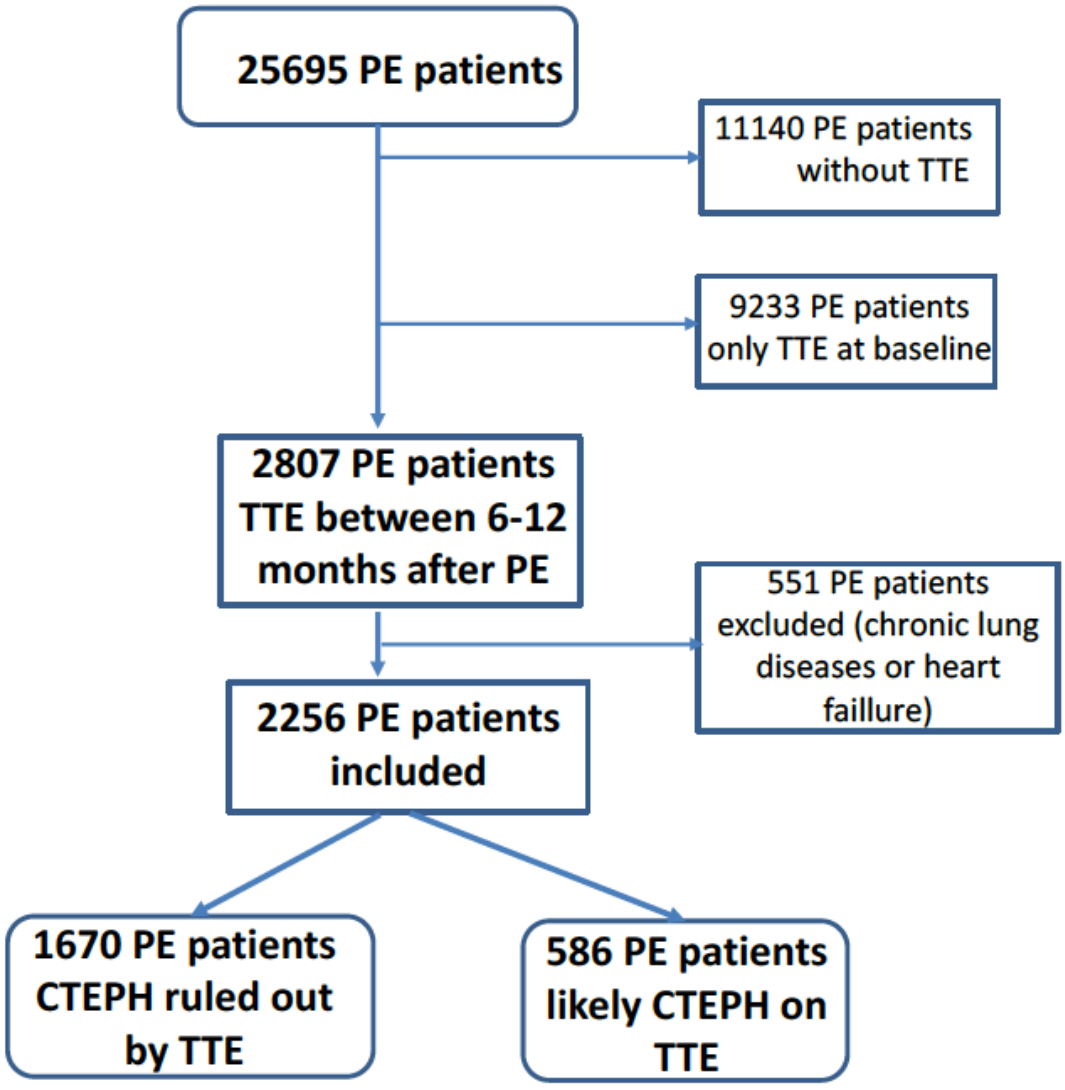
FIGURE 1


25695 PE patients
11140 PE patients without TTE
9233 PE patients only TTE at baseline
2807 PE patients TTE between 6-12 months after PE
551 PE patients excluded (chronic lung diseases or heart faillure)
2256 PE patients included
1670 PE patients CTEPH ruled out by TTE
586 PE patients likely CTEPH on TTE