



EDITORIAL COMMENT

Looking for the “magic formula” to restratify non-high risk pulmonary embolism: Are we missing the essential?



À procura da «fórmula mágica» para reestratificar a embolia pulmonar de não-alto risco: estamos a perder o que é essencial?

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In acute pulmonary embolism (PE), mortality varies significantly according to risk stratification. It stands at 30% on average in high risk PE and is very low in low-risk patients.¹ These data support current guideline recommendation to give reperfusion therapy in hemodynamically unstable patients and for those suffering from hemodynamic deterioration in spite of adequate anticoagulation.² However, whether hemodynamically stable acute PE patients with signs of right ventricle (RV) dysfunction and myocardial injury, categorized as intermediate-high risk acute PE, may also benefit from reperfusion therapy is an ongoing subject of debate. In fact, although most patients with intermediate-high risk PE evolve favorably under isolated anticoagulation, up to 10% may deteriorate clinically and be at a higher risk of mortality.³ In the FLASH registry, over one-third of PE patients were identified as intermediate risk with the presence of normotensive shock, characterized by a low cardiac index measured invasively.⁴

The major question is: in which situations is it clinically useful to use risk scores for the assessment of patients with PE?

In intermediate risk PE, risk scores could be helpful to better identify patients who are at a greater risk of unfavorable evolution under conservative treatment with isolated anticoagulation. But the fundamental question that scores must answer in this setting is whether a given patient with normotensive PE will benefit from more advanced intervention, either with a low dose of systemic thrombolysis or minimally invasive catheter-directed-therapy (CDT).

Several previous risk scores, such as BOVA⁵ and H-FABP (high-sensitivity troponin T)⁶ have been validated as prognostic scores in cohort studies, but their implications for patient management remain unclear.

In low-risk PE, the Pulmonary Embolism Severity Index (PESI) score allows the identification of a low-risk group (class I and II) in which it may be safe to be discharged early.⁷

In this issue of the Portuguese Journal of Cardiology, Gerardo et al.,⁸ created a new PoPE score to risk stratify patients admitted with hemodynamically stable PE from a derivation cohort of 835 patients. The authors intend to discover the “magic formula” to identify patients with normotensive PE with higher risk of mortality at 30 days. They

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created a composite score using five admission parameters available from noninvasive clinical assessments: modified shock index ≥ 1.1 , active cancer, altered mental state, lactate concentration ≥ 2.5 mmol/L and age ≥ 80 years. A good score to predict mortality in this setting should hold several key characteristics, all of which this new score contains:

1. *Accuracy and discriminatory power:* The PoPE score has a high level of accuracy in predicting all-cause mortality at 30 days. The statistical analysis was robust, and it was validated using appropriate methods to ensure its reliability. The score distinguishes between patients who are at high risk of mortality and those who are at low risk. It has a higher discriminatory power, measured by metrics such as the area under the receiver operating characteristic curve (AUC) of 0.83 (0.79–0.87), compared to other validated scores as PESI and sPESI.
2. *Simplicity:* The PoPE score is easy to calculate and friendly to use in clinical practice. Unlike the PESI score, which is complex to use because it comprises 11 clinical variables and stratifies patients into five severity classes, the PoPE score consists of a limited number of variables that are readily available at the admission and can be easily assessed without extensive testing.
3. *External validation:* the PoPE score was validated externally in an independent patient cohort with 280 patients from other institutions to confirm its predictive ability in different populations. Its performance in the validation cohort was deemed good with an AUC of 0.76 (0.71–0.82) and superior to PESI and sPESI. This step ensures the score's performance is not limited to the original derivation cohort and can be generalized to other settings (as mentioned by the authors – the validation cohort comprised higher risk patients).
4. *Clinical utility:* The score should provide information that can guide clinical decision-making. It should be a tool to help healthcare professionals to determine appropriate treatment strategies, allocate resources, and identify patients who may benefit from more intensive interventions or monitoring. And this is missing. The implication of this PoPE score for patient management remains unclear.

To date, only a combination of RV dysfunction on an echocardiogram (or CTPA) with a positive cardiac troponin test has been directly tested as a guide for early therapeutic decisions in the randomized controlled Pulmonary Embolism International Thrombolysis (PEITHO) trial. This was a large randomized controlled trial in normotensive PE patients, in which mortality was low in both groups (1.2% with thrombolysis vs. 1.8% with isolated anticoagulation) and thrombolysis with tenecteplase was associated with an unacceptable risk of bleeding.⁹ Thrombolysis should, therefore, be avoided in intermediate risk PE stratified based only on imaging and biomarkers. Another hypothesis raised by the PEITHO study is that risk stratification based only on right ventricular dysfunction and myocardial injury is likely insufficient to identify patients at higher risk in intermediate risk PE.

In the near future, there will be some properly built and powered randomized trials focused on clinical endpoints instead of the usual surrogate endpoint used in previous CDT

trials. These studies will investigate short- and long-term clinical outcomes. These landmark trials certainly will show us some light at the end of the tunnel regarding the role of endovascular intervention in the treatment of normotensive PE. HI-PEITHO trial is randomizing intermediate-high risk acute PE patients with at least two clinical criteria of severity (i.e., heart rate ≥ 100 bpm, systolic blood pressure ≤ 110 mmHg, respiratory rate >20 /min, and/or oxygen saturation on pulse oximetry $<90\%$ on room air) to treatment with a standardized protocol of ultrasound-facilitated catheter-directed thrombolysis plus anticoagulation versus anticoagulation alone.¹⁰

In HI-PEITHO the National Early Warning Score (NEWS), which was previously used to assess the severity of acute illness, is going to be used to classify the occurrence of clinical deterioration in hospitalized patients. NEWS comprises physiological measurements evaluated at the bedside – respiratory rate, oxygen saturations, supplemental oxygen need, temperature, systolic blood pressure, heart rate, and level of consciousness. HI-PEITHO could soon shed light on how to identify patients better who may clinically benefit from intervention, in addition to anticoagulation.

We are in an era where various scores are being created to find the “Holy Grail”. But we could be missing out on the essential: the clinical evaluation of the patient, the clinical instinct of their doctor, the continuous assessment of the patient's evolution at their bedside. . . in addition to the variables collected at admission and included in PoPE score; the patient's evolution under isolated anticoagulation in the first hours after admission (24–72 hours) is a determinant of the patient's short term risk.

In the PEITHO trial, the mean time between randomization and death or hemodynamic decompensation was 1.79 ± 1.60 days in the group randomized to heparin alone.⁹ A score measured at admission before starting anticoagulation may be insufficient and may be overestimating the patient's risk.

It is important to note that developing a mortality prediction score requires careful research, validation, and continuous evaluation. Clinical judgment should always be exercised when using any predictive tool, and the score should be considered as part of a comprehensive assessment that considers the individual patient's characteristics and clinical context. The decision to intervene should also rely on the experience of Pulmonary Embolism Response Teams (PERT), standardized protocols should be implemented and followed depending on the resources available.¹¹

While most relevant combination of clinical, imaging and biomarkers predictors of early PE-related death remain to be determined, numerous scores searching for a “magic formula” that identifies candidates for reperfusion treatment among patients with normotensive PE, will try to replace the essential: the fundamental value of bedside clinical evaluation of the patient and the decision-making process in a multidisciplinary team.

Conflicts of interest

The author has no conflicts of interest to declare.

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