THE IMPORTANCE OF CLINICAL PREDICTION MODELS IN NON-FATAL PULMONARY EMBOLISM: AN ANALYSIS OF THE BEST KNOWN CLINICAL SCORES

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THE IMPORTANCE OF CLINICAL PREDICTION MODELS IN NON-FATAL PULMONARY EMBOLISM: AN ANALYSIS OF THE BEST KNOWN CLINICAL SCORES (Abstract): The clinical evaluation in pulmonary embolism (PE) is the first instrument used by practitioners in the management of this potentially fatal pathology. The necessity of developing certain valid and especially affordable practical instruments has led to the emergence of various clinical prediction models. The purpose of this paper is to analyze the main clinical scores, as a diagnostic or a prognostic tool, with their strengths and weaknesses. The PESI score, while relatively recent, remains the most investigated and validated prognostic score for the identification of the mortality risk and major adverse events, with economic implications of health services reduction costs through the accurate identification of patients with a low risk who are candidates of early hospital discharge. The simplified Geneva score (with a similar accuracy as the Geneva one) identifies a high or low PE probability, especially in combination with D-dimers, with a prognosis value as well. The Wells and simplified Wells scores identify the high or low probability, being improved by the level of D-dimers, having similar results with the Geneva score. The LR-PED score, conceived as an identification score for low risk, uses biochemical and electrocardiographic markers, but is less validated. The Vienna Prediction Model is another system for the evaluation of the recurrence in which the level of D-dimers is the main prediction factor. Other scores were evaluated with a statistically low significance. The Geneva and the PESI scores remain the most valuable instruments of diagnosis and clinical prognostic, respectively. Keywords: PULMONARY EMBOLISM, CLINICAL SCORE, PROGNOSTIC, MORTALITY

Clinical prediction models have become more popular to aid clinical decision-making.

These models were developed to deliver a probability of having (a diagnostic prediction model) or developing (a prognostic prediction model) a certain outcome in an individual.

Pulmonary embolism (PE) is a potentially fatal condition, which’s diagnostic and treatment should be rapid, especially in the case of a massive PE. Both the European Society of Cardiology (ESC) guide and the American Heart Association (AHA)
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recommends the stratification of patients in patients with a high risk of mortality (mas- sive PE) (1, 2) and patients with non-fatal risk. The non-fatal group comprises 90% of the patients and shows an early mortality risk that varies from less than 1% (low risk) up to 15% (intermediate risk) (1, 2). Using researches dating back as early as the 1990s, but also recent imagistic and laboratory studies, the ESC guide regarding the PE management (2014) recommended that the patients without signs of shock and without increased biomarkers or echocardiographic aspects indicative of right ventricular dysfunction in sPESI score 0 be listed in the low risk group who benefits from early hospital discharge and home care (1). All these are recommendations and not clear indications due to the absence, until recently, of solid proof for selecting patients who may receive outpatient treatment (3). Unlike other diagnostic and prognosis instruments, these clinical scores are based on clinical data which may be applied in any medical unit. Thus, one can determine from the admission, using clinical scores, laboratory and imagistic tests, a profile of the low-risk patient who can receive outpatient care. Taking into consideration the more and more frequent evidence underlining the fact that the low risk subgroup and non-fatal PE benefit from outpatient treatment, British Thoracic Society confirms this recommendation, a measure which may lead to a substantial reduction of healthcare costs (4).

The identification of a valid and easy clinical score to the largest extent possible both from an economic point of view and from the perspective of access to various sophisticated diagnosis instruments, which can be a diagnostic and a prognostic tool at the same time, remains a challenge that this paper attempts to elucidate, by reviewing the main clinical prediction models. Multiple clinical prediction rules were discovered. Some of them, well-known as a diagnostic tool, now have a proved prognostic value, others were defined from the beginning as a prognostic tool. The patients with non-high risk PE can benefit from an accurate and relatively fast clinical examination in order to receive the best possible treatment.

Therapeutic strategies determined by the risk degree and the importance of clinical prediction models. The European PE guide divides patients into 3 risk groups: high, intermediate and low. High-risk patients are those diagnosed with elements of shock or hypotension (defined as systolic blood pressure under 90 mmHg or a decrease of the pressure by more than 40 mmHg in 15 minutes, which is not caused by the debut of an arrhythmia, hypovolemia or sepsis) and who receive thrombolytic therapy and/or hemodynamic and respiratory support (1). They are not covered by the current paper.

Patients with normal blood pressure with non-high risk fall into the intermediate risk group in the presence of dysfunction markers of the right ventricle (RV) (echocardiographic and/or positive BNP) and/or of myocardial lesion (positive I or T troponin). Hemodynamically stable patients without RV dysfunction elements or myocardial lesion show a low mortality risk (<1%). The injectable antigoagulant treatment is administered to all patients when there is a clinical suspicion of acute PE, even prior to the diagnostic confirmation, being followed by oral anticoagulants (1). Thus, the importance of clinical prediction scores is confirmed, as they may identify from the beginning a low mortality risk, the
patients being able to benefit from early discharge and outpatient care, with a direct impact on healthcare costs. Several early discharge criteria may be defined: absence of shock or hypotension, absence of RV dysfunction, absence of important co-morbidities (chronic heart failure, chronic pulmonary diseases, and chronic renal disease), low recurrence risk, exclusion of patent foramen ovale, absence of active bleeding and low hemorrhagic risk, absence of the necessity of intravenous analgesic administration and absence of oxygenotherapy indication (3). All of these provided there is a compliant patient who benefits from family support to continue proper treatment at home. But, taking into consideration that patients, not diseases, are treated, each with his/her own particularities, the determination of accurate and statistically well-documented clinical scores is a must. The controversial hypothesis of full treatment outside the hospital of certain well-selected patients has also been tested, provided there is an easy access to a hospital unit. The bleeding, recurrence or mortality risk was similar between the group which received full outpatient treatment and the hospitalized group (5). However, these studies failed to take into consideration less frequent PE complications, such as chronic pulmonary hypertension, arrhythmia or the necessity for inotropic support or thrombolysis, while rare in case of low-risk patients (6). Another argument for the early hospital discharge is the emergence of new oral anticoagulants which do not require laboratory monitoring or adjustment of doses for patients with venous thromboembolism. The potential of the new oral anticoagulants to treat low-risk patients and with early discharge criteria is to be evaluated in future studies. Antithrombotic treatment may have also a potentially beneficial role (7).

**Economic impact.** Early discharge of correctly evaluated low-risk PE patients is associated with a reduction of hospital costs, allowing the medical unit to use the saved funds for the more efficient and more complex treatment of serious cases. The cost-efficiency ratio of diagnosis and treatment in venous thromboembolism has been evaluated, but especially in deep thrombophlebitis (DVT) which has a similar anticoagulant treatment. A study revealed that the cost of hospital care for a DVT patient was higher for unfractionated heparin as compared to fractionated heparin and the cost of fractionated heparin administration in outpatient treatment decreased by almost a half (8). With regard to PE, it has been proven that the fractionated heparin treatment would be cost-saving if more than 8% would be eligible for early discharge or more than 5% of patients could receive outpatient treatment (9).

**DIAGNOSTIC CLINICAL PREDICTION RULES**

**The Geneva and Wells score.** The best known and most used are the Geneva and Wells scores. In a prospective study which comprised 296 PE diagnosed patients admitted at University Hospital of Geneva, followed up for a period of 3 months, six independent mortality predictors were identified as well as other adverse events (PE recurrence, major bleeding). These factors were validated in a study conducted in an emergency department, later to be named the Geneva prediction rule (10). The revised Geneva score comprises 8 variables with a different weight, which might be difficult to memorize and calculate in an emergency unit. The simplified Geneva
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score assigns 1 point for each factor used. Low probability is between 0-1 points, intermediate probability between 2-4 points and high probability over 5 points. The accuracy of the diagnosis and the clinical utility are not modified in case of the simplified Geneva score, being able to exclude PE when combined with a normal D-dimers value. The PE prevalence is similar to the original Geneva score and to the Wells score (11). Recently, the Geneva score was investigated in a large study, which evaluated 9 clinical scores as prognostic assessment tools in patients with pulmonary embolism (12). Out of these, the PESI and Geneva scores identified the in-hospital mortality < 1% (low-risk) for the PE patients. The identification of low recurrence risk seems to be superior with PESI score than Geneva score. However, 3 months-mortality was comparable between the 2 scores, both for the low-risk group (1.1% at PESI vs. 0% at Geneva) and for the high risk group (11.1% PESI vs. 14.3% Geneva). The use of both scores improves the prognosis evaluation. For instance, the mortality of patients with greater Geneva probability increased from 14.3% to 25% when the high PESI risk was added (13).

The Wells score, published in 2000, is based on a multicenter Canadian study and was developed as a clinical selection pre-test of patients with high PE probability. A Wells score higher than 2 is indicative of a high PE probability which requires imagistic explorations, while a score lower than 2 has a negative predictive value for PE of 95% (14). The simplified Wells score assigns 1 point for each variable, a score value higher than 1 suggesting PE probability (15). In the PIOPED II data, the CT positive predictive value for PE at patients with Wells scores lower than 2 was of 58% indicating that a large portion of the results from these patients are false-positive. The use of D – dimers tests in combination with the Wells score was suggested as a means to help with the patients’ selection. It was proved that a negative D-dimers result reduces the PE probability for any Wells score. The PE probability for patients with a score of <2, even with positive D-dimers, was of 7.0%. This is comparable to the PE rate for patients with a negative CT result (14). The Wells score accurately predicts PE probability at hospitalized patients and this population had a greater PE prevalence than other cohorts. However, the score has no prediction value to exclude a potentially fatal evolution (16).

Given the similarities between the Geneva and the Wells scores, various comparative analyses were conducted. A study that compared 4 clinical scores (the two ones and their simplified versions) concluded that they are similar in their ability to differentiate patients depending on the PE probability and in the patients’ proportion who required no imagistic investigation due to the low risk points of the scores with normal D-dimers. Although there were discrepancies at approximately 30% of the patients regarding the low or high probability, there were no differences in the failure rates when the clinic – D-dimers combination was used. The simplified Wells score had similar performances with the Wells score and the revised Geneva score (15). There are limitations, however. The Wells score includes clinical judgment, which is subjective and cannot be standardized (17). It also has no prognostic value. Moreover, it was suggested that the predictive value of this score derives precisely from its subjective component (18).
The Pulmonary Embolism Rule-out Criteria (PERC) rule. This score was obtained to exclude the PE diagnosis using anamnesis and the patient’s physical exam. A negative value implies: the clinical judgment of the physician regarding the probability lower than 15% of PE to which the following characteristics are added: age < 50, pulse < 100 beats/min, oxygen saturation > 94% in room air, absence of hemoptysis, absence of estrogen use, no PE antecedents or deep thrombophlebitis, no unilateral edema (objectified by the clinician), no recent surgical interventions or traumas (in the last 4 weeks, which involved endotracheal or spinal anesthesia) (19). Of a greater significance is the fact that this rule applies to a population with a PE prevalence lower than 10%. At this population, the sensitivity was of 100%, the specificity varying between 16-33% with a negative predictive value of 100% (19, 20, 21). In addition, it needs to be applied to low-risk patients, therefore another clinical score, such as the Wells score, should be calculated first. A single study used this score for patients with high risk as well and proved that the PERC is highly sensitive (100%) and has good negative predictive value (20). In case of the population with high PE prevalence, the PERC score, although combined with the revised Geneva score, could not exclude PE without further tests (22).

PROGNOSTIC CLINICAL PREDICTION RULES

The Pulmonary Embolism Prognostic Index (PESI) score. Various comparisons between clinical scores are difficult to interpret but it seems that PESI is the most studied with a total number of 22127 patients. PESI identified 43% of the patients with inter-hospital mortality less than 1%, defined by both guides (ESC and AHA) as low-risk. It comprises 11 clinical parameters with various degrees of prognosis. Depending on the score, the patient falls into one of the 5 classes, with mortality at 30 days ranging from 1.1% to 24.5% (23). Patients in the risk class I or II are low-risk and those in classes III-V are high-risk. However, the original score uses 11 clinical parameters and the final value requires difficult calculations which are hard to make in the clinical practice.

The simplified PESI (sPESI) was developed in 2010 and includes 6 out of the 11 original parameters, dividing patients into high-risk (1-6 points) and low-risk (0 points) patients (24). Both original and simplified PESI were included in the last ESC guidelines on the diagnosis and management of acute pulmonary embolism for risk stratification besides laboratory parameters and imaging tests.

A recent meta-analysis comprising 21 studies has comparatively analyzed the PESI versus sPESI accuracy in predicting adverse events (general mortality and PE related mortality, PE recurrence, non-fatal bleeding)(25). The PESI model also identifies patients with high-risk, a PESI high-risk score is a risk factor for mortality of all causes (AUC 0.78 (95% CI: 0.77 to 0.80)), PE related mortality (AUC 0.82 (95% CI: 0.75 to 0.89)) and significant adverse events. In addition, the sPESI group showed a similar accuracy with the PESI group (similar OR and AUC for PE related mortality, mortality of all causes and significant adverse events) in several studies (25, 26). sPESI was validated in a subsequent study which confirmed its applicability to an independent population (23). This model accurately identifies PE patients who show a low risk of fatal and
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non-fatal medical events: no patient from the class I died or showed PE recurrence or major bleeding at 90 days from the initial PE. Out of the class II patients, only 1% died and no patient showed adverse events. The negative predictive value for mortality among patients with low-risk (classes I and II) was of 98-99%. Thus, one can consider in these cases the possibility of early hospital discharge, depending on the patient’s particularities (23).

The biological markers of risk in PE are associated with a high risk of fatal events, but one of the most important benefits is their negative predictive value. The association of troponin with PESI score was studied in order to improve the risk evaluation. A study proved the superiority of PESI as compared to troponin I in the identification of low-risk patients. The combined prognosis value PESI + troponin I was not superior to PESI (27). The use of high-sensitive troponin added prognosis value to the PESI score (28). A T troponin ≥ 14pg/ml associated to sPESI ≥1, in case of PE hemodynamically stable patients, was an independent predictor of early death and complications. T troponin < 14 pg/ml and sPESI =0 were identified at 24% of the subjects for whom no adverse effects were mentioned.

Moreover, patients reclassified as high-risk showed a short-term increase of mortality of up to 50%. The modification of PESI and sPESI after 48 hours from the start of the treatment is correlated with subsequent mortality (29). Venetz et al. conducted a comparative study among patients with high and low risk using PESI, sPESI and 30 days mortality (30). Although sPESI accurately identified low risk of adverse events, PESI classified a higher proportion of low-risk patients, having a greater discriminating power than sPESI (6). A recent study has confirmed that the PESI score may also accurately predict long-term mortality (1 year) in case of patients without cancer. sPESI showed a similar accuracy at 3 and 6 months, but significantly lower at 1 year (31).

Compared to the ESC prognostic model, the proportion of patients classified as low-risk was smaller. sPESI indentified with more accuracy the low-risk group for whom outpatient treatment may be an option. sPESI is easy to apply, being routinely used in the clinical practice and takes into consideration both the PE severity and the associated co-morbidities without requiring complex laboratory or imagistic tests or other less affordable ones (32).

The Shock Index (the ratio between cardiac frequency and systolic blood pressure) is a simple method of predicting high risk of unfavorable events when its value exceeds 1. This value is related to inter-hospital mortality and reveals a negative prognosis in association with echocardiography (33). Analyzed in comparison with the Shock Index, sPESI showed greater prognosis accuracy in predicting 30 days mortality as well as in identifying low-risk patients, having a negative predictive value for death among those with higher risk (34).
The PESI and the Geneva scores are two clinical scores which identify both high risk of adverse events and low risk. PESI had a greater discriminatory power for predicting 30 days mortality than Geneva. Patients with PESI low-risk had a lower mortality and negative predictive value of death than the patients for whom the Geneva score was used (30-day mortality - PESI 0.9%; 95% CI, 0.3 to 2.2; vs. Geneva, 5.6%; 95% CI, 3.6 to 7.6 - p < 0.0001) (35). Uresandi et al. developed a prognostic clinical score (Spanish score) in a multicenter prospective study at PE patients (36). The score includes the following variables: recent severe bleedings, metastatic cancer, non-metastatic cancer, values of serum creatinine > 2 mg/dL, bed immobilization due to a recent medical condition, absence of surgical interventions in the last two months and age >60. The score classified 47.8% of patients as low-risk. Compared to the Spanish score, sPESI had a better sensitivity and negative predictive value, with a more accurate identification of low risk of adverse events (37). The Spanish score and PESI were formally applied in a randomized control trial aimed to select patients’ disposition for the initial treatment of PE. The study was prematurely stopped because of an unexpected high rate of adverse outcomes in included patients at low risk according to Spanish score, even if results were in favor of short hospital stay.(12)

The Low Risk Pulmonary Embolism Decision (LR-PED) rule. This score, recently identified, destined initially to identify eligible patients for early discharge and outpatient treatment, includes: age, preexisting heart failure, atrial fibrillation, heart rate, creatinine, glycemia, troponin I and protein C reactive upon admission. Compared to the sPESI and the Geneva score, it showed a greater sensitivity and negative predictive value for detecting patients with low risk (38). Despite the small dimension of the study lot and the lack of validation in an independent lot which diminishes the clinical applicability, the LR - PED score directs attention on the importance of combining the analysis parameters (troponin I, creatinine, protein C reactive and glycemia) on the heart rate (6).

Vienna Prediction Model is another system for the evaluation of recurrence at patients with PE or idiopathic deep vein thrombosis at the first episode. Age, sex, location of the thrombus, body mass index, V Leiden factor, prothrombin mutation and D-dimers were preselected as relevant risk factors as previously demonstrated. Only sex, thrombus location and D-dimers were identified as relevant predictors of recurrence. It was noticed that the association of the male sex and the localization of the embolism with recurrence risk diminishes in time, while the association with the D-dimers level remains stable. This model allows the prediction of the recurrence risk at various time intervals. Thus, D-dimers were repeatedly measured on a 2 years’ duration (39). The repetition of dosing D-dimers after the anticoagulants were stopped was studied before, proving that the persistence of a high level of D-dimers at 3 months from the cessation of the anticoagulant treatment was associated with a higher recurrence rate (40).

The Global Registry of Acute Coronary Events (GRACE) risk score is well-known for high diagnostic performance for adverse outcomes in acute coronary syndrome. Comparisons between GRACE and the other risk scores were performed and it has been shown that this risk score can accurately predict 30-day mortality in pa-
tients admitted for acute PE (41).

CONCLUSIONS

In the daily practice, the existence of scores made up of accessible clinical parameters determines the rapid initiation of optimum therapeutic measures, with the determination of the prognosis and possibly of the outpatient surveillance. The existence of multiple clinical scores may be confusing and time-consuming for a physician, so the large validation of one prediction model (with diagnostic and prognostic value) is required. The Geneva score meets the criteria for both a diagnostic and prognostic clinical rule. In the case of non-fatal PE, which may have sometimes an unpredictable evolution, the PESI and sPESI are the ones to assess the mortality risk and the risk of major adverse events. Certain scores failed to prove their efficiency fully until now, further studies being necessary. The availability of different clinical scores helps doctors to assess PE patients and establish immediate treatment (diagnostic scores) and longtime treatment (prognostic scores) with a favorable impact on the healthcare costs.

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