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Validity of four clinical prediction scores for pulmonary embolism in a sub-Saharan African setting: a protocol for a Cameroonian multicentre cross-sectional study

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ABSTRACT

Introduction Pulmonary embolism poses one of the most challenging diagnoses in medicine. Resolving these diagnostic difficulties is more crucial in emergency departments where fast and accurate decisions are needed for a life-saving purpose. Here, clinical pretest evaluation is an important step in the diagnostic algorithm of pulmonary embolism. Although clinical probability scores are widely used in emergency departments of sub-Saharan Africa, no study has cited their diagnostic performance in this resource-constrained environment. This study will seek to assess the performance of four routinely used clinical prediction models in Cameroonians presenting with suspicion of pulmonary embolism at the emergency department.

Methods and analysis It will be a cross-sectional study comparing the sensitivity, specificity, positive and negative predictive values and accuracy of the Wells, Simplified Wells, Revised Geneva and the Simplified Revised Geneva Scores to CT pulmonary angiography as gold standard in all consecutive consenting patients aged above 15 years admitted for clinical suspicion of pulmonary embolism to the emergency departments of seven major referral hospitals of Cameroon between 1 July 2019 and 31 December 2020. The area under the receiver operating curve, calibration plots, Hosmer and Lemeshow statistics, observed/expected event rates, net benefit and decision curve will be measured of each the clinical prediction test to ascertain the clinical score with the best diagnostic performance.

Ethics and dissemination Clearance has been obtained from the Institutional Review Board of the Faculty of medicine and biomedical sciences of the University of Yaounde I, Cameroon and the directorates of all participating hospitals to conduct this study. Also, informed consent will be sought from each patient or their legal next of kin and parents for minors, before enrolment into this study. The final study will be published in a peer-review journal and the findings presented to health authorities and healthcare providers.

Strengths and limitations of this study

- This is the first study to assess the diagnostic performance of four routine clinical probability scores (CPSs) for pulmonary embolism (PE) in sub-Saharan Africa, hence, may provide an insight on the CPS with the best diagnostic performance.
- Bias will be reduced by filling all the CPS before the conduct of a CT pulmonary angiography (CTPA), as well as blinding the results of CPS to the radiologists performing the CTPA.
- Robust statistical methods like the area under the receiver operating curve will be used to ascertain the test with the best diagnostic performance.
- Its main limitation is the inability to objectively assess the expertise of radiologists who will interpret the CTPA results, which is a paramount determinant of the amount of confirmed PE cases.
- Another drawback is the exclusion of D-dimer measurements which are of great significance in the risk stratification of PE.

BACKGROUND

Pulmonary embolism (PE) is a potentially lethal sequela of venous thromboembolism (VTE) with a reported 30-day mortality rate varying between 14% and 44%.[1–4] It poses considerable diagnostic difficulties in clinical practice and especially in emergency medicine, due to the polymorphism of its clinical manifestations and the lack of a pathognomic symptom or sign.[5] Hence, it is common for the diagnosis of PE to be easily overlooked[6 7] till necropsy where it has been reported in 53% of the dead people who had an autopsy.[8] Consequently, clinicians have developed a high index of clinical suspicion of PE over the last decade.[9] However, of all suspected PE patients, only 10%–15% would be confirmed during the diagnostic tests.[10] Overtesting leads to undue expenses, potential iatrogenic damages, such as contrast-induced allergic reactions, contrast-induced nephropathy[11] or radiation-induced solid tumours[12] from

multidetector CT pulmonary angiography (CTPA), its current gold-standard diagnostic test.[13] In an attempt to remedy the problem of undue investigations, several clinical probability scores (CPSs), among which the most widely used are the Wells,[14] Simplified Wells,[15] Revised Geneva,[16] Simplified Revised Geneva (SRG)[17] scores and the YEARS clinical decision rule,[18] were put forth to guide the choice of diagnostic testing depending on the assessed PE probability (low, intermediate or high).[13] Current guidelines recommend their use coupled with D-dimer to preclude patients with a low PE probability from further diagnostic tests, without compromising the patient's safety.[13] This diagnostic algorithm reduces the number of unnecessary CTPA by 35%, with only 1%–2% of missed cases in the group of patients with a low PE probability.[19] This is of invaluable economic interest in resource-limited emergency departments (EDs) of sub-Saharan Africa (SSA) where CTPA has recently been described to be financially and geographically inaccessible for the majority of patients with suspected PE.[20]

Globally, EDs are at the forefront of the management of patients with suspected PE.[21] Here, prompt and accurate ruling in or out the diagnosis of PE is vital for the timely diagnosis and treatment of PE. As mentioned above, the diagnosis of PE begins with the risk stratification through CPS to prevent patients with low PE probability from unnecessary further testings.[13 21] Although these clinical prediction models have been externally validated in high-income countries where they were designed,[22 23] the generalisation of their validity to SSA remains questionable due to lack of data in this regards. It is known that a CPS derived in a particular setting often performs less well when applied in another setting[24–27] due to discrepancies in disease prevalence and differences in clinicians' experiences of suspected cases.[24] Thus, generalising the external validity of CPS for PE to SSA without prior evidence is inappropriate given that several studies have showed blacks to have a 30%–60% increase in the incidence of PE,[28–30] as well as a 30% increase in PE-related mortality compared with other racial groups.[31]

Objectives

The study objectives will be to assess the diagnostic performance of the Original Wells, Simplified Wells, Revised Geneva and the SRG scores in a selected SSA population admitted to the ED with clinical suspicion of PE.

METHODS AND ANALYSIS

The final study will be reported in conformity to the Tripod checklist for prediction model validation.

Study design, setting and duration

This will be a cross-sectional multicentre study carried out in the EDs of seven major referral hospitals of Cameroon: the National Emergency Centre of Cameroon, the Gynaeco-obstetric and Paediatric Hospital of Yaoundé, the Yaoundé Central Hospital, the Yaoundé General Hospital, the University Hospital Centre of Yaounde, the Douala General Hospital and the Laquintinie Hospital of Douala between the period of 1 July 2019 and 31 December 2020. The Gynaeco-obstetric and Paediatric Hospital of Yaoundé is specialised in the management of all maternal and child diseases irrespective of the mother's and child's age. The other six hospitals are specialised in the management of all adults' as well of maternal and child diseases, irrespective of the adult's, mother's and child's ages. All seven hospitals are tertiary and university teaching hospitals in the cities of either Yaoundé or Douala of Cameroon. Averagely, each hospital manages 1000 patients per year.

Patient eligibility criteria

We will prospectively recruit all consecutive patients aged above 15 years who will be admitted to the aforementioned seven EDs for clinical suspicion of PE. Pregnant women will also be included. Case definition of clinical suspicion of PE will be any patient presenting with sudden dyspnoea, chest pain, haemoptysis or syncope. We will exclude the patients who will refuse to consent, those who will not undergo CTPA to rule in or rule out PE despite clinical suspicion, patients with contraindications to CTPA (haemodynamic instability, dehydration, altered renal function) and those with a diagnosis of PE documented before ED admission.

Sampling method

Assuming a prevalence rate of 61.5% for PE in Africa,[32] we used the Eng's formula[33] to obtain a minimum sample size of 364 participants through a consecutive sampling method.

Study procedure

We will approach all consecutive patients admitted for clinical suspicion of PE to obtain informed consent. Using a pilot-tested interview administered questionnaire (online supplementary file 1), each enrolled patient will be assessed for PE clinically probability before any other test to avoid bias, using four CPS, namely; the original Wells score, the simplified Wells score, the Revised Geneva score and the SRG score. The YEARS clinical rule, a CPS, will not be studied because it entails the measurement of D-dimers, which is relatively expensive and not available in all SSA laboratories.[18] Figure 1 illustrates the study procedure.

Definitions of terms

Patients will be considered to have chronic heart failure, cancer, history of previous deep venous thrombosis or PE or chronic pulmonary disease if these conditions will be known before ED admission. Recent surgery will be defined as any surgical intervention performed within the last 4 weeks before the patient's admission.

Diagnostic testing and assessment of potential sources of bias

The questionnaire will be filled and systematically reviewed for completeness before proceeding to further

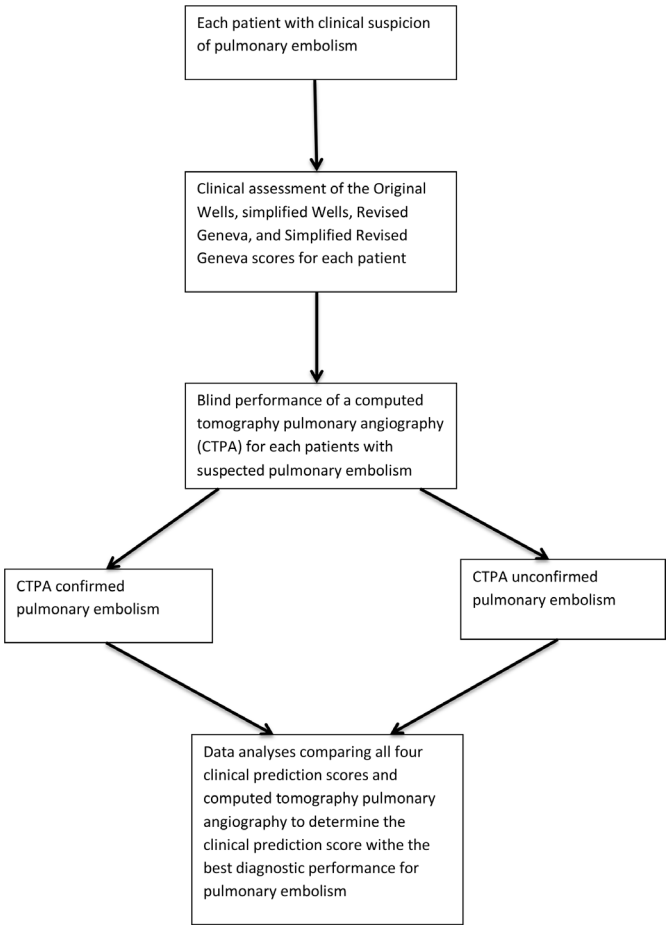

Figure 1 A flow chart illustrating the study procedure.

Table 1 The Original Wells score and Simplified Wells score for PE

Predictive variables	Original Wells score	Simplified Wells score
Previous PE or DVT	1.5	1
Heart rate >100 bpm	1.5	1
Recent surgery or immobilisation	1.5	1
Clinical signs of DVT	3	1
Alternative diagnosis less likely than PE	3	1
Haemoptysis	1	1
Cancer	1	1
	Pretest probability	**Pretest probability**
	0–1: low	≤1: PE unlikely (low)
	2–6: moderate	>1: PE likely (high)
	≥7: high	
	Dichotomised score	
	≤4: PE unlikely (low)	
	>4: PE likely (high)	

DVT, deep venous thrombosis; PE, pulmonary embolism.

diagnostic testing. After assessment of the clinical prediction of PE, all patients with none of the aforementioned contraindications to CTPA will undergo a CTPA to either rule in or rule out the diagnosis of PE. The diagnosis of PE will be established by the CTPA detection of an embolus in the pulmonary vasculature. Radiologists performing the CTPA will have a minimum of 10 years of clinical experience after qualifying to reduce the chances of the radiologists missing out the diagnosis of PE. The results of the CPS will be blinded to the radiologist to decrease the bias.

Data management and analysis

Using CTPA as the goal standard test, the sensitivity, specificity, positive predictive value, negative predictive value and accuracy of each CPS will be calculated. The sensitivity of each CPS will be calculated as the proportion of patients with CTPA confirmed PE who will have a PE likely probability. The specificity of each of the four CPS will be calculated as the proportion of patients with CTPA unconfirmed PE who will have a PE unlikely score. The positive predictive value will be calculated as the proportion of patients with PE likely score who will have CTPA confirmed PE. The negative predictive value of each CPS will be calculated as the proportion of patients with PE unlikely score who will have a CTPA unconfirmed PE. The accuracy of each CPS will be calculated as the proportion of true results (true positives and true negatives) or the number of correct clinical assessments divided by the number of all assessments. Data will be entered into the SPSS V.20.0 for analysis. Measures of discrimination, such as the area under the curve (AUC) and measures of calibration (calibration plots, Hosmer and Lemeshow statistics, observed/expected event rates, etc), would be used to better ascertain the performance of each CPS. Other analyses, such as the net benefit or decision curve, would also be measured. To ease analysis the predictive models were dichotomised as follows: Original Wells scores between 0–4 and >4 will be considered PE unlikely and PE likely, respectively (table 1); Simplified Wells scores between ≤1 and >1 will be considered as PE unlikely and PE likely, respectively (table 1); Revised Geneva scores between 0–5 and ≥6 will be considered PE unlikely and PE likely, respectively (table 2) and SRG scores between 0–2 and ≥3 will be considered PE unlikely and PE likely, respectively (table 2).

Patient and public involvement

Data will be collected directly from patients during the conduction of the study. The findings of this study will be presented at conferences, to relevant health authorities and will be published in a biomedical peer-reviewed journal.

Table 2 The Revised Geneva score and Simplified Revised Geneva score for PE

Predictive variables	Revised Geneva score	Simplified Revised Geneva score
Age >65 years	1	1
Active malignancy (or considered cure <1 year)	2	1
Recent surgery or fracture of the lower limbs within 1 month	2	1
Previous PE or DVT	3	1
Haemoptysis	2	1
Unilateral lower limb pain	3	1
Tenderness on lower limb deep venous palpation and unilateral oedema	4	1
Heart rate		
75–94 bpm	3	1
≥95 bpm	5	2
	Pretest probability	**Pretest probability**
	0–3: low	0–1: low
	4–10: moderate	2–4: moderate
	≥11: high	≥5: high
	Dichotomised score	**Dichotomised score**
	0–5: PE unlikely (low)	0–2: PE unlikely (low)
	≥6: PE likely (high)	≥3: PE likely (high)

DVT, deep venous thrombosis; PE, pulmonary embolism.

Ethics and dissemination

Also, informed consent will be sought from each patient or their legal next of kin and parental consent will be obtained for all minors. The final study will be published in a peer-review journal and the findings presented to health authorities and the healthcare providers.

DISCUSSION

PE is the most life-threatening complication of VTE. A recent systematic review on the epidemiology of venous thromboembolism in Africa found that the prevalence of PE ranges between 0.14% and 61.5%.[32] Furthermore, PE accounts for a mortality rate of 53% of autopsy reports.[8] These high prevalence rates and mortality rates of PE reiterates the burden of disease it poses. The ill health related to PE is further aggravated by the significant diagnostic challenge in clinical practice and particularly in emergency medicine, due to its polymorphic clinical presentations and absence of pathognomic clinical signs or symptoms. Hence, it is common for the diagnosis of PE to be easily missed out.[6 7] CTPA remains the imaging test to diagnose PE.[13] By paradox, the advent of CTPA let to a reduction in the prevalence of PE due to an overdiagnosis of PE as a result of an increased index of clinical suspicion of PE by clinicians.[9] However, CTPA is not void of complications. It may lead to contrast medium-induced nephropathy[11] or radiation medium-induced solid tumours.[12] To advert the sequelae of CTPA, sequential pretest testing using CPS has been introduced. Appropriate use of these CPS obviates the need of CTPA by 20%–30%, with an overall 3-month diagnostic failure rate below 1.5%.[18] Although CPS are routinely used in EDs of low-resource settings, few studies have cited their external validity in SSA. We intend to use robust statistical methods with the measurement of discrimination, such as AUC, measures of calibration (calibration plots, Hosmer and Lemeshow statistics, observed/expected event rates, etc), calculation of net benefit or decision curve, which would help ascertain the CPS with the best diagnostic performance for PE among all the four CPS assessed. The findings of this study may guide clinicians in making informed decisions in predicting PE diagnosis and identification of patients at the need of further testings or anticoagulants therapy in resource-challenged environments where CTPA is not always available or affordable to confirm the diagnosis of PE.

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REFERENCES

1 Mantilla CB, Horlocker TT, Schroeder DR, *et al*. Frequency of myocardial infarction, pulmonary embolism, deep venous thrombosis, and death following primary hip or knee arthroplasty. *Anesthesiology* 2002;96:1140–6.
2 Comfere TB, Sprung J, Case KA, *et al*. Predictors of mortality following symptomatic pulmonary embolism in patients undergoing noncardiac surgery. *Can J Anesth* 2007;54:634–41.
3 Sakon M, Kakkar AK, Ikeda M, *et al*. Current status of pulmonary embolism in general surgery in Japan. *Surg Today* 2004;34:805–10.
4 Heit JA, Silverstein MD, Mohr DN, *et al*. Predictors of survival after deep vein thrombosis and pulmonary embolism: a population-based, cohort study. *Arch Intern Med* 1999;159:445–53.
5 Bělohlávek J, Dytrych V, Linhart A. Pulmonary embolism, part I: epidemiology, risk factors and risk stratification, pathophysiology, clinical presentation, diagnosis and nonthrombotic pulmonary embolism. *Exp Clin Cardiol* 2013;18:129–38.
6 Barais M, Morio N, Cuzon Breton A, *et al*. "I Can't Find Anything Wrong: It Must Be a Pulmonary Embolism": Diagnosing Suspected Pulmonary Embolism in Primary Care, a Qualitative Study. *PLoS One* 2014;9:e98112.
7 Schiff GD, Hasan O, Kim S, *et al*. Diagnostic error in medicine: analysis of 583 physician-reported errors. *Arch Intern Med* 2009;169:1881–7.
8 Lindblad B, Eriksson A, Bergqvist D. Autopsy-Verified pulmonary embolism in a surgical department: analysis of the period from 1951 to 1988. *Br J Surg* 1991:1849–52.
9 Wiener RS, Schwartz LM, Woloshin S. Time trends in pulmonary embolism in the United States: evidence of overdiagnosis. *Arch Intern Med* 2011;171:831–7.
10 Le Gal G, Bounameaux H. Diagnosing pulmonary embolism: running after the decreasing prevalence of cases among suspected patients. *J Thromb Haemost* 2004;2:1244–6.
11 Mitchell AM, Kline JA. Contrast nephropathy following computed tomography angiography of the chest for pulmonary embolism in the emergency department. *J Thromb Haemost* 2007;5:50–4.
12 Cochran ST, Bomyea K, Sayre JW. Trends in adverse events after IV administration of contrast media. *American Journal of Roentgenology* 2001;176:1385–8.
13 Konstantinides SV, Torbicki A, Agnelli G, *et al*. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism: The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC) Endorsed by the European Respiratory Society (ERS). *Eur Heart J* 2014;35:3033–73.
14 Wells PS*et al*. Use of a clinical model for safe management of patients with suspected pulmonary embolism. *Ann Intern Med* 1998;129:997–1005.
15 Wells PS, Anderson DR, Rodger M, *et al*. Derivation of a simple clinical model to categorize patient's probability of pulmonary embolism: increasing the model's utility with the SimpliRED d-dimer. *Thromb Haemost* 2000:416–20.
16 Le Gal G, Righini M, Roy P-M, *et al*. Prediction of pulmonary embolism in the emergency department: the revised Geneva score. *Ann Intern Med* 2006;144:165–71.
17 Kline JA, Nelson RD, Jackson RE, *et al*. Criteria for the safe use of D -dimer testing in emergency department patients with suspected pulmonary embolism: a multicenter US study. *Ann Emerg Med* 2002;39:144–52.
18 van der Hulle T, Cheung WY, Kooij S, *et al*. Simplified diagnostic management of suspected pulmonary embolism (the years study): a prospective, multicentre, cohort study. *The Lancet* 2017;390:289–97.
19 Lucassen W, Geersing G-J, Erkens PMG, *et al*. Clinical decision rules for excluding pulmonary embolism: a meta-analysis. *Ann Intern Med* 2011;155:448.
20 Tambe J, Moifo B, Fongang E, *et al*. Acute pulmonary embolism in the era of multi-detector CT: a reality in sub-Saharan Africa. *BMC Med Imaging* 2012;12.
21 Hendriksen JMT, Geersing G-J, Lucassen WAM, *et al*. Diagnostic prediction models for suspected pulmonary embolism: systematic review and independent external validation in primary care. *BMJ* 2015;351.
22 Righini M, Bounameaux H. External validation and comparison of recently described prediction rules for suspected pulmonary embolism. *Curr Opin Pulm Med* 2004;10:345–9.
23 Hendriksen JMT, Geersing G-J, Lucassen WAM, *et al*. Diagnostic prediction models for suspected pulmonary embolism: systematic review and independent external validation in primary care. *BMJ* 2015.
24 Moons KGM, Kengne AP, Grobbee DE, *et al*. Risk prediction models: II. external validation, model updating, and impact assessment. *Heart* 2012;98:691–8.
25 Altman DG, Royston P. What do we mean by validating a prognostic model? *Stat Med* 2000;19:453–73.
26 Reilly BM, Evans AT. Translating clinical research into clinical practice: impact of using prediction rules to make decisions. *Ann Intern Med* 2006;144:201–9.
27 Justice AC, Covinsky KE, Berlin JA. Assessing the generalizability of prognostic information. *Ann Intern Med* 1999;130:515–24.
28 White RH, Keenan CR. Effects of race and ethnicity on the incidence of venous thromboembolism. *Thromb Res* 2009;123:S11–17.
29 Zakai N, Lutsey P, Folsom A, *et al*. Black-white differences in venous thrombosis risk: the longitudinal investigation of thromboembolism etiology (Lite). *Blood ASH Annual Meeting Abstracts* 2010;478.
30 Schneider D, Lilienfeld DE, Im W. The epidemiology of pulmonary embolism: racial contrasts in incidence and in-hospital case fatality. *J Natl Med Assoc* 2006;98:1967–72.
31 Ibrahim SA, Stone RA, Obrosky DS, *et al*. Racial differences in 30-day mortality for pulmonary embolism. *Am J Public Health* 2006;96:2161–4.
32 Danwang C, Temgoua MN, Agbor VN, *et al*. Epidemiology of venous thromboembolism in Africa: a systematic review. *J Thromb Haemost* 2017;15:1770–81.
33 Eng J. Sample size estimation: how many individuals should be studied? *Radiology* 2003;227:309–13.