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

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Keywords:	pulmonary embolism, Wells score, Simplified Wells score, Revised Geneva score, Simplified Revised Geneva score, emergency department

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Manuscripts

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

Introduction: Pulmonary embolism poses one of the most challenging diagnosis in medicine. Resolving these diagnostic difficulties is more crucial in emergency departments where fast and accurate decisions are needed to save lives. Here, clinical pretest evaluation is an important step in the diagnostic algorithm 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 accuracy of four routinely used clinical prediction models in Cameroonians presenting with pulmonary embolism in an acute setting.

Methods and analysis: It will be an analytic 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 computed tomography pulmonary angiography as gold standard in all consecutive consenting adults admitted for clinical suspicion of pulmonary embolism to the EDs of seven major referral hospital of Cameroon between July 1, 2019, and December 31, 2020. The area under the receiver operating curve of each the clinical prediction test will be calculated to best ascertain the most accurate test.

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 the directorates of all participating hospitals to conduct this study. Also, informed consent will be sought from each patients or their legal next of kin before enrollement into the study. The final study will be published in a peer-review journal and the findings presented to health authorities and the health providers.

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3 **Keywords** : pulmonary embolism, Wells score, Simplified Wells score, Revised Geneva
4 score, Simplified Revised Geneva score, emergency department, sub-Saharan African.
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10 **Strengths and Limitations of the study:**
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- 13 • This is the first study to assess the diagnostic performance of CPS for PE in SSA. The
14 study will provide insights on the test with the best pretest accuracy.
15
- 16 • The multi-centric design with samples from several major referral EDs of Cameroon
17 will ensure representative and generalizable findings.
18
- 19 • Bias will be reduced by completing the each CPS for all patients before conduction of
20 the CTPA and by blinding the results of CPS from the radiologists performing the
21 CTPA.
22
- 23 • Robust statistical methods like area under the receiver operating curve will be used to
24 ascertain the test with the best pretest accuracy
25
- 26 • Its main limitation is the inability to objectively assess the expertise of radiologists
27 interpreting the results of CTPA, which is a paramount determinant of the amount of
28 confirm PE cases. However, to curb this drawback only radiologists with a minimum
29 of 10 years of clinical experience after qualifying would interpret the results of CTPA
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50 **Background**
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53 Pulmonary embolism (PE) is a potentially lethal sequelae of venous thromboembolism
54 (VTE) with a reported 30-day mortality rate varying between 14-44% [1-4]. It poses
55 considerable diagnostic difficulties in clinical practice and especially in emergency medicine,
56 due to the polymorphism of its clinical manifestation and the lack of a pathognomonic symptom
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3 or sign [5]. Hence, it is common for the diagnosis of PE to be easily overlooked [6,7] till
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5 necropsy where it has been reported in 53% of autopsy reports [8]. Consequently, clinicians
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7 have developed a high index of clinical suspicion of PE over the last decade [9]. However, of
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9 all suspected PE patients, only 10-15% would be confirmed during diagnostic tests [10].
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11 Overtesting leads to undue expenses, potential iatrogenic damages such as contrast-induced
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13 allergic reactions, contrast-induced nephropathy[11] or radiation-induced solid tumors [12]
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15 from multi-detector computed tomography pulmonary angiography (CTPA), its current gold
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17 standard diagnostic test [13]. In an attempt to remedy the problem of undue investigations,
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19 several clinical probability scores (CPS), among which the most widely used are the
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21 Wells[14], simplified Wells[15], Revised Geneva [16] and Smplified Revised Geneva [17]
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23 scores, were put forth to guide the choice of diagnostic testing depending on the assessed PE
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25 probability (low, intermediate or high) [13]. Current guidelines recommend their use coupled
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27 with D-dimer to preclude patients with a low PE probability from further diagnostic tests,
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29 without compromising the patient's safety [13]. This diagnostic algorithm reduces the number
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31 of unnecessary CTPA by 35%, with only 1-2% of missed cases in the group of patients with a
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33 low PE probability [18]. This is of invaluable economic interest in resource-limited
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35 emergency departments (EDs) of sub-Saharan Africa (SSA) where CTPA, has recently been
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37 described to be financially and geographically inaccessible for majority of patients with
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39 suspected PE [19].

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41 Globally, EDs and primary healthcare centers are at the forefront of the mangement of
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43 patients with suspected PE[20]. Here, prompt and accurate ruling in or out the diagnosis of PE
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45 is vital for a timely diagnosis and treatment. As mentioned above, the diagnosis of PE begins
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47 with risk stratification through CPS to prevent patients with low PE probability from
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49 unnecessary further testings [13,20]. Although these clinical prediction models have been
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51 externally validated in of high-income countries where there were designed [21,22], the
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3 generalization of their validity to SSA remains questionable due to lack of data in this regards.
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5 It is known that CPS derived in a particular setting often perform less well when applied in
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7 another setting[23–26] due to discrepancies in disease prevalence and differences in
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9 clinicians' experience of suspected cases [23]. Thus, generalizing the external validity of CPS
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11 for PE to SSA without prior evidence is inappropriate given that several studies have showned
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13 blacks to have a 30-60% increase in the incidence of PE [27–29], as well as a 30 % increase
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15 in PE-related mortality compared to other racial groups[30].
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23 **Objectives**

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26 The study objectives will be to assess the diagnostic performance of the original Wells,
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28 simplified Wells, revised Geneva, and the simplified revised Geneva (SRG) scores in a
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30 selected sub-Saharan African population admitted to the ED with suspicion of PE.
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38 **Methods and analysis**

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41 This protocol is reported in accordance to the STROBE guidelines for cross-sectional studies
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43 (additional file 1). The final study will be reported in conformity to the Tripod checklist for
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45 prediction model validation.
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49 ***Study design, setting and duration***

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51 This will be a cross-sectional multicenter study carried out in the EDs of seven major referral
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53 hospital of Cameroon: the National Emergency Medicine Centre of Cameroon, the Gynaeco-
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55 obstetric and Paediatric Hospital of Yaoundé, the Yaoundé Central Hospital, the Yaoundé
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57 General Hospital, the University Hospital Centre of Yaounde, the Douala General Hospital
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59 and the Laquintinie Hospital of Douala Yaoundé Central Hospital between the period of July
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3 1, 2019, and December 31, 2020. All aforementioned hospitals are University Teaching
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5 hospitals in the cities of Yaounde and Douala of Cameroon.
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8 ***Patient eligibility criteria***

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10 We will prospectively recruit all consecutive patients aged above 15 years who will be
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12 admitted to the aforementioned seven EDs for clinical suspicion of PE. Case definition of
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14 clinical suspicion of PE will be any patient presenting with sudden dyspnoea, chest pain,
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16 haemoptysis or syncope. We will exclude patients who will refuse to consent, those who will
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18 not undergo CTPA to rule in or rule out PE despite clinical suspicion, patients with
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20 contraindications to CTPA (haemodynamic instability, dehydration, altered renal function)
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22 and those with a diagnosis of PE documented prior to ED admission.
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27 ***Sampling method***

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29 A consecutive convenience sampling method will be used.
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33 ***Study Procedure***

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35 We will approach all consecutive patients admitted for clinical suspicion of PE in order to
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37 obtain an informed consent. Using a pilot tested interview administered questionnaire, each
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39 enrolled patient will be assess for PE clinically probability before any other test to avoid bias,
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41 using four CPS, namely; the original Wells score, the simplified Wells score, the Revised
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43 Geneva score and the SRG Score.
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48 ***Definitions of Terms***

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50 Patients will be considered to have chronic heart failure, cancer, history of previous deep
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52 venous thrombosis (DVT) or PE, or chronic pulmonary disease if these conditions will be
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54 known prior to admission. Recent surgery will be defined as any surgical intervention
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56 performed within the last four weeks prior to the patient's admission.
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Diagnostic testing and assessment of potential sources of bias

Questionnaires will be completed and systematically reviewed for completeness before proceeding to further diagnostic testing. After assessment of the clinical prediction of PE, all patients with no contraindication such as dehydration and impaired renal function test, will undergo the goal standard diagnostic test, CTPA to either rule in or rule out the diagnosis of PE. The diagnosis of PE will be established by 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 and will be blinded to the results of CPS.

Data Management and Analysis

Using CTPA as the goal standard test, the sensitivity, specificity, positive predictive value, negative predictive value and accuracy of each clinical probability score will be calculated. The sensitivity of each CPS will be calculated as the proportion of patients with CTPA proven PE who will have a PE likely probability. The specificity of each the four CPS will be calculated as the proportion of patients with CTPA rule out 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 be ruled out of PE by CTPA. The accuracy of each clinical score 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 Statistical Package for Social Sciences (SPSS) version 20.0 for analysis. Measures of discrimination such as 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 accuracy of each CPS. To ease analysis the predictive models were dichotomized 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).
- SRG scores while 0-2 and ≥ 3 will be considered PE unlikely and PE likely respectively (Table 2).

Patient and Public Involvement

Unlike the public, patients will be involved in the conception and design of this protocol.

Ethics and dissemination

Clearance has been granted by the Institutional Review board of the Faculty of medicine and biomedical sciences of the University of Yaounde I, Cameroon and the the directorates of all participating hospitals to conduct this study. Also, informed consent will be sought from each patients or their legal next of kin before enrollement into the study. The final study will be published in a peer-review journal and the findings presented to health authorities and the health providers.

Discussion

PE is the most life threatening complication of VTE. It poses a significant diagnostic challenge in clinical practice and particularly in emergency medicine, due to its polymorphic clinical presentation and absence of pathognomic clinical signs. Although CPS are routinely used in EDs of low-resource settings, few studies have cited their external validity in SSA.

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3 We intend to use robust statistical methods with the measurement of discrimination such as
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5 area under the curve (AUC) and measures of calibration (calibration plots, Hosmer and
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7 Lemeshow statistics, observed/expected event rates, etc) which would help ascertain the
8
9 mosy accurate CPS amongst the four assessed. The findings of this study may guide
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11 clinicians in making informed decisions in predicting PE diagnosis and identifiation of
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13 patients at need of further testing or may be anticoagulants therapy in resource-challenged
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15 environments were CTPA is not always available or affordable to confirm the diagosis of PE.
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20 **List of Abbreviations**

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23 ED : Emergency department ; CPS : Clinical probability score ; CTPA : computed
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25 tomography pulmonary angiography ; PE : Pulmonary embolism ; SSA : sub-Sahara Africa :
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27 SRG : Simplified Revised Geneva.
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32
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34
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45
46 not-for-profit sectors.
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50 **Authors' Contributions:** AE and JNT: Study protocol conception, design and manuscript
51
52 writing. POE, JAMM and JZM: critically revised the manuscript for intellectual content. All
53
54 authors read and approved the final manuscript.
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58 **Competing interests:** The authors declare that they have no competing interests.
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3 **Data statement** : All data relevant to the study are included in the article or uploaded as
4
5 **supplementary information**. Any other information are available on request from the
6
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8 corresponding author at: joeltochie@gmail.com.
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40 **Table 1: The Original Wells score and Simplified Wells score for Pulmonary embolism**

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 immobilization	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	
	Dichotomized score:	
	≤ 4: PE unlikely (low)	
	>4: PE likely (high)	
DVT: Deep venous thrombosis	PE: Pulmonary embolism	

Table 2: The Revised Geneva score and Simplified Revised Geneva score for Pulmonary embolism

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
	Dichotomized score:	Dichotomized score:

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0 - 5: PE unlikely (low)
≥ 6: PE likely (high)

0 - 2: PE unlikely (low)
≥ 3: PE likely (high)

DVT: Deep venous thrombosis PE: Pulmonary embolism

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60STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	page 2 page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	page 3 to 5
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 5
Methods			
Study design	4	Present key elements of study design early in the paper	Page 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	Page 6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6 to 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6 7 and 8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	7 and 8 7 and 8 N/A 7 and 8 7 and 8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	N/A N/A N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest	N/A N/A
Outcome data	15*	Report numbers of outcome events or summary measures	N/A
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A N/A N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A

Discussion			N/A
Key results	18	Summarise key results with reference to study objectives	N/A
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	N/A
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	N/A
Generalisability	21	Discuss the generalisability (external validity) of the study results	N/A
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

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

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Primary Subject Heading:	Emergency medicine
Secondary Subject Heading:	Cardiovascular medicine, Respiratory medicine
Keywords:	pulmonary embolism, Wells score, Simplified Wells score, Revised Geneva score, Simplified Revised Geneva score, emergency department

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3 1 **The validity of four clinical prediction scores for pulmonary embolism in a sub-Saharan**
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5 2 **African setting: a protocol for a multicentre Cameroonian cross-sectional study.**
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1 **Abstract**

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

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

21 **Ethics and dissemination:** Clearance has been obtained from the Institutional Review Board
22 of the Faculty of medicine and biomedical sciences of the University of Yaounde I, Cameroon
23 and the directorates of all participating hospitals to conduct this study. Also, informed consent
24 will be sought from each patient or their legal next of kin and parents for minors, before

1 enrollment into this study. The final study will be published in a peer-review journal and the
2 findings presented to health authorities and healthcare providers.

3 **Keywords:** pulmonary embolism, Wells score, Simplified Wells score, Revised Geneva
4 score, Simplified Revised Geneva score, emergency department, African.

6 **Strengths and Limitations of the study:**

- 7 • This is the first study to assess the diagnostic performance of four routine clinical
8 probability scores (CPS) for pulmonary embolism (PE) in sub-Saharan Africa, hence,
9 may provide an insight on the CPS with the best diagnostic performance.
- 10 • The multi-centric design with samples from seven major referral emergency
11 departments of Cameroon will help to yield more generalizable findings.
- 12 • Bias will be reduced by filling all the CPS before the conduct of a computed
13 tomography pulmonary angiography(CTPA), as well as blinding the results of CPS to
14 the radiologists performing the CTPA.
- 15 • Robust statistical methods like the area under the receiver operating curve will be used
16 to ascertain the test with the best diagnostic performance
- 17 • Its main limitation is the inability to objectively assess the expertise of radiologists
18 who will interpret the CTPA results, which is a paramount determinant of the amount
19 of confirm PE cases.

21 **Background**

22 Pulmonary embolism (PE) is a potentially lethal sequelae of venous thromboembolism (VTE)
23 with a reported 30-day mortality rate varying between 14-44% [1–4]. It poses considerable
24 diagnostic difficulties in clinical practice and especially in emergency medicine, due to the

1 polymorphism of its clinical manifestations and the lack of a pathognomic symptom or sign
2 [5]. Hence, it is common for the diagnosis of PE to be easily overlooked [6,7] till necropsy
3 where it has been reported in 53% of dead people who had an autopsy [8]. Consequently,
4 clinicians have developed a high index of clinical suspicion of PE over the last decade [9].
5 However, of all suspected PE patients, only 10-15% would be confirmed during diagnostic
6 tests [10]. Overtesting leads to undue expenses, potential iatrogenic damages such as
7 contrast-induced allergic reactions, contrast-induced nephropathy[11] or radiation-induced
8 solid tumors [12] from multi-detector computed tomography pulmonary angiography
9 (CTPA), its current gold standard diagnostic test [13]. In an attempt to remedy the problem of
10 undue investigations, several clinical probability scores (CPS), among which the most widely
11 used are the Wells[14], Simplified Wells[15], Revised Geneva [16], Simplified Revised
12 Geneva [17] scores and the YEARS clinical decision rule[18], were put forth to guide the
13 choice of diagnostic testing depending on the assessed PE probability (low, intermediate or
14 high) [13]. Current guidelines recommend their use coupled with D-dimer to preclude patients
15 with a low PE probability from further diagnostic tests, without compromising the patient's
16 safety [13]. This diagnostic algorithm reduces the number of unnecessary CTPA by 35%, with
17 only 1-2% of missed cases in the group of patients with a low PE probability [19]. This is of
18 invaluable economic interest in resource-limited emergency departments (EDs) of sub-
19 Saharan Africa (SSA) where CTPA, has recently been described to be financially and
20 geographically inaccessible for the majority of patients with suspected PE [20].

21 Globally, EDs are at the forefront of the management of patients with suspected PE[21]. Here,
22 prompt and accurate ruling in or out the diagnosis of PE is vital for the timely diagnosis and
23 treatment of PE. As mentioned above, the diagnosis of PE begins with risk stratification
24 through CPS to prevent patients with low PE probability from unnecessary further testings
25 [13,21]. Although these clinical prediction models have been externally validated in high-

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3 1 income countries where there were designed [22,23], the generalization of their validity to
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5 2 SSA remains questionable due to lack of data in this regards. It is known that a CPS derived
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7 3 in a particular setting often performs less well when applied in another setting [24–27] due to
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9 4 discrepancies in disease prevalence and differences in clinicians' experiences of suspected
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11 5 cases [24]. Thus, generalizing the external validity of CPS for PE to SSA without prior
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13 6 evidence is inappropriate given that several studies have showed blacks to have a 30-60%
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15 7 increase in the incidence of PE [28–30], as well as a 30 % increase in PE-related mortality
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17 8 compared to other racial groups[31].
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10 **Objectives**

11 The study objectives will be to assess the diagnostic performance of the Original Wells,
12 Simplified Wells, Revised Geneva, and the Simplified Revised Geneva (SRG) scores in a
13 selected sub-Saharan African population admitted to the ED with clinical suspicion of PE.
14

15 **Methods and analysis**

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

18 ***Study design, setting and duration***

19 This will be a cross-sectional multicenter study carried out in the EDs of seven major referral
20 hospital of Cameroon: the National Emergency Centre of Cameroon, the Gynaeco-obstetric
21 and Paediatric Hospital of Yaoundé, the Yaoundé Central Hospital, the Yaoundé General
22 Hospital, the University Hospital Centre of Yaounde, the Douala General Hospital and the
23 Laquintinie Hospital of Douala between the period of July 1, 2019, and December 31, 2020.

1 The Gynaeco-obstetric and Paediatric Hospital of Yaoundé is specialized in the management
2 of all maternal and child diseases irrespective of the mother's and child's age. The other six
3 hospital are specialized in the management of all adults' as well of maternal and child
4 diseases, irrespective of the adult's, mother's and child's ages. All seven hospitals are tertiary
5 and university teaching hospitals in the cities of either Yaoundé and Douala of Cameroon.
6 Averagely, each hospital manages 1000 patients per year.

7 *Patient eligibility criteria*

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

15 *Sampling method*

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

18 *Study Procedure*

19 We will approach all consecutive patients admitted for clinical suspicion of PE to obtain
20 informed consent. Using a pilot-tested interview administered questionnaire (supplementary
21 1), each enrolled patient will be assess for PE clinically probability before any other test to
22 avoid bias, using four CPS, namely; the original Wells score, the simplified Wells score, the
23 Revised Geneva score, and the SRG Score. The YEARS clinical rule, a CPS, will not be

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3 1 studied because it entails the measurement of D-dimers which is relatively expensive and not
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5 2 available in all SSA laboratories[18]. Figure 1 illustrates the study procedure.
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8 ***Definitions of Terms***

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11 4 Patients will be considered to have chronic heart failure, cancer, history of previous deep
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13 5 venous thrombosis (DVT) or PE, or chronic pulmonary disease if these conditions will be
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15 6 known before ED admission. Recent surgery will be defined as any surgical intervention
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17 7 performed within the last four weeks before the patient's admission.
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20 ***Diagnostic testing and assessment of potential sources of bias***

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25 9 The questionnaire will be filled and systematically reviewed for completeness before
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27 10 proceeding to further diagnostic testing. After assessment of the clinical prediction of PE, all
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29 11 patients with none of the aforementioned contraindications to CTPA, will undergo a CTPA to
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31 12 either rule in or rule out the diagnosis of PE. The diagnosis of PE will be established by
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33 13 CTPA detection of an embolus in the pulmonary vasculature. Radiologists performing the
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35 14 CTPA will have a minimum of 10 years of clinical experience after qualifying to reduce the
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37 15 chances of the radiologists missing out the diagnosis of PE. The results of the CPS will be
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39 16 blinded to the radiologist to decrease the bias.
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44 ***Data Management and Analysis***

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47 18 Using CTPA as the goal standard test, the sensitivity, specificity, positive predictive value,
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49 19 negative predictive value and accuracy of each CPS will be calculated. The sensitivity of each
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51 20 CPS will be calculated as the proportion of patients with CTPA confirmed PE who will have a
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53 21 PE likely probability. The specificity of each the four CPS will be calculated as the proportion
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55 22 of patients with CTPA unconfirmed PE who will have a PE unlikely score. The positive
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57 23 predictive value will be calculated as the proportion of patients with PE likely score who will
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3 1 have CTPA confirmed PE. The negative predictive value of each CPS will be calculated as
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5 2 the proportion of patients with PE unlikely score who will have a CTPA unconfirmed PE. The
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7 3 accuracy of each CPS will be calculated as the proportion of true results (true positives and
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9 4 true negatives) or the number of correct clinical assessments divided by the number of all
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11 5 assessments. Data will be entered into the Statistical Package for Social Sciences (SPSS)
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13 6 version 20.0 for analysis. Measures of discrimination such as the area under the curve (AUC)
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15 7 and measures of calibration (calibration plots, Hosmer and Lemeshow statistics,
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17 8 observed/expected event rates, etc) would be used to better ascertain the performance of each
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19 9 CPS. Other analyses such as the net benefit or decision curve would also be measured. To
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21 10 ease analysis the predictive models were dichotomized as follows: Original Wells scores
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23 11 between 0-4 and > 4 will be considered PE unlikely and PE likely respectively (Table 1);
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25 12 Simplified Wells scores between ≤ 1 and > 1 will be considered as PE unlikely and PE likely
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27 13 respectively (Table 1); Revised Geneva scores between 0-5 and ≥ 6 will be considered PE
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29 14 unlikely and PE likely respectively (Table 2); and a SRG scores between 0-2 and ≥ 3 will be
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31 15 considered PE unlikely and PE likely respectively (Table 2).
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17 **Patient and Public Involvement**

18 Only patients admitted to the aforementioned seven EDs for suspicion of PE will be enrolled
19 into this study.

20 **Ethics and dissemination**

21 Clearance has been granted by the Institutional Review Board of the Faculty of Medicine and
22 Biomedical Sciences of the University of Yaounde I, Cameroon and the directorates of all
23 participating hospitals to conduct this study. Also, informed consent will be sought from each

1 patient or their legal next of kin and parental consent will be obtained for all minors. The final
2 study will be published in a peer-review journal and the findings presented to health
3 authorities and the healthcare providers.

4 **Discussion**

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

1 assessed. The findings of this study may guide clinicians in making informed decisions in
2 predicting PE diagnosis and identification of patients at the need of further testings or
3 anticoagulants therapy in resource-challenged environments where CTPA is not always
4 available or affordable to confirm the diagnosis of PE.

5 **List of Abbreviations**

6 ED : Emergency department ; CPS : Clinical probability score ; CTPA : computed
7 tomography pulmonary angiography ; PE : Pulmonary embolism ; SSA : sub-Sahara Africa :
8 SRG : Simplified Revised Geneva.

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12 conduct this study.

13 **Competing interests:** The authors declare that they have no competing interests.

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16 not-for-profit sectors.

17 **Authors' Contributions:** AE and JNT: Study protocol conception, design and manuscript
18 writing. POE, JAMM and JZM: critically revised the manuscript for intellectual content. All
19 authors read and approved the final manuscript.

20 **Competing interests:** The authors declare that they have no competing interests.

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3 1 **Data statement** : All data relevant to the study are included in the article or uploaded as
4
5 2 supplementary information. Any other information are available on request from the
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7 3 corresponding author at: joeltochie@gmail.com.
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28 **Table 1: The Original Wells score and Simplified Wells score for Pulmonary embolism**

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 immobilization	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
Dichotomized score:
 ≤ 4 : PE unlikely (low)
 >4 : PE likely (high)

DVT: Deep venous thrombosis PE: Pulmonary embolism

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Table 2: The Revised Geneva score and Simplified Revised Geneva score for Pulmonary embolism

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	4	1

1			
2			
3	oedema		
4	Heart rate		
5	75 – 94 bpm	3	1
6	≥ 95 bpm	5	2
7		Pretest probability;	Pretest probability;
8		0 – 3: low	0 – 1: low
9		4– 10: moderate	2– 4: moderate
10		≥ 11 : high	≥ 5 : high
11		Dichotomized score:	Dichotomized score:
12		0 - 5: PE unlikely (low)	0 - 2: PE unlikely (low)
13		≥ 6: PE likely (high)	≥ 3: PE likely (high)
14	<hr/>		
14	DVT: Deep venous thrombosis	PE: Pulmonary embolism	

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3 **Figure legend/caption**

4 Table 1: The Original Wells score and Simplified Wells score for Pulmonary embolism

5 Table 2: The Revised Geneva score and Simplified Revised Geneva score for Pulmonary
6 embolism

7 Figure 1 : A flow chart illustrating the study procedure.

8 supplementary 1 : Questionnaire

9

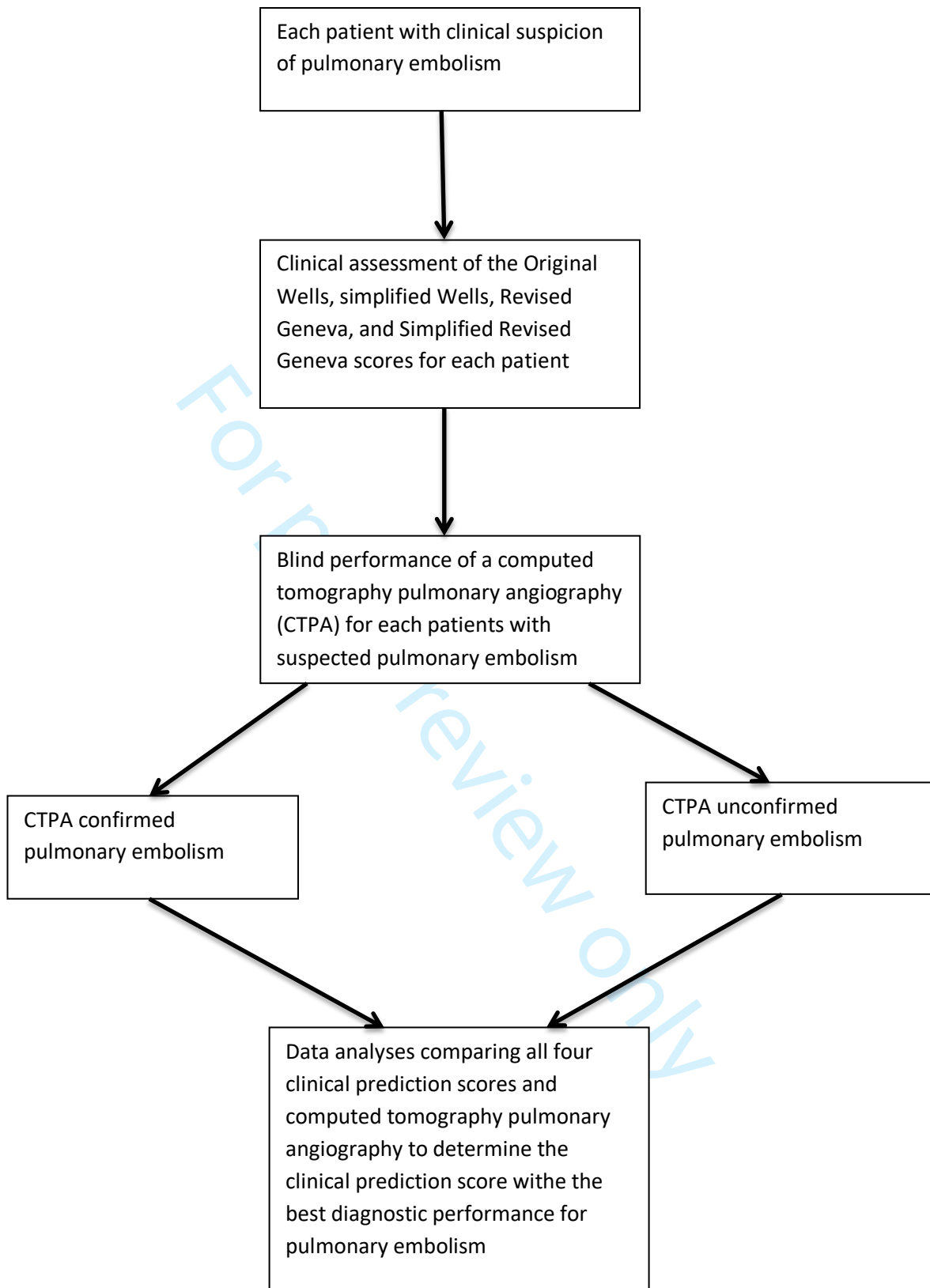


Figure 1 : A flow chart illustrating the study procedure.

Data collection form

1-Patient identification number

2-Name of patient.....

3- Patient's phone number.....

4-Next of kin phone's number

5Age of patient.....

6-Gender: M F

7-Date of admission.....

SECTION B – Presenting complaints12-Presenting complaint : chest pain syncope Dyspnoea haemoptysis

If others precise :

13- Duration of symptoms before admission:.....

SECTION C – Past History14- Medical: Yes No If yes Hypertension Diabetes HIV Deep venous thrombosis Pulmonary embolism
Stroke cancer others :.....15- Surgery within the last month: Yes No 16-Other predisposing factors : Obesity prolonged trps Use of hormonal contraceptives
Specify if others:.....**SECTION C – Physical examination**17-Vital sigs: Blood pressure.....mmHg Pulse.....beats per min respiratory ratebreat
per min SPO₂.....% Temperature.....°C**SECTION D– Evaluation of clinical probability scores for pulmonary embolism**

18- Original Wells et simplified Wells scores (circle the criteria found in the patient)

Questions	Original Wells score	Simplified Wells score
Previous thromboembolic disease	1.5	1
Heart rate > 100 beats per minute	1.5	1
Immobilization: bedrest ≥ 3 days or Surgery in the last 4 weeks	1.5	1
Signs and symptoms of deep venous thrombosis	3	1
Diagnostic alternative less likely than pulmonary embolism	3	1

Hemoptysis	1		1	
Malignancy: cancer treatment currently or in the last 6 months or receiving palliative care	1	<input type="checkbox"/>	1	<input type="checkbox"/>

Total Score	Pretest probability;	Probabilite du pretest;
	0 – 1: low	≤ 1: PE unlikely (low)
	2– 6: moderate	>1: PE likely (high)
	≥ 7 : high	
	Dichotomized score:	
	≤ 4: PE unlikely (low)	
	>4: PE likely (high)	

DVT: Deep venous thrombosis PE: Pulmonary embolism

19- The Revised Geneva score and Simplified Revised Geneva score for Pulmonary embolism
(circle the criteria found in the patient)

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
	Dichotomized score:	Dichotomized 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

20- Differential Diagnoses evoked: Pulmonary embolism Acute coronary syndrome

Others:.....

SECTION E – Findings on computed tomography angiography

21-Dilated right ventricle: Yes No

22-Leftward deviation of the interventricular septum : Yes No

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24-A thrombus seen in the pulmonary vessels: Yes No

25-Other Findings:.....

26-Conclusion of CT-scan results : Pulmonary embolism : Yes No

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STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	page 2 page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	page 3 to 5
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 5
Methods			
Study design	4	Present key elements of study design early in the paper	Page 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	Page 6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6 to 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6 7 and 8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	7 and 8 7 and 8 N/A 7 and 8 7 and 8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	N/A N/A N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest	N/A N/A
Outcome data	15*	Report numbers of outcome events or summary measures	N/A
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A N/A N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A

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Discussion			N/A
Key results	18	Summarise key results with reference to study objectives	N/A
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	N/A
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	N/A
Generalisability	21	Discuss the generalisability (external validity) of the study results	N/A
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-031322.R2
Article Type:	Protocol
Date Submitted by the Author:	29-Aug-2019
Complete List of Authors:	Esiéné, Agnès ; Universite de Yaounde I Faculte de Medecine et des Sciences Biomedicales, Department of Anesthesiology and Critical Care Owono Etoundi, Paul ; University of Yaoundé I, Department of Anesthesiology and Critical Care Tochie, Joel Noutakdie; Universite de Yaounde I Faculte de Medecine et des Sciences Biomedicales, Mbengono Metogo, Junette Arlette ; University of Yaoundé I, Department of Anesthesiology and Critical Care Ze Minkande, Jacqueline; University of Yaounde I, Department of Anesthesiology and Critical Care,
Primary Subject Heading:	Emergency medicine
Secondary Subject Heading:	Cardiovascular medicine, Respiratory medicine
Keywords:	pulmonary embolism, Wells score, Simplified Wells score, Revised Geneva score, Simplified Revised Geneva score, emergency department

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Manuscripts

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3 1 **The validity of four clinical prediction scores for pulmonary embolism in a sub-Saharan**
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5 2 **African setting: a protocol for a multicentre Cameroonian cross-sectional study.**
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9 3
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50 24 **Word count;** abstract: 297 words; manuscript: 2334 words
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1 **Abstract**

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

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

21 **Ethics and dissemination:** Clearance has been obtained from the Institutional Review Board
22 of the Faculty of medicine and biomedical sciences of the University of Yaounde I, Cameroon
23 and the directorates of all participating hospitals to conduct this study. Also, informed consent
24 will be sought from each patient or their legal next of kin and parents for minors, before

1 enrollment into this study. The final study will be published in a peer-review journal and the
2 findings presented to health authorities and healthcare providers.

3 **Keywords:** pulmonary embolism, Wells score, Simplified Wells score, Revised Geneva
4 score, Simplified Revised Geneva score, emergency department, African.

6 **Strengths and Limitations of the study:**

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

21 **Background**

22 Pulmonary embolism (PE) is a potentially lethal sequela of venous thromboembolism (VTE)
23 with a reported 30-day mortality rate varying between 14-44% [1–4]. It poses considerable
24 diagnostic difficulties in clinical practice and especially in emergency medicine, due to the

1 polymorphism of its clinical manifestations and the lack of a pathognomic symptom or sign
2 [5]. Hence, it is common for the diagnosis of PE to be easily overlooked [6,7] till necropsy
3 where it has been reported in 53% of dead people who had an autopsy [8]. Consequently,
4 clinicians have developed a high index of clinical suspicion of PE over the last decade [9].
5 However, of all suspected PE patients, only 10-15% would be confirmed during diagnostic
6 tests [10]. Overtesting leads to undue expenses, potential iatrogenic damages such as
7 contrast-induced allergic reactions, contrast-induced nephropathy[11] or radiation-induced
8 solid tumors [12] from multi-detector computed tomography pulmonary angiography
9 (CTPA), its current gold standard diagnostic test [13]. In an attempt to remedy the problem of
10 undue investigations, several clinical probability scores (CPS), among which the most widely
11 used are the Wells[14], Simplified Wells[15], Revised Geneva [16], Simplified Revised
12 Geneva [17] scores and the YEARS clinical decision rule[18], were put forth to guide the
13 choice of diagnostic testing depending on the assessed PE probability (low, intermediate or
14 high) [13]. Current guidelines recommend their use coupled with D-dimer to preclude patients
15 with a low PE probability from further diagnostic tests, without compromising the patient's
16 safety [13]. This diagnostic algorithm reduces the number of unnecessary CTPA by 35%, with
17 only 1-2% of missed cases in the group of patients with a low PE probability [19]. This is of
18 invaluable economic interest in resource-limited emergency departments (EDs) of sub-
19 Saharan Africa (SSA) where CTPA, has recently been described to be financially and
20 geographically inaccessible for the majority of patients with suspected PE [20].

21 Globally, EDs are at the forefront of the management of patients with suspected PE[21]. Here,
22 prompt and accurate ruling in or out the diagnosis of PE is vital for the timely diagnosis and
23 treatment of PE. As mentioned above, the diagnosis of PE begins with risk stratification
24 through CPS to prevent patients with low PE probability from unnecessary further testings
25 [13,21]. Although these clinical prediction models have been externally validated in high-

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3 1 income countries where they were designed [22,23], the generalization of their validity to
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5 2 SSA remains questionable due to lack of data in this regards. It is known that a CPS derived
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7 3 in a particular setting often performs less well when applied in another setting [24–27] due to
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9 4 discrepancies in disease prevalence and differences in clinicians' experiences of suspected
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11 5 cases [24]. Thus, generalizing the external validity of CPS for PE to SSA without prior
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13 6 evidence is inappropriate given that several studies have showed blacks to have a 30-60%
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15 7 increase in the incidence of PE [28–30], as well as a 30 % increase in PE-related mortality
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17 8 compared to other racial groups[31].
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10 **Objectives**

11 The study objectives will be to assess the diagnostic performance of the Original Wells,
12 Simplified Wells, Revised Geneva, and the Simplified Revised Geneva (SRG) scores in a
13 selected sub-Saharan African population admitted to the ED with clinical suspicion of PE.
14

15 **Methods and analysis**

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

18 ***Study design, setting and duration***

19 This will be a cross-sectional multicenter study carried out in the EDs of seven major referral
20 hospitals of Cameroon: the National Emergency Centre of Cameroon, the Gynaeco-obstetric
21 and Paediatric Hospital of Yaoundé, the Yaoundé Central Hospital, the Yaoundé General
22 Hospital, the University Hospital Centre of Yaounde, the Douala General Hospital and the
23 Laquintinie Hospital of Douala between the period of July 1, 2019, and December 31, 2020.

1 The Gynaeco-obstetric and Paediatric Hospital of Yaoundé is specialized in the management
2 of all maternal and child diseases irrespective of the mother's and child's age. The other six
3 hospitals are specialized in the management of all adults' as well of maternal and child
4 diseases, irrespective of the adult's, mother's and child's ages. All seven hospitals are tertiary
5 and university teaching hospitals in the cities of either Yaoundé and Douala of Cameroon.
6 Averagely, each hospital manages 1000 patients per year.

7 *Patient eligibility criteria*

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

15 *Sampling method*

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

18 *Study Procedure*

19 We will approach all consecutive patients admitted for clinical suspicion of PE to obtain
20 informed consent. Using a pilot-tested interview administered questionnaire (supplementary
21 1), each enrolled patient will be assessed for PE clinically probability before any other test to
22 avoid bias, using four CPS, namely; the original Wells score, the simplified Wells score, the
23 Revised Geneva score, and the SRG Score. The YEARS clinical rule, a CPS, will not be

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3 1 studied because it entails the measurement of D-dimers which is relatively expensive and not
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5 2 available in all SSA laboratories[18]. Figure 1 illustrates the study procedure.
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8 ***Definitions of Terms***

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11 4 Patients will be considered to have chronic heart failure, cancer, history of previous deep
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13 5 venous thrombosis (DVT) or PE, or chronic pulmonary disease if these conditions will be
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15 6 known before ED admission. Recent surgery will be defined as any surgical intervention
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17 7 performed within the last four weeks before the patient's admission.
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20 ***Diagnostic testing and assessment of potential sources of bias***

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25 9 The questionnaire will be filled and systematically reviewed for completeness before
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27 10 proceeding to further diagnostic testing. After assessment of the clinical prediction of PE, all
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29 11 patients with none of the aforementioned contraindications to CTPA, will undergo a CTPA to
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31 12 either rule in or rule out the diagnosis of PE. The diagnosis of PE will be established by
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33 13 CTPA detection of an embolus in the pulmonary vasculature. Radiologists performing the
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35 14 CTPA will have a minimum of 10 years of clinical experience after qualifying to reduce the
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37 15 chances of the radiologists missing out the diagnosis of PE. The results of the CPS will be
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39 16 blinded to the radiologist to decrease the bias.
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44 ***Data Management and Analysis***

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47 18 Using CTPA as the goal standard test, the sensitivity, specificity, positive predictive value,
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49 19 negative predictive value and accuracy of each CPS will be calculated. The sensitivity of each
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51 20 CPS will be calculated as the proportion of patients with CTPA confirmed PE who will have a
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53 21 PE likely probability. The specificity of each the four CPS will be calculated as the proportion
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55 22 of patients with CTPA unconfirmed PE who will have a PE unlikely score. The positive
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57 23 predictive value will be calculated as the proportion of patients with PE likely score who will
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3 1 have CTPA confirmed PE. The negative predictive value of each CPS will be calculated as
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5 2 the proportion of patients with PE unlikely score who will have a CTPA unconfirmed PE. The
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7 3 accuracy of each CPS will be calculated as the proportion of true results (true positives and
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9 4 true negatives) or the number of correct clinical assessments divided by the number of all
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11 5 assessments. Data will be entered into the Statistical Package for Social Sciences (SPSS)
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13 6 version 20.0 for analysis. Measures of discrimination such as the area under the curve (AUC)
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15 7 and measures of calibration (calibration plots, Hosmer and Lemeshow statistics,
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17 8 observed/expected event rates, etc) would be used to better ascertain the performance of each
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19 9 CPS. Other analyses such as the net benefit or decision curve would also be measured. To
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21 10 ease analysis the predictive models were dichotomized as follows: Original Wells scores
22
23 11 between 0-4 and > 4 will be considered PE unlikely and PE likely respectively (Table 1);
24
25 12 Simplified Wells scores between ≤ 1 and > 1 will be considered as PE unlikely and PE likely
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27 13 respectively (Table 1); Revised Geneva scores between 0-5 and ≥ 6 will be considered PE
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29 14 unlikely and PE likely respectively (Table 2); and SRG scores between 0-2 and ≥ 3 will be
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31 15 considered PE unlikely and PE likely respectively (Table 2).
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17 **Patient and Public Involvement**

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

21 **Ethics and dissemination**

22 Clearance has been granted by the Institutional Review Board of the Faculty of Medicine and
23 Biomedical Sciences of the University of Yaounde I, Cameroon and the directorates of all

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

5 **Discussion**

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

1 help ascertain the CPS with the best diagnostic performance for PE amongst all the four CPS
2 assessed. The findings of this study may guide clinicians in making informed decisions in
3 predicting PE diagnosis and identification of patients at the need of further testings or
4 anticoagulants therapy in resource-challenged environments where CTPA is not always
5 available or affordable to confirm the diagnosis of PE.

6 **List of Abbreviations**

7 ED : Emergency department ; CPS : Clinical probability score ; CTPA : computed
8 tomography pulmonary angiography ; PE : Pulmonary embolism ; SSA : sub-Saharan Africa :
9 SRG : Simplified Revised Geneva.

10

11 **Acknowledgments**

12 The authors thank all administrative staff of participating hospitals for authorizing us to
13 conduct this study.

14 **Competing interests:** The authors declare that they have no competing interests.

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19 writing. POE, JAMM and JZM: critically revised the manuscript for intellectual content. All
20 authors read and approved the final manuscript.

21 **Competing interests:** The authors declare that they have no competing interests.

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3 1 **Data statement** : All data relevant to the study are included in the article or uploaded as
4
5 2 supplementary information. Any other information are available on request from the
6
7 3 corresponding author at: joeltochie@gmail.com.
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10 11 4 12 13 5 **References**

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1 **Table 1: The Original Wells score and Simplified Wells score for Pulmonary embolism**

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 immobilization	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	
	Dichotomized score:	
	≤ 4: PE unlikely (low)	
	>4: PE likely (high)	

DVT: Deep venous thrombosis PE: Pulmonary embolism

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3 **1 Table 2: The Revised Geneva score and Simplified Revised Geneva score for Pulmonary**
4 **2 embolism**

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
	Dichotomized score:	Dichotomized 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		

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33 **5 Figure legend/caption**

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36 6 Table 1: The Original Wells score and Simplified Wells score for Pulmonary embolism

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38 7 Table 2: The Revised Geneva score and Simplified Revised Geneva score for Pulmonary
39 8 embolism

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41 9 Figure 1 : A flow chart illustrating the study procedure.

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44 10 supplementary 1 : Questionnaire

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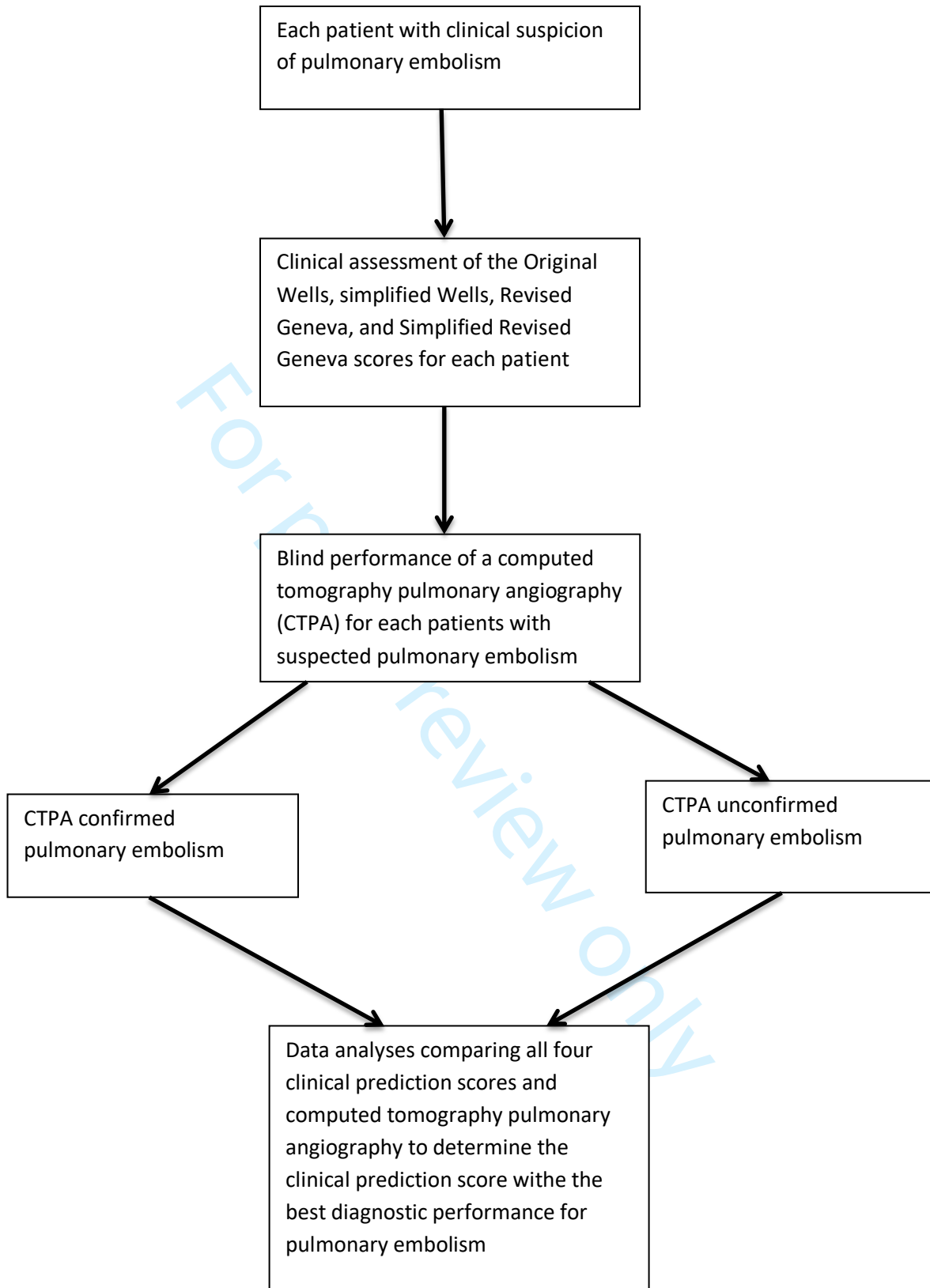


Figure 1 : A flow chart illustrating the study procedure.

Data collection form

1-Patient identification number

2-Name of patient.....

3- Patient's phone number.....

4-Next of kin phone's number

5Age of patient.....

6-Gender: M F

7-Date of admission.....

SECTION B – Presenting complaints12-Presenting complaint : chest pain syncope Dyspnoea haemoptysis

If others precise :

13- Duration of symptoms before admission:.....

SECTION C – Past History14- Medical: Yes No If yes Hypertension Diabetes HIV Deep venous thrombosis Pulmonary embolism
Stroke cancer others :.....15- Surgery within the last month: Yes No 16-Other predisposing factors : Obesity prolonged trps Use of hormonal contraceptives
Specify if others:.....**SECTION C – Physical examination**17-Vital sigs: Blood pressure.....mmHg Pulse.....beats per min respiratory ratebreat
per min SPO₂.....% Temperature.....°C**SECTION D– Evaluation of clinical probability scores for pulmonary embolism**

18- Original Wells et simplified Wells scores (circle the criteria found in the patient)

Questions	Original Wells score	Simplified Wells score
Previous thromboembolic disease	1.5	1
Heart rate > 100 beats per minute	1.5	1
Immobilization: bedrest ≥ 3 days or Surgery in the last 4 weeks	1.5	1
Signs and symptoms of deep venous thrombosis	3	1
Diagnostic alternative less likely than pulmonary embolism	3	1

Hemoptysis	1		1	
Malignancy: cancer treatment currently or in the last 6 months or receiving palliativecare	1	<input type="checkbox"/>	1	<input type="checkbox"/>

Total Score

Pretest probability;	Probabilite du pretest;
0 – 1: low	≤ 1: PE unlikely (low)
2– 6: moderate	>1: PE likely (high)
≥ 7 : high	
Dichotomized score:	
≤ 4: PE unlikely (low)	
>4: PE likely (high)	

DVT: Deep venous thrombosis PE: Pulmonary embolism

19- The Revised Geneva score and Simplified Revised Geneva score for Pulmonary embolism
(circle the criteria found in the patient)

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
	Dichotomized score:	Dichotomized 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

20- Differential Diagnoses evoked: Pulmonary embolism Acute coronary syndrome

Others:.....

SECTION E – Findings on computed tomography angiography

21-Dilated right ventricle: Yes No

22-Leftward deviation of the interventricular septum : Yes No

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24-A thrombus seen in the pulmonary vessels: Yes No

25-Other Findings:.....

26-Conclusion of CT-scan results : Pulmonary embolism : Yes No

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