jth

ORIGINAL ARTICLE

Assessing the clinical probability of pulmonary embolism during pregnancy: The Pregnancy-Adapted Geneva (PAG) score

Helia Robert-Ebadi[1] [ID] | Antoine Elias[2,3] | Olivier Sanchez[3,4,5] | Emmanuelle Le Moigne[6] | Jeannot Schmidt[3,7] | Catherine Le Gall[3,8] | Drahomir Aujesky[9] | Pierre-Marie Roy[3,10] | Thomas Moumneh[3,10] [ID] | Céline Chauleur[11,12,13] | Frederic Rouyer[14] | Grégoire Le Gal[15,16] | Marc Righini[1]

[1]Division of Angiology and Hemostasis, Faculty of Medicine, Geneva University Hospitals Geneva, Switzerland

[2]Médecine vasculaire, Centre Hospitalier de Toulon, Toulon, France

[3]F-CRIN INNOVTE, Saint-Etienne, France

[4]Service de Pneumologie et Soins Intensifs, Hôpital Européen Georges Pompidou, AP-HP, Université de Paris, Paris, France

[5]INSERM UMR S 1140, Paris, France

[6]EA3878 GETBO, Université de Brest, Brest, France

[7]Centre Hospitalier Universitaire de Clermont-Ferrand, Clermont-Ferrand, France

[8]Centre Hospitalier d'Argenteuil, Argenteuil, France

[9]Department of General Internal Medicine, Bern University Hospital, University of Bern, Bern, Switzerland

[10]Department of Emergency Medicine, UNIV Angers, UMR MitoVasc (CNRS 6015 - INSERM 1083), University Hospital of Angers, Angers, France

[11]INSERM U1059, Saint-Etienne, France

[12]University of Lyon, Saint-Etienne, France

[13]Department of Gynecology and Obstetrics, University Hospital, Saint-Etienne, France

[14]Emergency Department, Geneva University Hospitals, Geneva, Switzerland

[15]Department of Medicine, University of Ottawa, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada

[16]EA3878 University of Brest, Brest, France

Correspondence

Helia Robert-Ebadi, Division of Angiology and Hemostasis, Department of Medicine, Geneva University Hospitals and Faculty of Medicine, 4, rue Gabrielle-Perret-Gentil, CH-1211 Geneva 14, Switzerland.
Email: helia.robert-ebadi@hcuge.ch

Abstract

Background: The diagnosis of pulmonary embolism (PE) in pregnant women represents an ongoing challenge. As in the general population, the first step in pregnant women with suspected PE consists of assessing clinical pre-test probability (PTP). However, no dedicated clinical decision rule has been developed in this population.

Objective: To propose a new version of the Geneva score adapted to pregnant women with suspected PE.

Methods: Data from a multicenter, prospective management outcome study including 395 women with suspected PE, in whom PTP was assessed using the Geneva score, were used. We first removed items which were present in none of the patients

(cancer, age >65 years). Receiver operating characteristic (ROC) curve analysis was then performed for quantitative variables and the optimal threshold defined. The obtained Pregnancy-Adapted Geneva Score (PAG Score) comprised seven items, including an age 40 years or older and a heart rate >110 beats per minute.

Results: The PAG Score showed a high discriminative power to identify patients with a low, intermediate, or high PTP, associated with increasing prevalence of PE, 2.3%, 11.6%, and 61.5%, respectively. The ROC curves showed an area under the curve of 0.795 for the PAG Score compared to 0.684 for the Geneva score.

Conclusion: In pregnant women with suspected PE, the PAG Score shows a high discriminative power to identify patients at low, intermediate, or high PTP. It has the strength of being a fully objective decision rule, is clinically relevant, easy to compute, and should now be tested in a prospective outcome study.

KEYWORDS

diagnosis, pregnancy, probability, pulmonary embolism, venous thromboembolism

1 | INTRODUCTION

The diagnosis of pulmonary embolism (PE) relies on diagnostic strategies based on the sequential assessment of clinical pre-test probability (PTP), measurement of plasma D-dimer levels, and computed tomographic pulmonary angiography (CTPA) in selected cases.[1,2] PE diagnosis in pregnant women remains a challenge for physicians, because many of the symptoms often reported during physiological pregnancy, such as shortness of breath or tachypnea, may also suggest the diagnosis of PE.[3-5] Many physicians remain reluctant to use radiating imaging in pregnant women because of concerns about the long-term risks for the mother and the fetus. Although this risk is admittedly low, every effort to minimize radiation exposure during pregnancy should be encouraged. Optimizing clinical decision rules which can, in association with D-dimer, safely exclude PE without thoracic imaging, is therefore of particular importance in pregnant women.[6]

In non-pregnant patients with suspected PE, the assessment of clinical PTP is the first step of the diagnostic management.[1,2] It allows identification of a group of patients in whom a negative D-dimer safely rules out PE without imaging. It is also used for the interpretation of pulmonary ventilation/perfusion scan results.

Available clinical decision rules (CDR) have not been derived or validated on a large-scale basis in pregnant women.[7] This has been one of the reasons put forward for not using D-dimer in pregnant women, in addition to the reduced proportion of negative D-dimer during pregnancy. Recently, two prospective management outcome studies assessed diagnostic strategies in the specific setting of pregnant women with suspected PE.[8,9] These studies used two different pre-test assessment tools that had not been previously validated in a pregnant population: the pregnancy-adapted YEARS model in the ARTEMIS study and the Geneva Score in the CT-PE pregnancy study.[8,9]

Although the Geneva Score was able to identify three categories of pregnant women with an increasing prevalence of PE in the CT-PE pregnancy study, it includes items such as age >65 years or cancer,

---

ESSENTIALS

- The diagnosis of pulmonary embolism (PE) during pregnancy remains a challenge and no specifically derived clinical decision rule (CDR) is available.
- Data from a multicenter, prospective management outcome study were used to develop a pregnancy-specific CDR.
- The Pregnancy-Adapted Geneva (PAG) Score is highly discriminative to identify pregnant patients with a low, intermediate, or high clinical pre-test probability and displays an area under the curve of 0.795.
- The PAG Score is a fully objective decision rule, is clinically relevant, easy to compute, and should be tested in a prospective outcome study.

---

which are not relevant to this population.[8] Moreover, due to hemodynamic changes during pregnancy, the predictive ability for the presence of PE of some variables—such as a heart rate >75 beats per minute (bpm)—may differ in this setting. We therefore aimed to propose a Geneva Score adapted to pregnant women with suspected PE using data from the CT-PE pregnancy study.[8]

2 | METHODS

2.1 | Patients and settings

The prediction rule was derived from the CT-PE pregnancy study, a multicenter prospective outcome study designed to assess the safety of a PE diagnostic strategy in pregnant women.[8] This strategy was based on the sequential assessment of clinical PTP,

plasma D-dimer measurement, lower limb venous compression ultrasonography (CUS), and CTPA. Ventilation perfusion (V/Q) lung scan could be performed in case of inconclusive CTPA. All pregnant women with suspected PE presenting to the emergency department of 11 general and teaching hospitals in two countries (France and Switzerland) were eligible. PE suspicion was defined as acute onset of new or worsening shortness of breath or chest pain without any other obvious cause. Exclusion criteria were age <18 years, allergy to iodinated contrast agents, impaired renal function (defined by a creatinine clearance below 30 ml/min as per the Cockcroft-Gault formula), PE diagnosis made prior to presentation, indication for or already on therapeutic anticoagulation, and inaccessibility for follow-up. The study was approved by the ethics committee according to legislation at each study site. A written informed consent was obtained from all participating women. Between August 2008 and July 2016, 441 pregnant women were approached for participation to the study, of whom 395 were included.

The clinical PTP was determined using the revised Geneva Score.[10] A highly sensitive D-dimer test was performed in all women. PE was deemed excluded in women with a low or intermediate—that is, "non-high"—PTP and a negative D-dimer test (< 500 µg/L). Women with a high PTP and those with a non-high PTP but a positive D-dimer test underwent bilateral proximal CUS. Lack of compressibility of a deep vein was used as the diagnostic criterion for DVT. When a proximal DVT was found, PE was considered as confirmed without further testing. Women with a negative CUS underwent CTPA. The protocol for CTPA consisted of an evaluation of the pulmonary arteries up to and including the subsegmental vessels. In case of inconclusive CTPA, further testing with a V/Q lung scan was recommended. Pregnant women with a negative diagnostic work-up were considered as not having PE, were left without anticoagulant treatment, and underwent clinical follow-up for 3 months. The 3-month thromboembolic risk during follow-up in these patients was 0.0% (95% confidence interval [CI]: 0.0 to 1.0%).[8]

2.2 | Data analysis

The Geneva Score used in the CT-PE pregnancy study includes eight clinical items (see Table 1), with weighting for each item based on the regression coefficient obtained from a multivariate logistical variation analysis in non-pregnant patients.[10] Total score ranges from 0 to 22 points. Patients are classified into low (0–3 points), intermediate (4–10 points), and high (≥ 11 points) PTP categories.

Derivation of a CDR usually requires a first selection of potential candidate predictors through univariate analysis followed by multivariate analysis to select independent predictors. However, a commonly accepted rule of thumb is that performing a multivariate logistic model analysis for prediction purposes requires 5 to 10 events for each variable proposed to the model.[11,12] Only 28 women had confirmed PE in the CT-PE pregnancy study, precluding strict

TABLE 1 Patients' characteristics

Characteristics	
Female gender, n (%)	395 (100)
Age in years, median (IQR)	31 (27–36)
Trimester of pregnancy	
First, n (%)	83 (21.0)
Second, n (%)	170 (43.0)
Third, n (%)	142 (35.9)
BMI (kg/m^2)	25.9 (5.5)
Personal history of VTE, n (%)	29 (7.3)
Active malignancy, n (%)	0 (0.0)
Surgery within one month, n (%)	4 (1.0)
Bedridden for >72 hours during the last 4 weeks, n (%)	34 (8.6)
Chest pain, n (%)	260 (65.8)
Dyspnea, n (%)	292 (73.9)
Syncope, fainting, n (%)	59 (14.9)
Hemoptysis, n (%)	14 (3.5)
Clinical signs or symptoms of DVT, n (%)	57 (14.4)
Heart rate, bpm, mean (SD)	91 (17)
O2 saturation, %, mean (SD)	98.0 (1.8)

Abbreviations: BMI, body mass index; bpm, beats per minute; DVT, deep vein thrombosis; IQR, interquartile range; SD, standard deviation; VTE, venous thromboembolism.

adhesion to standard methods for CDR development. As such, we elected to adapt the Geneva Score rather than to fully derive a new CDR.

We planned to remove variables that would not be relevant to the pregnant women population; that is, variables not present in any of the included women. We computed the rate of missing data for each item to ensure that no variable from the score would be missing in more than 2% of included patients. We then analyzed the predictive ability of each individual item of the Geneva Score for the presence of PE.

For quantitative variables, that is, age and heart rate, we ran a receiver operating characteristic (ROC) curve analysis to determine if thresholds different from those used in the original score would have a better discriminative power. Quantitative variables were then dichotomized at their optimal cutoff and were assigned the same number of points as in the original score.

The new score obtained after these adaptations was then computed in all women included in the cohort. We assessed the prevalence of PE according to the number of points. We planned to determine cutoffs that would allow us to identify three groups of PTP. The low PTP group had to have a PE prevalence <10%, and the high PTP >50%, which corresponds to the usual prevalence observed in three-level PTP categories in PE diagnostic studies and guides the next steps of the diagnostic workup. We then reported the prevalence of PE in each of the three PTP groups along with the 95% CIs.

Finally, we ran ROC curve analyses to determine the area under the curve (AUC) of the Pregnancy-Adapted Geneva (PAG) Score and to compare its discriminant ability with the original score. Because of the low number of events, no repeated analysis in the same sample was performed to avoid overadjustment.

3 | RESULTS

3.1 | Study population

In the original CT-PE pregnancy study, 395 pregnant women with suspected PE were included. General characteristics are displayed in Table 2. PTP was assessed in all women using the Geneva Score, presented in Table 2. In the CT-PE pregnancy study, 192/395 (48.6%), 200/395 (50.6%), and 3/395 (0.8%) were classified in the low, intermediate, and high PTP categories, respectively, with corresponding PE prevalence of 7/192 (3.6%), 18/200 (9%), and 3/3 (100%). For seven of the eight items, data were available in 395/395 (100%) of patients. Heart rate (HR) was missing in five patients (1.2%).

3.2 | Development of the Pregnancy-Adapted Geneva Score

Two variables of the Geneva Score were not present in any of the pregnant women and were removed. The first was active malignancy, and the second was age >65 years. We nevertheless ran a ROC curve analysis to determine if a different age threshold would have some discriminative power. We found the most discriminative

point of the curve to be at age 40 years, with a specificity of 94% and a sensitivity of 18%. Among the 28 patients 40 years and older, 5 (17.9%) had PE, whereas in patients <40 years, 23/367 (6.3%) had PE. We therefore integrated an age 40 years or older to define the "positive" age item in the new score with the same weight as the original score (+1 point).

The ROC curve for HR showed the most discriminative cutoff point to be around 110 bpm, with a specificity of 91% and a sensitivity of 30%. Among patients with a HR >110 bpm, 9/43 (20.9%) had PE, whereas in patients with a HR ≤110 bpm, 18/347 (5.2%) had PE. We therefore integrated a threshold of >110 bpm to define a positive HR item of the new score with the same weight as the higher HR threshold in the original score (+5 points).

The remaining five items were categorical variables kept with the same point numbers as in the original score (Table 2). The PAG Score thus includes seven items, and the total number of points ranges from 0 to 20 points.

We computed the PAG Score in all included women. The proportion of confirmed PE according to the number of points is presented in Figure 1. To achieve our objective of PE obtaining a prevalence <10% among low PTP patients and >50% among high PTP patients, we chose a score ranging from 0 to 1 points to define low PTP, 2 to 6 points to define intermediate PTP, and ≥7 points to define high PTP. Patients' distribution and corresponding PE prevalence are presented in Table 3. Patients were categorized as having a low PTP in 67.9%, intermediate in 28.7%, and high in 3.3%. The corresponding PE prevalence was of 2.3%, 11.6%, and 61.5%, respectively (Table 3).

The ROC curves showed an AUC of 0.795 (95% CI 0.690–0.899) for the PAG Score compared to 0.684 (95% CI 0.563–0.805) for the Geneva Score.

TABLE 2 The Geneva Score and the Pregnancy-Adapted Geneva Score for assessment of pre-test clinical probability of PE in pregnant women

Geneva Score		Pregnancy-Adapted Geneva Score	
ITEM	POINTS	ITEM	POINTS
Age >65	+1	Age 40 years and older	+1
Active malignant condition	+2		
Surgery (under GA) or lower limb fracture in past month	+2	Surgery (under GA) or lower limb fracture in past month	+2
Previous DVT or PE	+3	Previous DVT or PE	+3
Unilateral lower limb pain	+3	Unilateral lower limb pain	+3
Hemoptysis	+2	Hemoptysis	+2
Pain on lower limb palpation and unilateral edema	+4	Pain on lower limb palpation and unilateral edema	+4
Heart rate 75–94	+3	Heart rate >110 bpm	+5
>=95	+5		
Maximal point number	22	Maximal point number	20
ROC curve AUC	0.684	ROC curve AUC	0.795
95% CI	0.563–0.805	95% CI	0.690–0.899

Abbreviations: AUC, area under the curve; CI, confidence interval; DVT, deep vein thrombosis; GA, general anesthesia; ROC, receiver operating characteristic; PE, pulmonary embolism.
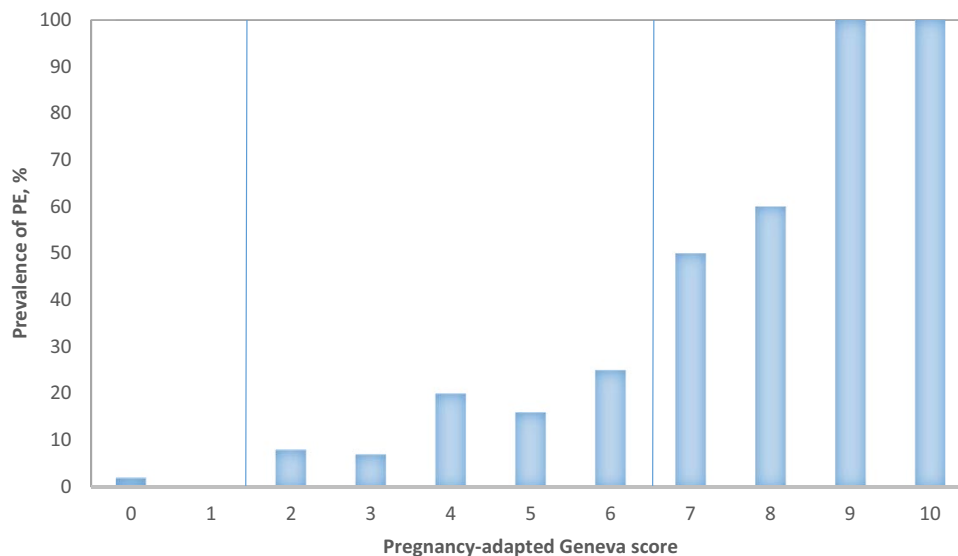
FIGURE 1 Prevalence of pulmonary embolism (PE) according to the number of points in the Pregnancy-Adapted Geneva Score. The vertical blue line represents the cut-offs for low, intermediate, and high clinical probabilities [Color figure can be viewed at wileyonlinelibrary.com]

The proportion of patients in whom a CTPA could be avoided when using the PAG Score in our cohort would have been of 11.3% (42/372 patients) compared to 11.6% with the Geneva Score used in the study (Figure 2).

4 | DISCUSSION

This work presents a clinical decision rule based on the Geneva Score for the assessment of PTP in pregnant women with suspected PE, the PAG Score. The analysis is based on the results of a large prospective cohort of pregnant women with suspected PE having undergone a full diagnostic work-up and a formal 3-month follow-up.[8]

Our results show that the PAG Score has a high discriminative power to classify patients in three categories of clinical PTP, namely low, intermediate, and high, associated with clinically meaningful increasing PE prevalence of 2.3%, 11.6%, and 61.5%, respectively.

The ROC curve shows that the PAG Score may have a better diagnostic accuracy than the Geneva Score used in this population, with AUC of 0.795 compared to an AUC of 0.684, respectively.

As opposed to other available PTP assessment rules,[13-15] this new score contains items which are all relevant to the setting of pregnant women. It represents a standardized tool for assessing PTP

of PE in this population, based exclusively on objectively assessed clinical items.

Given the lack of any validated probability scoring system at the time our group performed the CT-PE pregnancy study, we had decided to use the revised Geneva Score. We recognized that this was not optimal given that several items were not relevant to pregnancy (e.g., age >65 years, active malignancy). Nevertheless, in the original study, the Geneva Score was able to distribute patients in groups of low (48.6%), intermediate (50.6%), and high (0.8%) probability corresponding to an increasing prevalence of PE of 3.6%, 9.0%, and 100.0%, respectively.[8] However, admittedly, a score exclusively containing objective items relevant to this population was needed.

The main limitation of this work is that our data source included 395 patients, of whom 28 had PE. The significant variables could therefore not be entered in a multivariate logistic regression model, and all the steps of a formal derivation could not be followed. However, this limitation is inherent to this population of patients, as studies on PE diagnostic strategies are obviously more challenging to conduct during pregnancy than in the general population. This is highlighted by the fact that only two prospective studies have been published so far with fewer than 500 patients included in each study. Furthermore, the prevalence of confirmed PE is lower in pregnant women than in the general population, limiting the number of

TABLE 3 Patients' distribution and corresponding prevalence of PE according to the PAG Score

| Points	Category	Distribution	Distribution, %	Confirmed PE, n	Prevalence of PE, %	95% CI
0–1	Low	265/390	**67.9%**	6/265	**2.3%**	1.0–4.9%
2–6	Intermediate	112/390	**28.7%**	13/112	**11.6%**	6.9–18.9%
>=7	High	13/390	**3.3%**	8/13	**61.5%**	35.5–82.2%

Abbreviations: CI, confidence interval; PAG Score, Pregnancy-Adapted Geneva Score; PE, pulmonary embolism.

ROC Curve of the Geneva score

AUC 0.684 (95% CI 0.563-0.805)
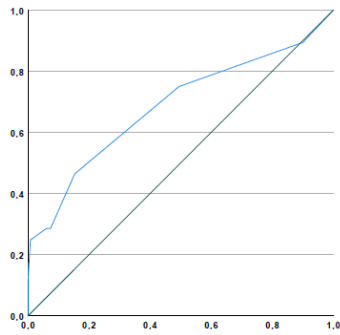
ROC Curve of the PA-Geneva score

AUC 0.795 (95% CI 0.690-0.899)
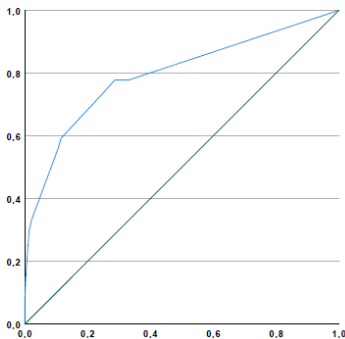
Comparative ROC curves of the PA-Geneva score (blue) and simplified PA-Geneva score (green)

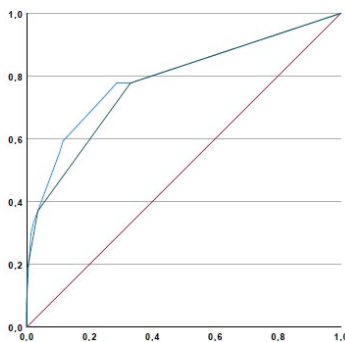AUC 0.795 (95% CI 0.690-0.899) and 0.774 (95% CI 0.670-0.877)

FIGURE 2 Receiver operating characteristic (ROC) curves of the Geneva Score and the Pregnancy-Adapted Geneva Score. AUC, area under the curve; CI, confidence interval; PA, Pregnancy-Adapted [Color figure can be viewed at wileyonlinelibrary.com]

patients with positive diagnoses available in the scientific literature for a derivation analysis. Notwithstanding this limitation, the accuracy of the score was assessed by calculating the ROC curve and analyzing the AUC.

The assessment of PTP in pregnant women with suspected PE is particularly challenging as many features of the clinical presentation can also be present in a physiological pregnancy, such as dyspnea, tachycardia, or lower limb edema. A fully objective clinical decision rule not relying on the emergency physician's experience in this specific population of patients is therefore highly appealing in clinical practice. The presented PAG Score fulfills these requirements, is clinically relevant, easy to compute, and should now be tested in a prospective outcome study.

ACKNOWLEDGEMENTS

CONFLICTS OF INTEREST

All authors declare that they have no conflicts of interest. The corresponding author had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

AUTHOR CONTRIBUTIONS

Helia Robert-Ebadi, Antoine Elias, Olivier Sanchez, Emmanuelle Le Moigne, Jeannot Schmidt, Catherine Le Gall, Drahomir Aujesky, Pierre-Marie Roy, Thomas Moumneh, Céline Chauleur, Frederic Rouyer, Grégoire Le Gal, Marc Righini: performed the conception and design, acquisition of data, analysis, and interpretation of data; and drafted the article. All authors provided final approval of the version to be published.

ORCID

Helia Robert-Ebadi https://orcid.org/0000-0003-3801-1269
Thomas Moumneh https://orcid.org/0000-0002-4229-9923

REFERENCES

1. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur Heart J*. 2020;41:543-603.
2. Lim W, Le Gal G, Bates SM, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: diagnosis of venous thromboembolism. *Blood Adv*. 2018;2:3226-3256.
3. Righini M, Le Gal G, Bounameaux H. Venous thromboembolism diagnosis: unresolved issues. *Thromb Haemost*. 2015;113:1184-1192.
4. Chan WS, Ray JG, Murray S, Coady GE, Coates G, Ginsberg JS. Suspected pulmonary embolism in pregnancy: clinical presentation, results of lung scanning, and subsequent maternal and pediatric outcomes. *Arch Intern Med*. 2002;162:1170-1175.
5. Wan T, Skeith L, Karovitch A, Rodger M, Le Gal G. Guidance for the diagnosis of pulmonary embolism during pregnancy: Consensus and controversies. *Thromb Res*. 2017;157:23-28.
6. Tromeur C, van der Pol LM, Le Roux PY, et al. Computed tomography pulmonary angiography versus ventilation-perfusion lung scanning for diagnosing pulmonary embolism during pregnancy: a systematic review and meta-analysis. *Haematologica*. 2019;104:176-188.
7. Chan WS. Can pregnancy-adapted algorithms avoid diagnostic imaging for pulmonary embolism? *Hematology Am Soc Hematol Educ Program*. 2020;2020:184-189.
8. Righini M, Robert-Ebadi H, Elias A, et al. Diagnosis of pulmonary embolism during pregnancy: a multicenter prospective management outcome study. *Ann Intern Med*. 2018;169:766-773.
9. van der Pol LM, Tromeur C, Bistervels IM, et al. Pregnancy-Adapted YEARS Algorithm for Diagnosis of Suspected Pulmonary Embolism. *N Engl J Med*. 2019;380:1139-1149.
10. Le Gal G, Righini M, Roy PM, et al. Prediction of pulmonary embolism in the emergency department: the revised Geneva score. *Ann Intern Med*. 2006;144:165-171.
11. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med*. 1996;15:361-387.
12. Wasson JH, Sox HC, Neff RK, Goldman L. Clinical prediction rules. Applications and methodological standards. *N Engl J Med*. 1985;313:793-799.
13. Robert-Ebadi H, Mostaguir K, Hovens MM, et al. Assessing clinical probability of pulmonary embolism: prospective validation of the simplified Geneva score. *J Thromb Haemost*. 2017;15:1764-1769.
14. Langlois E, Cusson-Dufour C, Moumneh T, et al. Could the YEARS algorithm be used to exclude pulmonary embolism during pregnancy? Data from the CT-PE-pregnancy study. *J Thromb Haemost*. 2019;17:1329-1334.
15. Kearon C, de Wit K, Parpia S, et al. Diagnosis of Pulmonary Embolism with d-Dimer Adjusted to Clinical Probability. *N Engl J Med*. 2019;381:2125-2134.