YEARS Algorithm in Pregnant Patients With Suspected Pulmonary Embolism

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Guest Contributor
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Editor's Note: *You are reading the 75th installment of Annals of Emergency Medicine Journal Club. As the Journal Club enters its second decade of publication, the format has been revised and will focus on a monthly succinct review of high-impact articles from this journal and other premier medical journals relevant to emergency medicine. The reviews are followed by questions demonstrating principles by which readers—be they clinicians, academics, residents, or medical students—may critically appraise the literature. We are interested in receiving feedback about this feature. Please e-mail journalclub@acep.org with your comments.*

ARTICLE IN REVIEW

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.

What Question Did This Investigation Aim to Answer?

In pregnant patients with suspected pulmonary embolism, what is the performance of the YEARS algorithm, including the incidence of symptomatic venous thromboembolism at 3-month follow-up and proportion of patients undergoing computed tomographic (CT) pulmonary angiogram?

What Study Design Did the Authors Choose?

Design: Prospective multicenter cohort.

Setting: The trial was conducted at 11 academic and 7 nonacademic teaching hospitals in the Netherlands, France, and Ireland.

Population: A total of 498 consecutive pregnant patients aged 18 years or older referred to the emergency department (ED) or obstetric ward for suspected pulmonary embolism.

Patients were excluded from the study if they had received full-dose therapeutic anticoagulation 24 hours or more before eligibility assessment, were unavailable for follow-up, had an allergy to iodinated contrast, or had a life expectancy of 3 months or less.

Intervention: Patients underwent the pregnancy-adapted YEARS algorithm, which began with assessment of the presence of the YEARS criteria (clinical signs of deep venous thrombosis, hemoptysis, and pulmonary embolism as the most likely diagnosis). Patients with signs of deep venous thrombosis underwent compression ultrasonography of the symptomatic leg and were treated if the result was positive. A D-dimer test was ordered for all patients, and if no YEARS criteria were met and the D-dimer result was less than 1,000 ng/mL or 1 or more YEARS criteria were met and the D-dimer result was less than 500 ng/mL, pulmonary embolism was excluded. Patients underwent CT pulmonary angiogram if the D-dimer level was elevated above these thresholds and pulmonary embolism was excluded if the CT pulmonary angiogram result was negative.

Primary and Secondary Outcomes: The primary outcome was incidence of symptomatic and objectively diagnosed venous thromboembolism during a 3-month follow-up period in patients not receiving anticoagulation. Venous thromboembolism diagnosis included any of the following: positive CT pulmonary angiogram result, high probability of a positive ventilation-perfusion lung scan result, incompletely compressible proximal vein (eg, popliteal vein or more proximal) or filling defect on ultrasonography, or pulmonary embolism found on autopsy or independent assessment. Secondary outcomes included hypothetical reductions in CT pulmonary angiogram use.

Sponsors: Authors reported receiving unrestricted grants from university hospitals.

How Did the Authors Interpret the Results?

The incidence of symptomatic venous thromboembolism at 3-month follow-up was 0.21% (95% confidence interval 0.04% to 1.2%), which fell below the a priori maximum threshold of 2.7%. One patient had a symptomatic venous thromboembolism, a popliteal deep venous thrombosis, diagnosed on day 90 of the follow-up period. Pulmonary embolism was initially excluded because this patient met 0 YEARS criteria, with a D-dimer level less than 500 ng/mL. Overall, use of the YEARS algorithm avoided CT pulmonary angiogram in approximately 40%

of patients. The algorithm was most efficient in patients in the first trimester, of whom 65% had pulmonary embolism excluded without imaging. Efficiency declined with increasing gestational age because 46% and 32% of patients had pulmonary embolism excluded without imaging in the second and third trimesters, respectively.

Conclusion: The YEARS algorithm safely excluded pulmonary embolism and reduced imaging for pregnant patients.

How Might This Study Affect Your Clinical Practice in the ED?

In this prospective cohort study, the YEARS algorithm was found to safely exclude pulmonary embolism in pregnant patients with suspected pulmonary embolism. The authors also reasonably proposed that use of the YEARS algorithm may reduce CT pulmonary angiogram by approximately 40% compared with the traditional and hypothetical scenario in which all patients would receive imaging. Although this algorithm appears safe, only 5.6% of imaging studies were positive for pulmonary embolism. This suggests providers overestimate the risk of pulmonary embolism in pregnant patients, and risk stratification and evaluation of suspected pulmonary embolism in this population requires further refinement.

DISCUSSION POINTS

1. *The primary outcome for the study was the incidence of objectively confirmed, symptomatic venous thromboembolism during the 3-month follow-up period for patients for whom pulmonary embolism was excluded. Discuss how this outcome differs from sensitivity, negative predictive value, and the limitations of this outcome for risk stratification, diagnostic testing, or both performed at a single point. Why do you think the authors chose this outcome measure?*

In this study, authors chose symptomatic venous thromboembolism during the follow-up period as the primary outcome. This differs from measures such as sensitivity and negative predictive value. Sensitivity reflects the probability a test is positive for patients who actually have the disease (eg, the probability a D-dimer result is positive in a patient who has a pulmonary embolism). Negative predictive value provides insight into how likely it is the patient does not have the disease if the test result is negative (eg, the likelihood the patient does not have a pulmonary embolism if the D-dimer result is negative). The study outcome of incident venous thromboembolism at 3-month follow-up is a surrogate for a true criterion standard. In this case, given the risks associated with CT pulmonary angiogram and preliminary data demonstrating safety, performing a CT pulmonary angiogram on all patients with possible pulmonary embolism would be unethical. This introduces the possibility of verification bias because not all patients received the criterion standard test (CT pulmonary angiogram); thus, some follow-up period was necessary to assess for pulmonary embolism missed in those in whom pulmonary embolism was excluded without CT pulmonary angiogram.

The outcome measured in this study is exhaustive because it captures the performance of the algorithm for detecting venous thromboembolism at not only the initial visit but also within a 3-month follow-up. A D-dimer test or CT pulmonary angiogram does not typically prognosticate risk of venous thromboembolism, but rather identifies presence of disease at a single point. Thus, the outcome chosen in this study may capture disease outside the scope of the index test to detect. Another limitation of this outcome is it relies on comprehensive follow-up of patients and could overestimate safety if lacking. However, in this study, only one patient was lost to follow-up, and the incidence of venous thromboembolism at follow-up, presuming this patient would receive a diagnosis of a venous thromboembolism, would be 0.42% (95% confidence interval 0.11% to 1.5%), well below the predefined safety threshold.

2. *The performance of a diagnostic test or clinical decision tool depends on the prevalence in a given population. The prevalence of pulmonary embolism in this population was 4%. Discuss how the YEARS algorithm might perform if in a higher-prevalence population. How might the efficiency of the algorithm (how many patients would be excluded without imaging) change in a lower-prevalence population?*

Because prevalence of a disease varies, the performance of a test or clinical decision tool may change. For example, with measures such as negative predictive value, as the prevalence of the disease decreases, the negative predictive value increases. This becomes important when one considers the implementation of a test or clinical decision tool in a population outside of the one in which it was initially evaluated. Few patients in this study population, only 4%, received a diagnosis of pulmonary embolism, similar to the prevalence found in other studies including pregnant patients.[1,2] In this case, the negative predictive value was 99.5%. However, the prevalence in studies conducted in the United States appears lower, at 2.8%, compared with just over 5% in other countries. In a population with a higher prevalence of disease, one would expect the negative predictive value to decrease, meaning clinicians may not be able to use the YEARS criteria to safely exclude pulmonary embolism in higher-risk populations. As an example, if the prevalence of pulmonary embolism were to increase from 4% to 10% or

even 20%, assuming the sensitivity and specificity of the YEARS algorithm remained stable, the negative predictive value would decrease to 98.6% and 97%, respectively. Readers interested in a more detailed discussion of negative predictive value should refer to the January 2016 *Annals* Journal Club.[3] In regard to the secondary outcome of this study, the proportion of patients for whom pulmonary embolism could be excluded without imaging, implementation of this algorithm in a setting with a lower prevalence of pulmonary embolism could result in increased rates of imaging. The D-dimer test is nonspecific, and the level normally increases throughout pregnancy.[4,5] Because this test is a key part of the YEARS algorithm, using the D-dimer test in a low-prevalence population could result in a higher proportion of patients unnecessarily referred for imaging.

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REFERENCES

1. Kline JA, Richardson DM, Than MP, et al. Systematic review and meta-analysis of pregnant patients investigated for suspected pulmonary embolism in the emergency department. *Acad Emerg Med*. 2014;21:949-959.
2. Righini M, Robert-Ebadi H, Elias A, et al. Diagnosis of pulmonary embolism during pregnancy. *Ann Intern Med*. 2018;169:766-773.
3. Silvestri D, Takhar SS. Sex, drugs, hepatitis C, and an urban emergency department: January 2016 *Annals of Emergency Medicine* Journal Club. *Ann Emerg Med*. 2016;67:138-140.
4. Kline JA, Williams GW, Hernandez-Nino J. D-dimer concentrations in normal pregnancy: new dignostic thresholds are needed. *Clin Chem*. 2005;51:825-829.
5. Murphy N, Broadhurst D, Khashan A, et al. Gestation-specific D-dimer reference ranges: a cross-sectional study. *BJOG*. 2015;122:395-400.

IMAGES IN EMERGENCY MEDICINE

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DIAGNOSIS:

Diffuse large B-cell lymphoma. Imaging of the neck revealed an enlarged cervical mass with mediastinal extension, compression of vascular structures, tracheal encasement with rightward deviation, and mass effect with laryngeal displacement. The patient underwent core-needle biopsy, revealing the diagnosis of diffuse large B-cell lymphoma. Further imaging for staging disclosed a renal mass, suggestive of metastatic disease. The patient was admitted and received intravenous dexamethasone and tailored chemotherapy, with a favorable response.

Diffuse large B-cell lymphoma is the most common subtype of non-Hodgkin's lymphoma, with typical onset during middle age.[1] It is considered an aggressive form of lymphoma, classically presenting with a rapidly enlarging, symptomatic nodal mass in the neck, abdomen, or mediastinum. Systemic "B" symptoms (eg, fever, weight loss, night sweats) are present in approximately 30% to 40% of patients.[2,3] Clinical presentation depends on the anatomic location of the mass, with laryngeal and tracheal displacement in our case. Diffuse large B-cell lymphoma has a 5-year overall survival rate of approximately 60% for individuals who are identified and treated aggressively; thus, early diagnosis is imperative in providing a positive outcome.[4]

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REFERENCES

1. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;127:2375-2390.
2. Anderson T, Chabner BA, Young RC, et al. Malignant lymphoma. 1. The histology and staging of 473 patients at the National Cancer Institute. *Cancer*. 1982;50:2699-2707.
3. Armitage JO, Weisenburger DD. New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. Non-Hodgkin's Lymphoma Classification Project. *J Clin Oncol*. 1998;16:2780-2795.
4. Smith A, Crouch S, Howell D, et al. Impact of age and socioeconomic status on treatment and survival from aggressive lymphoma: a UK population-based study of diffuse large B-cell lymphoma. *Cancer Epidemiol*. 2015;39:1103-1112.