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Letter to the Editors-in-Chief

A safe strategy to rule out pulmonary embolism: The combination of the Wells score and D-dimer test: One prospective study

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Pulmonary embolism (PE) is a potentially fatal disease with mortality of approximately 30%if left untreated [1]. Diagnosis is challenging for clinicians because clinical presentation is variable and nonspecific when it occurred individually [2]. Besides, there is no diagnostic test that combines sufficiently high sensitivity and specificity to be used alone in clinically suspected PE. Therefore, contemporary approaches depend on the sequential use of diagnostic tests including evaluation of clinical probability, fibrin D-dimer plasma measurement, lower limb venous compression ultrasonography, helical computed tomography and pulmonary angiogram. The effects of age on the characteristics of common diagnostic tests for clinically suspected PE have been discussed in one review [3]. D-dimer allows excluding PE in only 5% of patients aged 80 and older, compared with 60%younger than 40.In contrast, aging does not change the diagnostic accuracy of clinical probability assessment, nor appear to influence the diagnostic characteristics of CT. However, elderly patients are more likely to present with renal impairment and to develop contrast-induced nephropathy, which limits the use of CTPA in this age group.

Besides, the incidence of venous thromboembolism and the mortality of PE in elderly patients are significantly greater than in non-elderly patients [3]. And the increasing prevalence of other comorbidities, such as congestive heart failure or chronic obstructive pulmonary disease, leads to rising rate of misdiagnosis and missed diagnosis of PE. This prospective study aims to explore diagnostic values of the Wells scores, D-dimer test and their combination for suspected PE in hospitalized elderly patients.

From January 2008 to December 2015, a total of 1167 patients consecutively admitted to the geriatric department in Cangzhou Central Hospital, Hebei Province, China with clinically suspected PE were screened, of whom 319 (27.3%) were excluded because of predefined exclusion criteria: treatment with anticoagulant (vitamin K antagonists or heparin) at presentation ($n = 198$), contraindication to CTPA because of allergy to intravenous iodinated contrast or renal insufficiency ($n = 37$), and inability to return for follow-up ($n = 84$). 848 patients were finally enrolled in this study.

After written informed consent had been obtained, the characteristics including gender, age, main symptoms, signs, and risk factors were recorded for each suspected PE patient. Patients were then categorized as "PE unlikely" with the wells score of 4 or less points, or "PE likely" with a score of >4 points using a dichotomized version of the Wells score by two experiential physicians of geriatric department who were blinded to the final diagnosis. This cutoff was chosen because it has been shown to give an acceptable VTE diagnostic failure rate of 1.7% to 2.2% in combination with a normal D-dimer test result [4]. A second-generation latex agglutination D-dimer tests (immunoturbidimetric tests) was subsequently carried out. The level of D-dimer is defined as normal if <500 ng/ml. PE was diagnosed by using CTPA as a golden standard, and the signs are contrast material outlined central or eccentric partial filling defects, or filling defects occupying the total vessel section of main, lobar, segmental, and subsegmental artery. This study was conducted with the approval of the local institutional committees in adherence to the Declaration of Helsinki. During a 3-month follow-up period, all patients were interviewed by telephone by one study coordinator using a structured questionnaire and they were instructed to return to the clinic or to the emergency room in case of the occurrence of recurrent symptoms of the respiratory system or legs.

We evaluated the predictive values of the Wells score or D-dimer test alone and two kinds of combination tests, which were series testing and parallel testing. Patients were diagnosed PE when both the Wells score and D-dimer test had a positive result in series testing. And for parallel testing, PE was predicted when the result of the Wells score or D-dimer test was positive. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated.

Data are presented as means standard deviations or as percentage frequency. The sensitivity, specificity, PPV and NPV were calculated by using SPSS version 19.0. Chi-square test was used for comparison of categorical data, and Mann–Whitney *U* test was used for comparison of continuous variables. Statistical significance was accepted at $P < 0.05$.

A total of 848 patients (405 males and 443 females) with mean (standard deviation [SD]) age of 70.85 (5.43) were included in the analysis, of which 336 were diagnosed with PE after performing CTPA Supplementary Table 1. The overall prevalence of confirmed PE in our study was 39.6%, greater than previous studies [4], which may owe to transference from other primary hospitals. As Table 1 showed, the sensitivity and negative predictive value of D-dimer test was higher than the Wells score (93.2% vs. 90.8% and 93.2% vs. 91.4% respectively). However, with high false positive rate, the diagnostic accuracy of the Wells score or D-dimer test alone is unsatisfactory. The sensitivity and negative predictive value of parallel testing were 98.8% and 98.7% respectively, which were significantly elevated compared with the Wells score or D-dimer test alone and series testing. And none of the patients excluded PE by parallel testing suffered fatal PE, nonfatal PE, or deep vein thrombosis (DVT) during 3 months of follow-up. The specificity of parallel testing was lower than series testing (58.6% vs. 66.8%). Therefore, parallel testing with high sensitivity should be used as a simple screening test to diagnose acute and critical diseases and a negative result of parallel testing can safely exclude PE with a significantly high NPV.

When elderly patients present with unexplained shortness of breath or chest pain, it's a challenge to differentiate between common self-limiting diseases, such as myalgia or respiratory tract infections, and

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Table 1
The predictive values of the Wells score, D-dimer test and combination tests[d].

Variables	Sensitivity	Specificity	PPV	NPV
Wells score[a]	90.8	64.3	62.5	91.4
D-dimer	93.2	61.1	61.1	93.2
Series testing[b]	85.1	66.8	62.7	87.2
Parallel testing[c]	98.8	58.6	61.0	98.7

*PPV: positive predictive value; NPV: negative predictive value.
[a] There were no cases of major disagreements between the two Wells score assessors.
[b] Patients were diagnosed PE when both the Wells score and D-dimer test had a positive result.
[c] Patients were excluded PE when both the Wells score and D-dimer test had a negative result.

the rarer life threatening diseases such as PE. As a result, some clinicians may excessively perform CTPA, but only 10–15% of referred patients were actually diagnosed as having the condition, which unavoidably leads to unnecessary and expensive investigations and adds their associated risks. And CTPA can't be performed for patients in a critical condition or in some rural hospitals of China, which lack corresponding devices.

Despite the limited sensitivity and specificity of individual symptoms, signs, and common tests, the combination of findings evaluated by the use of prediction rules allows to classify patients with suspected PE into distinct categories of clinical or pre-test probability that correspond to an increasing actual prevalence of confirmed PE. The most widely known and validated prediction rule is the Wells score, which is simple and based on information that is easy to obtain [5], whereas the inclusion of a subjective parameter (PE more likely than alternative diagnosis) limits its standardization and accounts for its poor inter-observer reproducibility [6]. However, many clinical researches revealed that the Wells score had a better accuracy among most of the clinical assessments for predicting PE and the subjective criterion may be one of the most informative criteria [7].

Plasma D-dimer is a degradation product of cross-linked fibrin and its levels are elevated in the presence of an acute thrombosis because of simultaneous activation of coagulation and fibrinolysis. Nonetheless, fibrin is also produced in other conditions such as cancer, inflammation, bleeding, trauma and surgery [8]. Thus, the PPV of elevated D-dimer levels is low and D-dimer testing is not used for confirmation of PE. The D-dimer concentration increases with age and its specificity for embolism decreases, which makes the test less useful to exclude PE in older patients [9]. One proposed approach in the literature considered a 10 μg/l increase per patient year to be an appropriate new D-dimer coefficient [10]. The age adjusted D-dimer cut-off value improved clinical utility and did not come at the expense of safety.

The positive predictive values of the Wells score or D-dimer test alone, series testing and parallel testing were 62.5%, 61.1%, 62.7% and 61.0% respectively and the statistically significant was no difference. But the negative predictive values of the Wells score or D-dimer test alone was high. And for parallel testing, the negative predictive value, which means the Wells score and D-dimer test both had a negative result, was significantly improved (98.7%).

Several limitations should be acknowledged in our study. Firstly, this is a single-center study which may limit its generalizability although the number of included patients was considerable. Secondly, CTPA was the only standard to confirm or exclude PE, but the clinical outcome after a 3-month follow-up is widely accepted as an appropriate alternative to establish the safety of a diagnostic strategy. Thirdly, the clinical implication of subsegmental PE is controversial, which may affect the diagnostic values of this study. Moreover, it is argued that the D-dimer cutoff, which is 500 ng/ml in the present study, tends to be higher in elderly people [10], which may increase the pretest probability of diagnosing PE in individuals with a low to intermediate level of probability.

In conclusion, the combination of using the Wells score and D-dimer test is as effective as other complex diagnostic strategies in the evaluation and management of hospitalized elderly patients with clinically suspected PE. The impact of this finding on patient outcomes should be investigated in a prospective multi-center study.

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Conflicts of interest

All authors have declared no conflicts of interest.

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