Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editors-in-Chief

Validation of the YEARS algorithm and Wells' score with the age-adjusted cut-off to exclude pulmonary embolism in COVID-19 patients

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In COVID-19 patients it is difficult to diagnose pulmonary embolism (PE) due to the overlapping symptoms and elevated biomarkers. PE is a common complication in hospitalized COVID-19 patients, with an incidence of approximately 21 % [1]. In clinical practice, the YEARS algorithm [2] and Wells' criteria [3] with the age-adjusted D-dimer (AADD) cut-off [4] are often utilized to exclude clinically suspected PE in COVID-19 patients.

However, certain mechanisms of PE are different in COVID-19 patients compared with non-COVID-19 patients, which may affect the performance of these prediction rules. Reported PE in COVID-19 patients may often represent local pulmonary thrombosis, rather than an embolism from the deep venous circulation [5]. Furthermore, the hyperinflammatory state and coagulation activation in COVID-19 patients induces elevation of plasma D-dimer levels [5], complicating the possibility of excluding suspected PE without the use of CT-pulmonary angiography (CTPA).

A previous study [6] reported that PE could be ruled out in 29 % of patients with suspected COVID-19 when using the YEARS algorithm. Less is known about the performance of the YEARS and the age-adjusted Wells score in patients with confirmed COVID-19. Hence, we assessed the diagnostic performance of the YEARS algorithm and Wells score with the AADD threshold using data of patients with confirmed COVID-19.

We conducted this retrospective cohort study at the Northwest Clinics in Alkmaar, The Netherlands. The study was approved by the research board of the Northwest Clinics. The need to obtain written informed consent was waived for this observational study. We included consecutive COVID-19 patients, hospitalized between March 2020 and July 2021, with suspected PE, from the Procalcitonin Viral Infections (ProVIS) database. Suspected PE was defined as assessment of D-dimer concentration. Patients were managed in accordance with the hospital protocol: In the emergency room and general wards, D-dimer concentration were solely measured as an aid to rule out pulmonary embolism, and patients were subsequently managed in accordance with the YEARS algorithm [2] (Suppl. Fig. B.1). Patients with suspected PE in the intensive care unit were excluded, as the two prediction rules are not validated for this population [2,3]. Other exclusion criteria were patients with a known pregnancy, patients with a genetic thrombotic disease, and patients with therapeutic anticoagulant use for indications other than venous thromboembolism (VTE) or suspected VTE. Eligibility criteria of the ProVIS database are described in the supplementary material (Suppl. A).

YEARS scores were extracted from electronic medical records (EMR). Missing YEARS scores were calculated independently by two researchers (LH and ES), using available information in the EMR. All Wells scores were calculated using information from the EMR. Individual YEARS and Wells' items (Suppl. Fig. B.2) were defined in accordance with the definitions of Wells et al. [3], except for the item 'malignancy', which was defined as active malignancy or treatment for malignancy in the past 5 years. If the physician did not state information on an individual YEARS or Wells' item, the item was scored as 0. The subjective item 'PE is the most likely diagnosis/alternative diagnosis less likely' was defined as:

1. The physician specified in the EMR that PE was the most likely diagnosis, or
2. No other YEARS criteria were stated in the EMR, but a CTPA was performed with a d-dimer of <1000 μg/l within 24 h of the D-dimer measurement.

If the above criteria were not met, this subjective item was scored as 0.

Wells' AADD cut-off levels were calculated in patients aged >50 years by multiplying age in years by 10 μg/l [4]. D-dimer levels were measured using a HemosIL D-Dimer HS 500 immunoassay (ACL-TOP analyzer, Werfen, Bedford, USA).

Primary outcomes were efficiency and failure rate of the YEARS algorithm and Wells' criteria with the AADD cut-off. Efficiency was defined as the proportion of patients in whom PE could be excluded at baseline using the clinical prediction rules, without the use of CTPA. The failure rate was defined as the proportion of patients that developed VTE within 3 months after previous PE exclusion at baseline. PE diagnosis after a repeated D-dimer measurement was regarded as diagnostic failure. A maximum failure rate of 3 % was deemed acceptable [5].

Statistical analyses were performed using IBM SPSS statistics 25.0 (IBM Corp, Armonk NY). Efficiency and failure rates were calculated using descriptive statistics, confidence intervals were calculated using

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Clopper-Pearson tests, and median D-dimer concentrations were compared using Mann-Whitney-*U* tests. Statistical significance was set at a two-sided p value of $p < 0.05$. Missing YEARS and Wells scores were calculated as described above, and patients who were transferred during their hospital admission were excluded from the analyses.

In total, 539 patients were included. The mean age was 63 years (SD 14.74), 61.4 % were men. The inclusion flowchart and baseline characteristics table are presented in Suppl. Fig. B.3, Table B.1. Median D-dimer levels were higher in patients with PE at baseline, compared with patients without PE (5460 μg/l vs. 810 μg/l, $p < 0.001$) (Fig. 1). The overall incidence of PE was 11.9 % (64 patients), of which 34 patients (6.3 %) were diagnosed at baseline. Another 34 patients (6.3 %) developed VTE within 3 months after baseline PE exclusion (PE: $n = 30$, DVT: $n = 4$). One hundred ninety-five patients (36.2 %) attended a follow-up post-COVID-19 appointment 3 months after hospital discharge. Seventy-eight patients (14.5 %) died within 3 months of hospital admission.

YEARS scores were stated in the EMR of 111 patients (20.6 %). At baseline, 396 patients (73.5 %) did not meet any YEARS criteria (Table 1). Of this group, 226 patients (57.1 %) had a D-dimer concentration of <1000 μg/l. Overall, 143 patients (26.5 %) had ≥1 YEARS criteria, of which 16 patients (11.2 %) presented with a D-dimer concentration below 500 μg/l. PE could be excluded in 242 out of 539 patients without CTPA, resulting in an efficiency of 44.9 % (95 % CI, 40.6–49.2 %). Thirty-seven protocol violations occurred: 13 patients without YEARS criteria and D-dimer concentration < 1000 μg/l underwent CTPA. All patients with a D-dimer concentration > 500 μg/l and ≥1 YEARS criteria underwent CTPA, and 12 patients with a D-dimer >1000 μg/l did not undergo CTPA.

Of the 242 patients in whom PE was excluded at baseline with a negative YEARS algorithm, 16 (6.6 %) patients developed VTE within 3 months. Another (6.4 %) patients in whom PE was excluded with CTPA at baseline developed VTE within 3 months. The failure rates of patients managed without CTPA and with CTPA were therefore 6.6 % (95 % CI, 3.8–10.5 %) and 6.4 % (95 % CI, 3.9–9.8 %), respectively.

Fifty-three patients (9.8 %) had a Wells score of >4 and 486 patients (90.2 %) had a Wells score of ≤4 (Table 1). Of the 486 patients with Wells score ≤ 4, PE could be excluded in 175 patients using the AADD cut-off. The efficiency was 175/539 (32.5 %, 95 % CI: 28.536.6 %).

Ten patients in whom PE was previously excluded developed VTE within 3 months of initial presentation. The failure rate was 10/175 (5.7 %, 95 % CI 2.8–10.3 %) in patients managed without CTPA. In patients who underwent CTPA, the failure rate was 24/364 (6.6 %, 95 % CI 4.3–9.7 %).

Table 1
Wells scores, YEARS scores, and D-dimer concentrations in COVID-19 patients with or without pulmonary embolism at baseline.

	PE excluded ($n = 505$)	PE ($n = 34$)
YEARS score		
0	378 (74.9 %)	18 (52.9 %)
≥1	127 (25.1 %)	16 (47.1 %)
Wells score		
≤4	467 (92.5 %)	19 (55.9 %)
>4	38 (7.5 %)	15 (44.1 %)
D-dimer concentration (μg/l)		
<500	116 (23.0 %)	0 (0.0 %)
500–1000	204 (40.4 %)	3 (8.8 %)
1000–2000	127 (25.1 %)	8 (23.5 %)
2000–3000	20 (4.0 %)	1 (67.6 %)
>3000	38 (7.5 %)	22 (64.7 %)

Abbreviations: PE, pulmonary embolism.

In patients who underwent CTPA at baseline, a follow-up VTE event occurred at a median of 7.5 days (IQR 6–12.25) after the initial CTPA. Overall, 22 follow-up VTE events occurred during the initial hospital admission (64.7 %), of which 9 patients (26.5 %) developed VTE during ICU admission. The remaining 13 follow-up VTE events occurred after discharge (38.2 %). Characteristics of patients with VTE at follow-up are presented in Suppl. Table B.2–3.

This retrospective study assessed the diagnostic value of the YEARS algorithm and Wells' criteria with the AADD cut-off in COVID-19 patients with suspected PE. The high failure rates observed after a recent negative CTPA, a negative YEARS algorithm, as well as a negative AADD cut-off using Wells' criteria, indicate that a new assessment of the clinical probability of PE in COVID-19 patients is needed in case of newly suspected PE after the recent PE exclusion using either method.

The efficiency of the YEARS algorithm (44.9 %) was comparable to the efficiency described in the YEARS study (48 %) [2], and the efficiency of Wells' criteria with the AADD cut-off (33.2 %) was comparable to a previous meta-analysis (33 %, 95 % CI 25–42 %) [7]. However, despite the exclusion of PE with or without a negative CTPA, 6.3 % of

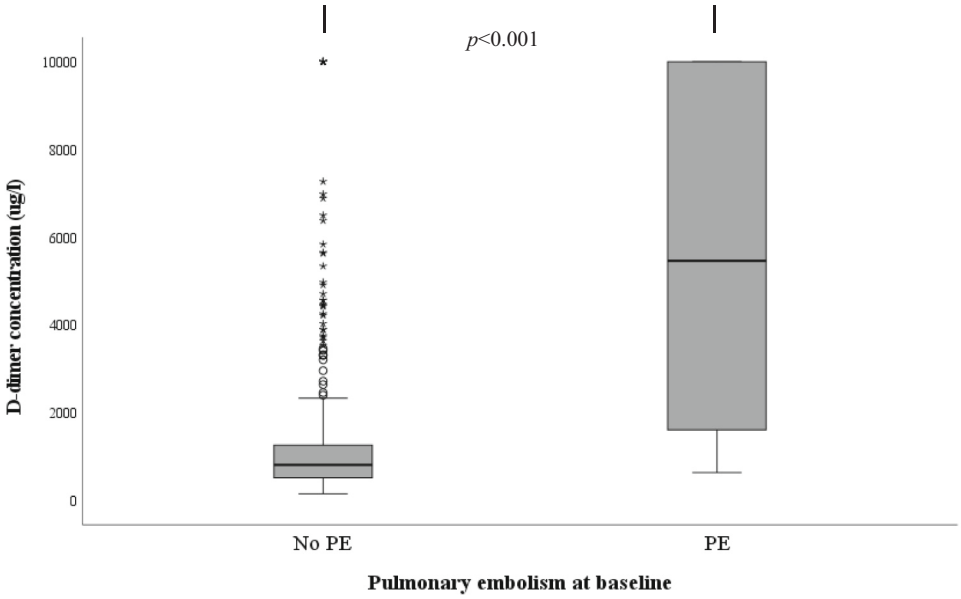

Fig. 1. Median D-dimer levels in patients with pulmonary embolism (PE) at baseline (PE: $n = 34$) vs. patients in whom PE was excluded at baseline, using a negative D-dimer cut-off or negative CTPA (No PE: $n = 505$).
Legend: ° = Mild outlier, * = Extreme outlier.
Abbreviations: PE, pulmonary embolism.

patients developed VTE within 3-months. Patients with a negative CTPA at baseline were diagnosed with VTE within a median of only 7.5 days, indicating that VTE may occur rapidly after an earlier exclusion of PE. Failure rates of the prediction rules were comparable in patients in whom PE was excluded with a negative CTPA (YEARS: 6.4 %, Wells: 6.6 %) and patients in whom PE was excluded without CTPA (YEARS: 6.6 %, Wells: 5.7 %). In line, a prospective multicenter study [8] evaluating the efficiency and failure rate of the YEARS rule in patients with suspected PE and suspected COVID-19 found a high failure rate of the YEARS algorithm (8.8 %, 95 % CI 4.3–16 %) in patients managed with a negative CTPA. In contrast to our study, the authors reported a lower failure rate in patients managed with a negative YEARS algorithm (1.8 %, 95 % CI 0.04–7.8 %). Nevertheless, the confidence interval of this failure rate exceeded the maximum accepted failure rate of 3 % [8]. A more recent retrospective study [9] included 300 COVID-19 patients who underwent both CTPA and D-dimer testing for suspected PE, and reported that both the AADD Wells' criteria and YEARS algorithm could reduce the number of CTPA by 19 %. However, the AADD Wells' criteria and the YEARS algorithm would have led to 11.4 % and 7.1 % missed diagnoses of PE, respectively. The authors did not assess 3-month failure rate after a negative CTPA. To summarize, the findings in our study and previous studies suggest that follow-up VTE events in COVID-19 patients may represent a combination of diagnostic failure of the clinical prediction rules, as well as formation of new clots due to further progression of COVID-19-associated inflammation and systemic coagulopathy [10].

A strength of this study was that all patients were actively managed using the YEARS algorithm, and protocol violations occurred in only 37 cases (6.9 %). A major limitation was the retrospective design, as YEARS and Wells scores were often calculated, relying on accurate record-keeping to calculate these scores. Because the follow-up was incomplete, the post-discharge PE rate may be underestimated. However, one-third of the patients attended a follow-up appointment 3 months post-discharge, and we aimed to prevent loss of follow-up by excluding patients who were transferred to another hospital during their hospital admission.

In conclusion, the high failure rates after a negative YEARS algorithm, a negative AADD cut-off using Wells' criteria, as well as a negative CTPA, suggest that follow-up VTE events in COVID-19 patients may represent failure of the clinical prediction rules in combination with formation of new clots. Physicians should remain attentive of follow-up VTE after recent PE exclusion in COVID-19 patients.

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Authorship details

EMS, SS and WGB designed the present study. LMH conducted the ProVIS study and set up the ProVIS database. EMS and LMH conducted data extraction. EMS performed the data analyses and wrote the manuscript. LMH, WGB, SS and HRB contributed to the drafting and editing of the manuscript. LM supervised the data analyses.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2022.09.011.

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