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

Systematic screening for pulmonary embolism using the YEARS algorithm in patients with suspected COVID-19 in the Emergency Department

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Pulmonary embolism (PE) is a prevalent and potentially life-threatening complication of COVID-19 [1]. To prevent further respiratory deterioration, early detection of concomitant PE is required, preferably upon hospital admission. In this study, we evaluated the diagnostic yield of systematic screening for PE in the Emergency Department (ED) in a consecutive cohort of patients with suspected COVID-19 who were admitted for hospital care.

We included all patients who were admitted to a large teaching hospital in the Netherlands via the ED between April 7th and May 31st 2020 and who met the WHO case definition for suspected COVID-19 [2]. All patients were evaluated according to a prespecified clinical protocol, including systematic history taking, laboratory testing, computed tomography (CT) of the chest, and SARS-CoV-2 reverse transcriptase-polymerase chain reaction (RT-PCR).

In the ED, all patients were screened for PE according to the YEARS algorithm [3]. This algorithm consists of three clinical items (clinical signs of deep vein thrombosis, hemoptysis, and PE as the most likely diagnosis) with simultaneous D-dimer testing (using CS2500 blood coagulation analysers, Sysmex Corporation, Kobe, Japan). Contrast-enhanced CT-pulmonary angiography (CTPA) was performed in patients with 0 YEARS items and D-dimer ≥1000 ng/mL, and in patients with ≥1 YEARS items and D-dimer ≥500 ng/mL. Patients who had D-dimer values below these cut-off values were considered to have PE excluded and underwent a non-contrast-enhanced chest-CT as part of the clinical protocol. Patients were excluded if they were already receiving a therapeutic dose of anticoagulant drugs for another indication, or in case of contraindication to CTPA (e.g., allergy to iodinated contrast agents, impaired renal function, or inability to cooperate) or to anticoagulant treatment because of active major bleeding.

Systematic PE screening using the YEARS algorithm was performed in all patients who met the WHO case definition for suspected COVID-19 [2]. Yet, a definite diagnosis of COVID-19 (defined as either a positive SARS-CoV-2 RT-PCR or a COVID-19 CT-classification score (CO-RADS) [4] 4 or 5 on chest-CT obtained at the ED) could only be established after full diagnostic work-up, including PE screening. To identify risk factors for PE (which might provide clues to limit the required number of CTPAs in the future), we performed regression analyses on the data of the patients that underwent CTPA. Associations with $p < 0.10$ in the univariate logistic regression models and those considered biologically plausible were included in the multivariate logistic regression model (using SPSS v.26.0, IBM corp., Armonk, USA). The study was approved by the local ethical committee (METCZ20200076).

In total, 920 patients with suspected COVID-19 were admitted for hospital care via the ED. 214 patients were excluded because of the use of anticoagulant drugs ($n = 190$) or protocol violation due to unavailability of D-dimer values ($n = 24$). The remaining 706 patients were included in the present study (Supplemental Fig. A).

Following the YEARS algorithm, PE was considered ruled out (without CTPA) in 273 out of 706 patients (38.7%). CTPA was indicated in 433 patients (61.3%). However, 15 of those patients were excluded for CTPA because of contraindications to CTPA (impaired renal function ($n = 8$), allergy to iodinated contrast (n = 2), or inability to cooperate (n = 1)) or to anticoagulant therapy because of active bleeding ($n = 4$). Unfortunately, protocol violation occurred in 25 patients (5.8%) who did not undergo CTPA for unknown reasons. Thus, 666 patients were included in the present analyses, 393 in the CTPA group and 273 in the non-CTPA group.

The characteristics of the study population are provided in Supplementary Table A. Patients in the CTPA group were older (mean age 69.5 vs. 61.2 years, $p < 0.001$) and had a lower BMI (26.3 vs. 27.7 kg/m^2, $p = 0.002$) than those in the non-CTPA group. Patients in the CTPA group more often had a history of chronic kidney disease (7.4% vs. 3.3%, $p = 0.03$), but the prevalence of other comorbidities did not differ significantly.

Of the 393 patients who underwent CTPA, PE was confirmed in 51 (13%), resulting in a number needed to test (NNT) by CTPA of 7.7. The overall prevalence of PE among all COVID-19 suspected patients at the ED, including the 273 patients in whom PE was considered to be ruled out based on the YEARS algorithm, was 7.7% (51 out of 666).

D-dimer level was significantly higher in patients with PE (median 5402 μg/L; range 620 to >35,000 μg/L) compared to patients without PE (median 2281 μg/L; range 509 to >35,000 μg/L, $p = 0.007$) (Fig. 1). The lowest D-dimer level among patients with PE was 1258 μg/L for patients who met no YEARS items and 619 μg/L for patients who met ≥1 YEARS items.

After full work-up including PE screening, COVID-19 was diagnosed

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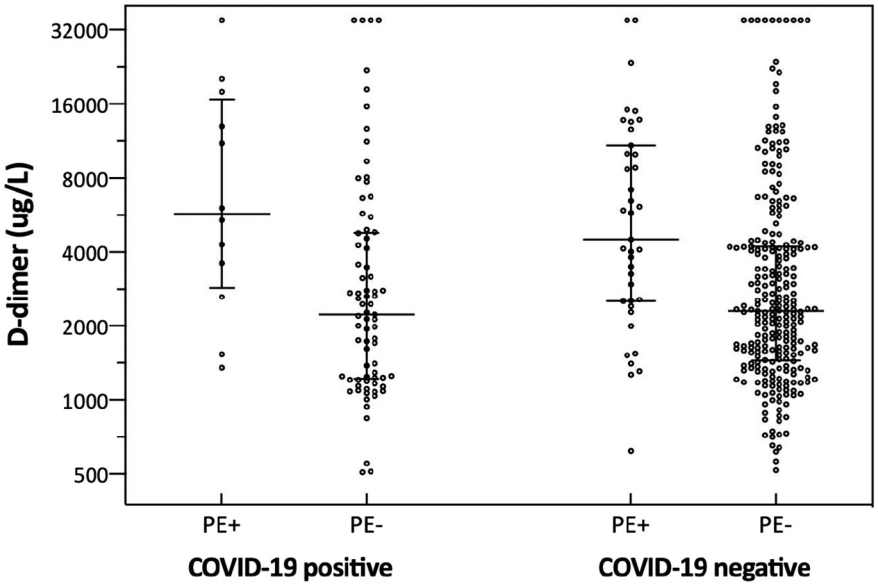

Fig. 1. Scatter plot of the D-dimer levels in COVID-19 positive and COVID-19 negative patients with and without PE on a base-2 log scale. Each dot represents one patient. Horizontal lines show the median, error bars show the interquartile range. PE, pulmonary embolism.

in 89 patients (22.6%) in the CTPA group and 81 (29.7%) in the non-CTPA group ($p = 0.04$, Supplementary Table B). The PE prevalence in patients finally diagnosed with COVID-19 did not differ from patients without COVID-19 (7.1% vs. 7.9%, $p = 0.73$). There were no significant differences in D-dimer levels between patients with COVID-19 and those without (median [IQR] 998 [549–2651] vs. 1317 [605–3179] μg/L, $p = 0.91$).

Only D-dimer was associated with the presence of PE, both in univariate (OR 1.07 for every 1000 μg/L increase, 95%CI 1.05–1.09, $p \leq 0.001$) and multivariate regression analyses (OR 1.07 for every 1000 μg/L increase, 95%CI 1.02–1.13, $p = 0.007$, Table 1). No other demographic, clinical, or laboratory characteristics were found to be associated with PE.

In the first study that systematically screened for PE in ED patients with (suspected) COVID-19, we found an overall PE prevalence of 7.7%. Except for D-dimer, no other risk factors for PE were identified. One out of 7.7 CTPAs that were indicated according to the YEARS algorithm were positive for PE. Therefore, we believe that this is a feasible approach for early PE detection in these patients.

Due to systematic screening in a well-defined time-point in the course of disease (upon hospital admission), the present study allows a more accurate estimation of the PE prevalence than previous studies. Almost all previous studies were heterogenic with regard to setting and time-point and lacked systematic screening for PE as CTPA was only performed in case of clinical suspicion [1]. Since signs and symptoms of PE are non-specific and largely overlap those of COVID-19, ruling out PE on clinical grounds is not feasible in COVID-19 patients. Naturally, in the present study we cannot rule out PE with certainty in patients with low D-dimer values in whom CTPA was not indicated according to the YEARS algorithm. Given the potential side-effects, performing CTPA in

Table 1
Regression analysis for factors associated with PE in COVID-19 suspected patients at the ED.

Variables	Univariate analysis			Multivariate analysis		
	Odds ratio	95%CI	*P*-value	Odds ratio	95%CI	*P*-value
Age (years)						
<60	Reference					
60–75	0.79	0.37–1.67	0.54			
≥75	0.68	0.32–1.43	0.31			
Age per 5 years	0.95	0.86–1.04	0.24	0.95	0.82–1.11	0.53
Male sex	1.07	0.59–1.93	0.83			
BMI (kg/m^2)						
<25	Reference					
25–30	1.73	0.91–3.32	0.10	2.84	0.95–8.47	0.06
≥30	0.78	0.30–2.01	0.62			
Current smoker	0.82	0.31–2.18	0.69	0.72	0.24–2.21	0.57
Chronic comorbidity						
COPD	0.41	0.14–1.18	0.10	0.84	0.21–3.42	0.81
Malignant neoplasms	0.96	0.27–3.33	0.94			
Vital signs						
Heart rate > 90 bpm	1.03	0.57–1.86	0.91			
COVID-19 infection	1.06	0.53–2.12	0.87			
Cytokine storm syndrome	0.94	0.37–3.33	0.96			
Laboratory results						
CRP > 100 mg/L	1.05	0.55–2.01	0.88			
Ferritin >400 μg/L	1.01	0.56–1.84	0.97			
D-dimer per 1000 μg/L	1.07	1.05–1.09	<0.001	1.07	1.02–1.13	0.006

CI, confidence interval; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein.

patients with a very low pre-test probability for PE was considered undesirable. Moreover, the overwhelming number of patients with (suspected) COVID-19 resulted in logistic constraints to perform CTPA in all patients. However, despite this potential bias, the present study used a validated algorithm [3] and provides a much more reliable estimation of the true PE prevalence, than previous studies that lacked systematic screening and were thus highly susceptible to inclusion and selection bias [5].

Since inflammation induces an increase in D-dimer levels, questions have been raised about the efficacy of the currently used D-dimer threshold in COVID-19 patients. Several studies have advocated the use of a higher D-dimer cut-off (between 2500 and 2900 μg/L) based on the highest "Youden's index" for an optimal cut-off point [6,7]. However, these higher D-dimer thresholds yield a sensitivity of 80–83%, implying a substantial proportion (17–20%) of PEs will remain undiagnosed. In our cohort, adjusting the D-dimer threshold from 1000 to 2500 μg/L would have resulted in missing approximately 20% of the PEs (Fig. 1). Hence, we believe that it is well justified to opt for a threshold with a sensitivity and a negative predictive value close to 100%. In our data, the lowest D-dimer value among patients with PE who met zero YEARS items was 1258 μg/L, which is close to the threshold of 1000 μg/L used in the YEARS algorithm. Accordingly, we do not advocate raising the D-dimer threshold in ED patients with (suspected) COVID-19.

We found no significant difference in PE prevalence between patients with and without COVID-19, which is in line with several other studies [8,9]. Since these studies mainly included patients with respiratory symptoms, alternative causes of their respiratory symptoms, including PE, should be present if COVID-19 was ruled out. Moreover, a report of the Danish population-based registry, mainly containing non-hospitalized patients, also showed that VTE risks in COVID-19 patients were comparable to that in COVID-19-negative and influenza patients [10]. The first published studies on PE in COVID-19 were predominantly performed in ICU patients, which led to the assumption that PE is highly prevalent among COVID-19 patients. In contrast with these severely ill (ICU) patients, the PE prevalence is apparently much lower in (suspected) COVID-19 patients at presentation in the ED.

Limitations of this study include the exclusion of patients with contraindications to CTPA or anticoagulant therapy. However, as this applied to only 15 patients, significant influence on the results appears unlikely. Moreover, the prevalence of PE in patients already using anticoagulant drugs remains unclear, as those patients were excluded.

This is the first study that used a systematic screening strategy based on the YEARS algorithm to evaluate the PE prevalence in ED patients with suspected COVID-19. In our opinion, this is a feasible approach for early PE detection in order to reduce morbidity and mortality in these patients.

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.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2021.09.010.

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