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Predictive scores for the diagnosis of Pulmonary Embolism in COVID-19: A systematic review

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ABSTRACT

Objectives: During the COVID-19 pandemic, several studies described an increased chance of developing pulmonary embolism (PE). Several scores have been used to predict the occurrence of PE. This systematic review summarizes the literature on predicting rules for PE in hospitalized COVID-19 patients (HCPs).
Methods: PUBMED and EMBASE databases were searched to identify articles (1 January 2020-28 April 2021) presenting data pertaining to the use of a prediction rule to assess the risk for PE in adult HCPs. The investigated outcome was the diagnosis of PE. Studies presenting data using a single laboratory assay for PE prediction were excluded. Included studies were appraised for methodological quality using the Newcastle - Ottawa Quality Assessment Scale for Cohort Studies (NOS).
Results: We obtained a refined pool of twelve studies for five scoring systems (Wells score, Geneva score, CHADS2/CHA2DS2VASc/M-CHA2DS2VASc, CHOD score, Padua Prediction Score), and 4,526 patients. Only one score was designed explicitly for HCPs. Three and nine included studies were prospective and retrospective cohort studies, respectively. Among the examined scores, the CHOD score seems promising for predictive ability.
Conclusion: New prediction rules, specifically developed and validated for estimating the risk of PE in HCP, differentiating ICU from non-ICU patients, and taking into account anticoagulation prophylaxis, comorbidities, and the time from COVID-19 diagnosis are needed.

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Introduction

One and a half years after the beginning of the coronavirus disease 2019 (COVID-19) pandemic, the high morbidity and mortality across the world is still a concern. To date, more than 255 million confirmed cases have been reported, including more than 5.1 million deaths (WHO, 2021). An extenuating effort in research and clinical efforts led to improvements in diagnostic strategies and therapeutics; however, World Health Organization (WHO) data about the case fatality rate across countries are disturbing (Ioannidis, 2021).

Among factors contributing to a worse prognosis in COVID-19 patients, an important role is the increased chance of developing pulmonary embolism (PE) (Klok et al., 2020). As already well known, immobility, inflammatory state, and altered coagulation are factors associated with increased chances of developing deep vein thrombosis (DVT) and PE (Elias et al., 2016). All these factors are common in symptomatic COVID-19 patients, especially during the severe disease state; since the beginning of the pandemic, several studies and case series described the occurrence of PE (Danzi et al., 2020; Suh et al., 2021). Indeed, according to the latest meta-analysis by Suh and colleagues, PE and DVT occurred in 16.5% and 14.8% of patients hospitalized for COVID-19, respectively (Liao et al., 2020; Suh et al., 2021). Notably, more than half of the patients with PE lacked DVT (Suh et al., 2021).

In COVID-19, two distinct pathophysiological mechanisms are believed to independently and simultaneously cause PE: immobility and local immune thrombosis (Van Dam et al., 2020). The first

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pathological mechanism is characterized by blood stasis, the leading risk factor for thromboembolic genesis. The second is to be ascribed to pulmonary microvascular endothelial damage, associated with systemic and local proinflammatory factors, in turn leading to a coagulation cascade. Evidence suggests that some patients respond to the infection by an immune overactivation, leading to the so-called “cytokine storm” and to activation of the coagulation system, in turn increasing the risk for Acute Respiratory Distress Syndrome (ARDS), Disseminated Intravascular Coagulation (DIC) and PE (Liu et al., 2020). Of note, COVID-19 related PE most commonly involves the basal lung lobes, precisely in areas of ground-glass opacities (GGO) (Van Dam et al., 2020; Mueller-Peltzer et al., 2020).

Thrombotic lesions found in COVID-19-related PE more frequently involve distal, peripheral arteries of the lungs when compared to PE found in non-COVID-19 patients (Van Dam et al., 2020). Together with a typically decreased total clot burden, as expressed through the Qanadli score (Qanadli et al., 2001), these elements brought researchers to hypothesize a different PE phenotype in COVID-19 patients (Van Dam et al., 2020).

PE in COVID-19 patients is seen at various phases during the illness and can occur despite thromboembolic prophylaxis with low molecular weight heparin (LMWH) (Helms et al., 2020). The insidious onset of PE has led to the need for clinicians to frequently monitor D-dimer , inflammatory markers, and clinical symptoms to identify early signs of PE, promptly perform imaging diagnostics, and eventually start anti-thrombotic treatment.

Before the COVID-19 pandemic, the most used scores to predict PE in the general population were the Geneva and the Wells scores, used either alone or combined with D-dimer (Guo et al., 2015). Several scores have been adapted or used after the beginning of the COVID-19 pandemic due to the increasing occurrence of PE in hospitalized COVID-19 patients (HCP). However, several flaws hamper the extensive use of predictive scores, especially in the context of COVID-19: i) the uneven predictive ability of available scores, in terms of sensitivity and specificity; ii) some of these scores contain variables that are not screened outside of a few limited settings, such as in the case of interleukins; iii) predictive scores are often developed in the context of research projects and are seldom validated in clinical settings.

Despite these limitations, using scores to identify patients at risk for this complication could represent an added value to the clinical management of COVID-19.

Since a wide variety of predictive scores are available, with different sensitivities and specificities, tested in several settings in patients with heterogeneous clinical characteristics, we performed a systematic review of published data on a prognostic model to predict the risk for PE in COVID-19. We aimed at providing a comprehensive picture of predictive values, including the pros and cons of each score, and to give suggestions on their use in clinical practice.

Methods

Article identification

Studies concerning the use of at least one prediction rule to assess the risk for PE in HCPs were identified through computerized literature searches using free text searching, MEDLINE (National Library of Medicine Bethesda MD), EMBASE, and by reviewing the references of the retrieved articles.

Index search terms included the Medical Subject Heading "Covid-19," "pulmonary embolism," and "score." The search term lines are available in the supplementary material.

The search was restricted to English language articles. The literature search period ranged from 1 January 2020 to 28 April 2021. No attempt was made to obtain information about unpublished studies. Reviewed articles were recorded in a master log, and any reason for exclusion from the analysis was documented in the rejected log. The systematic review was reported according to the 2020 Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines (Page et al., 2021).

Inclusion and exclusion criteria

Studies were considered eligible if they presented data about using a prediction rule to assess the risk for PE in adult HCPs with laboratory-confirmed SARS-CoV2 infection. The investigated outcome was the diagnosis of PE. Studies presenting data on using a single laboratory assay for PE prediction, such as D-dimer , C-reactive protein (CRP), ferritin, etc., and imaging diagnostics alone, such as Lung Ultrasound (LUS), were excluded.

Observational studies were considered eligible if randomized controlled trials (RCTs) were unavailable. Reviews, letters, editorials, abstracts, and case reports were excluded. Studies gathering data for less than ten patients were excluded as well.

Data extraction

Data extraction was performed independently by two investigators (S.A.M. and L.V.R). Each investigator was blinded to the other investigator’s data extraction. In the case of disagreement between the two reviewers, a third reviewer was consulted (MAC). Data from each study were entered into a standardized form, verified for consistency and accuracy, and entered into a computerized database.

Abstracted information included: country and period in which patients’ enrollment took place; number and setting of enrolled patients; patient characteristics, including relevant demographic variables; criteria for selecting patients to be assessed with imaging studies; imaging technique used to assess the presence of PE; the number of patients with PE confirmed at imaging; the number of patients completing follow up; type of scores used for the prediction, including the reported threshold, statistical information about the predictive ability of the score used with sensitivity/specificity and/or AUC of the Receiver Operating Characteristic (ROC) when available.

No automatic tool was used during any phase of the present study.

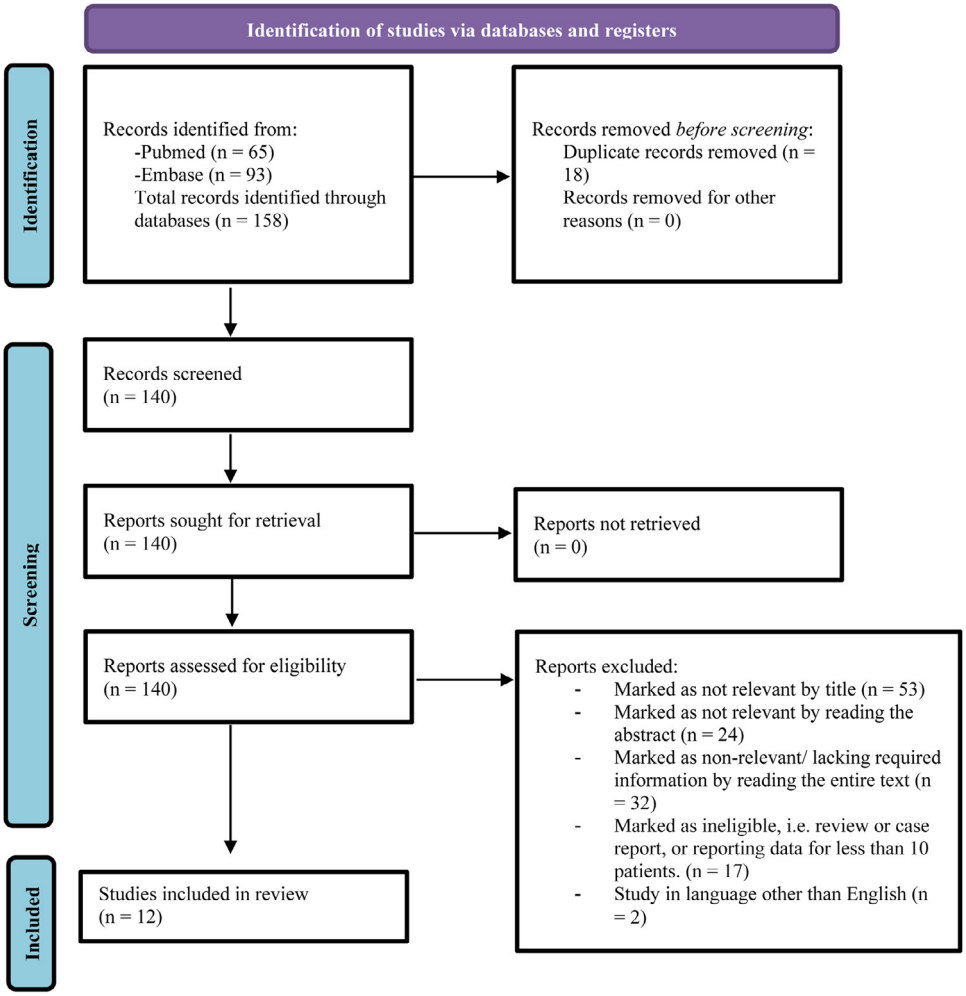
Quality assessment

Included studies were appraised for methodological quality independently by two authors (S.A.M. and L.V.R.) without blinding to journal or study authorship. If required, discrepancies were resolved by discussion or involvement of a third review author.

The quality of observational studies was assessed using the Newcastle - Ottawa Quality Assessment Scale for Cohort Studies (NOS). Detailed assessment of the risk of bias via NOS table is available in the supplemental material in S1.

Results

Our search retrieved 158 articles, of which twelve were eventually included (Whyte et al., 2020; Baccellieri et al., 2021; Monfardini et al., 2020; Zotzmann et al., 2020; Kirsch et al., 2021; Melazzini et al., 2020; García-Ortega et al., 2021; Fang et al., 2020; Scardapane et al., 2021; Polo Friz et al., 2021; Kampouri et al., 2020; Caro-Codón et al., 2021), comprising 4,526 HCPs. Figure 1 shows the selection process of studies included in the systematic review.



Figre 1. PRISMA chart for identification of studies.

Study description

A summary description of the included studies is reported in Table 1 and Table 2. Among the twelve studies, three prospective cohort and nine retrospective cohort studies were included. Eleven studies assessed the presence of PE using CTPA; one used perfusion (Q)-single-photon emission computed tomography (Q/SPECT) instead.

Table S1 shows the quality appraisal of the included studies.

In our search, five prediction rules were identified. Only one was explicitly designed for HCPs; the remaining were already in use before the COVID-19 pandemic. Table 3 reports the prediction rules and the variables included in these scoring systems. The Wells score was the most frequently used, found in eight out of twelve studies.

Kirsch et al. validated the utility of the Wells score in predicting PE in a retrospective cohort of 64 HCPs (median age 54.9 years, 54.7% males), twelve of whom developed PE. In this study, a Wells score above four was significantly associated with PE development (p= 0.04), even though four out of twelve patients with PE had a score of zero (Kirsch et al., 2021). The AUC-ROC curve for the prediction of PE in HCPs, calculated for an optimal value of Wells score between one and two, was 0.54 (Kirsch et al., 2021).

Another study found no significant correlation between Wells score and PE in a cohort of 43 HCPs (median age 65 years, 51.16% males) (Scardapane et al., 2021). Similar findings were confirmed by Whyte and colleagues in a cohort of 214 HCPs (median age 61 years, 60.28% males). These authors did not find a significant association between the Wells score and the probability of having PE. Of the main components of the Wells score, only the presence of DVT signs and symptoms was found to be significantly associated with PE ($p = 0.0017$) (Whyte et al., 2020).

In a retrospective cohort study of 34 HCPs (median age 61 years, 77% males) with a moderate-to-high pre-test probability of PE, as suggested by Wells score $\geq$ 4, 76% of the subjects showed signs of PE on a computerized tomographic pulmonary angiogram (CTPA) ($n = 26$) (Monfardini et al., 2020).

In a retrospective study of 443 HCPs (median age 68.68 years, 57.7% males), Kampouri et al. found that a Wells score $\geq$ 2 in combination with a D-dimer value $\geq$ 3000 ng/L provided a very specific predictive rule with a sensitivity of 57.1%, and a specificity of 91.6%. A Wells score $\geq$ 2 combined with a D-dimer value $\geq$ 1000 ng/L provided a more sensitive prediction rule, with a sensitivity of 92.9% and a specificity of 46.9%. Furthermore, PE was less likely upon admission in cases where the Wells score was $\leq$ 2 and the D-dimer value was $\leq$ 1000 ng/ml (Kampouri et al., 2020).

Zotzmann et al. evaluated all patients retrospectively with SARS-CoV2 associated ARDS admitted to ICU (20 HCPs, median age 61.6 years, 70% males) utilizing the Wells score plus Lung Ultrasound (LUS). The study reports a predictive ability approaching 100% of sensitivity and 80% specificity when a threshold of $>$ 2 for the Wells score was used and predicted PE with an AUC of 0.944.

Table 1
Characteristics of studies included in the systematic review.

Author [ref]	Time frame for enrolling patients	Country	Study design	Sex (% of males)	Age (years, median)	Total number of included HCPs	Total number of HCPs with PE	Selection of cohort	Setting
Whyte et al., 2020	March to May 2020	UK	Retrospective cohort	60.28	61.05	214	80	All patients undergoing CTPA	Mixed, including ICU
Baccellieri et al., 2021	April 2020	Italy	Prospective cohort	71	62	200	35	Consecutive HCPs	Mixed, including ICU
Monfardini et al., 2021	March 2020	Italy	Retrospective cohort	NA	NA	34	26	All patients undergoing CTPA	Mixed, including ICU
Zotzmann V. et al., 2020	March to May 2020	Germany	Retrospective cohort	70	61.6	20	12	All patients with ARDS, a CTPA, a LUS	ICU only
Kirsch B. et al., 2021	February to July 2020	USA	Retrospective cohort	54.7	54.9	64	12	All patients undergoing CTPA	Mixed, including ICU
Melazzini F. et al., 2020	March to April 2020	Italy	Retrospective cohort	68	70	259	4	All HCPs	Mixed, including ICU
Garcia-Ortega A. et al., 2021	March to April 2020	Spain	Prospective cohort	71	65.4	73	26	All patients undergoing CTPA + D-dimer	Mixed, including ICU
Fang C. et al., 2020	March to April 2020	UK	Retrospective cohort	64.51	59.2	93	41	All patients undergoing CTPA	Mixed, including ICU
Scardapane et al., 2021	March to April 2020	Italy	Retrospective cohort	51.16	65	43	15	All patients undergoing CTPA	Wards admitting COVID-19 patients besides ICU
Scardapane et al., 2021	March to April 2020	Italy	Retrospective cohort	51.16	65	43	15	All patients undergoing CTPA	Wards admitting COVID-19 patients besides ICU
H Polo Fritz et al., 2021	April 2020	Italy	Retrospective cohort	27	71.7	41	8	All patients undergoing CTPA + reduction in p/f ratio >30%	Wards admitting COVID-19 patients besides ICU
Kampouri et al., 2020	February to April 2020	Switzerland	Retrospective cohort	57.78	68.68	443	27	All HCPs	Mixed, including ICU
Caro-Codòn et al., 2021	March to April 2020	Spain	Prospective cohort	54.9	62.3	3042	75	All COVID-19 patients accessing ER	Mixed, including ICU

Key: HCPs= hospitalized COVID-19 patients; PE= Pulmonary embolism; ICU= Intensive care unit; CTPA= CT pulmonary angiogram; ARDS= Acute respiratory distress syndrome; LUS= Lung ultrasound; COVID-19 (coronavirus disease 2019).

Table 2
Prediction ability of scores in included studies

Author [ref]	Score, Threshold	Threshold used in the study	Sensitivity	Specificity	AUC ROC	p-value (univariate association between PE and score)	Relevant information derived from the study
Whyte et al., 2020	Wells, ≥ 4	≥4	NA	NA	NA	0.951	Wells score was not able to predict PE in HCPs
Baccellieri et al., 2021	Padua, ≥4	≥4	NA	NA	NA	0.026	Padua score ≥ 4 was significantly associated with PE on univariate analysis
Monfardini et al., 2021	Wells, ≥ 4	≥4	NA	NA	NA	NA	Among patients with Wells ≥ 4, 76% had PE on imaging; 24% had imaging negative for PE
Zotzmann V. et al., 2020	Wells + Lung US	≥2	100%	80%	0.944	0.042	Wells score ≥2 + positive lung US is able to predict PE in HCPs
Kirsch B. et al., 2021	Wells, ≥ 4	>4	NA	NA	0.54	0.04	Wells score was associated with PE in HCPs; nevertheless, it was not able to predict it.
Melazzini F. et al., 2020	Padua, ≥4	>4	NA	NA	NA	0.4	100% with PE had Padua >4 (only 4 patients had pulmonary embolism among the sample).
Garcia-Ortega A. et al., 2021	CHOD score	0-2: 4.5% PE; 3-5: 36.8% PE; 6-7: 100% PE	NA	NA	0.86	HR (p = 0.036); Room-air SatO2 (p = 0.041); D-dimer (p = 0.022); CRP (p = 0.037)	CHOD score was able to predict PE in HCPs
Fang C. et al., 2020	Wells, ≥ 4	>4	NA	NA	NA	0.801	Wells score was not able to predict PE in HCPs
Scardapane et al., 2021	Wells, ≥ 4	Wells, ≥ 4	NA	NA	NA	Wells (0.17)	Wells score did not correlate to PE in HCPs
Scardapane et al., 2021	Revised Geneva ≥ 4	Revised Geneva ≥ 4	NA	NA	Revised Geneva (0.727)	Revised Geneva (p = 0.013)	Revised Geneva score was able to predict PE in HCPs
H Polo Fritz et al., 2021	"Simplified Wells", ≥ 2	"Simplified Wells", ≥ 2	"Simplified Wells", ≥ 2 + age adjusted D-dimer : 88%	"Simplified Wells", ≥ 2 + age adjusted D-dimer : 18%	NA	0.851	"Simplified" Wells score was not able to predict PE in HCPs
Kampouri et al., 2020	Wells ≥ 4 + d dimer	Wells ≥ 2 + d dimer ≥ 3000 ng/L	57.10%	91.6%	NA	NA	When diagnostic imaging for PE is not possible, empiric therapeutic anticoagulation should be considered if Wells score ≥ 2 + D-dimer ≥ 3000 ng/L
Caro-Codòn et al., 2021	CHADS2, CHA2DS2-VASc and the M-CHA2DS2VASc; ≥ 2	CHADS2, CHA2DS2-VASc and the M-CHA2DS2VASc; ≥ 2	NA	NA	(0.497), CHA2DS2-VASc (0.490) and the M-CHA2DS2VASc (0.541)	NA	No tested score was able to predict PE in HCPs

Key: AUC-ROC= Area under curve – receiver operating characteristics; PE= Pulmonary embolism; HCPs= hospitalized COVID-19 patients; NA= Not Available; US= Ultrasound; CHOD = C-reactive protein, Heart rate, Oxygen saturation, D-dimer ; HR= Heart rate; CRP= C-reactive protein; CHA2DS2-VASc= CHF, Hypertension, Age, Diabetes, Stroke, Vascular diseases.

Table 3
Prediction rules for PE in HCPs: included variables and value attributed to each included variable.

	WELLS SCORE	REVISED GENEVA SCORE	PADUA SCORE	M-CHA2DS2-VASC	CHOD score
Variables included	**Numeric value attributed to each included variable**				
Acute infection/Autoimmune disease			1		
D-dimer ≥ 956 ng/mL					2
Thrombophilia			3		
O2 Sat ≤ 92%					2
Blood Pressure (↑)/(↓)				1	
HR (↑)/(↓)*	1.5	3-5			2
Diabetes				1	
CRP ≥ 50mg/L					1
Cardiac or Respiratory Failure			1	1	
BMI>30			1		
Lower limb pain		3			
Lower limb edema		4			
Previous DVT/PE	1.5	3	3	2	
Clinical signs of DVT	3				
PE is the most likely diagnosis	3				
Surgery/fracture lower limb <1mo prior	1.5	2	2		
Hypomobility < 3 days prior			3		
Hemoptysis	1	2			
Stroke/MI			1	2	
Active malignancy	1	2	3		
Gender				1	
Vasculopathy				1	
HRT			1		
Age (↑)		1	1	0-2	
SCORE RANGE	0-12.5	0-22	0-20	0-9	0-7
THRESHOLD	> 4	moderate risk > 4; high risk > 11	> 4	> 2	moderate risk > 3; high risk > 5

Key: CHA2DS2-VASc= CHF, Hypertension, Age, Diabetes, Stroke, Vascular diseases; CHOD = C-reactive protein, Heart rate, Oxygen saturation, D-dimer ; HR = Heart Rate; CRP= C-reactive protein; BMI= Body mass index; DVT = Deep Vein Thrombosis; PE = Pulmonary Embolism; MI= Myocardial Infarction; HRT = Hormone Replacement Therapy.

* Note: In the CHOD score, points for heart rate are attributed when ≥ 90bpm; in the revised Geneva score, the same applies if 75-94bpm (3 points) or ≥ 95bpm (5 points).

Furthermore, the Wells score was found significantly higher in PE patients than non-PE patients (2.7 ± 0.8 vs. 1.7 ± 0.5 respectively, p= 0.042) (Zotzmann et al., 2020).

Fang and colleagues performed a retrospective analysis of COVID-19 patients undergoing CTPA. In this study, based on a cohort of 93 HCPs (median age 59.2 years, 64.51% males) who underwent a CTPA (41 positive for PE), a high Wells score was not able to predict PE (Fang et al., 2020).

Polo Fritz and colleagues performed a similar study, based on 41 HCPs (median age 71.7 years, 73% females) undergoing CTPA. Eight patients were found to have PE at imaging. The Wells score was found not clinically useful (Polo Friz et al., 2021).

Two studies evaluated the use of the Padua Prediction Score (PPS).

Baccellieri and colleagues, in a prospective study including 200 consecutive HCPs (median age 62 years, 71% males), found an association between PE and the PPS ≥ 4 by univariate analysis (p= 0.026) (Baccellieri et al., 2021).

Melazzini et al. confirmed similar findings in a retrospective cohort study involving 259 COVID-19 patients (median age 70 years, 68% males); in this study, no patient with PE had a PPS below 4. Nevertheless, it is worth mentioning that only four patients in the examined cohort were diagnosed with PE (Melazzini et al., 2020).

Scardapane et al. reported the ability of the revised Geneva score in predicting PE in a retrospective cohort with 43 COVID-19 patients, all undergoing CTPA as inclusion criteria. In this cohort, 35% of patients had PE. The Revised Geneva Score was significantly higher in PE patients than in non-PE patients (mean 4±2 vs. 2 ± 2, p= 0.01). The AUC-ROC for the predictive ability of the Revised Geneva score was 0.727 (95% CI of 0.525-0.929) (Scardapane et al., 2021).

Caro-Codòn and colleagues published a prospective observational study including 3042 COVID-19 patients (median age 62.3 years, 54.9% males) and assessing the utility of CHADS2, CHA2DS2-VASc, and the M-CHA2DS2VASc, acronyms made of the variables used for its calculation, i.e., congestive heart failure, hypertension, age ≥ 75 years, diabetes, TIA/Stroke/Thromboembolism, vascular disease, age 65-75, gender category; the M version is designed to assign an extra point for male sex (Melgaard et al., 2015). No score showed a significant correlation with PE in COVID-19 patients. All three above-mentioned scores showed poor predictive value for PE (AUC 0.497, 0.490, and 0.541, respectively) (Caro-Codón et al., 2021).

Our search identified only one study designed to predict PE in HCPs, i.e., the CHOD score, acronym of CRP concentration + Heart rate + Oxygen saturation + D-dimer levels. Patients with an elevation in D-dimer were randomly selected from a cohort of 372 HCPs; 73 patients were included (median age 65.4 years, 71% males) and underwent CTPA assessment. PE was diagnosed in 35.6% of them. A multivariate analysis showed that heart rate [Hazard ratio (HR), 1.04], oxygen saturation in room-air (spO2) (HR, 0.87), D-dimer (HR, 1.02), and CRP levels (HR, 1.01) at the time of admission, were independent predictors of PE in HCPs. The AUC-ROC method was used to determine the diagnostic value of each selected quantitative variable, and dichotomized variables were included in another multivariable logistic regression to construct the CHOD score. This score showed a high predictive value (AUC-ROC of 0.86; 95% CI: 0.8 to 0.93) (García-Ortega et al., 2021). Furthermore, the CHOD score was able to stratify patients into three risk groups, low (0-2 points), moderate (3-5 points), and high risk (more than 5 points), with a PE rate of 4.5%, 36.8%, and 100%, respectively (García-Ortega et al., 2021).

Discussion

The importance of assessing a predictive score for PE stems from the need to promptly diagnose acute thrombotic complications in HCPs, thus reducing an adverse outcome. Indeed, routinely

performing CTPA for all HCPs would be costly, time-consuming, poorly feasible, and risky for both patients and operators. Candidate selection for contrast imaging is, therefore, a clinical decision based on experience, observation, and laboratory findings. *Ad hoc* prediction tools could help select patients who would benefit from CTPA more efficaciously.

Our systematic review found twelve studies assessing the role of five clinical scores in predicting PE in HCPs.

The most frequently used score in studies included in our systematic review was the Wells score. It has been extensively used to predict PE for over twenty years and is still used today for stratifying the general population into three groups. i.e., low (1.3% prevalence), moderate (16.2% prevalence), and high risk (37.5% prevalence), according to their pre-test chance of developing PE (Wells et al., 1997). The score had an AUC of the ROC calculated for predicting PE in the general population of 0.632 (CI 0.574–0.691) (Coelho et al., 2020).

In the studies included in our review, heterogeneous results on the Wells score were obtained. Five studies did not report a significant association between this score and the risk of PE in HCPs. The only study reporting the AUC of the ROC for Wells score predicting ability for PE in HCPs was calculated to be equal to 0.54 when used alone (Kirsch et al., 2021).

It has been hypothesized that the low prediction ability of the Wells score in HCPs might be correlated with the PE pathophysiological mechanism in HCPs. Indeed, PE might result from direct endothelial cell injury by viral action or from an inflammatory reaction secondary to the alveolar damage (Scardapane et al., 2021). Therefore, scores designed for investigating PE as a principal diagnosis, rather than a complication of another pathology (i.e., COVID-19), may not be the best option in these patients (Fang et al., 2020). This hampers the predictive ability of the Wells score, mainly because it stems from the assumption that PE results from a DVT. COVID-19-related PE is most frequently a pulmonary local phenomenon and not a result of immobilization or DVT. In fact, 85% of PE cases were not associated with DVT at US of the lower limbs, as described by Monfardini and colleagues (Monfardini et al., 2020).

Regardless of the use in HCPs, the main limitation of the Wells score pertains to the inclusion of a subjective opinion of the physician among variables, i.e., "PE is the most likely diagnosis," as already described by Klok and colleagues (Klok et al., 2008). Especially in COVID-19 management, physicians will most often suspect PE if patients present with hypoxemia and tachycardia, *de facto* limiting the utility of this score in predicting PE (Kirsch et al., 2021).

A non-accurate history taking could also lead to a miscalculation of the Wells score, as highlighted by Whyte and colleagues, who found a poor predictive ability in HCPs (Whyte et al., 2020).

Of note, it has been reported that the concomitant use of the Wells score and D-dimer would enhance the sensitivity and specificity of the test (Zhang et al., 2020; Girardi et al., 2020; Touhami et al., 2018; Kampouri et al., 2020).

Regarding other scores utilized in studies included in our review, the usefulness of PPS in predicting PE in HCPs was evaluated in two studies (Baccellieri et al., 2021; Melazzini et al., 2020). The PPS has been validated before COVID-19 to identify the need for anticoagulation in hospitalized patients based on their risk of VTE (Barbar et al., 2010). Results appear to confirm the utility of PPS in HCPs only when the score is $\geq$4. Nevertheless, a more extensive prospective study would be necessary to clarify the predictive ability of PPS in predicting PE in HCPs.

The revised Geneva score includes risk factors, such as age, previous PE/DVT, surgery in the month before the admission, active malignant condition, and symptoms, including hemoptysis and unilateral lower-limb pain. In the general population, a score below 4 suggests a low clinical probability of PE (<10%); a score between 4 and 10 defines an intermediate-risk group (10-60%), and a score $\geq$ 11 a high-risk group (>60%) (Le Gal et al., 2006; Wicki et al., 2001). In HCPs, the performance of the revised Geneva score appears to be reasonably satisfactory, with an AUC of the ROC of 0.727; however, the variable with the highest predictivity in this study was the mean D-dimer value (Scardapane et al., 2021).

CHA2DS2-VASc is a score used in atrial fibrillation to clinically stratify patients according to their risk of developing ischemic stroke or thromboembolism (Lip et al., 2010). Caro-Codón and colleagues evaluated these scores in HCPs reporting poor predictive ability and no correlation between CHADS2, CHA2DS2-VASc, and the M-CHA2DS2VASc and PE (Caro-Codón et al., 2021). Thus, their usefulness for predicting PE in HCPs is very limited, and these scores do not deserve to be further assessed in HCPs.

Among the examined scores, the CHOD score seems promising in terms of predictive ability. This score was developed explicitly for HCPs and is calculated on a few routinely extracted elements. However, only one study described its use, and no validation study was developed yet.

It is worth highlighting that included studies showed several flaws. First of all, most of these studies enrolled subjects who already underwent CTPA, undermining the correct representation of the at-risk population, thus introducing a potential selection bias. Moreover, most studies were retrospective, and importantly, not designed to evaluate the score's predictive ability. Many of them did not report all relevant data for evaluating the predictive ability of scores and often lacked a multivariate analysis.

An additional limitation is represented by the study population; most of the studies included a mixed cohort, i.e., ICU and non-ICU patients, hampering the possibility to evaluate the role of scores in predicting PE in critically ill patients. Furthermore, the LMWH prophylaxis effect on preventing PE was not evaluated systematically. Most of the studies were issued in the early period of introduction of LMWH prophylaxis to all HCPs (Kulkarni et al., 2020); therefore, LMWH prophylaxis may not have been routinely performed in the clinical practice for HCPs.

PE is substantially contributing to the severity burden of COVID-19, both in the short and the long term. As the majority of PE cases in COVID-19 do not result from DVT, new prediction rules, specifically developed and validated for estimating the risk of PE in COVID-19, are needed. Findings of the CHOD score seem interesting, but future studies are needed to validate such scores in clinical practice on a larger scale. Scores should differentiate ICU from non-ICU patients and should consider anticoagulation prophylaxis, comorbidities exposing the HCP to an increased risk of developing PE, and the time from COVID-19 diagnosis.

Authors' Contributions

NP and LVR conceived and designed the study. LVR, SAM, and DRD were responsible for data collection. LVR and MAC wrote the initial manuscript. NP, MAC, and LVR critically revised the manuscript. All authors have read and approved the final manuscript.

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Declaration of competing interest

NP received honoraria for lectures from MSD, Pfizer, Johnson & Johnson, Becton & Dickinson, Shionogi; the other authors have no competing interests.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2021.11.038.

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