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Redefining the Wells criteria for pulmonary embolism to include Covid-19

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Pulmonary embolism (PE) is a potentially life-threatening clinical condition that occurs when there is a disruption to blood flow in the pulmonary artery or its branches by a thrombus that originated elsewhere in the body, usually from a deep vein thrombosis (DVT), but it can also occur due to embolization from other material into the pulmonary circulation such as air, fat, or tumor cells. (1) PE can present variably and nonspecifically, with findings that include but are not limited to cough, shortness of breath, tachycardia, pleuritic chest pain, hemoptysis, presyncope, syncope, and even hemodynamic instability and cor pulmonale. (2) The risk of mortality from PE is up to 30% in untreated PE and 8% in PE with timely treatment. (3,4) Furthermore, PE is associated with 100,000 deaths in the United States annually. (5) Therefore, early recognition is crucial to prevent drastic complications.

Several risk scores have been developed to assist in the recognition of PE. The Pulmonary Embolism Rule-out Criteria (PERC), initially created in 2004, derived a scoring system using 8 important variables to allow the clinician to rule out PE if no criteria are positive and the pretest probability is <15% with the goal of decreasing unnecessary testing for PE in emergency room settings. (6) The Geneva Criteria is similar, using 8 objective variables, to help predict the likelihood of PE on presentation. (7) Lastly, one of the most commonly used scores is the Wells criteria for pulmonary embolism, which objectifies the risk of PE using seven variables: clinical signs and symptoms of DVT, PE is the most likely diagnosis or equally likely, heart rate >100 beats per minute, immobilization of at least 3 days or surgery in the previous 4 weeks, previous objectively diagnosed PE or deep vein thrombosis, hemoptysis, and malignancy with treatment within 6 months or palliative. (8) This particular scoring system and the clinical variables selected were validated in a study after logistic regression analysis was performed on 40 clinical variables with these 7 prospectively validated in inpatients and outpatients with suspected PE as they were determined to have the highest odds ratios of all the variables analyzed. (8,9)

The accuracy of Wells criteria for pulmonary embolism has been validated by numerous external studies. One of the most robust of these is known as the Christopher study. (8,10) In this prospective cohort study of 3,306 patients with suspected PE at 12 centers in the Netherlands, using this clinical decision rule with these particular variables and their assigned scores, a clinical decision rule score of 4 or less points were determined as “unlikely” to have PE while scores greater than 4 were determined as “likely” to have PE. (10) Using the clinical decision rule, a total of 2,206 patients were identified as unlikely to have PE while 1,100 were identified as likely to have PE. The 2,206 patients identified as unlikely to have PE then underwent D-dimer testing. If the D-dimer test result was within the reference range (less than 500 ng/ml), PE was excluded as a diagnosis; this occurred in 1,057 patients. In this group, 5 nonfatal venous thromboembolism (VTE) events occurred during the 3-month follow-up period. The remaining 1,149 patients in this category had D-dimer test results greater than 500 ng/ml and thus met the indication to undergo computed tomography (CT) along with the 1,100 pa-

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tients determined as likely to have PE (clinical decision rule score greater than 4). Thus, a total of 2,249 patients met the indication to undergo CT. Of these, 1,505 patients had PE excluded, 674 patients had PE confirmed, 20 patients had inconclusive results, and 50 patients did not undergo CT. Of the 1,505 patients that had PE excluded on CT, at 3-month follow-up 11 patients had nonfatal VTE and 7 patients had fatal PE. Of the 674 patients with confirmed PE, at 3-month follow-up 9 patients had nonfatal VTE and 11 had fatal PE. Of the 20 patients with inconclusive CT results, at 3-month follow-up, 1 patient had nonfatal VTE. Of the 50 patients who did not undergo CT, 1 had nonfatal VTE and 1 had fatal PE. Regarding the discriminatory performance of the clinical decision rule developed by Wells, the area under the receiver operating curve (ROC) of the original Wells rule was 0.744 (95% CI, 0.724-0.764). (9)

A systematic review and meta-analysis comparing the above scoring criteria showed that they have comparable accuracy with the most extensively validated rules being the Wells score and the Geneva criteria. (11)

Since the emergence of Coronavirus 2019 (Covid-19), several studies have reported a higher risk of PE in patients with Covid-19. It is thought that the Covid-19 virus induces coagulopathy by direct infection of endothelial cells via angiotensin-converting enzyme 2 (ACE 2) receptors resulting in a massive release of plasminogen activators and cell damage. (12) A study by Xie et al. attempted to elucidate the short-term risk of VTE in patients with ambulatory Covid-19. Using a cohort of outpatient 18,818 Covid-19 positive patients compared to matched uninfected participants, it was found that Covid-19 infection was associated with an increased risk of VTE in the first 30 days after symptoms onset (incidence rate 50.99 per 1000 person-years in infected patients vs. 2.37 per 1000 person-years in non-infected patients). (13) Additional independent risk factors for VTE formation in Covid-19 positive patients were older age, male sex, and obesity. They also found the risk of VTE was greatly reduced in patients who were fully vaccinated. (13) In studies looking at critically ill patients, it has been identified that there was a connection between Covid-19 infection and VTE; however, it has been hard to quantify the incidence as critically ill patients are complex and changes in Covid-19 management may influence the rate of thrombosis. In a multicenter retrospective study by Al Samkari et al. involving 400 hospitalized Covid-19 patients of the 36% who became critically ill, 9.5% had confirmed or suspected venous or arterial thrombotic events, which was lower than reported in previous studies. (14)

As such, several studies have recommended anticoagulation of patients with Covid-19 to prevent VTE. A multiplatform trial published in 2021 in the New England Journal of Medicine (NEJM) looked at using therapeutic dose anticoagulation for critically ill patients hospitalized with Covid-19. (15) Patients were risk stratified into severe disease (intensive care unit [ICU] level care) or moderate disease (hospitalized but not critically ill). These patients were randomly assigned to receive either therapeutic dose anticoagulation with low-molecular-weight heparin or usual care thromboprophylaxis for up to 14 days or until recovery (defined as a hospital discharge or discontinuation of supplemental oxygen for at least 24 hours). The primary outcome was organ support-free days at day 21. This trial was stopped when the prespecified criteria for the superiority of therapeutic dose anticoagulation were met. (15) In non-critically ill patients, therapeutic anticoagulation increased the probability of survival until hospital discharge and reduced the need for ICU-level organ support compared to thromboprophylaxis; this was true regardless of the baseline D-dimer level. There was an increased incidence of major bleeding in the anticoagulation group (1.9% vs. 0.9%). (15) However, the authors did not find a benefit in critically ill patients, defined as those requiring ICU-level care at enrollment. (15) In these patients, there has been a debate about the benefit of anticoagulation, and the timing of starting anticoagulation seems to be a major determinant of the benefits. A multicenter retrospective cohort study by Al-Banaa et al. which included 578 critically ill patients admitted to the ICU found that when adjusted for characteristics associated with mortality (i.e., older age, gender, body mass index [BMI], race, comorbidities, and disease severity), a higher anticoagulant dose “therapeutic” was independently associated with lower inpatient mortality. (16) Guidelines published by the American Society of Hematology (ASH) last updated in February 2022 acknowledged the increased risk of VTE in Covid-19 in select patient populations but recommended against empiric therapeutic anticoagulation for VTE prevention in critically ill populations citing no benefit for preventing the progression of Covid-19 or death. (17) It did however conditionally suggest using therapeutic intensity over prophylactic intensity anticoagulation for patients with Covid-19 without suspected or confirmed VTE. (17) Similarly, the recommendations from the National Institutes of Health (NIH) recommend the use of therapeutic heparin in patients with D-dimers above the upper

limit of normal who require low-flow oxygen and who do not have an increased risk of bleeding. (18) It is important to note that one limitation of these studies was that a majority of them were performed prior to Omicron and even Delta strain outbreaks. Nonetheless, the evidence is overwhelmingly supportive of the association between Covid-19 and VTE. Therefore, this important thrombogenic risk factor should be included in future risk stratification of patients presenting with symptoms and signs suggestive of PE. We suggest redefining the Wells score to include Covid-19 and suggest naming the modified score as "the Wells-19 score". Prospective studies are encouraged to investigate and validate the proposed score.

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