The diagnostic management of suspected pulmonary embolism in special patient populations

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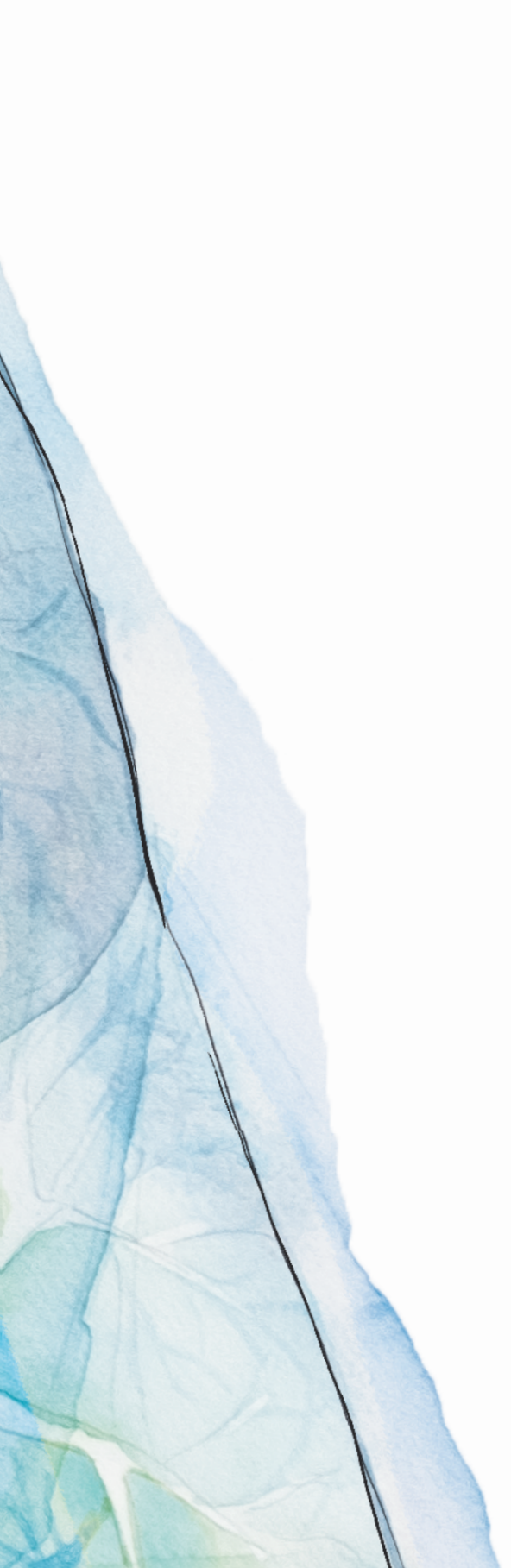

1

General introduction and outline of this thesis

GENERAL INTRODUCTION AND OUTLINE OF THIS THESIS

Pulmonary embolism (PE) is a serious and sometimes life-threatening condition that refers to a blood clot that occludes the arteries of the lung.[1] PE is a clinical presentation of venous thromboembolism (VTE), which also comprises deep-vein thrombosis (DVT) of the extremities.[1] Annual incidence rates of PE range from 39 to 115 per 100,000 population[2] and VTE is globally the third most common cause of cardiovascular mortality, exceeded only by stroke and myocardial infarction.[3] Early diagnosis and initiation of adequate treatment is of paramount importance, since delay in diagnosis and treatment initiation will result in poor outcome.

The list of predisposing factors for VTE is extensive, including surgery, cancer, inflammatory disorders, (respiratory tract) infections and pregnancy.[4] Since the outbreak of the new coronavirus-induced severe acute respiratory disease (COVID-19), many studies have reported high incidences of VTE in hospitalized patients with COVID-19, aggravated by admittance to the Intensive Care Unit (ICU).[5-10] An accurate and timely diagnosis of VTE in patients with COVID-19 is of importance too, as VTE is a key contributor to the rapid deterioration of patients with severe COVID-19.

Despite all improvements over the past decades, diagnosing PE is still a difficult process due to the non-specific symptoms, which can frequently overlap with symptoms of other cardiopulmonary diseases.[11] Currently recommended diagnostic strategies for suspected acute PE consist of standardized assessment of the clinical pre-test probability (CPTP) using validated clinical decision rules (CDRs) and D-dimer testing.[1] PE is considered safely ruled out in patients with a non-high CPTP and a normal D-dimer test. Imaging tests as computed tomography pulmonary angiography (CTPA) are required in the case of a high CPTP and/or abnormal D-dimer test to confirm the diagnosis.[12,13] Recently, D-dimer thresholds dependent on age and CPTP were developed (i.e. applying a higher threshold in patients above 50 years of age and in patients with low CPTP, respectively).[14-17] These adapted D-dimer thresholds improve the efficiency of the diagnostic strategy and reduce the need for imaging tests, thereby minimizing the exposure to potentially harmful radiation and contrast material.[18,19] The focus of this thesis is twofold and concentrates on the diagnostic management of patients with suspected PE and venous thrombotic complications in patients with COVID-19.

The first part of this thesis describes the challenges of diagnosing PE in general and in specific clinically relevant patient subgroups. **Chapter 2** focuses on the diagnostic challenges in patients with cancer, elderly patients and patients with renal insufficiency. Diagnosing PE in these patients is particularly challenging, for multiple reasons. First

of all, imaging tests are often relatively contra-indicated or known to yield more non-diagnostic test results.[20] D-dimer levels are often elevated in the absence of thrombosis, thereby limiting the ability to rule out PE without imaging in these patients.[20-22] Importantly, as adapted D-dimer thresholds improve efficiency of the CDR/D-dimer combination, this chapter reviews the available evidence on applying age-adjusted or CPTP-dependent D-dimer thresholds in these patients. Unfortunately, studies on strategies with adapted D-dimer thresholds in patient subgroups are limited and the studies that are available present inconclusive or conflicting results, as they were often underpowered to perform reliable subgroup analyses. To address this knowledge gap, we set out to evaluate the safety and efficiency of various diagnostic strategies for suspected PE across clinically relevant patient subgroups defined by sex, age, cancer, and previous VTE in a large international individual patient data meta-analysis (IPDMA). Diagnostic strategies under evaluation in this study were the Wells rule and revised Geneva score with fixed and adapted D-dimer thresholds, and the YEARS algorithm, a strategy with a D-dimer threshold dependent on CPTP. The results of this meta-analysis with individual patient data from 20,553 patients with suspected PE are presented in **Chapter 3**.

Chapter 4 concentrates on the diagnostic approach of suspected PE in patients during pregnancy. Pulmonary embolism is a dreaded complication of pregnancy as it is one of the leading causes of maternal death in developed countries.[23] The threshold to test for PE during pregnancy is low, but uncertainty exists about whether non-invasive diagnostic strategies can be applied safely during pregnancy. This chapter describes the results of an IPDMA evaluating the performance of non-invasive diagnostic strategies for ruling out PE in pregnant patients. More recently, a new diagnostic strategy for suspected PE was developed. This new strategy, called the 4-Level Pulmonary Embolism Clinical Probability Score (4PEPS), integrates different aspects from the currently available strategies.[24] In **Chapter 5**, we externally validated the 4PEPS in a post-hoc analysis of the YEARS study.[16] An overview of the most widely used and validated diagnostic strategies for suspected PE, with their specific advantages and disadvantages, is given in **Chapter 6**. This chapter serves as a practical guide for clinicians on the best diagnostic approach of patients with suspected PE, overall and across patient subgroups. In **Chapter 7**, we evaluated the performance of the generic National Early Warning Score (NEWS) compared to the (simplified) Pulmonary Embolism Severity Index ((s)PESI) for prediction of early ICU admission and mortality in patients with a recent diagnosis of acute PE.

The second part of this thesis focuses on venous thrombotic complications in hospitalized patients with COVID-19. Despite all the evidence on the high thrombotic risk in patients with COVID-19, it was unknown how this risk compared to the thrombotic risk in patients hospitalized with other virus infections, as some studies suggested a

SARS-COV-2 virus specific procoagulant effect.[25-27] Therefore, the aim of **Chapter 8** was to evaluate the incidence of venous and arterial thrombotic complications in hospitalized patients with influenza as compared to that observed in hospitalized patients with COVID-19. Although frequently encountered, guidance on the best diagnostic approach of suspected PE in the setting of COVID-19 was lacking. Diagnosing PE in patients with COVID-19 is particularly challenging as symptoms of both conditions show wide overlap, elevated D-dimer levels are a common finding in the absence of thrombosis[10] and imaging tests may not always be feasible due to severe renal insufficiency or hemodynamic instability. Moreover, especially at the beginning of the pandemic, there were concerns about performing imaging tests in COVID-19 patients posing a risk towards infection transmission to other patients and healthcare staff. **Chapter 9** describes these difficulties and discusses available evidence and guidelines on the application of non-invasive diagnostic strategies for ruling out PE in patients with COVID-19. Until recently, diagnostic strategies for suspected PE were not prospectively validated in the setting of COVID-19. In **Chapter 10**, we present the results of a prospective multicenter study evaluating the YEARS algorithm in patients with (suspected) COVID-19 and clinically suspected PE.

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