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Delayed anticoagulation is associated with poor outcomes in high-risk acute pulmonary embolism

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ABSTRACT

Purpose: Early diagnosis and timely treatment are essential to improve the outcomes of pulmonary embolism (PE), but no study has investigated the impact of anticoagulation timing on clinical outcomes in high-risk acute PE patients. We analyzed the relationship between early anticoagulation initiation and in-hospital mortality in high-risk acute PE patients at the intensive care unit (ICU) of a teaching hospital.
Materials and methods: Seventy-three PE patients admitted to the ICU were included in this retrospective study. Demographic, clinical, radiological, and therapeutic data were collected on ICU admission, and the timings of diagnosis and anticoagulation initiation were analyzed.
Results: The number of survivors was 67. The median time from hospital arrival to the start of anticoagulation therapy was significantly lower in survivors (3.6 [2.6-5.0] hours) than nonsurvivors (5.7 [4.5-14.9] hours; $P = .03$). However, the median time required to achieve a therapeutic anticoagulation level was comparable between survivors and nonsurvivors (12.0 [9.5-19.5] vs 16.4 [10.7-27.4] hours; $P = .488$). Ventilatory support and vasopressor use were found to be associated with higher in-hospital mortality.
Conclusions: Delayed anticoagulation is an important prognostic factor of poor outcomes in high-risk acute PE patients.

1. Introduction

Acute pulmonary embolism (PE) continues to be an important cause of in-hospital mortality despite recent advances in diagnostics, especially computed tomographic (CT) pulmonary angiography, and therapeutic modalities, and it may become rapidly fatal if not diagnosed and treated early [1–6]. The 2014 European Society of Cardiology guidelines for the management of PE categorize this condition as high, intermediate, and low risk. High-risk patients, who have shock or hypotension, have a greater than 15% mortality rate during the first 30 days after PE, whereas intermediate-risk patients, who have right ventricular dysfunction or myocardial injury, have a 3% to 15% and low-risk patients have a less than 1% mortality rate [7,8]. Both the 2014 guidelines of the European Society of Cardiology and the 2012 guidelines of the American College of Chest Physicians recommend immediate anticoagulation with unfractionated heparin for the treatment of high-risk PE.

Study has proposed the presence of a "golden hour" for timely management of high-risk PE, which can affect outcomes like trauma, myocardial infarction, and stroke [9]. Several reports focusing on treatment of PE using unfractionated heparin have found that the timing of anticoagulation is related to the outcome [10,11]. However, to our knowledge, no study has investigated the relationship between the timing of anticoagulation and the outcome of acute high-risk PE. Smith et al [11] reported an association between early anticoagulation and reduced mortality among patients with acute PE, but not all the patients had high-risk PE and 23% of them did not even require intensive care unit (ICU) admission. Al Otair et al [12] reported the clinical and demographic characteristics of patients with acute PE admitted to the ICU, but they did not consider the impact of the timing of anticoagulation on the outcome. Data on the predictive risk factors of in-hospital mortality in ICU patients with acute PE are also limited. Because high-risk PE patients are fragile and have hemodynamic instability, immediate anticoagulation and identification of prognostic factors are important for improving their clinical status. Therefore, in the present study, we examined how the timing of anticoagulation is related to mortality among patients with acute PE admitted to the cardiac or medical ICU,

Abbreviations: IVC, inferior vena cava; IQR, interquartile range; CHF, chronic heart failure; COPD, chronic pulmonary obstructive disease; CT, computed tomography; ICU, intensive care unit; ED, emergency department; PE, pulmonary embolism; SBP, systolic blood pressure; aPTT, activated partial thromboplastin time; RV, right ventricle; LV, left ventricle.

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specifically the period from the hospital visit to the start of anticoagulation (time to anticoagulation). Furthermore, we attempted to identify risk factors and clinical and demographic characteristics of patients with acute PE admitted to the cardiac or medical ICU as well as factors associated with a poor prognosis.

2. Materials and methods

This study was approved by the institutional review board. We retrospectively reviewed a cohort of adult patients with a primary diagnosis of PE who were admitted to a teaching hospital during a 4-year period. *Acute PE* was defined as a filling defect seen on CT angiography in patients presenting to the emergency department (ED) or cardiologic outpatient clinic with symptoms consistent with pulmonary artery hypoperfusion or infarction (ie, dyspnea, chest pain, lightheadedness, or syncope). Patients were excluded if they were admitted to the general ward, if diagnosis and treatment procedures were conducted before hospital arrival, or if anticoagulation was contraindicated. Patients who refused treatment, those initially treated with low–molecular-weight heparin, or those who were diagnosed with sepsis during the same hospitalization period were also excluded. The decision regarding ICU admission was based on the presence of shock or hypotension in the ED (systolic blood pressure [SBP] <90 mm Hg for at least 10 minutes or the need for inotropic support). All patients were initially treated on the basis of a weight-based intravenous (IV) heparin nomogram similar to the one described by Raschke et al [13].

A data entry form was designed to collect demographic, clinical, and laboratory data on arrival to the hospital. This form included age; sex; clinical presentation; risk factors (*obesity* defined as body mass index >25, immobility, recent surgery within 8 weeks, trauma, and current cigarette smoking); and comorbidities, namely, coronary artery disease, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), cancer, nephritic syndrome, connective tissue diseases, antiphospholipid syndrome, history of venous thromboembolism or coagulopathy, and cerebrovascular diseases. In addition, vital signs (heart rate, SBP, body temperature, and respiratory rate), electrocardiographic and laboratory findings (white blood cell count; levels of D-dimer, troponin T, and creatinine; and arterial blood gas concentration), and echocardiographic findings (presence of right ventricular [RV] dysfunction and left ventricular [LV] ejection fraction) were recorded. A *positive troponin T level* was defined as greater than 0.014 ng/mL; and a *positive D-dimer level*, as greater than 500 ng/mL. Thrombolytic agent (tissue plasminogen activator) use, inferior vena cava (IVC) filter insertion, and surgical embolectomy were noted as other therapeutic modalities. Medical records were reviewed to determine the initial time of starting anticoagulation therapy (IV heparin) and the time to achieve a therapeutic activated partial thromboplastin time (aPTT). The primary outcome was in-hospital all-cause mortality, and the secondary outcomes were hospital and ICU lengths of stay and the factors associated with in-hospital mortality. The time of heparinization was determined by reviewing the drug administration records and documentation from the ED or admitting physicians. Laboratory draw times were reviewed to determine the interval between hospital arrival and the time of the first achievement of *therapeutic aPTT*, which was defined as 1.5 times the baseline aPTT or at least 50 seconds, similar to the one described by Smith et al [11]. A *hemorrhagic event when the patient was on IV heparin* was defined as acute blood loss of at least 2 g/dL of hemoglobin that required cessation of heparin and transfusion.

All data were analyzed using SPSS 18.0 for Windows (SPSS, Chicago, IL) except the cutoff points regarding time to anticoagulation, which were examined using SAS version 9.2 (SAS Institute, Cary, NC). To derive the cutoff point, we used the technique of Contal and O'Quigley with the log-rank test statistic to estimate the cut point and its significance [14]. The log-rank test and Kaplan-Meier analysis were used to examine the associations between the time to start anticoagulation and in-hospital survival. Median values are reported with interquartile ranges (IQRs) because the data were not normally distributed. Categorical data were analyzed using Fisher exact test or the χ^2 test, and continuous data were analyzed using the Mann-Whitney test. To determine in-hospital mortality predictors, the parameters were first evaluated using univariate logistic regression analysis. Odds ratios were computed together with their 95% confidence intervals. *P* values less than .05 were considered statistically significant.

3. Results

Search of the Severance Hospital electronic medical records yielded 73 patients who met the aforementioned criteria for acute PE between 2008 and 2012 (Fig. 1). The number of survivors was 67. The median age was 69 years (IQR, 50.5-75.0), and 49.3% patients were men. The in-hospital mortality rate was 8.2%. The patients were admitted to the ICU for hypotension, hypoxemia, RV dysfunction, or comorbidities. Dyspnea, chest pain, and cough were the main presenting symptoms in 64 (87.7%), 25 (34.2%), and 9 (12.3%) patients, respectively. The median hospital length of stay was 9.0 days (IQR, 6.0-11.5), and the median ICU length of stay was 2.0 days (IQR, 1.0-3.0). The median time from hospital arrival to CT diagnosis was 2.7 hours (IQR, 2.1-4.3), and at least 16 patients (21.9%) were administered IV heparin before CT diagnosis.

The clinical presentations, risk factors, and comorbidities of the study group are shown in Table 1. Obesity was the most common risk factor, followed by malignancy (53.4% and 16.4%, respectively). Delayed anticoagulation and low initial systolic blood pressure were univariate predictors of in-hospital mortality in the present cohort (Table 2). The median time from hospital arrival to the start of anticoagulation therapy was significantly lower in survivors (3.6 [2.6-5.0] hours) than nonsurvivors (5.7 [4.5-14.9] hours; $P = .03$; Fig. 2). However, the median time from hospital arrival to achievement of therapeutic aPTT was similar between survivors and nonsurvivors (12.0 [9.5-19.5] vs 16.4 [10.7-27.4] hours; $P = .488$). Twelve patients did not receive IV heparin within 6 hours from admission, and this delay was caused by delayed diagnostic results because of unusual symptoms, known underlying disease, delayed recovery from shock, or refusal to undergo diagnostic testing for several hours. Three patients were intubated and 11 needed vasopressor supports, both of which were associated with high in-

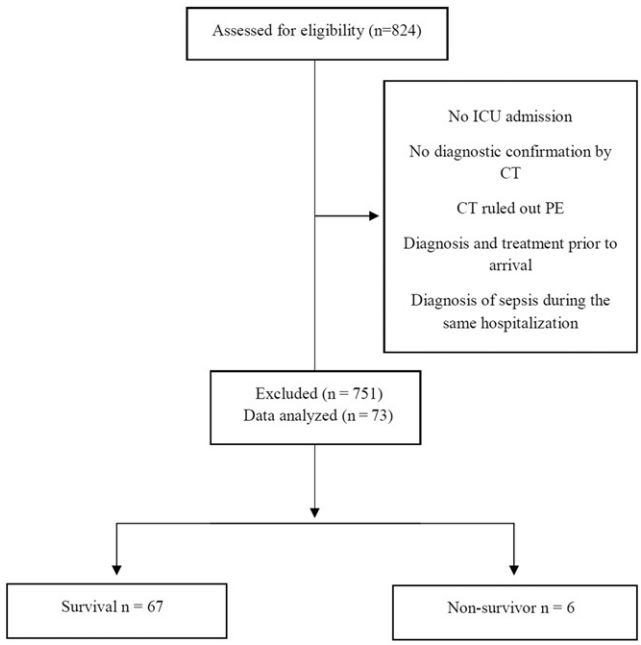

Fig. 1. Patient enrolment into the study (using CONsolidated Standards of Reporting Trials [CONSORT] recommendations).