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D-Dimer and thrombus burden in acute pulmonary embolism ☆

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ABSTRACT

Background: Thrombus burden in pulmonary embolism (PE) is associated with higher D-Dimer-levels and poorer prognosis. We aimed to investigate i) the influence of right ventricular dysfunction (RVD), deep venous thrombosis (DVT), and high-risk PE-status on D-Dimer-levels and ii) effectiveness of D-Dimer to predict RVD in normotensive PE patients.
Methods: Overall, 161 PE patients were analyzed retrospectively, classified in 5 subgroups of thrombus burden according to clinical indications and compared regarding D-Dimer-levels. Linear regression models were computed to investigate the association between D-Dimer and the groups. In hemodynamically stable PE patients, a ROC curve was calculated to assess the effectiveness of D-Dimer for predicting RVD.
Results: Overall, 161 patients (60.9% females, 54.0% aged >70 years) were included in this analysis. The D-Dimer-level was associated with group-category in a univariate linear regression model (β 0.050 (95%CI 0.002–0.099), P = .043). After adjustment for age, sex, cancer, and pneumonia in a multivariate model we observed an association between D-Dimer and group-category with borderline significance (β 0.047 (95%CI 0.002–0.096), P = .058). The Kruskal-Wallis test demonstrated that D-Dimer increased significantly with higher group-category.
In 129 normotensive patients, patients with RVD had significantly higher D-Dimer values compared to those without (1.73 (1.11/3.48) vs 1.17 (0.65/2.90) mg/l, P = .049). A ROC curve showed an AUC of 0.61, gender non-specific, with calculated optimal cut-off of 1.18 mg/l. Multi-variate logistic regression model confirmed an association between D-Dimer >1.18 mg/l and RVD (OR2.721 (95%CI 1.196–6.190), P = .017).
Conclusions: Thrombus burden in PE is related to elevated D-Dimer levels, and D-Dimer values >1.18 mg/l were predictive for RVD in normotensive patients. D-Dimer levels were influenced by DVT, but not by cancer, pneumonia, age, or renal impairment.

1. Introduction

An acute pulmonary embolism (PE) is a crucial event and a cardiovascular emergency with high morbidity and mortality [1-6]. Pathologically, thrombotic material (embolus) occludes partly the pulmonary artery bed [1,4,6,7]. Large pulmonary artery emboli with >50% occlusion of the pulmonary vascular tree are commonly accompanied by right ventricular dysfunction (RVD) and a consecutively impaired left ventricular filling resulting in reduction of cardiac output with arterial hypotension and syncope/collapse [1,2,4,7-13]. These signs of hemodynamic compromise are connected with elevated morbidity and mortality [1-4,6,7,10-12,14-18].

D-Dimer is one of the diagnostic parameters for PE and deep venous thrombosis (DVT) [7,19,20]. Plasma D-Dimer is a degradation product of cross-linked fibrin [7,21-23] and D-Dimer values are elevated in the presence of acute clots due to the simultaneous activation of coagulation and fibrinolysis [7,22]. Normal D-Dimer values exclude an acute PE in hemodynamically stable patients with high probability [7,21].

Computed tomography (CT) studies suggest that higher D-dimer levels are associated with significantly higher clot burden in pulmonary arteries [24-26].

In addition, some study results have revealed that elevated D-Dimer levels were related to an increased mortality rate or complications [22,23,27-31]. In two previously published papers concerning our study cohort we found apparently contrary results. In the first paper no association was identified between D-Dimer and RVD among patients with PE who were hemodynamically stable or un-stable [6];

☆ The study was conducted in St. Vincenz and Elisabeth Hospital Mainz (KKM).

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whereas in a second paper a relationship was detected between D-Dimer and PE severity status, according to recent European Society of Cardiology (ESC) guidelines [7] in patients with PE who were hemodynamically stable [32].

To summarize these results, we hypothesized that D-Dimer levels are obviously related to clot burden in the pulmonary artery bed, but may also be affected by thrombus burden in the deep veins due to DVT.

Thus, the objectives of this current study were to investigate the influence of DVT, RVD, and high-risk PE status on the D-Dimer level in patients with PE as well as D-Dimer level to predict RVD in normotensive patients with PE.

2. Methods and patients

Consecutive patients with a confirmed diagnosis of acute PE were included in a retrospective analysis. All patients were treated at the Internal Medicine Department of our hospital in the 5-year period between May 2006 and June 2011. The patients with PE were identified by a search of the hospital information system database for the diagnostic code of PE (ICD-Code: I26).

Studies in Germany involving retrospective analysis of diagnostic standard data do not require an ethics statement.

2.1. Included subjects

Patients were eligible for this study based on the following:

i. if the diagnosis of PE was confirmed by a detected filling defect in the pulmonary artery system on a CT pulmonary angiogram of the chest, a scintigraphic ventilation-perfusion (V/Q) scan read as high probability for PE, or positive venous ultrasound/phlebography of an extremity consistent with deep venous thrombosis (DVT) in patients with typical symptoms of PE (chest pain or dyspnoea) and positive D-dimer levels;
ii. if patients were treated in the Internal Medicine Department of the hospital;
iii. if patients were at least 18 years old;
iv. if the patients had D-Dimer levels measured during the acute phase.

All CT, scintigraphic, and phlebography images were analyzed by experienced radiologists.

2.2. Routine diagnostic strategy

The routine diagnostic strategy followed the recommendations of the ESC guidelines from 2008 [7]. In hemodynamically stable patients with suspected PE the CT scan was the primary diagnostic tool to confirm PE diagnosis. In cases of impaired renal function a V/Q scan was used to make the diagnosis. In a minority of patients, especially in multi-morbid patients with suspected PE, a confirmed DVT with additional typical symptoms of PE and positive D-Dimer value were considered adequate to establish the diagnosis of PE. Transthoracic echocardiography (TTE) and laboratory examinations of cardiac troponin I (cTnI) were intended for all patients with suspected and confirmed PE, but were not performed in all patients with PE.

2.3. Definitions

2.3.1. Definition of cardiac injury

Myocardial injury was defined as cTnI elevation >0.4 ng/ml according to the American Heart Association (AHA) scientific statement from 2011 [33].

2.3.2. Definition of right ventricular dysfunction (RVD)

RVD was defined according to the AHA scientific statement [33] as a quotient of right ventricular (RV) septal-lateral diameter/left ventricular (LV) septal-lateral diameter >0.9 in the four-chamber view on TTE or CT [33]. Additionally, RVD was defined as RV hypokinesis and tricuspid regurgitation or a systolic pulmonary artery pressure >30 mm Hg on TTE [33].

2.3.3. High-risk PE

Patients with PE with a systolic blood pressure <90 mm Hg at admission were classified as high-risk PE according to the definition from the recent and current ESC guidelines [7,34] and the AHA scientific statement [33].

2.3.4. Elevated creatinine

An elevation in creatinine was defined according to gender as >1.3 mg/dl in men and >1.1 mg/dl in women.

2.3.5. Tachycardia

Tachycardia comprised a heart rate ≥100 beats per minute.

2.4. Study outcome measures

The study outcomes were all-cause in-hospital death and occurance of RVD.

2.5. Study groups

The patients with PE in our study were classified into 5 subgroups according to suspected thrombus/embolus clot burden according to clinical indications. The lowest clot burden was expected in hemodynamically stable PE patients without both RVD and DVT. These patients were included in group 1. The second group comprised hemodynamically stable PE patients with DVT, but without RVD. Group 3 consisted of hemodynamically stable PE patients with RVD, but without DVT. The fourth group included hemodynamically stable PE patients with both RVD and DVT. The highest clot burden was suspected in group 5 comprising the patients with high-risk PE [7].

2.6. Statistics

We compared the 5 groups using the chi-squared test to analyze the trend between the groups for categorical variables and the Kruskal-Wallis test to compare the groups regarding the D-Dimer values. Univariate and multivariate (adjusted for age, sex, cancer, and pneumonia) linear regression models were provided to investigate the association between the D-Dimer values and the groups regarding increasing clot burden. Results were presented as Beta coefficients (β) and 95% confidence intervals (CI). We computed univariate logistic regression models in order to analyze the associations between D-Dimer and the parameters age >70 years, sex, creatinine elevation, VTE events in patients' medical history, pneumonia, DVT, and cancer. Results were presented as Odds Ratios (OR) and 95%CI.

For the second part of the study, we focused on hemodynamically stable PE patients with an accurate TTE. Among these, we compared normotensive patients with and without RVD regarding D-Dimer and the outcome of in-hospital death. We computed a multivariate logistic regression model (adjusted for age, creatinine kinase, creatinine, and tachycardia) to investigate the association between D-Dimer and RVD in these patients.

In addition, we performed receiver operating characteristic (ROC) curves with areas under the curves (AUC) and Youden indices to test the effectiveness of D-Dimer values to predict RVD in TTE.

The software SPSS® (version 22.0; SPSS Inc., Chicago, Illinois) was used for the majority of computerized analysis. For the calculation of the ROC curve with AUC and Youden cut-off values, R version 2.14.1

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