Original Article

Predictors for Prognosis in Patients With Nonfatal Pulmonary Embolism: A Registry-Based Cohort Study

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Abstract

The article's aim was to determine predictors for short- and long-term prognosis of patients with pulmonary embolism (PE). Cohort prospective study based on the National registry on venous thromboembolism. Eighty-four patients with PE, on age 60.3 + 12.5 years, were selected and followed up in a prospective study. Pulmonary embolism was confirmed by computed tomography angiography in all the patients, while deep venous thrombosis was confirmed by ultrasound in 21 patients. Study population was followed up for 6.7 months. Multivariate regression analysis was done where right ventricular (RV) diameter (mean 37.5 mm), systolic pulmonary artery pressure (68 ± 23 mm Hg) measured by echocardiography, D-dimer level at baseline 2654.5 ± 420.3 ng/mL, number of comorbidities (2.4 ± 0.7), and present symptoms (3.1 ± 0.9) entered the model. The model was age-adjusted. D-dimer level was revealed as a predictor for the length of hospitalization ($\beta = .25$, $P = .05$) and RV diameter as a factor for duration of anticoagulation ($\beta = .29$, $P = .05$). Our results imply that the baseline measurement of these parameters independently influence both the short-term and long-term prognosis of patients with nonfatal PE.

Keywords

pulmonary embolism, venous thromboembolism, prognosis, D-dimers, echocardiography

Introduction

Pulmonary embolism (PE) is a fatal condition, especially in the first month. Mortality is between 3% in those patients with isolated deep venous thrombosis (DVT), up to 11% in patients presented clinical PE. The long-term prognosis (from 1-12 months) is determined with rate of recurrence and bleeding. Many models included comorbidities and risk factors to determine the probability of occurrence (Wels, Geneve), and prognosis of this condition (Pulmonary Embolism Severity Index score and Computerized registry of patients with venous thromboembolism [RIETE]). D-Dimer levels could be used for diagnosis of venous thromboembolism (VTE). Echocardiographic parameters (right ventricular diameter, tricuspid annular plane systolic excursion, and tricuspid regurgitation) by European and American Societies have been demonstrated as useful tools in high-risk PE for its diagnosis.[1-3] The article was aimed to determine predictors for short- and long-term prognosis of patients with PE.

Patients and Methods

Eighty-four patients with PE, from the National registry on VTE (age 60.3 + 12.5 years), were selected in a prospective study. The National registry is a multicenter nonrandomized survey of patients with PE with or without DVT. Pulmonary embolism was confirmed by computed tomography (CT) angiography in all of them, and DVT was confirmed by ultrasound in 21 patients.

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Inclusion Criteria

Consecutive patients with symptomatic PE, with or without DVT were included. Venous thromboembolism was confirmed by compression ultrasound (for DVT) and multislice CT scan (PE). All patients (or their relatives) provided written or oral consent for participation in the registry, in accordance with local ethics committee requirements.

The following baseline data were collected at the time of inclusion in the study: age; gender; body weight; clinical presentation (DVT or PE as the first presentation); presence of comorbidities including chronic heart or lung disease; recent major bleeding (<30 days prior to VTE); concomitant medications, including antiplatelet drugs, statins, or steroids; presence of major provoking risk factors for VTE including active cancer (defined as newly diagnosed cancer, metastatic cancer, or cancer undergoing treatment), recent immobility (defined as nonsurgical patients assigned to bed rest with bathroom privileges for $\geq$4 days 2 months prior to VTE), surgery (2 months prior to VTE), leg trauma or fracture, use of hormonal therapy, pregnancy, or puerperium; and laboratory results including full blood count and serum creatinine levels (Table 1). Information on thrombophilia testing, when available, was also documented.

Treatment and Follow-Up

Eighty-four consequent patients with PE, from the National registry on VTE (age 60.3 + 12.5 years), were selected in a prospective study. The study population was followed up for 6.7 months.

Patients were managed according to the clinical practice of each participating hospital (ie, there was no standardization of treatment). The type, dose, and duration of anticoagulant therapy were recorded. Nine (10.71%) patients were treated with novel anticoagulants (NOAC) (rivaroxaban), 49 (58.33%) patients with unfractionated heparin, and 26 (30.96%) patients with low-molecular heparin, in the acute phase. Treatment was observed as NOAC in 19% (16 patients) and vitamin K antagonists in 81% (68 patients).

Patients were followed up for the first month and up to 6 months in the outpatient clinic. During each visit, any signs or symptoms suggesting PE recurrences or bleeding and complications were noted. Each episode of clinically suspected recurrent PE was evaluated by repeat compression ultrasonography, lung scans, helical-CT scan, or pulmonary angiography as appropriate. Length of hospitalization during the acute phase and total duration of anticoagulation were followed up by the physician, according to clinical stability of patient and level of the D-dimer test. Negative D-dimer tests after 3 to 6 months follow-up were criteria to stop anticoagulation. Most outcomes were classified as reported by the clinical centers. However, if staff at the coordinating center were uncertain how to classify a reported outcome, that event was reviewed by a central adjudicating committee (less than 10% of events).

Table 1. Basic Characteristics of Study Population.

Variables	Value
Age, years	60.26 + 13.54
D-dimer, ng/mL	2654.46 + 1309.67
RV diameter, mm	29.38
Length of hospitalization, days	12.11
SPAP, mm Hg	68 + 23
No symptoms	2.67
Creatinine	105 + 12 mmol/L
Leukocytes	9.5 + 1.3 × 1000/mm^3
Platelets	307 + 23 × 1000/mm^3

Abbreviations: RV, right ventricular; SPAP, systolic pulmonary artery pressure.

Multivariate regression analysis was done, where variables from Table 1, right ventricular (RV) diameter (mean 37.5 mm, where 39 patients were with RV diameter >30 mm), systolic pulmonary artery pressure (68 $\pm$ 23 mm Hg, 25 patients with value >40 mm Hg), as measured by echocardiography, D-dimers level at baseline 2654.5 $\pm$ 420.3 ng/mL, number of comorbidities (2.4 $\pm$ 0.7), and occurred symptoms (3.1 $\pm$ 0.9), entered the model. The model was age adjusted.

Results

During the 6 months, 3 adverse events were observed (2 of major bleeding or 2.4%, and 1 of recurrent PE or 1.2%). D-Dimer and number of symptoms entered the model for VTE recurrence (Table 2), despite creatinine level and comorbidities entered model for major bleeding (nonfatal). No independent predictor was found for these adverse events by multivariate model. Herein, D-dimer was revealed as a predictor for length of hospitalization ($\beta = .25$, $P = .05$), where parameters from Table 1 were input into a 1-month follow-up model. Right ventricular diameter was determined as a factor for duration of anticoagulation ($\beta = .29$, $P = .05$), after the ruling out use of D-dimers in 6 months follow-up (presented in Table 3). Our results imply that baseline measurement of these parameters independently influence the 6-month prognosis of patients with nonfatal PE (Table 4).

Discussion

In real clinical practice, more than half of patients with VTE and unprovoked events and more than third of these patients with a transient risk factor receive anticoagulant treatment for more than 12 months. The American College of Chest Physicians (ACCP) guidelines recommend a 3-month treatment duration for patients with VTE, secondary to transient risk factors, and to recommend considering lifelong treatment duration for patients with unprovoked VTE or with cancer.[1] Thus, we found that the duration of anticoagulant therapy often exceeded the recommendations, particularly in patients with transient risk factors for VTE. These ACCP guidelines remain firm in the revisited recommendations of 2016.[2] Our data suggest that in real life, physicians appear to be more concerned

Table 2. Predictive Model for Pulmonary Embolism Recurrence and Major Bleeding.[a]

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std Error	β	*t*	Sig
1	(Constant)	8.307	2.585		3.213	.002
	D-Dimer	0.032	0.022	.197	1.441	.156
	Number of symptoms	0.101	0.054	.253	1.868	.067
	Creatinine[b]	0.525	0.645	.102	0.815	.419
	Comorbidities[b]	−2.228	1281	−.213	−1.739	.088

Abbreviations: Std, standard; Sig, significance.
[a]D-dimer and number of symptoms entered the model for VTE recurrence, despite creatinine level and comorbidities entered model for major bleeding (nonfatal).
[b]coefficient of prediction.

Table 3. Predictive Model for 6 Months Follow-Up of Nonfatal Pulmonary Embolism in a Term for Length of Hospitalization and Duration of Anticoagulation.[a]

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std Error	β	*t*	Sig
1	(Constant)	5.208	2.947		1.767	.083
	Age	.019	.042	.056	0.444	.659
	SPAP	.031	.022	.193	1.397	.169
	D-dimer	.001	.000	.255	2.006	.050
	RV	.097	.053	.248	1.814	.046

Abbreviations: RV, right ventricular; Sig, significance; SPAP, mean systolic pulmonary artery pressure measured by echocardiography; Std, standard.
[a]Age, SPAP, and D-dimer entered in a model for length of hospitalization. Right ventricular baseline diameter was predictor in a model for duration of anticoagulation.

Table 4. Predictive Model for 6 Months Follow-Up of Nonfatal Pulmonary Embolism.

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std Error	β	*t*	Sig
1	(Constant)	8.307	2.585		3.213	.002
	SPAP	0.032	0.022	.197	1.441	.156
	RV	0.000	0.004	.293	1.968	.047
	No symptoms	0.525	0.645	.102	0.815	.419
	Comorbidities	−2.228	1.281	−.213	−1.739	.088

Abbreviations: Std, standard error; Sig, significance; SPAP, mean systolic pulmonary artery pressure measured by echocardiography; RV, right ventricular diameter baseline diameter; No symptoms, number of symptoms.

about the risk of bleeding than about the risk of recurrent PE episode after discontinuing therapy. Yet, in our study population, the rate of PE recurrences and the rate of major bleeding during the course of anticoagulation were not significantly different: major (but nonfatal) bleeds clearly was 2.4% and recurrent embolism 1.2%.

The European Society of Cardiology (ESC) in 2014 hoped to cement the concept of intermediate-risk PE, with their 2014 guidelines critically reviewing the combinations of imaging (echocardiographic or CT angiography) parameters and laboratory biomarkers that can be used to detect right ventricular dysfunction and/or myocardial injury.[3] Taking into account that both imaging and laboratory tests have shown consistent prognostic value, individually and in concordance with each other,[4,5] the ESC guidelines aimed to discourage uncritical time and resource-consuming laboratory and echocardiographic testing in every confirmed patient with PE with no prior triage and instead suggested a stepwise classification of early risk.[3] Lankeit et al in 201, specifically took the risk stratification value of the biomarker N-terminal probrain natriuretic peptide together with a clinical score and the echocardiographic measurement of right ventricular dysfunction to optimize their model of risk stratification.[4] Jiménez et al in 2013 used a derivation and validation cohort to design a final model to use multiple biomarkers along with a clinical score and lower limb ultrasound testing.[5] In this regard, it was proposed that D-dimer testing may identify patients in whom anticoagulation can be safely discontinued, particularly, with serial

measurements combined with evidence of residual thrombosis.[6] Palareti et al in 2014 used persistently negative D-dimer values to discontinue half of the suitable patients, while monitoring all the patients with lower limb ultrasound testing. Their values reaffirmed that serial D-dimer values hold a firm predictive value for recurrent VTE. Likewise, recurrence scores have a place in the prognosis of VTE, where Tosetto et al evaluated a proposed recurrence score in therapy,[7] Eichinger et al and Rodger et al both used D-dimer measurements to supplement the prognostic value of their recurrence scores.[7-9] However, a recently published prospective management study questioned the safety of the strategy to discontinue anticoagulant therapy some months after a DVT or PE event.[10] In 410 adults aged 75 years or younger with such a first unprovoked proximal DVT or PE, who had completed 3 to 7 months of anticoagulant therapy, warfarin was stopped if D-dimer test results were negative and was not restarted if results were still negative after 1 month. The study showed that the risk for recurrence was, at least in men, not low enough to justify the discontinuation of anticoagulant therapy; there was imprecision and uncertainty in the female population.[10] Studies are not being done only in the field of biomarkers. Echocardiographic parameters as independent predictors are readily being explored,[11] with an emphasis on different populations[12,13] as well as different combinations of echocardiographic parameters and risk scores as prognostic factors.[14] Many studies in recent years have explored the balance between keeping patients anticoagulated and thrombosis free as opposed to the associated risk of bleeding. Kaatz et al in 2012 explored the challenge of counterbalancing recurrent VTE risk and the risk of bleeding in regard to treatment duration. They concluded that there were notable discrepancies between the observed results and the current guidelines, thereby suggesting further exploration.[15] Similarly, Ageno et al in 2015 analyzed the lack of a firm duration of receiving oral anticoagulants and extrapolated that major bleeding occurred more often than recurrent VTE in patients who had transient risk factors and that fatal bleeding was more frequent than fatal recurrent pulmonary thrombembolism in all population groups, asking the question whether some patients are exposed to an unnecessary risk of bleeding.[16] Moustafa et al in 2017 also built on top of the risk assessment of anticoagulated patients for both VTE recurrences and bleeding events in a subset of populations. They took patients from the RIETE registry, defined 15 000 patients as either more or less sickly (fragile), and the follow-up concluded that these fragile patients, when on anticoagulation, had fewer VTE recurrences and more bleeding events than their nonfragile counterparts.[17] Another study, by Jiménez et al in 2016, relied on the RIETE registry for a large-scale evaluation of mortality after a PE event. They analyzed the temporal trends in risk-adjusted rates in all-cause mortality and PE-related mortality up to 30 days after diagnosis between time frames from 2001 and 2013. They came to the conclusion that there was a decrease in hospital stay, an increase in the use of low-molecular-weight heparin as opposed to unfractionated heparin, an increase in the use of thrombolytic therapy and the implementation of surgical embolectomy, and resultantly all-cause, short-term mortality decreased from 6.6% to 4.9%, and rates of PE-related mortality decreased from 3.3% to 1.8%.[18] Douma et al, in 2012, looked at the viability of reducing the value of the D-dimer cutoff for exclusion of patients older than 50 years suspect for nonhigh probability DVT, in 5 cohorts, from the conventional cutoff value of 500 μg/L to an age-adjusted D-dimer cutoff (patient's age × 10 μg/L in patients >50 years). The results showed a negligible difference in failure rates, between 0.3% and 1.7%, for the age-adjusted cutoff in comparison with 0.2% to 1.6% for the conventional cutoff, proving the effectiveness and applicability of the age-adjusted cutoff.[19] An ongoing prospective cohort study is investigating the value of a rule combining clinical data and D-dimer levels for prediction of a low recurrence risk after unprovoked VTE (NCT00261014). In summary, we consider 2 studies analyzing the prognostic value of bleeding scores. First, the prospective observational cohort study done by Klok et al in 2016 took 5 different bleeding prediction scores that were pitted against each other, with only the HAS-BLED showing good prognostic value after the first week but with none of the scores showing any relevant prognostic value.[20] Second, Riva et al in 2014 analyzed bleeding risk scores and evaluated that only HAS-BLED and the ACCP score held any statistical value but also affirmed that none of the bleeding scores performed better than chance.[21] Both authors stated that the scientific world must look to create new prediction rules in the prediction of bleeding post-VTE.

Our present study has several limitations. A clear limitation present is in relation to the treatment approach. Namely, patients were not treated with a similar approach.[22] There were clear variations present in the treatment plan in accordance with the presence of silent PE at baseline, and this is likely to have been influenced by a physician's assessment of a patient's risk of death. Although treatment varied by the physician's assessment of a patient's risk, it is not likely that local treatment practices exist, as the multiple centers from which the data originates follow the same guidelines. Another possible limitation may be that although the centers included in the study are overall typical centers that would treat PE and VTE patients, any centers involved with the national registry are probably at least partially more inclined to evidence-based management of PE and VTE as opposed to other treatment centers in the country. Similar to the previously cited article, for the same reasons, our results may not be fully replicable in all hospitals in the nation.[13] Since the analysis is done from registry, potential future research can aim to include different imaging parameters in potential diagnostic management studies and consequent follow-up of the patients.

Conclusion

Our results confirmed the predictive value of D-dimers when considered alongside echocardiographic parameters, in relation to the short- and long-term prognosis of patients with nonfatal

PE, in terms of length of hospitalization and duration of anticoagulation.

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