Journal of Thrombosis and Haemostasis, **7**: 1795–1801 DOI: 10.1111/j.1538-7836.2009.03576.x

ORIGINAL ARTICLE

D-dimer levels and 15-day outcome in acute pulmonary embolism. Findings from the RIETE Registry

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To cite this article: Lobo JL, Zorrilla V, Aizpuru F, Grau E, Jiménez D, Palareti G, Monreal M and the RIETE Investigators. D-dimer levels and 15-day outcome in acute pulmonary embolism. Findings from the RIETE Registry. *J Thromb Haemost* 2009; **7**: 1795–801.

Summary. *Background:* A number of variables have been evaluated for risk stratification in patients with acute pulmonary embolism (PE). Whereas increased D-dimer levels have been associated with mortality at 3 months, its role in predicting short-term outcome (the period of time during which any therapeutic decision has to be taken) remains unclear. *Methods:* RIETE is an ongoing, prospective registry of consecutive patients with acute venous thromboembolism. We assessed the prognostic value of D-dimer levels at baseline, measured with an automated latex agglutination test (IL Test D-dimer®), on the 15-day outcome in patients with acute PE. Overall mortality, fatal PE and major bleeding rates were compared by quartile. *Results:* As of February 2008, 1707 patients with acute PE underwent D-dimer testing. Of these, 72 patients (4.2%) died during the first 15 days, 11 (0.6%) had recurrent PE, and 29 (1.7%) had major bleeding. Overall mortality increased with increasing D-dimer levels, from 2.7% in the first quartile (< 1050 ng mL^{-1}) to 7.0% in the fourth quartile (≥ 4200 ng mL^{-1}). The rates of fatal PE and major bleeding also increased. On multivariate analysis, patients with D-dimer levels in the fourth quartile had an increased risk for overall death (odds ratio, 1.8; 95% CI, 1.1–3.2), fatal PE (odds ratio, 2.0; 95% CI, 1.0–3.8) or major bleeding (odds ratio, 3.2; 95% CI, 1.5–7.0). *Conclusions:* PE patients with D-dimer levels in the fourth quartile had an increased incidence of overall death, fatal PE and major bleeding within 15 days both before and after multivariate adjustment.

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Received 29 April 2009, accepted 6 August 2009

Introduction

The use of thrombolysis and the selection of acute pulmonary embolism (PE) patients for outpatient therapy are controversial issues. There is growing evidence that outpatient therapy with low-molecular-weight heparin (LMWH) is effective and safe for many patients with PE [1,2]. Conversely, the benefit of early thrombolysis or other aggressive therapies over heparin appears to only be clear in those patients with a high risk of death during hospital stay [3–9]. However, because thrombolytic therapy doubles the risk of major bleeding [7], careful and simple risk assessment is paramount in the selection of the appropriate treatment strategy for high-risk patients.

A number of clinical models, including serum cardiac biomarkers, echocardiography and chest computed tomography (CT) have been evaluated for risk stratification, but have given conflicting results [10–19]. Increased D-dimer levels at baseline in patients with PE have been associated with thrombus extension and increased mortality at 3 months [20–26], but its ability to predict short-term outcome remains unclear.

The RIETE (Registro Informatizado de Enfermedad TromboEmbólica) initiative is an ongoing, multicenter, international (Spain, France, Italy, Israel and Brazil) observational registry, designed to gather data on the clinical characteristics, treatment patterns and outcome in consecutive patients with symptomatic, objectively confirmed, acute venous thromboembolism [14,15]. The aim of the present study was to assess the predictive value of D-dimer levels measured at baseline for the 15-day outcome in a series of consecutive patients with acute PE.

Patients and methods

Study design

The study population includes consecutive patients with symptomatic PE, confirmed by objective tests (pulmonary angiography, lung scintigraphy or helical CT), that underwent

testing with a turbidimetric immunoassay test (IL Test D-dimer®, Instrumental Laboratory SpA, Milano, Italy) at baseline [27]. Blood specimens were obtained by phlebotomy prior to starting treatment with anticoagulants or thrombolytic agents. Patients with no D-dimer testing and those with D-dimer performed by other assays were excluded. Patients were also excluded if they were currently participating in a therapeutic clinical trial. All patients provided oral consent to their participation in the registry, according to the requirements of the Ethics Committee within each hospital. The therapeutic approach was the decision of the attending physician.

Patients were divided into quartiles according to their D-dimer levels at baseline, and their event rates within 15 days of PE diagnosis were compared by quartile (Table S1). The major outcome was overall mortality; secondary outcomes were fatal PE and major bleeding. Causes of death were determined by the attending physicians. In case of doubt, they addressed the case-report to the Adjudication Committee of the RIETE Registry. Fatal PE, in the absence of autopsy, was defined as any death appearing shortly after PE diagnosis, in the absence of any alternative cause of death. Bleeding complications were classified as 'major' if they were overt and required a transfusion of two or more units of blood, or were retroperitoneal, spinal or intracranial, or were fatal.

Variables and definitions

The following parameters were recorded: patient's baseline characteristics; clinical status, including any coexisting or underlying conditions such as chronic heart or lung disease; risk factors for PE; the type and dose of treatment received upon PE diagnosis; and the outcome during the first 15 days. Immobilized patients were defined in this analysis as non-surgical patients who had been immobilized (i.e. total bed rest with bathroom privileges) for ≥ 4 days in the 2-month period prior to PE diagnosis. Surgical patients were defined as those who had undergone an operation in the 2 months prior to VTE diagnosis.

Data collection and monitoring in RIETE

The attending physicians ensured that eligible patients were consecutively enrolled. Data were recorded on to a computer-based case report form at each participating hospital and submitted to a centralized coordinating centre through a secure website. Encryption of data was used to enhance confidentiality and security. Data quality was regularly monitored and documented electronically to detect inconsistencies or errors, which were resolved by the local coordinators. Data quality was also monitored by periodic visits to participating hospitals, by contract research organizations that compare the medical records with the data in the web. A data audit was performed at periodic intervals. Patient identities remain confidential as they are identified by a unique number assigned by the study coordinating centre responsible for all data management.

Statistical analysis

Odds ratios and corresponding 95% confidence intervals (CI) were calculated for categorical variables. First, the influence of a number of variables on the risk of overall death, fatal PE or major bleeding was tested by a chi-square test for categorical variables, and Student's *t*-test for continuous variables. A *P*-value < 0.05 was considered statistically significant. Candidate variables were selected from clinical variables based on published literature. To measure predictors of outcome, a multivariate analysis was carried out using a forward stepwise logistic regression analysis. Significance level of $P < 0.10$ was considered to include variables and $P > 0.15$ to exclude variables in the final multivariate model. D-dimer levels entered in the model dichotomized as quartile 4 vs. quartile 1–3. Finally, to assess the accuracy of predicting mortality, we assessed the sensitivity, specificity, positive and negative predictive values. All analyses were completed with the Statistical Package for Social Sciences (SPSS) program (version 16.0 for Windows, 2008; SPSS Inc., Chicago, Illinois, USA).

Results

As of February 2008, 10293 consecutive patients with symptomatic PE had been enrolled in RIETE. Of these, 1707 (17%) underwent D-dimer testing using the IL Test D-dimer® (and were included in the study), 5876 (57%) underwent testing with other reagents, and 2710 (26%) were not tested. Fewer patients that underwent D-dimer testing had chronic lung disease, recent immobility, cancer, atrial fibrillation, fatal bleeding, fatal PE or overall death than those patients that were not tested (Table 1). There were no significant differences in baseline characteristics or outcomes between patients tested with the IL Test D-dimer® or with other reagents.

The study population included 765 males and 942 females, aged 14–99 years (mean, 70 years). PE diagnosis was confirmed in 1294 patients (75.8%) with a positive CT scan, in 369 (21.6%) with a high-probability ventilation-perfusion lung scan, and in 44 (2.6%) with intermediate-probability lung scan plus evidence of deep vein thrombosis in the lower limbs. Seventy-two patients (4.2%) died during the first 15 days. Of these, 36 (50%) died of the initial PE, three (4.2%) died of recurrent PE, and one patient died of bleeding. Twenty-nine patients (1.7%) had major bleeding (six had fatal bleeding) but only one of these died during the 15-day study period.

Overall mortality increased with increasing D-dimer levels, from 2.7% in the first quartile (< 1050 ng mL^{-1}) to 7.0% in the fourth quartile (≥ 4200 ng mL^{-1}). The rates of fatal PE and major bleeding also increased with increasing D-dimer levels (Table 2). Patient age, heart rate, hypoxemia, abnormal creatinine levels, and the use of thrombolytic therapy also increased with increasing D-dimer levels (Table 2).

On univariate analysis, female patients and those with chronic heart failure, abnormal creatinine levels, recent immobility, cancer, hypotension, tachycardia, atrial fibrillation and D-dimer levels in the fourth quartile had an increased 15-day

Table 1 Clinical characteristics, therapeutic strategies and outcome in all patients with acute PE, according to D-dimer testing at baseline

	D-dimer IL-test	D-dimer, other reagents	No D-dimer testing
Patients, *n*	1707	5876	2710
Clinical characteristics			
Gender (male)	765 (45%)	2664 (45%)	1274 (47%)
Mean age (years ± SD)	70 ± 15	68 ± 17‡	68 ± 16
PE characteristics			
Systolic BP < 100 mmHg	138 (8.1%)	420 (7.1%)	212 (7.8%)
Arterial PO_2 < 60 mmHg	547 (42%)	1913 (41%)	830 (43%)
15-day outcome			
Major bleeding	29 (1.7%)	105 (1.8%)	54 (2.0%)
Recurrent PE	9 (0.5%)	37 (0.6%)	28 (1.0%)*
Fatal, initial PE	36 (2.1%)	131 (2.2%)	79 (2.9%)*
Fatal, recurrent PE	3 (0.2%)	25 (0.4%)	8 (0.3%)
Overall death	72 (4.2%)	244 (4.2%)	182 (6.7%)‡

Comparisons between patients: *$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$.
Patients with D-dimer tested with IL-test were compared with those tested with other reagents. Patients not tested were compared with those tested.
SD, standard deviation; VTE, venous thromboembolism; BP, blood pressure; PE, pulmonary embolism.

Table 2 Clinical characteristics, therapeutic strategies and outcome in 1707 patients with acute PE, according to their D-dimer levels at baseline

	1st quartile	2nd quartile	3rd quartile	4rth quartile	*P* trend
Patients, *n*	413	440	428	426	
D-dimer levels (ng mL^{-1})	< 1050	1050–2150	2151–4199	≥ 4200	
Clinical characteristics					
Gender (males)	204 (49%)	197 (45%)	186 (44%)	178 (42%)	0.027
Mean age (years ± SD)	66 ± 16	70 ± 15	70 ± 15	74 ± 12	< 0.001
Body weight (kg ± SD)	74 ± 14	75 ± 14	74 ± 16	73 ± 12	N.S.
Underlying conditions					
Chronic lung disease	47 (12%)	64 (15%)	45 (11%)	38 (9.2%)	N.S.
Chronic heart failure	31 (7.9%)	31 (7.4%)	25 (6.1%)	26 (6.3%)	N.S.
Creatinine levels > 1.2 mg dL^{-1}	65 (16%)	91 (21%)	81 (19%)	113 (27%)	0.001
Risk factors					
Postoperative	59 (14%)	52 (12%)	64 (15%)	42 (9.9%)	N.S.
Immobility ≥ 4 days	94 (23%)	116 (26%)	105 (25%)	125 (29%)	N.S.
Cancer	72 (17%)	84 (19%)	79 (18%)	96 (23%)	N.S.
Idiopathic (none of the above)	174 (42%)	180 (41%)	173 (40%)	163 (38%)	N.S.
Prior VTE	56 (14%)	74 (17%)	59 (14%)	56 (13%)	N.S.
PE characteristics					
Systolic BP < 100 mmHg	22 (5.3%)	43 (9.8%)	32 (7.5%)	41 (9.6%)	N.S.
Heart rate > 100 bpm	84 (21%)	144 (33%)	145 (34%)	159 (37%)	< 0.001
Atrial fibrillation	33 (8.7%)	36 (8.9%)	44 (11%)	49 (12%)	N.S.
PO_2 < 60 mmHg (n = 1292)	111 (36%)	147 (43%)	122 (38%)	167 (51%)	0.002
Treatment					
Initial therapy, LMWH	391 (95%)	399 (91%)	396 (92%)	398 (93%))	N.S.
Median LMWH dose (IU d^{-1})	14261	14866	14324	14243	N.S.
Thrombolytics	5 (1.2%)	7 (1.6%)	14 (3.3%)	15 (3.5%)	0.010
Inferior vena cava filter	4 (1.0%)	5 (1.1%)	3 (0.7%)	11 (2.6%)	N.S.
15-day outcome					
Major bleeding	4 (1.0%)	2 (0.5%)	8 (1.9%)	15 (3.5%)	0.001
Fatal bleeding	2 (0.5%)	0	1 (0.2%)	3 (0.7%)	N.S.
Recurrent PE	3 (0.7%)	0	4 (0.9%)	4 (0.9%)	N.S.
Fatal, initial PE	4 (1.0%)	8 (1.8%)	7 (1.6%)	17 (4.0%)	0.005
Fatal, recurrent PE	1 (0.2%)	0	2 (0.5%)	0	N.S.
Overall death	11 (2.7%)	15 (3.4%)	16 (3.7%)	30 (7.0%)	0.002

SD, standard deviation; VTE, venous thromboembolism; BP, blood pressure; PE, pulmonary embolism; LMWH, low-molecular-weight heparin.

mortality, while those with idiopathic PE had a lower death rate (Table 3). Female patients and those with abnormal creatinine levels, immobility, hypotension, tachycardia or D-dimer levels in the fourth quartile also had an increased incidence of fatal PE, while those with idiopathic PE had a lower rate. Finally, female patients, or those aged > 70 years, with chronic heart failure, abnormal creatinine levels or D-dimer levels in the fourth quartile had an increased incidence of

Table 3 Univariate analysis of the risk for overall death or fatal PE

	Overall death			Fatal PE		
	Yes	No	Odds ratio (95% CI)	Yes	No	Odds ratio (95% CI)
Patients, *n*	72	1635		39	1668	
Clinical characteristics						
Age > 70 years	49 (68%)	984 (60%)	1.4 (0.9–2.3)	25 (64%)	1008 (60%)	1.2 (0.6–2.3)
Gender (males)	23 (32%)	742 (45%)	0.6 (0.3–0.9)	10 (26%)	755 (45%)	0.4 (0.2–0.9)
Body weight < 60 kg	11 (15%)	179 (11%)	1.5 (0.7–2.8)	3 (7.7%)	187 (11%)	0.7 (0.2–2.2)
Underlying conditions						
Chronic lung disease	9 (13%)	185 (12%)	1.1 (0.5–2.3)	6 (17%)	188 (12%)	1.5 (0.6–3.7)
Chronic heart failure	9 (13%)	104 (6.6%)	2.1 (1.0–4.4)	5 (14%)	108 (6.7%)	2.2 (0.8–5.8)
Creatinine levels > 1.2 mg dL^{-1}	28 (39%)	322 (20%)	2.6 (1.6–4.2)	13 (33%)	337 (20%)	2.0 (1.0–3.9)
Risk factors						
Postoperative	6 (8.3%)	211 (13%)	0.6 (0.3–1.4)	3 (7.7%)	214 (13%)	0.6 (0.2–1.8)
Immobility ≥ 4 days	36 (50%)	404 (25%)	3.0 (1.9–4.9)	22 (56%)	418 (25%)	3.9 (2.0–7.3)
Cancer	29 (40%)	302 (18%)	3.0 (1.8–4.8)	12 (31%)	319 (19%)	1.9 (0.9–3.7)
Idiopathic	13 (18%)	677 (41%)	0.3 (0.2–0.6)	6 (15%)	684 (41%)	0.3 (0.1–0.6)
Prior VTE	5 (7%)	240 (15%)	0.4 (0.2–1.1)	4 (10%)	241 (14%)	0.7 (0.2–1.9)
PE characteristics						
SBP < 100 mmHg	13 (18%)	125 (7.6%)	2.7 (1.4–5.0)	9 (23%)	129 (7.7%)	3.6 (1.7–7.7)
Heart rate > 100 bpm	38 (53%)	494 (30%)	2.6 (1.6–4.2)	20 (51%)	512 (31%)	2.3 (1.2–4.4)
Atrial fibrillation	16 (25%)	146 (9.6%)	3.1 (1.7–5.7)	7 (19%)	155 (10%)	2.2 (0.9–5.0)
PO_2 < 60 mmHg (n = 1292)	26 (46%)	521 (42%)	1.2 (0.7–2.0)	13 (39%)	534 (42%)	0.9 (0.4–1.8)
Treatment						
Initial therapy, LMWH	52 (74%)	1532 (94%)	0.2 (0.1–0.3)	25 (67%)	1559 (93%)	0.1 (0.07–0.3)
Mean LMWH dose (IU/kg/d)	12782	13788	P = 0.005	13275	13762	P = NS
Thrombolytic therapy	5 (7%)	36 (2%)	3.3 (1.3–8.7)	4 (10%)	37 (2%)	5.0 (1.7–14.9)
Inferior vena cava filter	1 (1.4%)	22 (1.3%)	1.0 (0.1–7.2)	0	23 (1.4%)	0.98 (0.97–0.99)
D-dimer levels (ng mL^{-1})						
1st quartile (< 1050)	11 (15%)	402 (25%)	1.0	5 (19%)	408 (24%)	1.0
2nd quartile (1050–2150)	15 (21%)	425 (26%)	1.3 (0.6–2.8)	8 (20%)	432 (26%)	1.5 (0.5–4.7)
3rd quartile (2151–4219)	16 (22%)	412 (25%)	1.4 (0.7–3.1)	9 (23%)	419 (25%)	1.8 (0.6–5.3)
4th quartile (≥ 4200)	30 (42%)	396 (24%)	2.8 (1.4–5.6)	17 (44%)	409 (24%)	3.4 (1.2–9.3)

SD, standard deviation; VTE, venous thromboembolism; SBP, systolic blood pressure; bpm, beats per minute; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; CI, confidence intervals.

major bleeding (Table 4). Multivariate analysis confirmed that patients with D-dimer levels in the fourth quartile had an increased risk for overall death (odds ratio, 1.8; 95% CI, 1.1–3.2), fatal PE (odds ratio, 2.0; 95% CI, 1.0–3.8) or major bleeding (odds ratio, 3.2; 95% CI, 1.5–7.0), as shown in Table 5. After excluding those patients that received thrombolytic therapy or a vena cava filter, the odds ratios were: 1.8 (95% CI, 1.1–3.2) and 2.2 (95% CI, 1.1–4.3), respectively.

The sensitivity, specificity, positive predictive value and negative predictive value for predicting overall death in patients with D-dimer levels in the fourth quartile were: 42% (95% CI, 30–56), 76% (95% CI, 74–78), 7% (95% CI, 5–9) and 97% (95% CI, 96–98), respectively. For fatal PE the values were: 44% (95% CI, 28–59), 75% (95% CI, 73–78), 4% (95% CI, 2–6) and 98% (95% CI, 98–99), respectively.

Discussion

Our findings reveal that D-dimer levels at baseline are significantly associated with overall mortality, fatal PE and major bleeding complications within 15 days. The observation that PE patients with increased D-dimer levels at baseline have a worse outcome within 3 months is certainly not new [20,21], but our current study demonstrates that D-dimer levels may predict the short-term prognosis of PE, the period of time during which any therapeutic decision has to be taken. Interestingly, PE patients with D-dimer levels in the fourth quartile not only had an increased risk for overall death or fatal PE, but also an increased risk for major bleeding. D-dimer levels increased with the patient age, the presence of renal insufficiency or the severity of the PE event, and the worse outcome in these patients persisted after multivariate adjustment for these variables.

The only study also showing a correlation between high D-dimer levels and 15-day mortality was performed in 262 patients with less likely clinical probability of PE (Wells score < 4 points), and who were derived from a diagnostic management study that excluded patients with a life expectancy < 3 months, were pregnant or who were hemodynamically unstable [22]. Our findings may be applicable for all patients with acute PE.

A number of studies have found that PE patients with increased D-dimer levels have a higher extension of the PE and more proximal location of thrombus [23–26]. Thus, the association between increased D-dimer levels and PE-related mortality makes sense. It may be more difficult to explain why

Table 4 Multivariate analysis of the risk for overall death, fatal PE or major bleeding in the 1707 patients with acute PE

	Odds ratio (95% CI)	*P* value
Overall death		
Gender (females)	2.0 (1.1–3.3)	0.026
Creatinine levels > 1.2 mg dL^{-1}	2.7 (1.5–4.9)	0.001
Immobility ≥ 4 days	2.9 (1.7–5.1)	< 0.001
Cancer	3.8 (2.1–6.8)	< 0.001
Systolic blood pressure < 100 mmHg	2.2 (1.1–4.5)	0.035
Heart rate > 100 beats per minute	2.1 (1.2–3.7)	0.008
Atrial fibrillation	2.5 (1.3–4.8)	0.007
D-dimer, 4th quartile (≥ 4200 ng mL^{-1})	1.8 (1.1–3.2)	0.032
Fatal PE		
Gender (females)	2.0 (1.0–4.8)	0.043
Immobility ≥ 4 days	3.2 (1.7–6.2)	< 0.001
Systolic blood pressure < 100 mmHg	2.5 (1.1–5.6)	0.025
D-dimer, 4th quartile (≥ 4200 ng mL^{-1})	2.0 (1.0–3.8)	0.044
Major bleeding		
Gender (females)	2.5 (1.0–5.0)	0.061
Creatinine levels > 1.2 mg dL^{-1}	2.0 (0.9–4.3)	0.095
Thrombolytic therapy	6.7 (2.2–20)	0.001
D-dimer, 4th quartile (≥ 4200 ng mL^{-1})	3.2 (1.5–7.0)	0.002

PE, pulmonary embolism; SBP, systolic blood pressure; CI, confidence intervals.

PE patients with increased D-dimer levels at presentation (i.e. before any treatment) also had an increased incidence of major bleeding. To our knowledge, this is a previously unreported association, and now needs to be validated in further studies. A risk of subsequent bleeding in these patients would be expected to be associated with treatment, especially thrombolysis. However, multivariate analysis corrected for the effect of thrombolysis on D-dimer levels, so the association of D-dimers with major bleeding in our study was independent and not influenced by thrombolysis. A possible explanation is that the clinical conditions (and associated co-morbidities) at presentation are more serious in PE patients. Consequently, more aggressive treatments (with increased subsequent risk of bleeding) are used and/or there is a higher frequency of other underlying disease that may contribute to bleeding.

A number of variables, including serum cardiac biomarkers, echocardiography and CT-scan have been evaluated in the risk-assessment of patients with acute PE [10–19]. D-dimer tests are inexpensive, fast, simple, routinely performed in patients with suspected PE in many centres, and seem to predict the likelihood of fatal PE and major bleeding. A fully standardized rule exclusively based on objective clinical items, the Pulmonary Embolism Severity Index (PESI), has been extensively

Table 5 Univariate analysis of the risk for developing major bleeding in 1707 patients with acute PE

	Yes	No	Odds ratio (95% CI)
Patients, *n*	29	1678	
Clinical characteristics			
Age > 70 years	23 (79%)	1010 (60%)	2.5 (1.0–6.2)
Gender (males)	9 (31%)	756 (45%)	0.5 (0.2–1.2)
Body weight < 60 kg	6 (21%)	184 (11%)	2.1 (0.8–5.3)
Underlying conditions			
Chronic lung disease	1 (3.4%)	193 (12%)	0.3 (0.04–2.0)
Chronic heart failure	6 (21%)	107 (6.6%)	3.8 (1.5–9.6)
Creatinine levels > 1.2 mg dL^{-1}	11 (38%)	339 (20%)	2.4 (1.1–5.1)
Risk factors			
Postoperative	4 (14%)	213 (13%)	1.1 (0.4–3.2)
Immobility ≥ 4 days	11 (38%)	429 (26%)	1.8 (0.8–3.8)
Cancer	7 (24%)	324 (19%)	1.3 (0.6–3.1)
Prior VTE	3 (10%)	242 (14%)	0.7 (0.2–2.3)
None of the above	9 (31%)	681 (41%)	0.6 (0.3–1.4)
PE characteristics			
SBP < 100 mmHg	3 (10%)	135 (8.0%)	1.3 (0.4–4.4)
Heart rate > 100 bpm	10 (34%)	522 (31%)	1.1 (0.5–2.5)
Atrial fibrillation	2 (6.9%)	160 (10%)	0.7 (0.2–3.0)
PO_2 < 60 mmHg (n = 1292)	13 (52%)	534 (42%)	1.5 (0.7–3.3)
Treatment			
Thrombolytic	4 (14%)	37 (2.2%)	7.1 (2.3–21.4)
Initial therapy, LMWH	23 (79%)	1561 (93%)	0.3 (0.1–0.7)
Mean LMWH dose (IU/kg/d)	13318	13767	*P* = N.S.
Inferior vena cava filter	5 (17%)	18 (1.1%)	19 (6.6–56)
D-dimer levels (ng mL^{-1})			
1st quartile (< 1050)	4 (14%)	409 (24%)	1
2nd quartile (1050–2150)	2 (6.9%)	438 (26%)	0.5 (0.1–2.6)
3rd quartile (2151–4200)	8 (28%)	420 (25%)	1.9 (0.6–6.5)
4th quartile (≥ 4200)	15 (52%)	411 (24%)	3.7 (1.2–11)

VTE, venous thromboembolism; SBP, systolic blood pressure; bpm, beats per minute; LMWH, low-molecular-weight heparin; CI, confidence intervals.

validated for assessing patients with a low mortality risk who may be suitable for home management [28]. Whether the combination of PESI and D-dimer levels might more accurately identify low-risk patients with PE than each test individually, requires further examination.

Our study has some limitations. First, the low proportion of patients with PE that could be included in the analysis, because only a small proportion (17%) of patients with PE in the RIETE registry had D-dimer testing using the IL test. This, and the fact that patients who had the IL test differed from those that did not undergo D-dimer testing, increases the risk of selection bias. In addition, our findings may not apply to patients analysed using other reagents. Second, the 4.2% death rate in our series is lower than the 5.0–15% rates observed in other studies [29,30], but these differences may be due to either different observation periods (15 days in our study) or the need for objective confirmation of PE diagnosis in RIETE. Third, some patients with severe PE may have died before getting an objective confirmation, or were not enrolled because they could not give informed consent. Fourth, although D-dimer levels had a higher sensitivity for predicting death than other variables, it remains comparatively low, and the positive predictive values are very low and very close. Thus, physicians should also consider using other methods to detect patients at high risk of death (i.e. echocardiography and cardiac biomarkers). Finally, the physicians who assessed outcomes were not blinded to patients' D-dimer results.

In summary, PE patients with D-dimer levels in the fourth quartile are at an increased risk for overall death, fatal PE or major bleeding during the first 15 days. Our data suggest that D-dimer testing (using IL test) may help identify those patients with acute PE that should be treated in hospital.

Acknowledgements

We express our gratitude to Sanofi-Aventis Spain for supporting this Registry with an unrestricted educational grant. We also express our gratitude to Bayer Schering Pharma for supporting this Registry. Bayer Schering Pharma's support was limited to the international part of RIETE (excluding patients from Spain), which accounts for 9.4% of the total patients included in the RIETE Registry. We also thank the Registry Coordinating Center, S & H Medical Science Service, for their quality control, logistic and administrative support.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

Appendix

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. STROBE Statement—checklist of items that should be included in reports of observational studies.

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