Supplementary Appendix

Hospital volume and outcomes for acute pulmonary embolism: analysis from the RIETE registry

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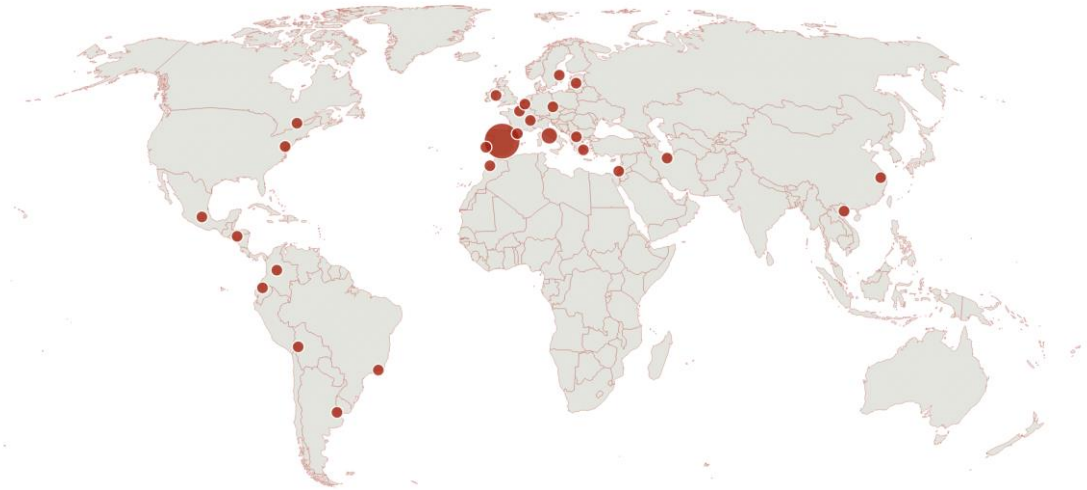
Figure. Sites of the RIETE registry



B. Methods:

B1. Inclusion criteria for RIETE (1)

Acute objectively confirmed DVT or acute objectively confirmed PE[a, b]

Availability of data for at least 54 core variables and minimum of 3-month follow-up

Abbreviations: RIETE, Registro Informatizado Enfermedad TromboEmbolica; DVT, deep vein thrombosis; PE, pulmonary embolism.

[a] Not mutually exclusive (i.e. patients may have both DVT and PE but will not be double counted).

[b] In more recent years, those with superficial vein thrombosis, splanchnic vein thrombosis (i.e. thrombosis involves thrombosis in the mesenteric, splenic or portal veins), retinal vein thrombosis and cerebral vein thrombosis have been separately enrolled.

B2. Exclusion criteria for RIETE (1)

Enrolment in any treatment trial (VTE or other conditions) in a blinded fashion

Previous enrolment in the registry

Lack or withdrawal of patient consent

Abbreviations: RIETE, Registro Informatizado Enfermedad TromboEmbolica; VTE, venous thromboembolism.

B3. Data collected in RIETE

Patients enrolled in RIETE had data collected from around the time of VTE diagnosis that included but were not limited to: age; gender; body weight; presence of coexisting conditions such as chronic heart or lung disease; recent major bleeding (<30 days prior to the index VTE event); presence of risk factors for PE including active cancer (defined as newly diagnosed cancer or cancer undergoing treatment [i.e. surgery, chemotherapy, radiotherapy, hormonal, or supportive therapy]), recent immobility (defined as non-surgical patients assigned to bed rest with bathroom privileges for ≥4 days in the 2-months prior to VTE diagnosis), surgery (defined as those who had undergone major surgery in the 2 months prior to VTE); clinical signs and symptoms on admission, including heart rate, systolic blood pressure and arterial oxyhemoglobin saturation; and laboratory results at hospital admission that included hemoglobin, platelet count and serum creatinine.

B4. Ascertainment of PE cases

We randomly chose four Spanish hospitals per hospital volume quarter. The completeness of case ascertainment by registry hospitals was determined by comparing the number of symptomatic PE cases entered into the registry with the number of symptomatic PE cases reported to the Spanish National Patient Registry (**SNPR**) during 2017, thus the Spanish National Patient Registry was regarded as the gold standard. To quantify completeness, we calculated the percent difference between the number of cases entered in the registry relative to the number of cases in the Spanish National Patient Registry:

$$\text{Percent difference (\%)} = ([\text{registry} - \text{SNPR}] / \text{SNPR}) \times 100.$$

B5. Definition of inappropriate management

Inappropriate management was defined as any of the following:

1. Use of intravenous unfractionated heparin (**UFH**) in a patient i) without severe renal failure (i.e., creatinine clearance < 30 mL/min), ii) without severe obesity (i.e., body weight > 120 kilograms), and iii) without unstable PE (defined as cardiogenic shock, systolic blood pressure < 90 mmHg, or use of inotropic or vasopressor support) (2); or use of low-molecular-weight heparin (**LMWH**) in a patient i) with severe renal failure, ii) severe obesity, or iii) unstable PE (3).
2. Use of thrombolytic therapy in a hemodynamically stable patient who did not deteriorate soon after diagnosis (2, 4); or no use of thrombolytic therapy in a hemodynamically unstable patient without major contraindications owing to bleeding risk (2, 4, 5).
3. Insertion of an inferior vena cava (**IVC**) filter in a patient without a contraindication to anticoagulant therapy (2, 4, 5); or no insertion of an inferior vena cava filter in a patient with a contraindication to anticoagulant therapy (4-6).

B6. Definition of recurrent VTE and major bleeding

Recurrent symptomatic VTE was defined as a recurrent PE, or a new or a recurrent distal or proximal lower extremity DVT, within 1 month after study entry with acute PE. For the recurrent PE diagnosis, we required the presence of a new perfusion defect involving 75% or more of a lung segment on V/Q scintigraphy, or a new intraluminal filling defect or an extension of a previous filling defect on PE-protocol chest CT (6). For a new or recurrent DVT, we required the appearance of a new noncompressible vein segment, or a 4-mm or more increase in the diameter of a thrombus on complete compression ultrasound (7).

We defined major bleeding episodes as those that required a transfusion of at least 2 units of blood, were retroperitoneal, spinal or intracranial, or were fatal (8).

B7. Propensity score analysis

We used inverse probability weighted regression adjustment (**IPWRA**) that was based on propensity score to construct a weighted cohort of patients who differed with respect to the volume of the hospital where they were managed but were similar with respect to other measured characteristics (9, 10). To calculate the inverse probability of weights, we estimated each patient's propensity to be treated in the corresponding volume hospital quarter, using a multinomial logistic regression model that included predictor variables that had been selected on the basis of their a priori possibility of confounding the relationship between hospital volume and outcome (age, sex, cancer, immobilization, chronic lung disease, chronic heart disease, heart rate, systolic blood pressure, sPESI, creatinine levels, and hemoglobin levels). Inverse probability weighted regression adjustment that was based on the propensity score was then used as the primary tool to adjust for differences between the low-volume (quarter 1) and high-volume (quarter 4) groups. This approach, which was implemented to create balance, involved weighting each patient in a high-volume hospital by the inverse of the probability that he or she would belong to a high-volume hospital and weighting each patient who belonged to a low-volume hospital by the inverse of the probability that he or she would belong to a low-volume hospital (11).

C. Results:

Table S1. Ascertainment of PE cases

Hospital	PE cases in RIETE 2017	PE cases in SNPR 2017	Percent difference
Quarter 4 (>40 patients/yr)			
Total	357	422	-15.4
Hospital 1	47	57	-17.5
Hospital 2	70	88	-20.4
Hospital 3	98	111	-11.7
Hospital 4	142	166	-14.5
Quarter 3 (>25-40 patients/yr)			
Total	140	170	-17.6
Hospital 5	29	31	-6.5
Hospital 6	33	45	-26.7
Hospital 7	38	47	-19.1
Hospital 8	40	47	-14.9
Quarter 2 (15-25 patients/yr)			
Total	78	93	-16.1
Hospital 9	16	19	15.8
Hospital 10	18	20	-10.0
Hospital 11	21	25	-16.0
Hospital 12	23	29	-20.7
Quarter 1 (<15 patients/yr)			
Total	27	33	-18.2
Hospital 13	10	12	-16.7
Hospital 14	7	9	-22.2
Hospital 15	6	6	0
Hospital 16	4	6	-33.3

Abbreviations: PE, pulmonary embolism; RIETE, Registro Informatizado Enfermedad TromboEmbolica; SNPR, Spanish National Patient Registry.

Table S2. Inappropriate management of acute PE

Variable	*Hospital volume quarters*			
	Q1 ***(<15 patients/yr)***	***Q2*** ***(15-25 patients/yr)***	***Q3*** ***(>25-40 patients/yr)***	***Q4*** ***(>40 patients/yr)***
Anticoagulant therapy				
No UFH in a patient with severe renal insufficiency, severe obesity, unstable PE, n/N (%)	187/1,633 (11.5%)	164/1,544 (10.6%)	135/1,907 (7.1%)	119/2,812 (4.2%)
UFH in a patient without severe renal insufficiency, severe obesity, unstable PE, n/N (%)	206/6,963 (3.0%)	178/6,586 (2.7%)	188/7,843 (2.4%)	209/9,969 (2.1%)
Reperfusion therapy				
No reperfusion in an unstable patient, n/N (%)	461/587 (78.5%)	366/472 (77.5%)	487/686 (71.0%)	680/963 (70.6%)
Reperfusion in a stable patient, n/N (%)	208/8,009 (2.6%)	100/7,658 (1.3%)	127/9,064 (1.4%)	100/11,818 (0.8%)
Inferior vena cava filter				
No filter in a patient with contraindication to anticoagulation, n/N (%)	526/637 (82.6%)	383/502 (76.3%)	634/783 (81.0%)	938/1,239 (75.7%)
Filter in a patient without contraindication to anticoagulation, n/N (%)	119/7,959 (1.5%)	105/7,628 (1.4%)	106/8,967 (1.2%)	122/11,542 (1.1%)
Inappropriate management, n (%)	**1,512 (17.6%)**	**1,251 (15.4%)**	**1,453 (14.9%)**	**1,821 (14.2%)**

Abbreviations: PE, pulmonary embolism; UFH, unfractionated heparin.

Table S3. Multivariable logistic regression models*

Variable	Quarter 1 (<15 patients/yr)	Quarter 2 (15-25 patients/yr)	Quarter 3 (>25-40 patients/yr)	Quarter 4 (>40 patients/yr)
Model 1 (unadjusted)				
Odds ratio (95% CI)				
30-day PE-related mortality	1.0	0.68 (0.43 to 1.09)	0.63 (0.37 to 1.09)	0.67 (0.37 to 1.23)
30-day all-cause mortality	1.0	0.78 (0.53 to 1.14)	0.81 (0.51 to 1.28)	0.94 (0.56 to 1.59)
7-day PE-related mortality	1.0	0.65 (0.41 to 1.06)	0.70 (0.40 to 1.21)	0.71 (0.38 to 1.31)
7-day all-cause mortality	1.0	0.77 (0.50 to 1.20)	0.80 (0.49 to 1.33)	0.89 (0.51 to 1.57)
30-day nonfatal VTE recurrences	1.0	0.78 (0.51 to 1.18)	0.71 (0.45 to 1.12)	0.82 (0.51 to 1.32)
30-day nonfatal major bleeding	1.0	0.97 (0.74 to 1.28)	0.95 (0.68 to 1.31)	1.16 (0.82 to 1.63)
Model 2 (adjusted for age and sex)				
Odds ratio (95% CI)				
30-day PE-related mortality	1.0	0.65 (0.41 to 1.02)	0.59 (0.35 to 1.01)	0.62 (0.34 to 1.11)
30-day all-cause mortality	1.0	0.74 (0.51 to 1.06)	0.73 (0.47 to 1.13)	0.87 (0.52 to 1.44)
7-day PE-related mortality	1.0	0.62 (0.38 to 1.00)	0.68 (0.40 to 1.17)	0.64 (0.35 to 1.17)
7-day all-cause mortality	1.0	0.73 (0.48 to 1.11)	0.73 (0.44 to 1.19)	0.82 (0.48 to 1.42)
30-day nonfatal VTE recurrences	1.0	0.79 (0.52 to 1.20)	0.68 (0.43 to 1.08)	0.84 (0.52 to 1.35)
30-day nonfatal major bleeding	1.0	0.95 (0.72 to 1.25)	0.90 (0.65 to 1.24)	1.11 (0.79 to 1.55)
Model 3 (adjusted for age, sex, cancer, immobilization, chronic lung disease, chronic heart disease, heart rate, systolic blood pressure, creatinine levels, and hemoglobin levels)				
Odds ratio (95% CI)				
30-day PE-related mortality	1.0	0.65 (0.42 to 1.01)	0.61 (0.38 to 1.00)	0.56 (0.33 to 0.96)
30-day all-cause mortality	1.0	0.68 (0.48 to 0.97)	0.74 (0.49 to 1.11)	0.78 (0.49 to 1.23)
7-day PE-related mortality	1.0	0.65 (0.41 to 1.02)	0.68 (0.42 to 1.11)	0.61 (0.35 to 1.04)
7-day all-cause mortality	1.0	0.72 (0.48 to 1.07)	0.72 (0.46 to 1.12)	0.76 (0.47 to 1.25)
30-day nonfatal VTE recurrences	1.0	0.82 (0.54 to 1.23)	0.74 (0.48 to 1.14)	0.76 (0.49 to 1.19)
30-day nonfatal major bleeding	1.0	0.91 (0.70 to 1.20)	0.90 (0.66 to 1.23)	1.07 (0.77 to 1.48)
Model 4 (adjusted for age, sex, cancer, immobilization, chronic lung disease, chronic heart disease, heart rate, systolic blood pressure, sPESI, creatinine levels, and hemoglobin levels)				
Odds ratio (95% CI)				
30-day PE-related mortality	1.0	0.66 (0.43 to 1.01)	0.61 (0.38 to 0.99)	0.56 (0.33 to 0.95)
30-day all-cause mortality	1.0	0.68 (0.48 to 0.97)	0.73 (0.19 to 1.10)	0.78 (0.50 to 1.22)
7-day PE-related mortality	1.0	0.65 (0.41 to 1.02)	0.68 (0.42 to 1.11)	0.60 (0.35 to 1.03)

7-day all-cause mortality	1.0	0.72 (0.48 to 1.07)	0.72 (0.46 to 1.12)	0.76 (0.47 to 1.24)
30-day nonfatal VTE recurrences	1.0	0.82 (0.54 to 1.23)	0.74 (0.48 to 1.14)	0.76 (0.49 to 1.19)
30-day nonfatal major bleeding	1.0	0.92 (0.70 to 1.20)	0.90 (0.66 to 1.22)	1.07 (0.77 to 1.47)
Model 5 (adjusted for age, sex, cancer, immobilization, chronic lung disease, chronic heart disease, heart rate, systolic blood pressure, sPESI, creatinine levels, hemoglobin levels, and hospital status)				
Odds ratio (95% CI)				
30-day PE-related mortality	1.0	0.66 (0.43 to 1.01)	0.60 (0.37 to 0.98)	0.54 (0.32 to 0.93)
30-day all-cause mortality	1.0	0.68 (0.48 to 0.97)	0.72 (0.48 to 1.09)	0.77 (0.48 to 1.21)
7-day PE-related mortality	1.0	0.64 (0.41 to 1.02)	0.65 (0.40 to 1.07)	0.57 (0.33v0.98)
7-day all-cause mortality	1.0	0.72 (0.48 to 1.07)	0.69 (0.44 to 1.09)	0.73 (0.44 to 1.20)
30-day nonfatal VTE recurrences	1.0	0.80 (0.53 to 1.20)	0.67 (0.44 to 1.02)	0.66 (0.42 to 1.03)
30-day nonfatal major bleeding	1.0	0.91 (0.70 to 1.20)	0.89 (0.66 to 1.22)	1.05 (0.75 to 1.46)

Abbreviations: CI, confidence interval; PE, pulmonary embolism; VTE, venous thromboembolism.

* All these models accounted for clustering of patients within hospitals and hospitals clustered within countries.

Table S4. Sensitivity analyses of falsification endpoints*

Variable	Quarter 1 (<15 patients/yr)	Quarter 2 (15-25 patients/yr)	Quarter 3 (>25-40 patients/yr)	Quarter 4 (>40 patients/yr)
Odds ratio (95% CI)				
90-day cancer-related mortality	1.0	1.52 (1.06 to 2.19)	1.57 (1.05 to 2.33)	1.52 (1.00 to 2.31)
90-day chronic heart disease-related mortality	1.0	1.25 (0.65 to 2.40)	1.05 (0.52 to 2.09)	0.86 (0.42 to 1.73)
90-day infection-related mortality	1.0	1.06 (0.61 to 1.82)	0.86 (0.48 to 1.55)	1.34 (0.74 to 2.44)

Abbreviations: CI, confidence interval.

***** Adjusted for age, sex, cancer, immobilization, chronic lung disease, chronic heart disease, heart rate, systolic blood pressure, sPESI, creatinine levels, and hemoglobin levels at hospital admission. Confidence intervals (**CI**) and P values take into account clustering according to center.

Table S5. Propensity score analysis

30-day outcome	*RR*	*95% CI*	*P value*
PE-related death	0.60	0.37-0.90	0.05
Death	0.84	0.58-1.20	0.33
Recurrent VTE	0.82	0.46-1.45	0.50
Major bleeding	1.03	0.80-1.36	0.78

Abbreviations: RR, relative risk; CI, confidence interval; PE, pulmonary embolism; VTE, venous thromboembolism.

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