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Epidemiology, patterns of care and mortality for patients with hemodynamically unstable acute symptomatic pulmonary embolism

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ABSTRACT

Background: Limited information exists about the epidemiology, management and outcomes of hemodynamically unstable patients with acute pulmonary embolism (**PE**). We aimed to evaluate the prevalence and outcomes of unstable PE, and to assess the acute management in routine clinical practice.
Methods: This study included 34,380 patients from the RIETE registry with PE between 2001 and 2016. Primary outcomes included all-cause and PE-specific 30-day mortality. We used multivariable adjustments to calculate hazard ratios among unstable patients who did and did not receive reperfusion.
Results: Overall, 1207 patients (3.5%) presented with hemodynamic instability. All-cause 30-day mortality was 14% and 5.4% in those with versus those without hemodynamic instability ($P < 0.001$). Two hundred and thirty eight (20%) unstable patients received reperfusion therapy. After multivariable adjustment, reperfusion therapy was associated with non-significantly reduced 30-day all-cause mortality (hazard ratio [**HR**] 0.71; 95% CI, 0.45 to 1.10; $P = 0.12$), and significantly reduced 30-day PE-related mortality (HR 0.56; 95% CI, 0.31 to 0.99; $P = 0.04$). When limiting the adjusted analyses to unstable patients with right ventricular dysfunction, the difference was significant for both all-cause (HR 0.65; 95% CI, 0.42 to 1.00; $P = 0.05$) and PE-related mortality (HR 0.52; 95% CI, 0.30 to 0.92; $P = 0.02$).
Conclusions: In a multinational registry of patients with PE, prevalence of hemodynamic instability was 3.5%, with high associated 30-day mortality rates. Although use of reperfusion was associated with lower mortality rates, particularly in patients with right ventricular dysfunction, it was used in only a fifth of patients.

1. Introduction

Hemodynamically unstable acute pulmonary embolism (**PE**) is a cardiovascular emergency, associated with high risk of death from worsening right ventricle (**RV**) failure and cardiogenic/obstructive shock, with an in-hospital mortality rate > 15% [1–3]. Prior investigations from existing PE registries have provided some important insights into unstable PE [4–6]. However, most of such studies included a limited number of patients with hemodynamically unstable PE, and were conducted when novel reperfusion approaches were not available or played a limited role in the management of these patients [4, 5].

Over the past two decades, there have been advances in the treatment of unstable PE, with emergence of additional data for systemic or catheter-based thrombolytic therapy (with or without ultrasound assistance) [7–10], re-emergence of surgical thrombectomy [11], and use of percutaneous thrombectomy, extracorporeal membrane oxygenation and inferior vena cava filters in certain subgroups

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[12]. Emergence of PE response teams and its counterparts have facilitated evaluation and delivery of therapies for severe PE [13]. Yet, there remains limited contemporary information about the epidemiology, treatment pattern, and outcomes of patients with unstable PE.

Accordingly, this study used the data from the Registro Informatizado de la Enfermedad TromboEmbólica (**RIETE**), a large ongoing, multicenter, multinational, prospective registry of consecutive patients with objectively confirmed, acute venous thromboembolism (**VTE**) [14–16] to determine the epidemiology, treatment patterns, and associated outcomes for patients with hemodynamically unstable PE (i.e., systolic blood pressure < 90 mm Hg) in routine clinical practice.

2. Methods

2.1. Study design

We used the prospectively collected data from patients enrolled in the RIETE registry. All patients provided written or oral informed consent for participation in the registry in accordance with local ethics committee requirements. For preparation of this manuscript, we followed the Strengthening the Reporting of Observational Studies in Epidemiology (**STROBE**) statement guidelines for observational cohort studies [17].

2.2. Data source

Previous publications have described the design and conduct of the RIETE registry [18, 19]. Briefly, at each participating RIETE site, investigators aimed to enroll consecutive patients that had confirmed acute symptomatic or asymptomatic VTE.

2.3. Eligibility

This current study included patients from RIETE who had a diagnosis of acute symptomatic PE from January 1, 2001, through December 31, 2016. Confirmatory testing consisted of high probability ventilation-perfusion (**V/Q**) scintigraphy [20], positive contrast-enhanced, PE-protocol, helical chest computerized tomography (**CT**) [single or multi-detector CT] for PE [21], or a non-diagnostic V/Q lung scan and confirmed lower limb deep vein thrombosis (**DVT**) on venous compression ultrasound [22].

2.4. Definitions

We defined unstable PE as the presence of arterial hypotension (systolic blood pressure < 90 mm Hg for a time period >15 min) at the time of diagnosis of PE [3, 5].

We defined myocardial injury as an elevation in cardiac troponins (i.e., cTnI > 0 ng/mL) [23]. This study defined echocardiographic RV dysfunction as the presence of at least two of the following: dilatation of the RV (end-diastolic diameter of >30 mm from the parasternal view or the RV appearing larger than the left ventricle from the subcostal or apical view), hypokinesis of the RV free wall (any view), or tricuspid regurgitant jet velocity of >2.6 m/s [24].

2.5. Variables

Patients enrolled in RIETE had data collected from around the time of VTE diagnosis that included but were not limited to: demographics, body weight, presence of coexisting conditions such as chronic heart or lung disease, recent (<30 days prior to VTE) major bleeding, active cancer (defined as newly diagnosed cancer or cancer undergoing treatment [i.e. surgery, chemotherapy, radiotherapy, hormonal, or support 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 (including hemoglobin, platelet count and serum creatinine).

2.6. Study outcomes

The primary outcomes were 30-day all-cause and PE-specific mortality (defined as death 30 days following the diagnosis of PE). To better understand the association between specific phases of treatment and mortality, we examined rates of death from any cause within 7 days following the diagnosis of PE. We also examined PE-related mortality through 7-days and through 30-days after diagnosis. The RIETE investigators used medical record review to assess vital status. For patients that died, further medical record review, and proxy interviews when necessary, assisted with determining date and cause of death. For deaths confirmed by autopsy or those following a clinically severe PE, either initially or shortly after an objectively confirmed recurrent event, in the absence of any alternative diagnosis, the investigators were instructed to judge death as due to fatal PE. We chose 7-day and 30-day mortality assessment periods because recent trials and observational studies suggest that most of the fatal events occur soon (i.e., during the first 30 days) after diagnosis of PE and initiation of treatment [15]. In addition, we examined the rates of VTE recurrences and also bleeding events within 30 days following the diagnosis of PE.

2.7. Statistical analysis

We used chi-square or Fisher's exact tests to compare categorical data between groups. We used the Shapiro-Wilk test to assess continuous data for a normal distribution. We used two-tailed unpaired *t*-tests to compare parametric continuous data between two unpaired groups, and we used the Mann-Whitney *U* test for non-parametric data comparisons. We also used these tests to explore differences between the patients with unstable PE who did and did not receive reperfusion therapies. Data were unadjusted unless specifically stated otherwise. We used Cox proportional hazard models to evaluate the association between reperfusion and the outcome measures in the subgroup of unstable patients with acute PE. A manual backward stepwise approach was used to develop the multivariable models. In the full model, covariates determined a priori to be associated with mortality (i.e., age, male sex, recent bleeding, heart rate, and arterial oxygen saturation) and covariates with imbalance between the groups at baseline were considered for inclusion. Variables that showed evidence of confounding (i.e., the coefficient of the variable group changed by >10% when removing that variable from the full model) for the effect of reperfusion on the outcome undergoing analysis were not removed from the model. Specific candidate variables were forced, one at a time, into the full model to assess their effects. To test the robustness of the models, the effects of excluding patients without echocardiographic right ventricular dysfunction, were assessed.

We conducted statistical analyses with the use of STATA version 13.1 (STATA Corp, College Station, Texas). All hypothesis tests were two-sided, with a significance level of 0.05.

3. Results

We identified 69,480 patients with objectively confirmed VTE enrolled in RIETE during the study period. After exclusion of 1825 (2.6%) patients who had asymptomatic VTE, and 33,275 (48%) patients who had isolated DVT (i.e., without symptomatic PE), the study cohort consisted of 34,380 patients (16,038 men and 18,342 women) with confirmed acute symptomatic PE.

Overall, 1207 patients (3.5%; 95% confidence interval [**CI**], 3.3% to 3.7%) had unstable PE and 33,173 did not. Patients with unstable PE differed significantly from those with stable PE in preexisting medical conditions, and in relevant clinical, physiologic and laboratory parameters. Patients with unstable PE had a higher prevalence of chronic heart disease, recent surgery, cancer, immobilization, and recent major bleeding compared to those with stable PE. Of note, hypoxemia (i.e., oxygen saturation < 90%), myocardial injury (shown as elevation in cardiac troponins) and syncope were more frequent in the unstable subgroup (Table 1).

3.1. Treatment modalities

Treatment was significantly different between the two groups: 20% (238/1207) of patients with unstable PE received reperfusion therapies, compared with 3.0% (983/33,173) of patients with stable PE. Approximately 6% of patients with unstable PE were treated with an inferior vena cava filter, compared to 2.8% of patients with stable PE.

In the unstable group, 217 (18%) patients received systemic thrombolysis, 26 (2.2%) underwent surgical embolectomy, and 6 (0.5%) received catheter-based therapies. Patients with unstable PE who received reperfusion therapy differed significantly from those who did not receive reperfusion therapy in preexisting medical conditions, and in relevant clinical, physiologic and laboratory parameters. Patients who received reperfusion were younger than patients who did not receive reperfusion, and had higher heart rate, and more frequently presented with hypoxemia, myocardial injury and syncope, compared with unstable patients who did not receive reperfusion (Table 2). Interestingly, the two treatment groups had similar proportions of male gender, history of heart failure, chronic obstructive pulmonary disease, recent surgery, recent major bleeding, and similar baseline creatinine levels.

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Table 1
Baseline characteristics and treatment information for patients with acute symptomatic pulmonary embolism.

	All patients $N = 34,380$	Unstable PE $N = 1207$	Stable PE $N = 33,173$	*P* value
Clinical characteristics				
Age, years (mean ± SD)	67.3 ± 16.3	68.1 ± 17.1	67.2 ± 17.0	0.09
Age > 65 years	21,712 (63%)	768 (64%)	20,944 (63%)	0.74
Male sex	16,038 (47%)	515 (43%)	15,523 (47%)	<0.01
Weight, kg (mean ± SD)	75.8 ± 16.1	73.0 ± 15.9	75.9 ± 16.1	<0.001
Risk factors for VTE				
History of VTE	5073 (15%)	125 (10%)	4948 (15%)	<0.001
Cancer[a]	7671 (22%)	310 (26%)	7361 (22%)	<0.01
Recent surgery[b]	4092 (12%)	182 (15%)	3910 (12%)	<0.01
Immobilization[c]	7769 (23%)	422 (35%)	7347 (22%)	<0.001
Comorbid diseases				
Recent major bleeding[b]	806 (2.3%)	50 (4.1%)	756 (2.3%)	<0.001
Chronic obstructive pulmonary disease (**COPD**)	4917 (14%)	183 (15%)	4734 (14%)	0.38
Congestive heart failure	3162 (9.2%)	144 (12%)	3018 (9.1%)	<0.01
Concomitant DVT, *n*/*N*	13,093/21,251 (62%)	418/685 (61%)	12,675/20,566 (62%)	0.75
Clinical symptoms and signs at presentation				
Syncope	5036 (15%)	518 (43%)	4518 (14%)	<0.001
Chest pain	15,875 (46%)	447 (37%)	15,428 (46%)	<0.001
Dyspnea	27,625 (80%)	962 (80%)	26,663 (80%)	0.25
Heart rate ≥ 110/minute	6986 (20%)	580 (48%)	6406 (19%)	<0.001
Arterial oxyhemoglobin saturation < 90%	6443 (19%)	407 (34%)	6036 (18%)	<0.001
Echocardiography and cardiac biomarkers, n (%)				
RV dysfunction ($n = 29,646$)	14,606/29,646 (49%)	613/1080 (57%)	13,993/28,566 (49%)	<0.001
BNP > 100 pg/mL ($n = 2706$)	1776/2706 (66%)	63/86 (73%)	1713/2620 (65%)	0.13
cTnI > 0 ng/mL ($n = 15,418$)	5273/15,418 (34%)	369/652 (57%)	4904/14,766 (33%)	<0.001
Laboratory findings				
Hemoglobin, g/dL (mean ± SD)	13.1 ± 2.9	12.3 ± 2.1	13.1 ± 2.9	<0.001
Creatinine, mg/dL (mean ± SD)	1.2 ± 2.7	1.4 ± 1.0	1.2 ± 2.7	<0.001
Treatment				
Reperfusion therapy	1221 (3.6%)	238 (20%)	983 (3.0%)	<0.001
Insertion of an IVC filter	1015 (2.9%)	68 (5.6%)	947 (2.8%)	<0.001

Abbreviations: PE, pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; BNP, brain natriuretic peptide; cTnI, cardiac troponin I; IVC, inferior vena cava.

[a] Active or under treatment in the last year.

[b] In the previous month.

[c] Immobilized patients are 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 month prior to PE diagnosis.

3.2. Outcomes

Outcomes data were available for all patients through the 30-day study follow-up. Overall, 1954 out of 34,380 patients died (5.7%; 95% CI, 5.4% to 5.9%). Over 50% of deaths (998 of 34,380 patients; 2.9%; 95% CI, 2.7% to 3.1%) were attributable to PE, and 956 patients (2.8%; 95% CI, 2.6% to 3.0%) died from other causes. The 30-day mortality rates were 14% (95% CI, 12% to 16%) and 5.4% (95% CI, 5.1% to 5.6%) in patients with unstable and stable PE, respectively (Table 3). PE was the cause of death in 67% of the patients with unstable PE and in 49% of the patients with stable PE. Recurrent PE was detected within 30 days in 0.2% and 0.6%, and bleeding complications occurred in 6.2% versus 3.6%, respectively, in patients with unstable versus stable PE.

In the subgroup of patients with unstable PE, all-cause mortality within 30-days of PE diagnosis occurred in 25 patients (11%; 95% CI, 6.9% to 15%) who received reperfusion therapy, and in 143 patients (15%; 95% CI, 13% to 17%) who did not receive reperfusion. After multivariable adjustment, reperfusion therapy was associated with non-significantly reduced 30-day all-cause mortality (adjusted hazard ratio [HR] 0.71; 95% CI, 0.45 to 1.10; $P = 0.12$) (Fig. 1, Panel A). PE-related mortality within 30-days of PE diagnosis occurred in 15 patients (6.3%; 95% CI, 3.6% to 10%) with unstable PE who received reperfusion therapy, and in 98 patients (10%; 95% CI, 8.3% to 12%) with unstable PE who did not receive reperfusion. The risk-adjusted PE-related mortality rate was lower for reperfusion than no reperfusion (HR 0.56; 95% CI, 0.31 to 0.99; $P = 0.04$) (Fig. 1, Panel B). In an exploratory analysis among unstable patients with echocardiographic evidence of right ventricular dysfunction, using the same multivariable model, reperfusion was associated with significantly reduced 30-day all-cause mortality (adjusted HR 0.65; 95% CI, 0.42 to 1.00; $P = 0.05$) and 30-day PE-related mortality (adjusted HR 0.52; 95% CI, 0.30 to 0.92; $P = 0.02$). All-cause mortality within 7-days of PE diagnosis occurred in 23 patients (9.7%; 95% CI, 6.2% to 14%) with unstable PE who received reperfusion therapy, and in 87 patients (9.0%; 95% CI, 7.2% to 11%) with unstable PE who did not receive reperfusion. Recurrent VTE within 30-days of PE diagnosis occurred in 3 patients (1.3%; 95% CI, 0.3% to 3.6%) entering the study with unstable PE who received reperfusion, and in 0 patients (0%; 95% CI, 0% to 0.4%) with unstable PE who did not receive reperfusion. Seventy-five patients (6.2%; 95% CI, 4.9% to 7.7%) with unstable PE suffered a major bleeding episode. Major bleeds within 30-days of PE diagnosis occurred in 33 patients (14%; 95% CI, 9.7% to 19%) with unstable PE who received reperfusion, and in 42 patients (4.3%; 95% CI, 3.1% to 5.8%) with unstable PE who did not receive reperfusion (adjusted HR 2.26; 95% CI, 1.41 to 3.62; $P < 0.01$).

4. Discussion

In this large multi-center multinational study unstable PE occurred in 3.5% of patients with acute symptomatic PE, with a 30-day mortality rate of approximately 14%. Over half of the deaths were attributable to PE in the overall cohort, while among those with hemodynamically unstable PE, other causes accounted only for a third of deaths. Patients

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Table 2
Clinical characteristics of patients with unstable PE who did or did not receive reperfusion therapies.

	Received reperfusion therapies $N = 238$	Did not receive reperfusion therapies $N = 969$	*P* value
Clinical characteristics			
Age, years (mean ± SD)	62.4 ± 17.1	69.5 ± 16.8	<0.001
Age > 65 years	118 (50%)	650 (67%)	<0.001
Male gender	97 (41%)	418 (43%)	0.51
Weight, kilograms (mean ± SD)	76.1 ± 16.7	72.2 ± 15.6	<0.01
Risk factors for VTE			
History of VTE	16 (6.7%)	109 (11.2%)	0.04
Cancer[a]	39 (16%)	271 (28%)	<0.001
Recent surgery[b]	34 (14%)	148 (15%)	0.76
Immobilization[c]	76 (32%)	346 (36%)	0.29
Comorbid diseases			
Recent major bleeding[b]	8 (3.4%)	42 (4.3%)	0.59
Chronic obstructive pulmonary disease (**COPD**)	28 (12%)	155 (16%)	0.11
Congestive heart failure	21 (8.8%)	123 (13%)	0.12
Concomitant DVT, *n/N*	94/148 (63%)	324/537 (60%)	0.51
Clinical symptoms and signs at presentation			
Syncope	146 (61%)	372 (38%)	<0.001
Chest pain	98 (41%)	349 (36%)	0.15
Dyspnea	202 (85%)	760 (78%)	0.06
Heart rate ≥ 110/minute	157 (66%)	423 (44%)	<0.001
Arterial oxyhemoglobin saturation (SaO2) < 90%	102 (43%)	305 (31%)	<0.001
Echocardiography and cardiac biomarkers, n (%)			
RV dysfunction ($n = 1080$)	181/226 (80%)	432/854 (51%)	<0.001
BNP > 100 pg/mL ($n = 2706$)	22/30 (73%)	41/56 (73%)	1.0
cTnI > 0 ng/mL ($n = 15{,}418$)	107/156 (69%)	262/496 (53%)	<0.01
Laboratory findings			
Hemoglobin, g/dL (mean ± SD)	12.8 ± 2.2	12.2 ± 2.1	<0.01
Creatinine, mg/dL (mean ± SD)	1.4 ± 0.8	1.4 ± 1.1	0.23
Treatment			
Insertion of an IVC filter	18 (7.6%)	50 (5.2%)	0.16

Abbreviations: PE, pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; BNP, brain natriuretic peptide; cTnI, cardiac troponin I; IVC, inferior vena cava.
[a] Active or under treatment in the last year.
[b] In the previous month.
[c] Immobilized patients are 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 month prior to PE diagnosis.

with unstable PE had markedly worse outcomes compared to those with stable PE. Among patients with hemodynamically unstable PE, particularly in those with associated RV dysfunction, reperfusion therapies were associated with reduced PE-associated mortality rates. However, only 20% of patients with unstable PE received reperfusion therapies, and use of other advanced PE therapies remained similarly rare.

Table 3
Clinical events after diagnosis and treatment for patients with acute symptomatic pulmonary embolism.

	All patients $N = 34{,}380$	Unstable PE $N = 1207$	Stable PE $N = 33{,}173$	*P* value
30-day outcomes				
Primary outcome, *n* (%)				
All-cause death	1954 (5.7%)	168 (14%)	1786 (5.4%)	<0.001
PE-related death	998 (2.9%)	113 (9.4%)	885 (2.7%)	<0.001
Secondary outcomes, *n* (%)				
Recurrent PE	201 (0.6%)	3 (0.2%)	198 (0.6%)	0.17
Major bleeding	1274 (3.7%)	75 (6.2%)	1199 (3.6%)	<0.001
7-day outcomes				
Primary outcome, *n* (%)				
All-cause death	815 (2.4%)	110 (9.1%)	705 (2.1%)	<0.001
PE-related death	560 (1.6%)	79 (6.5%)	481 (1.4%)	<0.001
Secondary outcomes, *n* (%)				
Recurrent PE	69 (0.2%)	0 (0%)	69 (0.2%)	0.21
Major bleeding	602 (1.7%)	55 (4.6%)	547 (1.6%)	<0.001

Abbreviations: PE, pulmonary embolism.

The prevalence of unstable PE in the study cohort (3.5%) was similar to that of EMPEROR registry, in which 3.1% of patients with confirmed PE had a systolic blood pressure <90 mm Hg [6], and lower than the 4.5% reported in ICOPER [4]. This discrepancy between the studies may be explained at least in part by the inclusion of major PE first discovered by autopsy in ICOPER [3]. Moreover, ICOPER also included patients that had a subjective diagnosis of PE made by the attending physician, despite a lack of objective confirmation. Further, with recent implementation of computed tomography pulmonary angiography -a more sensitive diagnostic technology- in recent years, it is likely that some less severe PEs are introduced in the overall case mix of patients with PE, thereby lowering the relative frequency of unstable PEs [25].

Hemodynamic status remains the most important short-term prognostic factor for patients with acute PE. The high risk of PE-related death in patients with PE and associated hypotension or shock may lower the threshold of aggressive treatment (e.g., thrombolysis) [1, 2]. In the absence of large randomized clinical trials that demonstrate the benefit of thrombolytic therapy on mortality, the American College of Chest Physicians (ACCP) guidelines and the American Heart Association Scientific Statement recommended the use of thrombolytic therapy for patients with acute symptomatic PE and hemodynamic instability that do not have major contraindications owing to bleeding risk [1, 12]. Intriguingly, we found that only 20% of the patients with unstable PE received reperfusion therapies. Lin et al. reported in their retrospective analysis of patients with confirmed PE that only 7 patients (12%) with unstable PE received thrombolytic therapy [6]. In ICOPER, two thirds

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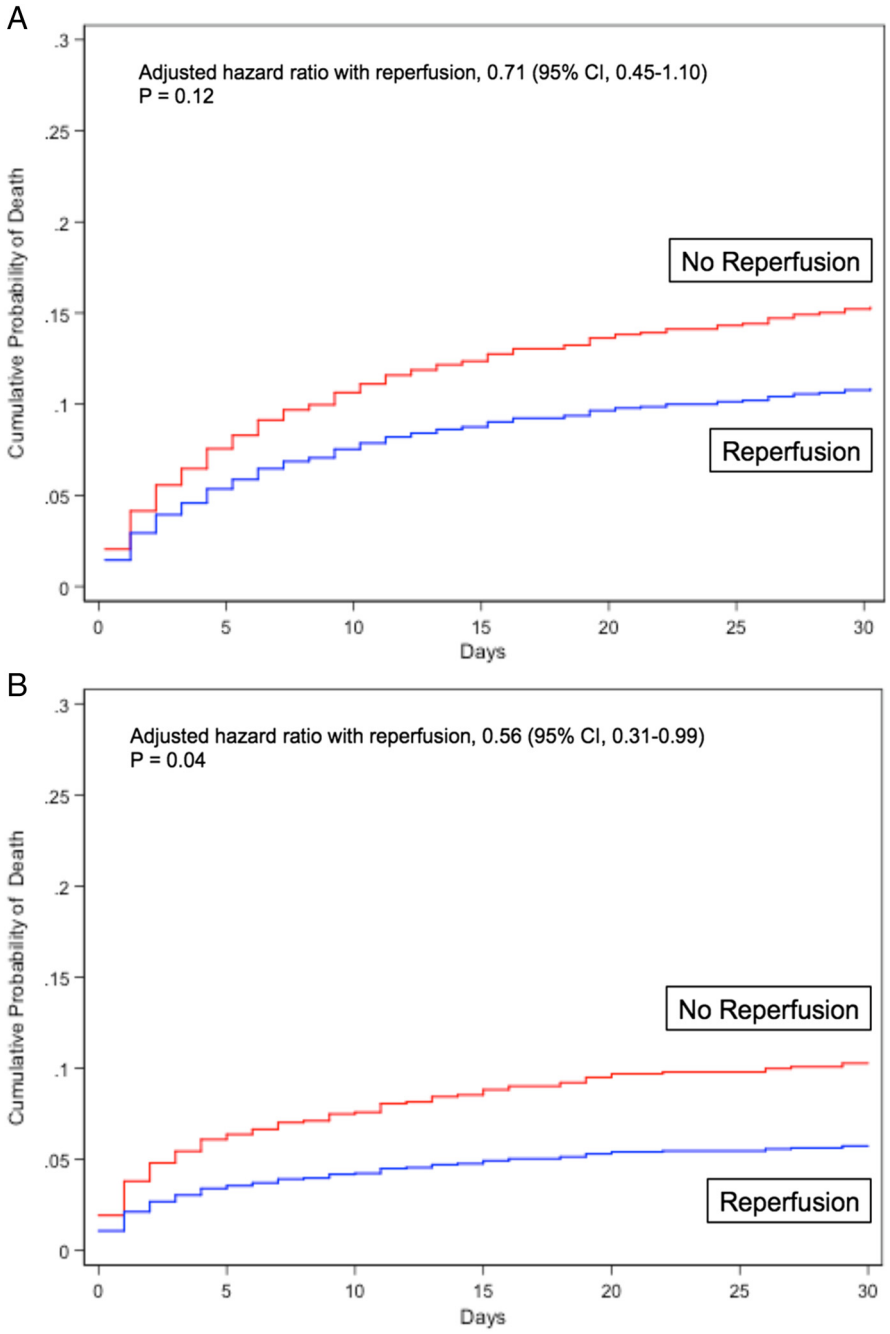

Fig. 1. Panel A. Rates of 30-day all-cause mortality in the unstable PE population, from an adjusted analysis. Panel B. Rates of 30-day PE-related mortality in the unstable PE population, from an adjusted analysis.

of the patients with massive PE did not receive thrombolysis or embolectomy [4]. Unfortunately, we were not able to explore the exact reasons for withholding thrombolysis, catheter embolectomy, or surgery in each patient. We may hypothesize that in some cases patients improved with fluids and vasopressor support, other patients had contraindications to thrombolysis or surgical or percutaneous interventions, some were considered to have high bleeding risk, some had refused therapy, and in some others the decisions were based on attending physician preferences or availability of advanced therapies. However, our review of common factors contributing to withholding of advanced therapies (including rates of severe renal dysfunction, recent surgery, and recent major bleeding), did not detect a clinically large difference between hemodynamically unstable patients who received reperfusion therapies, compared with those who did not. Our findings are representative of current clinical practice in >20 countries around the world. While we cannot comment on treatment appropriateness per patient, collectively, our findings provide sufficient empiric evidence to suspect under-utilization of advanced therapies in several of hemodynamically unstable patients with PE.

Unstable PE continues to have a high mortality [26]. In our study, use of reperfusion therapies was associated with a significant reduction in short-term PE-related mortality after adjusting for potential confounders. The results were consistent and more robust in those with hypotension and evidence of right ventricular dysfunction. In contrast, thrombolysis did not improve survival in ICOPER and EMPEROR, as well as a prior investigation from RIETE [18]. In these studies, the lack of association between use of thrombolysis and prognosis may have been due to a lack of statistical power, as all the three had suggestive effect sizes, but

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with wider confidence intervals. In addition, the previous RIETE study did not use a standard definition for hemodynamically unstable PE. The larger sample size in the present study, the adjustment for potential confounders, and the robustness of the findings in supplemental analyses, provides further evidence supporting the concept that reperfusion therapies might improve survival in patients with unstable PE. Alternatively, the adjusted risk of major bleeding among unstable patients who received reperfusion therapies was about 2 times higher than in unstable patients who did not receive reperfusion. Taken together, these results suggest that improved methods of risk stratification might help to identify subgroups of patients at high risk of death and low risk of bleeding that might have a favorable risk to benefit ratio for treatment with reperfusion therapies.

This study has some limitations. First, the single data point of initial blood pressure used to define unstable PE may have affected our analysis. However, based on current guidelines and the published literature, the diagnosis of unstable PE is based on the presence of hypotension at the time of PE diagnosis. Because delay in the initiation of fibrinolysis may lead to irreversible shock and poor outcomes in patients with unstable PE, our definition seemed nevertheless reasonable. Second, the RIETE database did not prospectively collect data on the reasons that led clinicians to choose or withhold aggressive therapy. However, within the limits of available data, including factors such as history of recent surgery and recent bleeding, among others, we did not identify major clinically significant differences to account for infrequent use of thrombolytic therapy in hemodynamically unstable patients with PE. Further, although data in this registry allowed us to adjust for a number of key variables, the possibility of residual confounding still remains. However, consistent associations in our supplemental analyses (some were, in fact, stronger) indicate the robustness of the findings and the soundness of the conclusions. Finally, it is possible that not all patients with PE in participating centers were enrolled. However, RIETE, by design and by agreement with enrolling investigators makes every effort to enroll consecutive patients from the practice of RIETE investigators. Periodic audits from the RIETE coordinating center have been consistent with this notion and a previous study found that the information in the RIETE registry is very similar to that observed in the administrative database from the Spanish Ministry of Health [27]. RIETE investigators are from diverse backgrounds, including from general medicine, hematology, pulmonary, cardiology, and vascular medicine specialties in general hospitals, tertiary care centers, and centers of excellence for cardiopulmonary conditions. Therefore, we believe that our sample is representative of real-world practice.

In conclusion, in a large registry from 325 hospitals in 24 countries, hemodynamically unstable PE was found in 3.5% of patients. Such patients had markedly worse outcomes compared with other patients with PE. Although reperfusion therapy was associated with lower PE-related mortality rates, particularly in those with associated RV dysfunction, only a fifth of hemodynamically unstable patients received advanced therapies. These findings indicate the potential for improvement in the management of patients with unstable PE.

Author contributions

Study concept and design: Jimenez, Barrios, Yusen, Monreal.

Acquisition of data; *analysis and interpretation of data*; *statistical analysis*: Jimenez, Bikdeli, Barrios, Quezada, Yusen, Monreal.

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The corresponding author, David Jiménez, had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Conflict of interest statement

None reported.

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Appendix A

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