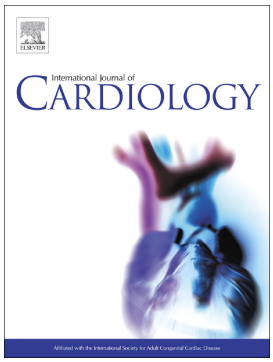

Systolic blood pressure and mortality in acute symptomatic pulmonary embolism

Andrés Quezada, David Jiménez, Behnood Bikdeli, Lisa Moores, Mateo Porres-Aguilar, Mario Aramberri, Jorge Lima, Aitor Ballaz, Roger D. Yusen, Manuel Monreal, the RIETE investigators

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Systolic blood pressure and mortality in acute symptomatic pulmonary embolism

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ABSTRACT

Background: The optimal cutoff for systolic blood pressure (**SBP**) level to define high-risk pulmonary embolism (**PE**) remains to be defined.

Methods: To evaluate the relationship between SBP levels on admission and mortality in patients with acute symptomatic PE, the current study included 39,257 consecutive patients with acute symptomatic PE from the RIETE registry between 2001 and 2018. Primary outcomes included all-cause and PE-specific 30-day mortality. Secondary outcomes included major bleeding and recurrent VTE.

Results: There was a linear inverse relationship between admission SBP and 30-day all-cause and PE-related mortality that persisted after multivariable adjustment. Patients in the lower SBP strata had higher rates of all-cause death (reference: SBP 110-129 mmHg) (adjusted odds ratio [**OR**] 2.9; 95% confidence interval [**CI**], 2.0-4.2 for SBP <70 mmHg; and OR 1.7; 95% CI, 1.4-2.1 for SBP 70-89 mmHg). The findings for 30-day PE-related mortality were similar (adjusted OR 4.4; 95% CI, 2.7-7.2 for SBP <70 mmHg; and OR 2.6; 95% CI, 1.9-3.4 for SBP 70-89 mmHg). Patients in the higher strata of SBP had significantly lower rates of 30-day all-cause mortality compared with the same reference group (adjusted OR 0.7; 95% CI, 0.5-0.9 for SBP 170-190 mmHg; and OR 0.6; 95% CI, 0.4-0.9 for SBP >190 mmHg). Consistent findings were also observed for 30-day PE-related death.

Conclusions: In patients with acute symptomatic PE, a low SBP portends an increased risk of all-cause and PE-related mortality. The highest mortality was observed in patients with SBP <70 mmHg.

Abstract word count: 242

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INTRODUCTION

Pulmonary embolism (**PE**) remains a major health issue (1). Acute PE represents the third most common cause of vascular death worldwide (2). Prior studies have demonstrated that low systolic blood pressure (**SBP**) is associated with high risk of death from worsening right ventricle (**RV**) failure and cardiogenic/obstructive shock in patients with acute symptomatic PE (3-5). On the basis of these studies, experts and professional societies have recommended the use of thrombolytic therapy (or surgical thrombectomy) for patients with acute symptomatic PE and haemodynamic instability (i.e., SBP <90 mmHg) who do not have a prohibitive risk (e.g. major contraindications owing to bleeding risk) (6-8).

Predicting the likelihood of short-term PE-related mortality for a given SBP level is of utmost importance, in order to identify individual patients at high risk of PE-related death and low risk of bleeding that might have a favorable risk to benefit ratio for treatment with reperfusion therapies. By consensus, prior studies defined hemodynamically unstable PE as a SBP <90mmHg (3-5). However, most of such studies included a limited number of patients (usually <3,000 patients), and the majority of them focused on the outcome of all-cause mortality, which does not reflect the impact of pharmacological and interventional treatments in patients with acute symptomatic PE as well as PE-related death. It remains to be determined if an alternative SBP cut-off at presentation could more accurately capture the patients at risk, ideally identifying best candidates for advanced therapies (9). In addition, there is lack of data with respect to PE outcomes in the group of patient who have elevated SBPs at presentation.

To address this critical knowledge gap, this study used the data from the Registro Informatizado de la Enfermedad TromboEmbólica (**RIETE**), a large ongoing, multi-center, multinational, prospective registry of consecutive patients with objectively confirmed, acute venous thromboembolism (**VTE**) (10-12) (1) to determine the relationship between admission SBP levels and short-term mortality and other important clinical outcomes, and (2) to define the optimal cutoff for SBP to identify high-risk PE.

METHODS

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 (13).

Data source

Previous publications have described the design and conduct of the RIETE registry (14, 15). Briefly, at each participating RIETE site, investigators aimed to enroll consecutive patients who had confirmed acute symptomatic or asymptomatic VTE.

Eligibility

This current study included patients from RIETE who had a diagnosis of acute symptomatic PE from January 1, 2001, through August 31, 2018. Confirmatory testing consisted of high probability ventilation-perfusion (**V/Q**) scintigraphy (16), positive contrast-enhanced, PE-protocol, helical chest computerized tomography (**CT**) [single or multi-detector CT] for PE (17), or a non-diagnostic V/Q lung scan and confirmed lower limb deep vein thrombosis (**DVT**) on venous compression ultrasound (18).

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, SBP, and arterial oxyhemoglobin saturation), and laboratory results at hospital admission (including hemoglobin, platelet count, and serum creatinine). Markers of right ventricular dysfunction (either by echocardiography or CT) and cardiac biomarkers (cardiac troponins or brain natriuretic peptides [**BNP**]) were recorded where available.

Blood pressure measurement

This study measured SBP around the time of PE diagnosis. Most of the times SBP was measured at the time of admission to the Emergency Department, though the RIETE protocol did not require a strict time window for measurement of vital signs.

Study outcomes

The primary outcomes were 30-day all-cause and PE-specific mortality. The RIETE investigators used medical record review to assess vital status. For patients who died, further medical record review, and proxy interviews when necessary, assisted with determining the 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. In addition, we examined the rates of nonfatal VTE recurrences and major bleeding events within 30 days following the diagnosis of PE.

Statistical analysis

We compared the baseline demographics and clinical characteristics among patients categorized by the following admission SBP levels: less than 70, 70 to less than 90, 90 to less than 110, 110 to less than 130, 130 to less than 150, 150 to less than 170, 170 to less than 190, and 190 or greater mmHg. We then used hierarchical logistic regression (with hospital site as a random effect to account for clustering across centers) to assess the association between admission SBP and outcomes, after adjustment for potential patient-level confounders.

For multivariable models, we considered factors previously demonstrated to be prognostically significant or thought to be clinically important, and covariates identified in bivariate analyses as predictors of mortality. The following models were generated sequentially to determine the successive influence of potential confounders on the relationship between admission SBP (reference group, 110-129 mmHg) and mortality: (1) unadjusted; (2) adjusted only for age and sex; and (3) adjusted for age, sex, and the following covariates: coexisting conditions (i.e., cancer, immobilization, chronic lung disease, chronic heart disease), severity of PE (i.e., heart rate, arterial oxyhemoglobin saturation, simplified Pulmonary Embolism Severity Index [**sPESI**] [19]), and laboratory results (i.e., creatinine levels, hemoglobin levels) at hospital admission.

We assessed the sensitivity of our findings by repeating the primary analysis under varying assumptions about the study population in a sensitivity analysis for PE-related mortality. Sensitivity analyses comprised the exclusion of outlier hospitals (those with too few or too many patients), exclusion of patients younger than 50 years old, and exclusion of patients who received reperfusion therapies.

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.

RESULTS

Study population

The final analysis included 39,257 adults at 353 hospitals participating in the RIETE registry that had a diagnosis of acute symptomatic PE during the time period of January 1, 2001, through August 31, 2018 (**eFigure**).

Patient characteristics

The distribution of admission SBP measurements approximated that of a normal distribution, with a mean admission SBP level of 129.3 mmHg (SD, 24.0

mmHg), and a median admission SBP level of 130.0 mmHg (IQR, 114.0-143.0 mmHg).

Baseline characteristics of the 39,257 study patients by strata of admission SBP levels are shown in **Table 1**. The relationship between SBP levels and baseline variables was complex: U-shaped for age; and inverted U-shaped for other variables (cancer, and elevated BNP). Patients in the lower SBP levels strata had a higher relative frequency of being male, having previous surgery, immobilization, and recent bleeding compared with patients in the higher SBP strata. Patients in the lower SBP strata had a lower prevalence of previous VTE, chronic lung disease, and chronic heart disease compared to patients in the higher SBP strata. Patients in the lower SBP strata had more signs of clinical severity (tachycardia, hypoxemia, higher sPESI scores, right ventricle dysfunction, and myocardial injury), and laboratory abnormalities (renal failure, anemia) compared to the higher quartiles. Use of thrombolytic therapy and insertion of an inferior vena cava (**IVC**) filter was more frequent in patients in the lower strata compared to patients in the higher strata (**Table 1**). In the RIETE registry, only 26 (1.9%; 95% confidence interval [**CI**], 1.3-1.8%) unstable patients with acute PE underwent surgical embolectomy.

Association of admission blood pressure and outcomes

The entire cohort had a 30-day all-cause mortality of 5.4% (2,139 of 39,257 patients), and a 30-day PE-related mortality rate of 1.7% (668 of 39,257 patients) (**Table 2**).

Patients in the lower strata of SBP levels had significantly higher rates of 30-day all-cause death compared to patients with SBP 110-129 mmHg (reference category) (adjusted odds ratio [**OR**] 2.9; 95% CI, 2.0-4.2 for SBP <70 mmHg, and OR 1.7; 95% CI, 1.4-2.1 for SBP 70-89 mmHg] (**Table 2**). Patients in the higher strata of SBP had significantly lower rates of 30-day all-cause mortality compared with the same reference group (adjusted OR 0.7; 95% CI, 0.5-0.9 for SBP 170-190 mmHg, and OR 0.6; 95% CI, 0.4-0.9 for SBP >190 mmHg] (**Table 2**). Consistent findings were also observed for 30-day PE-related death. As compared with patients in the reference stratum of SBP, patients with SBP <70

mmHg, and patients with SBP 70-89 mmHg had a 4.4- and 2.6-fold greater risk of 30-day PE-related death, respectively. Alternatively, patients with SBP 170-190 mmHg, and patients with SBP >190 mmHg had a nonsignificant reduction in the adjusted odds of 30-day PE-related death of 30%. Analyses of the SBP-mortality by decile of SBP are shown in **Figure 1**. A definitive SBP threshold where mortality rates plateaued did no appear to exist, with mortality differences being greatest for SBP <70 mmHg.

Of the 39,257 patients with acute symptomatic PE, 256 (0.6%; 95% CI, 0.6-0.7%) had an episode of nonfatal recurrence, and 1,145 (2.9%; 95% CI, 2.7-3.1%) had a nonfatal major bleeding event within the first 30 days after initiation of therapy. After adjustment for all covariates, we did not find a significant relationship between admission SBP levels and risk for recurrence (adjusted OR 2.2; 95% CI, 0.5-9.2 for SBP <70 mmHg) or major bleeding (adjusted OR 1.5; 95% CI, 0.7-3.3 for SBP <70 mmHg) (**Table 2**).

To explore the sensitivity of our findings, we repeated the analysis with varying assumptions about the patient population and hospitals (**Table 3**). Our results were not affected by the exclusion of younger patients (i.e., age less than 50 years), patients who received reperfusion therapies, or exclusion of the outlier hospitals.

DISCUSSION

In this cohort study of patients with acute symptomatic PE, we found an inverse linear relationship between admission SBP levels and 30-day all-cause and PE-related mortality, after use of various adjustment techniques. The highest mortality was observed among patients with admission SBP <70 mmHg, with lower mortality rates observed for SBP of at least 130 mmHg. In contrast, compared with the normal SBP group, the risk of recurrent VTE or major bleeding was not significantly higher in low or high SBP groups.

The association between SBP level on hospital admission and prognosis of patients with acute PE is not new. In fact, hemodynamic status remains the

most important short-term prognostic factor for patients with acute PE (20). However, this study is among the first that is adequately powered to evaluate the association between the full range of admission SBP and mortality following acute PE, and confirms that having a low SBP (<110 mmHg) was associated with an increased risk for death (both all-cause and PE-related mortality). In addition, having high SBP levels (>130 mm Hg) was associated with lower risks. In our study, patients with lower SBP were also those with more signs of clinical severity (tachycardia, hypoxemia, high-risk sPESI, right ventricle dysfunction, and myocardial injury). All these variables have been associated with worse outcomes in patients with acute PE (21, 22) and are likely to carry residual confounding, accounting, in part, for the reported associations.

In this study, we expanded previous reports by providing the full range of admission SBP and mortality following acute PE, and could serve as a resource to inform discussions around PE management, including use of thrombolytic therapies. These findings have important practical implications. Many practice guidelines use a SBP <90 mmHg as the main criterion for identifying patients with acute PE who should receive thrombolytic therapy (7, 8). However, according to our data, a SBP <90 mmHg increased the risk of 30-day PE-related mortality by 2.6-fold (absolute risk, 13.6%), while thrombolysis increased the risk of major bleeding by 2.2-fold (absolute risk, 15.4%) compared with anticoagulation in 280 patients with unstable PE from 3 real-life registries (23). These analyses also could be useful for research purposes, and the advance of design and analysis of clinical trials in PE. For example, they could provide a more evidenced informed approach to patient selection in trials of reperfusion treatments.

Unlike other cardiovascular diseases, in patients with acute PE the association between SBP and mortality did not show a J-shape association. In fact, our study showed that high SBP levels were protective for all-cause and PE-related mortality. Elevated blood pressure levels on admission in patients with PE could be reflective of underlying hypertension, sympathetic surge, or a mixture of the two. Our study suggests that such a profile is indicative of markedly better outcomes. Studies of patients with atrial fibrillation treated with vitamin K

antagonists (**VKA**) have demonstrated that higher levels of SBP were associated with an increased risk for hemorrhagic complications (24). However, we failed to confirm these data in the population of patients with acute symptomatic PE. Similar to our results, Kooiman et al. found that hypertension (i.e., SBP >160 mmHg) was not an independent predictor of major bleeds during VKA treatment for acute VTE (25).

This study has several limitations. First, although SBP was measured around the time of PE diagnosis, the RIETE protocol did not require a strict time window for measurement of SBP and other vital signs. Further, there were no subsequent measurements of SBP in RIETE. In addition, RIETE does not include information related to use of vasopressors. Therefore, it is possible that some patients with PE receiving vasopressor therapy have been misclassified as having a normal blood pressure. However, the direction of this bias is toward null. In fact, despite this limitation, we noticed a strong association between reported SBPs and short-term outcomes.

In conclusion, in a large study of patients with acute PE, there was a negative linear association between SBP at presentation and all-cause, as well as PE-related mortality. Although standard dichotomization of SBP (I.e., SBP <90 vs. $\geq$ 90 mmHg) may be useful for guideline recommendations, our results will allow for more accuracy regarding clinical decision-making. Standardization of timing for measurement of SBP, and assessment of the prognostic significance of its serial measurement in a formal study in future can further elucidate the impact of isolated and serial SBP measurements on outcomes of patients with PE.

Author contributions

Study concept and design: Quezada, Jimenez, Bikdeli, Moores, Monreal.

Acquisition of data; analysis and interpretation of data; statistical analysis: Quezada, Jimenez, Bikdeli, Moores, Porres-Aguilar, Aramberri, Lima, Ballaz, Yusen, Monreal.

Critical revision of the manuscript for important intellectual content: Quezada, Jimenez, Bikdeli, Moores, Porres-Aguilar, Aramberri, Lima, Ballaz, Yusen, Monreal.

Study supervision: Jiménez, Monreal.

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

Dr. Bikdeli reports that he serves as experts on behalf of plaintiffs in litigation related to a specific type of IVC filters. The current study is the idea of the investigators and not performed at the request of a third party.

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Appendix

Coordinator of the RIETE Registry: Manuel Monreal.

RIETE Steering Committee Members: Paolo Prandoni, Benjamin Brenner and Dominique Farge-Bancel.

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RIETE Registry Coordinating Center: S & H Medical Science Service.

APPENDIX

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Ruiz J, Ruiz-Sada P, Sahuquillo JC, Sala-Sainz MC, Salgueiro G, Sampériz A, Sánchez-Cámara S, Sánchez-Martínez R, Sánchez-Muñoz-Torrero JF, Sancho T, Soler S, Suárez S, Suriñach JM, Tiberio G, Tolosa C, Torres MI, Trujillo-Santos J, Uresandi F, Valero B, Valle R, Vela JR, Vidal G, Villares P; ARGENTINA: Gutiérrez P, Vázquez FJ, Vilaseca A; BELGIUM: Vanassche T, Vandenbriele C, Verhamme P; CZECH REPUBLIC: Hirmerova J, Malý R; ECUADOR: Salgado E; FRANCE: Benzidia I, Bertoletti L, Bura-Riviere A, Debourdeau P, Farge-Bancel D, Helfer H, Hij A, Mahé I, Moustafa F; GERMANY: Schellong S; ISRAEL: Braester A, Brenner B, Tzoran I; IRAN: Sharif-Kashani B; ITALY: Barillari G, Bilora F, Bortoluzzi C, Brandolin B, Ciammaichella M, Dentali F, Di Micco P, Imbalzano E, Landolfi R, Maida R, Mastroiacovo D, Mumoli N, Pace F, Pesavento R, Pomero F, Prandoni P, Quintavalla R, Rocci A, Siniscalchi C, Tufano A, Visonà A, Vo Hong N, Zalunardo B; LATVIA: Kalejs RV, Skride A, Strautmane S; REPUBLIC OF MACEDONIA: Bosevski M, Zdraveska M; SWITZERLAND: Bounameaux H, Mazzolai L; USA: Bikdeli B, Caprini J, Tafur AJ; VIETNAM: Bui HM.

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Figure 1. Adjusted associations between systolic blood pressure and A) all-cause mortality and B) PE-related death. All models are adjusted for age, sex, cancer, immobilization, chronic lung disease, chronic heart disease, heart rate, arterial oxyhemoglobin saturation, simplified Pulmonary Embolism Severity Index, creatinine levels, and hemoglobin levels at hospital admission.

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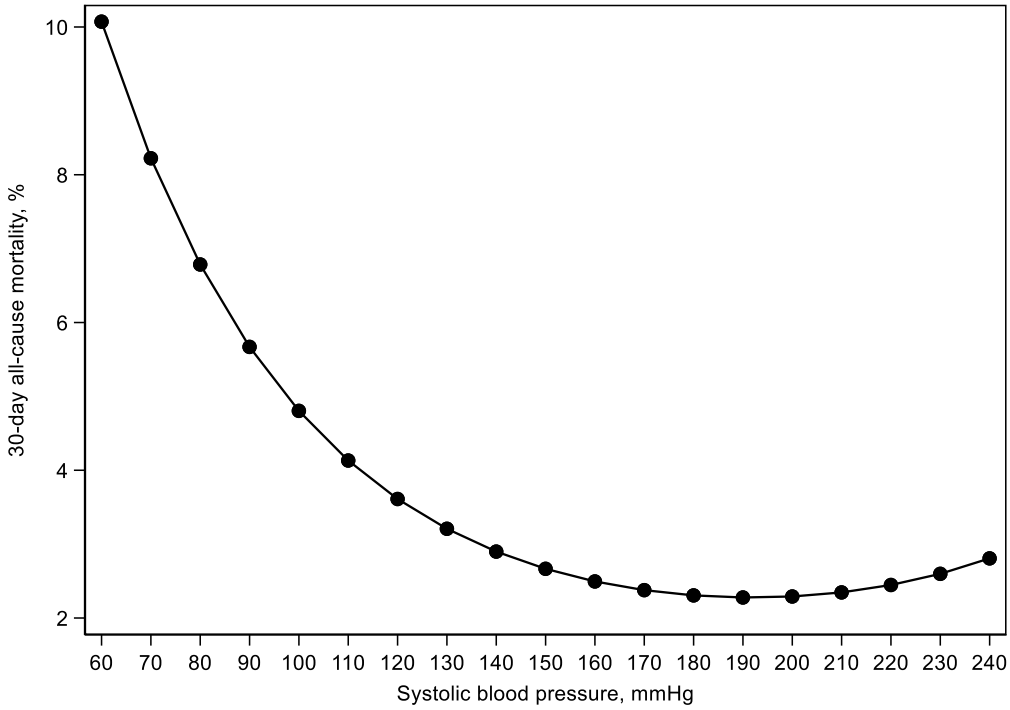
Figure 1.

A)



B)

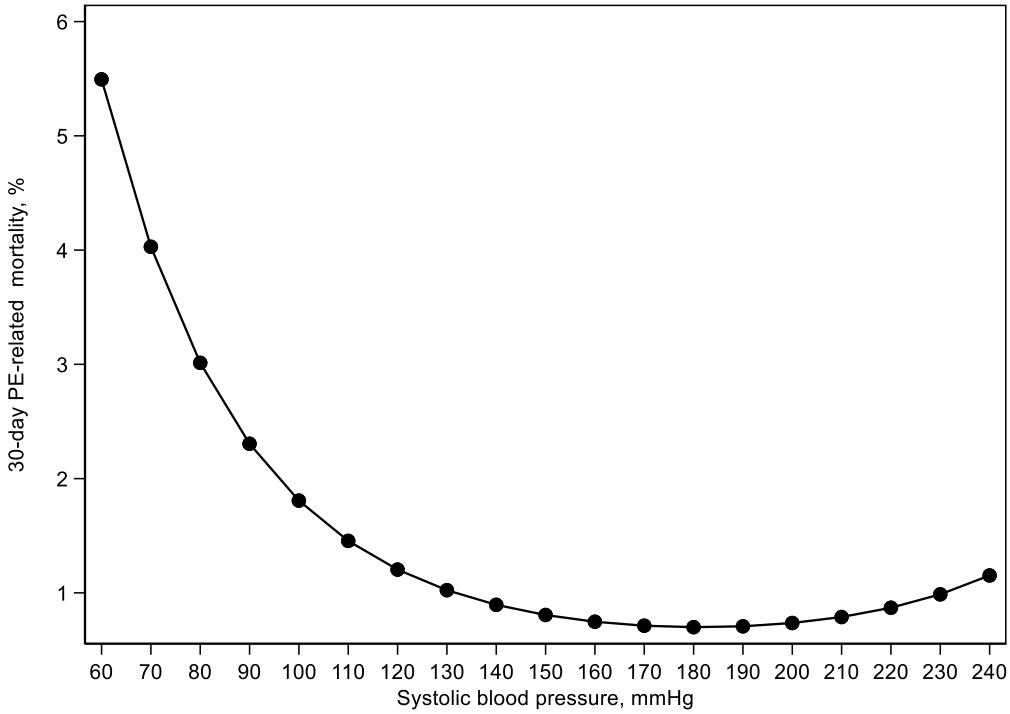


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Table 1. Baseline characteristics by admission systolic blood pressure

	Admission systolic blood pressure, mmHg								
Characteristic	**<70**	**70-<90**	**90-<110**	**110-<130**	**130-<150**	**150-<170**	**170-<190**	**≥190**	**P value**
Clinical characteristics,									
No. (%) of patients	206 (0.5)	1,147 (2.9)	5,087 (13)	12,941 (33)	12,149 (31)	5,373 (14)	1,780 (4.5)	574 (1.5)	
Age, years (mean ± SD)	68.9 (16.4)	67.8 (17.3)	65.9 (18.1)	64.3 (18.3)	67.7 (16.2)	71.4 (13.6)	73.1 (12.6)	74.7 (11.3)	<0.001
Age > 80 years, n (%)	56 (27)	299 (26)	1,193 (23)	2,650 (20)	2,780 (23)	1,449 (27)	536 (30)	190 (33)	<0.001
Male gender, n (%)	100 (49)	485 (42)	2,186 (43)	6,180 (48)	6,010 (50)	2,408 (45)	775 (44)	223 (39)	<0.001
Weight, kilograms (mean ± SD)	75.5 (14.8)	73.0 (16.6)	72.8 (15.6)	75.6 (15.9)	77.6 (16.5)	77.4 (16.4)	77.0 (16.8)	76.1 (14.9)	<0.001
Risk factors for VTE,									
History of VTE, n (%)	18 (8.7)	126 (11)	626 (12)	1,830 (14)	1,885 (16)	881 (16)	262 (15)	86 (15)	<0.001
Cancer, n (%) †	45 (22)	297 (26)	1,347 (27)	3,025 (23)	2,581 (21)	1,040 (19)	333 (19)	106 (18)	<0.001
Recent surgery, n (%) ‡	28 (14)	175 (15)	628 (12)	1,666 (13)	1,421 (12)	505 (9.4)	126 (7.1)	49 (8.5)	<0.001
Immobilization for ≥ 4 days, n (%) §	75 (36)	385 (34)	1,455 (29)	2,979 (23)	2,422 (20)	1,041 (19)	353 (20)	114 (20)	<0.001
Comorbid diseases,									
Chronic lung disease, n (%)	27 (13)	180 (16)	810 (16)	1,793 (14)	1,672 (14)	734 (14)	264 (15)	82 (14)	<0.01
Chronic heart disease, n (%)	16 (7.8)	141 (12)	616 (12)	1,049 (8.1)	1,017 (8.4)	439 (8.2)	185 (10)	61 (11)	<0.001
Recent major bleeding, n (%)	12 (5.8)	52 (4.5)	152 (3.0)	342 (2.6)	245 (2.0)	108 (2.0)	24 (1.3)	7 (1.2)	<0.001
Clinical symptoms and signs at presentation,									
Pulse, beats (mean ± SD)	107.5 (30.7)	106.0 (24.6)	96.7 (21.3)	91.6 (19.5)	90.9 (18.8)	91.4 (19.3)	92.5 (19.4)	93.3 (20.0)	<0.001
Pulse ≥ 110 beats/min, n (%)	107 (52)	547 (48)	1,480 (29)	2,385 (18)	1,996 (16)	966 (18)	350 (20)	127 (22)	<0.001
Arterial oxyhemoglobin saturation (SaO_2) < 90%, n (%)	57 (28)	376 (33)	1,195 (23)	2,126 (16)	1,936 (16)	913 (17)	309 (17)	116 (20)	<0.001
sPESI (19)									
Low-risk, n (%)	0 (0)	0 (0)	998 (20)	4,888 (38)	4,604 (38)	1,910 (36)	570 (32)	165 (29)	-
High-risk, n (%)	206 (100)	1,147 (100)	4,089 (80)	8,053 (62)	7,545 (62)	3,463 (64)	1,210 (68)	409 (71)	<0.001
Echocardiography and cardiac biomarkers, n (%)									
RV dysfunction (n = 17,079)	75 (63)	318 (55)	997 (42)	1,746 (31)	1,570 (31)	619 (28)	211 (28)	62 (27)	<0.001
BNP > 100 pg/mL (n = 3,041)	8 (62)	62 (74)	288 (74)	609 (65)	610 (62)	267 (62)	107 (66)	22 (51)	<0.01
cTnI > 0 ng/mL (n = 18,410)	78 (71)	370 (57)	1,121 (44)	2,109 (36)	1,850 (33)	852 (33)	292 (34)	83 (31)	<0.001
Laboratory findings,									
Abnormal creatinine levels (> 2 mg/dL)	84 (41)	382 (33)	1,200 (24)	2,217 (17)	2,085 (17)	956 (18)	348 (20)	127 (22)	<0.001
Hemoglobin, g/dL (mean ± SD)	12.4 (2.1)	12.3 (2.1)	12.6 (2.1)	13.0 (3.4)	13.2 (2.4)	13.3 (2.8)	13.4 (2.9)	13.5 (5.5)	<0.001
Procedures,									
Systemic thrombolysis, n (%)	53 (26)	155 (14)	213 (4.2)	218 (1.7)	162 (1.3)	50 (0.9)	13 (0.7)	1 (0.2)	<0.001
IVC filter insertion, n (%)	9 (4.4)	66 (5.8)	171 (3.4)	391 (3.0)	325 (2.7)	121 (2.3)	37 (2.1)	12 (2.1)	<0.001

Abbreviations: SD, standard deviation; VTE, venous thromboembolism; sPESI, simplified Pulmonary Embolism Severity Index; RV, right ventricle, BNP, brain natriuretic peptide; cTnI, cardiac troponin I; IVC, inferior vena cava.

[†]Active or under treatment in the last year

[‡]In the previous month

[y]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

Table 2. Event rates and logistic regression models for mortality, and separately for recurrence and bleeding, by admission systolic blood pressure

Characteristic	**<70**	**70-<90**	**90-<110**	**110-<130**	**130-<150**	**150-<170**	**170-<190**	**≥190**
No. (%) of patients	206 (0.5)	1,147 (2.9)	5,087 (13)	12,941 (33)	12,149 (31)	5,373 (14)	1,780 (4.5)	574 (1.5)
30-day all-cause mortality								
No. of deaths	39	145	491	687	481	203	72	21
Mortality, (%)	18.9	12.6	9.6	5.3	4.0	3.8	4.0	3.7
30-day all-cause mortality, OR (95% CI)								
Model 1, unadjusted	4.2 (2.9-5.9)	2.6 (2.1-3.1)	1.9 (1.7-2.1)	1 [Reference]	0.7 (0.6-0.8)	0.7 (0.6-0.8)	0.8 (0.6-1.0)	0.7 (0.4-1.1)
Model 2, adjusted for age and sex	3.7 (2.6-5.4)	2.4 (2.0-2.9)	1.8 (1.6-2.1)	1 [Reference]	0.7 (0.6-0.8)	0.6 (0.5-0.7)	0.6 (0.5-0.8)	0.5 (0.3-0.8)
Model 3, adjusted for all covariates[a]	2.9 (2.0-4.2)	1.7 (1.4-2.1)	1.5 (1.3-1.7)	1 [Reference]	0.7 (0.6-0.8)	0.7 (0.6-0.8)	0.7 (0.5-0.9)	0.6 (0.4-0.9)
30-day PE-related death								
No. of deaths	21	70	178	199	117	56	20	7
Mortality, (%)	10.2	6.1	3.5	1.5	1.0	1.0	1.1	1.2
30-day PE-related death, OR (95% CI)								
Model 1, unadjusted	7.3 (4.5-11.6)	4.2 (3.1-5.5)	2.3 (1.9-2.8)	1 [Reference]	0.6 (0.5-0.8)	0.7 (0.5-0.9)	0.7 (0.5-1.2)	0.8 (0.4-1.7)
Model 2, adjusted for age and sex	6.5 (4.0-10.4)	3.8 (2.9-5.1)	2.2 (1.8-2.7)	1 [Reference]	0.6 (0.5-0.7)	0.6 (0.4-0.8)	0.6 (0.4-0.9)	0.6 (0.3-1.3)
Model 3, adjusted for all covariates[a]	4.4 (2.7-7.2)	2.6 (1.9-3.4)	1.8 (1.5-2.2)	1 [Reference]	0.6 (0.5-0.8)	0.6 (0.5-0.9)	0.7 (0.4-1.1)	0.7 (0.3-1.4)
30-day recurrent VTE								
No. of events	3	14	34	83	81	28	11	2
Event rate, (%)	1.5	1.2	0.7	0.6	0.7	0.5	0.6	0.3
30-day recurrent VTE, OR (95% CI)								
Model 1, unadjusted	2.3 (0.7-7.3)	1.9 (1.1-3.4)	1.0 (0.7-1.6)	1 [Reference]	1.0 (0.8-1.4)	0.8 (0.5-1.2)	1.0 (0.5-1.8)	0.5 (0.1-2.2)
Model 2, adjusted for age and sex	2.5 (0.8-8.0)	2.1 (1.2-3.7)	1.1 (0.7-1.6)	1 [Reference]	1.1 (0.8-1.5)	0.9 (0.6-1.4)	1.2 (0.6-2.2)	0.7 (0.2-2.8)
Model 3, adjusted for all covariates[a]	2.2 (0.5-9.2)	1.7 (0.8-3.4)	1.0 (0.6-1.7)	1 [Reference]	1.1 (0.7-1.6)	1.2 (0.7-1.9)	1.2 (0.7-2.3)	0.7 (0.2-3.0)
30-day major bleeding								
No. of events	13	52	170	350	336	150	53	21
Event rate, (%)	6.3	4.5	3.3	2.7	2.8	2.8	3.0	3.7
30-day major bleeding, OR (95% CI)								

Model 1, unadjusted	2.4 (1.4-4.3)	1.7 (1.3-2.3)	1.2 (1.0-1.5)	1 [Reference]	1.0 (0.9-1.2)	1.0 (0.8-1.2)	1.1 (0.8-1.5)	1.4 (0.9-2.1)
Model 2, adjusted for age and sex	2.3 (1.3-4.0)	1.6 (1.2-2.2)	1.2 (1.0-1.5)	1 [Reference]	1.0 (0.8-1.1)	0.9 (0.8-1.1)	1.0 (0.7-1.3)	1.2 (0.7-1.8)
Model 3, adjusted for all covariates[a]	1.5 (0.7-3.3)	1.3 (0.9-1.9)	1.1 (0.9-1.4)	1 [Reference]	1.0 (0.9-1.3)	0.9 (0.7-1.2)	1.0 (0.7-1.4)	1.1 (0.6-2.0)

Abbreviations: OR, odds ratio; PE, pulmonary embolism; VTE, venous thromboembolism.

[a] Includes age, sex, and the following covariates: coexisting conditions (i.e., cancer, immobilization, chronic lung disease, chronic heart disease), severity of PE (i.e., heart rate, arterial oxyhemoglobin saturation, simplified Pulmonary Embolism Severity Index [sPESI]), and laboratory results (i.e., creatinine levels, hemoglobin levels) at hospital admission.

Table 3. Sensitivity analysis for PE-related mortality rates*

Model	No. of patients	No. of hospitals	Odds ratio (95% CI)
Main model	39,270	353	4.4 (2.7-7.2)
Excluding outlier hospitals†	33,142	231	3.9 (2.2-7.0)
Excluding hospitals with an annualized volume less than 5 patients per year	36,585	256	3.3 (1.9-5.8)
Excluding hospitals with an annualized volume more than 80 patients per year	34,295	344	3.9 (2.2-6.8)
Excluding patients less than 50 years old	30,770	345	4.6 (2.8-7.7)
Excluding patients less than 65 years old	24,803	338	4.1 (2.3-7.2)
Excluding patients who received reperfusion therapies‡	35,962	345	2.9 (1.5-5.7)

* Odds ratios and 95 percent confidence intervals (**CIs**) are presented comparing the lowest decile of systolic blood pressure (<70 mmHg) with the reference group (110-130 mmHg). Models were adjusted for age, sex, cancer, immobilization, chronic lung disease, chronic heart disease, heart rate, arterial oxyhemoglobin saturation, sPESI, creatinine levels, and hemoglobin levels at hospital admission. Confidence intervals take into account clustering according to center.

† Hospitals that were outliers in terms of volume were excluded because their annualized volume was less than 5 or greater than 80 patients per year.

‡ Systemic thrombolysis, catheter-directed therapy, or surgical embolectomy.

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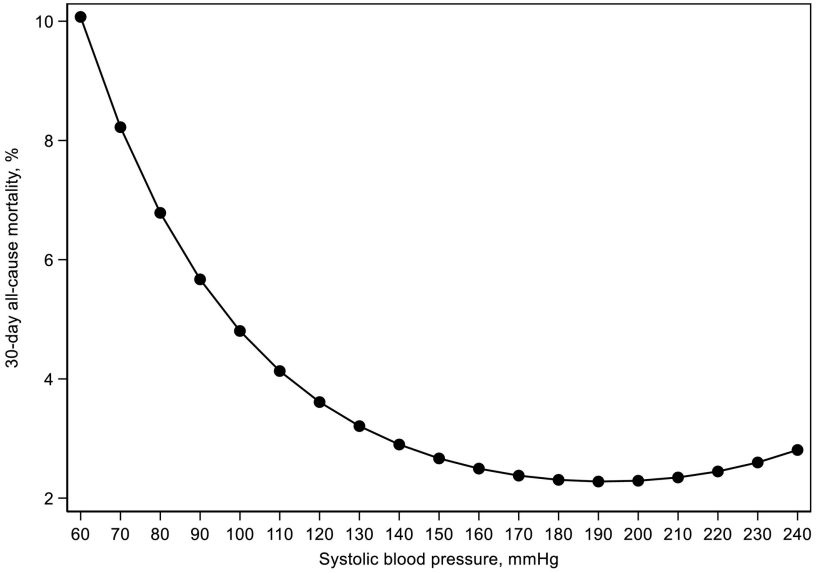
HIGHLIGHTS

- The optimal cutoff for systolic blood pressure (**SBP**) level to define high-risk pulmonary embolism (**PE**) remains to be defined.
- There is a linear inverse relationship between admission SBP and 30-day all-cause and PE-related mortality.
- The highest mortality is observed in patients with SBP <70 mmHg.

A)


10
8
6
4
2
30-day all-cause mortality, %
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Systolic blood pressure, mmHg

B)

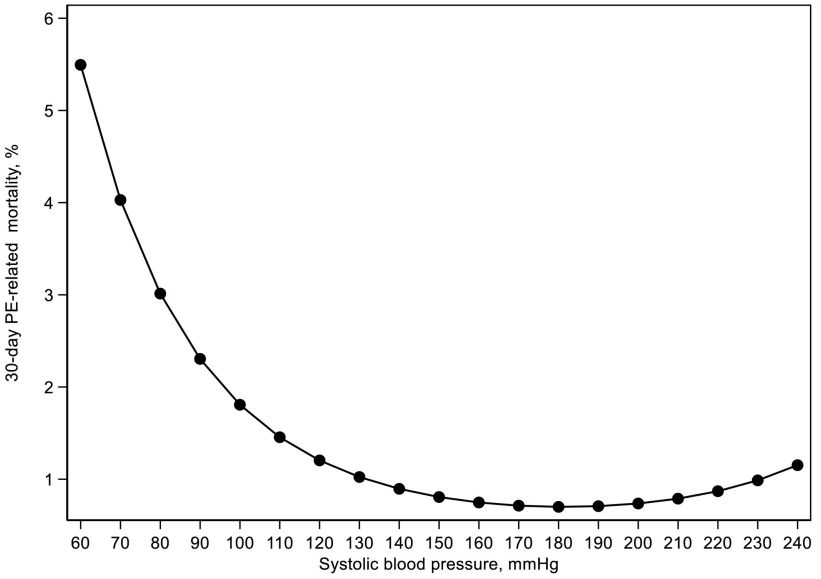
6
5
4
3
2
1
30-day PE-related mortality, %
60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220 230 240
Systolic blood pressure, mmHg

Figure 1