

ORIGINAL ARTICLE

Right ventricular dysfunction on echocardiography to predict mortality in acute pulmonary embolism: an individual patient data meta-analysis

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Abstract

Background: In patients with acute pulmonary embolism (PE), echocardiography is currently used to detect right ventricular dysfunction (RVD) and to guide risk stratification and treatment decisions. However, the prognostic value of individual RVD parameters in echocardiography, as well as their combinations, remains uncertain.

Objectives: To assess the association between individual RVD parameters on echocardiography and short-term all-cause death and PE-related death, and to evaluate whether combinations of parameters improve risk stratification.

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Methods: We performed an individual patient data meta-analysis of studies reporting on echocardiographic findings and 30-day mortality in patients with acute PE. Outcomes included short-term all-cause death and PE-related death.

Results: Overall, 9233 patients were included, with a 7% rate (95% CI, 6%-9%) of short-term all-cause death. Tricuspid annular plane systolic excursion < 16 mm, an estimated pulmonary artery pressure > 30 mm Hg, a right-to-left ventricle diameter ratio > 1, RV hypokinesis, paradoxical septal motion, and dilated RV were associated with short-term all-cause death and PE-related death in univariate analysis. Among 8905 patients with at least 3 RVD parameters assessed, having a single abnormal parameter was not associated with short-term all-cause death (odds ratio [OR], 1.17; 95% CI, 0.92-1.47), whereas having 2 (OR, 1.52; 95% CI, 1.19-1.54) or 3 or more parameters was (OR, 2.33; 95% CI, 1.79-3.03). Among the couple of parameters, a trend toward an increasing association with death was observed for the combination of right-to-left ventricle diameter ratio > 1 and tricuspid annular plane systolic excursion < 16 mm (OR, 2.49; 95% CI, 1.23-5.01) compared with either parameter alone.

Conclusion: In acute PE patients, RVD parameters from echocardiography are associated with short-term all-cause and PE-related death. The combination of at least 2 RVD parameters identifies PE patients at an increased risk for death.

KEYWORDS

echocardiography, pulmonary embolism, right ventricular dysfunction, mortality

1 | INTRODUCTION

Pulmonary embolism (PE) is a potentially life-threatening disease [1]. Right ventricular (RV) failure plays a crucial role in the occurrence of death in patients with acute PE, and it is advocated to identify those at an increased risk of death. In fact, risk stratification should inform decision-making for patients with acute PE regarding disposition, treatment, and early discharge. However, evidence-based harmonization of guidelines on strategies for risk stratification is awaited [2].

Several studies reported on the association between RV dysfunction (RVD) on echocardiography and short-term all-cause death in patients with acute PE. However, the definition of RVD is highly heterogeneous across clinical practice and clinical studies, which may explain the discrepancies in the available results [3]. In fact, different measures of RVD on echocardiography may have varying accuracies in predicting prognosis [3,4].

This individual patient data meta-analysis (IPDMA) aimed to assess the role of individual RVD parameters on echocardiography and their combinations in predicting short-term all-cause death and PE-related death, and to support the standardization of the definition of RVD in this setting (PROSPERO CRD42022384200).

2 | METHODS

The study was designed as an IPDMA of observational studies and followed the Meta-Analysis of Observational Studies in Epidemiology

and Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Individual Participant Data (PRISMA-IPD) [5].

2.1 | Search strategy and selection criteria

PubMed and Embase were searched from inception to November 2023 for studies reporting on the prognostic role of RVD on echocardiography in patients with acute PE (International Prospective Register of Systematic Reviews [PROSPERO] CRD42022384200). The search strategy is reported in the [Supplementary Methods](#). Two investigators (L.A.C. and M.V.U.) independently reviewed titles and abstracts and determined study eligibility. Candidate records were then reviewed and selected for data retrieval; discrepancies were resolved through discussion with a third researcher (C.B.). Studies were eligible for the IPDMA if the following were satisfied: (a) inclusion of patients with confirmed acute PE; (b) echocardiography performed early after PE diagnosis (within 72 hours); (c) available data concerning short-term all-cause (ie, within the first 30 days) and/or PE-related death. The lead investigators of the selected studies were invited to provide deidentified individual patient data (IPD) of the study patients. Individual patient information was collected ([Supplementary Method](#)). Data on all the available parameters of RVD on echocardiography (RV diameter, RV-to-left ventricle [LV] diameter ratio, qualitative RV free wall hypokinesis, estimated pulmonary artery pressure [PAP], tricuspid annular plane systolic excursion [TAPSE],

McConnell's sign, inferior vena cava collapsibility, tricuspid regurgitation peak gradient, and paradoxical septum movement) were collected. The risk of bias for the included studies was independently assessed using Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) [6]. IPD were centrally homogenized and merged into a pooled database housed at the University of Perugia. Variables were identified, measurements verified, and comparisons with individual reports were made. Discrepancies with published data were resolved by contacting the principal investigators.

2.2 | Study outcome

The primary study outcome was short-term all-cause death. The secondary outcome was short-term PE-related death. For the

purpose of this study, short-term all-cause death was defined as death occurring in-hospital or within 30 days following the diagnosis of acute PE. If both were available, the 30-day outcome was used for analysis. The definition of PE-related death was retained as per the original criteria used in the individual studies.

2.3 | Statistical analyses

We conducted an IPDMA of studies reporting on echocardiographic findings and short-term all-cause death in patients with acute PE. Echocardiographic parameters of RVD were analyzed as binary variables (present/absent) based on predefined cutoffs from current European guidelines: TAPSE < 16 mm, RV diameter > 30 mm, systolic PAP > 30 mm Hg, and RV-to-LV ratio > 1.

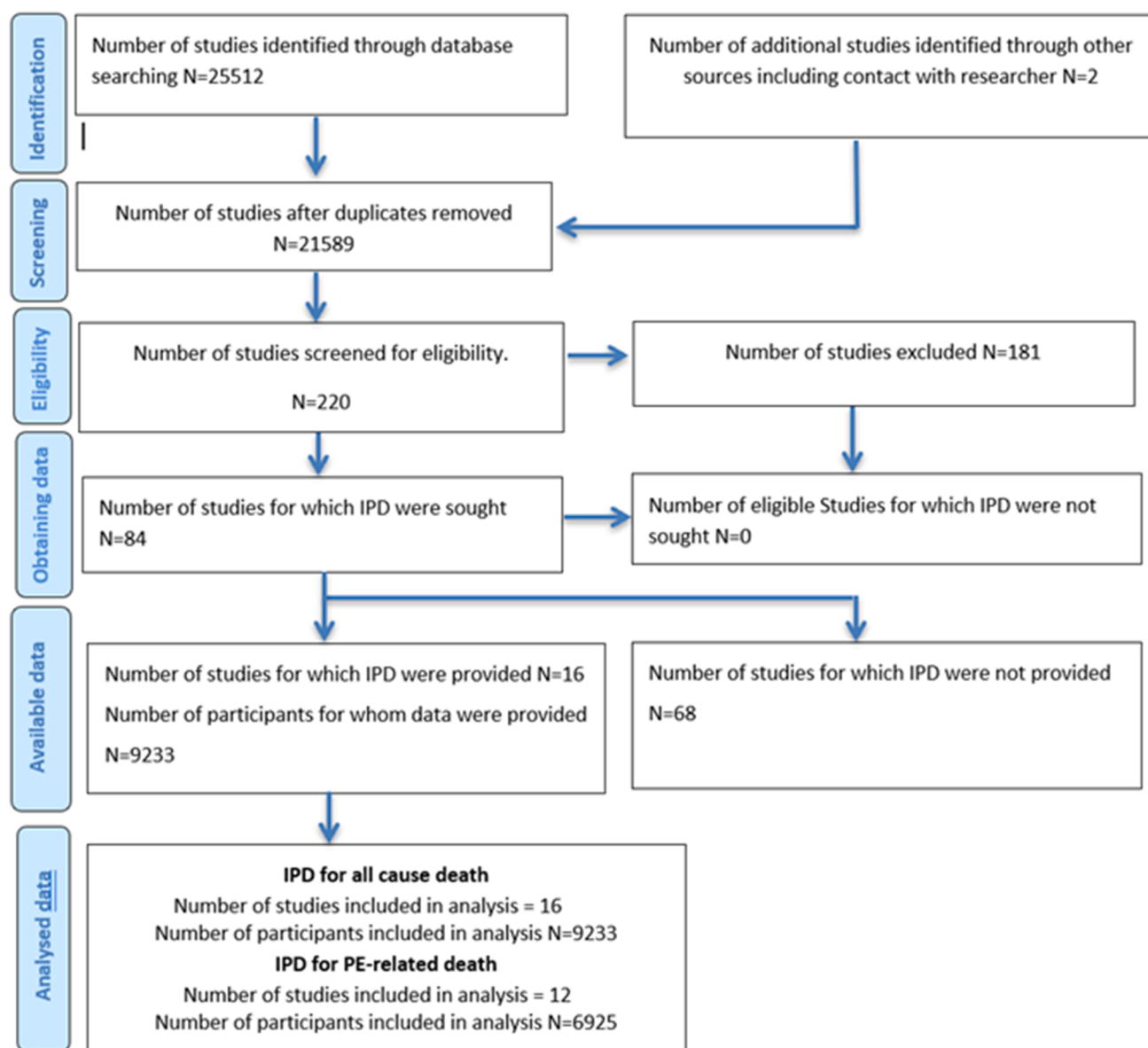


FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of individual patient data meta-analysis. IPD, individual patient data; PE, pulmonary embolism.

Separate datasets were created for each RVD parameter by excluding studies in which the parameter was systematically missing. Within each dataset, missing values were handled nonsystematically via multiple imputations, preserving the clustering of the original study ([Supplementary Methods](#)) [7]. The prognostic value of each RVD parameter was assessed individually and in combinations. To explore additive risk, we examined the number of abnormal RVD findings per patient (none, 1, 2, or ≥ 3) and also evaluated the predictive value of specific pairs of parameters, avoiding potentially collinear combinations.

Patients were considered hemodynamically stable according to the original study definitions. Baseline characteristics were summarized using appropriate descriptive statistics. Whenever possible, the simplified PE Severity Index (sPESI) was recalculated from baseline data; otherwise, it was considered as reported in the original study.

Primary analysis was conducted using a one-stage IPDMA approach via generalized linear mixed-effects models, including a random effect for each study. A 2-stage IPDMA was performed as a confirmatory analysis. Heterogeneity was assessed by τ^2 and a model-based I^2 in the one-stage model, and by Cochran's Q (chi-squared), I^2 , and τ^2 in the 2-stage model; 95% prediction intervals were reported for both. To explore potential interactions between echocardiographic parameters, logistic regression models including interaction terms between combinations of parameters were calculated.

Continuous RVD parameters were modeled as linear predictors of short-term all-cause death in logistic regression. Linearity assumptions were assessed using a logistic regression model for each continuous parameter. For selected variables, continuous measures were also categorized into normal, moderately abnormal, and severely abnormal values based on predefined thresholds.

Diagnostic performance (sensitivity, specificity, positive predictive value [PPV], and negative predictive value [NPV]) of each RVD parameter was evaluated using receiver operating characteristic curves. Optimal thresholds were determined via Youden's index to visually summarize discrimination performance, without threshold optimization. Sensitivity analyses were conducted stratified by hemodynamic status, sPESI score, and cancer status.

The remaining details of the Methods section are provided in the [Supplementary Methods](#).

3 | RESULTS

3.1 | Included studies

Eighty-four studies fulfilled the inclusion criteria. After contacting the lead authors, 16 IPD datasets were obtained and pooled into a joint database comprising 9233 patients with acute PE ([Figure 1](#)) [8–23].

Characteristics of the included studies and the risk-of-bias assessment are reported in [Supplementary Tables S1](#) and [S2](#). Seven studies included all-comers with PE, whereas 9 included only hemodynamically stable patients. Echocardiography was obtained mainly within 24 to 48 hours following the diagnosis of PE.

Study outcomes were reported at 30 days, 5 days, or during hospital stay in 5, 2, and 9 studies, respectively. For studies providing original outcome data at 5 days, unpublished data on study outcome events at 30 days were required and used in the present study. The proportion of missing data for each variable across the individual studies is reported in [Supplementary Table S3](#). Among the RVD parameters, the highest proportion of missing values was observed for estimated PAP (32.4%).

3.2 | Patients

The main features of the study patients are reported in [Table 1](#).

RVD parameters reported in at least 2 studies and considered for analyses were TAPSE < 16 mm, estimated PAP > 30 mm Hg, RV-to-LV diameter ratio > 1, RV free wall hypokinesis, McConnell's sign, paradoxical septal motion, and RV diameter > 30 mm. RV free wall hypokinesis and McConnell's sign – both qualitative indicators of regional wall motion abnormality – were pooled into a single variable ("RV hypokinesis") for the primary analyses.

TABLE 1 Characteristics of study patients (N = 9233).

Characteristics	N studies with data available; N patients	N (%)
Female sex	16; 9233	4710 (51.0)
Age (y), median (IQR)	16; 9231	69 (55–78)
Age > 80 y	16; 9231	1367 (14.8)
Systolic blood pressure < 90 mm Hg	15; 8275	429 (4.6)
HR > 110 bpm	15; 8623	1777 (19.2)
Oxygen saturation < 90%	14; 3539	643 (7.0)
Cancer	14; 7013	1584 (17.2)
Cardiopulmonary disease	16; 5951	1343 (22.6)
Chronic heart failure ^a	12; 5771	554 (9.60)
Chronic lung disease ^a	13; 6192	931 (10.1)
sPESI > 0	16; 9233	4250 (46.0)
Short-term all-cause death at 30 d	15; 9154	648 (7.0)
PE-related death at 30 d	11; 6925	281 (3.0)
RV-to-LV > 1 apical 4-chamber	12; 8586	2407 (26.1)
TAPSE < 16 mm	11; 6207	1392 (18.6)
RV diameter > 30 mm	10; 5541	2363 (36.2)
RV hypokinesis	10; 5058	1194 (23.6)
Paradoxical septum motion	7; 3972	658 (12.7)
Estimated PAP > 30 mm Hg	5; 5342	1675 (43.1)

HR, heart rate; PAP, estimated pulmonary artery pressure; PE, pulmonary embolism; RV, right ventricle; RV-to-LV, right-to-left ventricle diameter ratio; sPESI, simplified Pulmonary Embolism Severity Index; TAPSE, tricuspid annular plane systolic excursion.

^a Cardiopulmonary disease (1343/5951).

3.3 | RVD parameters and death in all-comers and in hemodynamically stable patients

Each of the assessed RVD parameters was associated with an increased risk of short-term all-cause death and an increased risk of PE-related death in all-comers (Table 2). These findings were confirmed in 2-stage IPD meta-analyses, which showed consistent results (Supplementary Figure S1).

Pooled PPV and NPV and receiver operating characteristic curves of each RVD parameter for short-term all-cause death and PE-related death in all-comers are reported in Table 3 and Supplementary Figures S2 and S3.

After adjusting for hemodynamic instability, the association between individual RVD parameters and short-term all-cause death or PE-related death was confirmed, except for RV diameter > 30 mm (Supplementary Table S4). In this analysis, the association between RV diameter > 30 mm and PE-related death was confirmed after the exclusion of 1 study with a low ranking in the quality assessment (odds ratio [OR], 2.06; 95% CI, 1.35-3.14).

In hemodynamically stable patients, reduced TAPSE, an RV-to-LV diameter ratio > 1, RV hypokinesis, and paradoxical septal motion were associated with an increased risk of short-term all-cause death (Supplementary Table S5). PPV and NPV of RVD parameters for short-term all-cause death in hemodynamically stable patients are reported in Table 3 and Supplementary Table S6.

3.4 | Severity of RVD and clinical outcome

Combinations of parameters available for interaction analyses were: RV hypokinesis and RV dilation (6 studies, 3154 patients); RV-to-LV diameter ratio > 1 and TAPSE < 16 mm (10 studies, 5462 patients); and RV-to-LV diameter ratio > 1 and RV hypokinesis (8 studies, 3527 patients; Figure 2). A trend toward a stronger association with death was observed for the combination of RV-to-LV diameter ratio > 1 and TAPSE < 16 mm, and for RV hypokinesis and RV-to-LV diameter ratio > 1 compared with either parameter alone or normal parameters. No incremental prognostic value was observed for any of the other tested combinations.

Overall, 13 studies (8905 patients) reported on at least 3 RVD parameters per patient. In these patients, the increasing number of RVD parameters (1, 2, or at least 3) was associated with an increasing risk of short-term all-cause death and of PE-related death (Table 4).

3.5 | RV-to-LV diameter ratio, TAPSE, RV diameter, and PAP: analyses of continuous values

Continuous values of RV-to-LV diameter ratio, TAPSE, RV diameter, and PAP were available for 3187, 4696, 3056, and 2864 patients, respectively. All patients with PAP available as a continuous value were hemodynamically stable. Increasing values of the RV-to-LV

TABLE 2 Short-term all-cause death and pulmonary embolism-related death in all-comers by right ventricular dysfunction parameters: incidence rates and univariate comparisons.

RVD parameter	Incidence rates, WMI		Estimated risk		I ² (%) ^a for short-term all-cause death/ PE-related death
	Short-term all-cause death % (95% CI)	PE-related death % (95% CI)	Short-term all-cause death OR (95% CI/PI)	PE-related death OR (95% CI/PI)	
All-comers					
TAPSE < 16 mm vs ≥16 mm	10.6 (3.3-17.9) vs 5.8 (3.9-7.5)	5.8 (0.9-10.6) vs 1.9 (0.4-3.4)	1.78 (1.46-2.16/1.33-2.45)	2.22 (1.58-3.17/1.58-3.17)	0/0
RV-to-LV > 1.0 vs ≤1.0	9.1 (5.8-12.5) vs 5.9 (2.9-9.9)	5.6 (3.5-7.7) vs 1.3 (0.07-3.5)	1.59 (1.33-1.92/1.25-1.92)	2.59 (1.88-3.57/1.90-3.89)	0/0
RV hypokinesis (RV free wall or McConnell's sign), present vs absent	12.1 (6.6-17.6) vs 6.8 (3.7-9.9)	7.1 (2.9-11.3) vs 2.9 (0.2-6.2)	1.79 (1.45-2.21/1.51, 2.54)	2.42 (1.82-3.21/1.81, 3.75)	0/0
Paradoxical septum motion, present vs absent	10.9 (2.5-24.5) vs 6.9 (3.9-9.8)	8.0 (5.2-10.9) vs 4.3 (3.4-5.1)	1.44 (1.10-1.87/0.35-8.66)	2.09 (1.38-3.17/0.09-39.33)	25/59
RV diameter > 30 mm vs ≤30 mm	7.6 (0.1-15.0) vs 6.5 (4.4-8.6)	4.9 (2.5-12.3) vs 3.5 (2.5-9.58)	1.29 (1.05-1.59/0.54-2.62)	1.42 (1.00-2.02/0.17-16.24)	33/57
Estimated PAP ≤ 30 vs >30 mm Hg	8.0 (4.2-11.8) vs 5.7 (3.5-7.7)	4.3 (0.1-8.6) vs 2.4 (0.1-4.9)	1.52 (1.20-1.91/0.86-1.85)	1.79 (1.20-2.50/1.30-6.71)	0/0

OR, odds ratio; PAP, estimated pulmonary artery pressure; PE, pulmonary embolism; PI, prediction interval; RV, right ventricle; RVD, right ventricular dysfunction; RV-to-LV, right-to-left ventricle diameter ratio; sPESI, simplified Pulmonary Embolism Severity Index; TAPSE, tricuspid annular plane systolic excursion; WMI, weighted mean incidence.

^a I² was derived from random-effects models.

TABLE 3 Accuracy of individual echocardiographic parameters in predicting short-term all-cause death and pulmonary embolism-related death in all-comers and in hemodynamically stable patients.

Short-term all-cause death	All-comers		HD stable	
	PPV (95% CI)	NPV (95% CI)	PPV (95% CI)	NPV (95% CI)
TAPSE < 16 mm	0.14 (0.12-0.16)	0.94 (0.94-0.95)	0.08 (0.07-0.09)	0.95 (0.94-0.96)
RV-to-LV > 1	0.11 (0.09-0.12)	0.94 (0.94-0.95)	0.08 (0.07-0.08)	0.96 (0.95-0.97)
RV hypokinesis (RV free wall or McConnell's sign)	0.12 (0.11-0.14)	0.93 (0.92-0.93)	0.13 (0.11-0.16)	0.94 (0.94-0.95)
Paradoxical septum motion	0.10 (0.09-0.12)	0.95 (0.94-0.96)	0.08 (0.07-0.10)	0.94 (0.93-0.96)
RV diameter > 30 mm	0.10 (0.09-0.12)	0.96 (0.95-0.96)	0.09 (0.08-0.11)	0.96 (0.95-0.97)
Estimated PAP >30 mm Hg	0.09 (0.074-0.10)	0.94 (0.93-0.95)	0.11 (0.09-0.13)	0.95 (0.94-0.96)
PE-related death				
TAPSE < 16 mm	0.04 (0.03-0.05)	0.98 (0.98-0.99)	0.05 (0.04-0.07)	0.98 (0.97-0.98)
RV-to-LV > 1	0.05 (0.046-0.06)	0.99 (0.98-0.99)	0.05 (0.04-0.06)	0.98 (0.97-0.98)
RV hypokinesis (RV free wall or McConnell's sign)	0.06 (0.05-0.07)	0.99 (0.98-0.99)	0.06 (0.05-0.08)	0.97 (0.96-0.98)
McConnell's sign	0.12 (0.07-0.19)	0.97 (0.95-0.98)	0.08 (0.04-0.15)	0.96 (0.94-0.98)
Paradoxical septum motion	0.12 (0.09-0.17)	0.96 (0.95-0.97)	0.06 (0.03-0.09)	0.97 (0.97-0.98)
RV diameter > 30 mm	0.05 (0.04-0.07)	0.98 (0.98-0.99)	0.04 (0.03-0.05)	0.96 (0.96-0.97)
Estimated PAP > 30 mm Hg	0.05 (0.044-0.06)	0.98 (0.97-0.98)	0.04 (0.03-0.05)	0.97 (0.86-0.98)

HD, hemodynamically; NPV, negative predictive value; PAP, estimated pulmonary artery pressure; PE, pulmonary embolism; PPV, positive predictive value; RV, right ventricle; RV-to-LV, right-to-left ventricle diameter ratio; TAPSE, tricuspid annular plane systolic excursion.

diameter ratio (OR, 1.66; 95% CI, 1.03-2.65; $P = .03$) and decreasing values of TAPSE (OR, 0.92; 95% CI, 0.89-0.94; $P < .001$) were associated with a risk of short-term all-cause death in all-comers, whereas this was not the case for RV diameter (Figure 3A). The analysis of continuous values for hemodynamically stable patients is reported in Figure 3B.

Continuous values were then categorized into normal, moderately abnormal, or severely abnormal. A trend toward a linear increase in mortality was confirmed across categories of TAPSE (TAPSE 10-16 mm: OR, 2.20; 95% CI, 1.74-2.78; TAPSE < 10 mm: OR, 3.02; 95% CI, 1.74-5.24), RV-to-LV diameter ratio (RV-to-LV 1-1.5: OR, 1.60; 95% CI, 1.17-2.20; RV-to-LV > 1.5: OR, 1.53; 95% CI, 0.76-3.07), and PAP (PAP 36-45 mm Hg: OR, 1.50; 95% CI, 1.07-2.10; PAP > 45 mm Hg: OR, 1.86; 95% CI, 1.21-2.87) in all-comers (Supplementary Figures S4 and S6) and in hemodynamically stable patients (Supplementary Figure S5).

3.6 | Role of RVD parameters in patients' subgroups

Consistently with the main results, associations between individual echocardiographic parameters and short-term all-cause death were confirmed in studies conducted after 2019 (TAPSE < 16 mm vs ≥ 16 mm: OR, 1.54; 95% CI, 1.09-2.17; RV-to-LV diameter ratio > 1.0 vs ≤ 1.0 : OR, 1.43; 95% CI, 1.02-2.01; RV diameter > 30 mm vs ≤ 30 mm: OR, 1.34; 95% CI, 0.93-1.94).

In patients with sPESI = 0, all RVD parameters, except estimated PAP > 30 mm Hg, were associated with an increased risk of short-term all-cause death. Analyses in patients with sPESI ≥ 1 or sPESI ≥ 1 but no cancer are reported in Supplementary Table S7.

4 | DISCUSSION

Our IPDMA, which includes more than 9200 patients with acute PE who received early echocardiography, provides robust evidence on the association between single parameters of RVD and short-term all-cause or PE-related death. These associations were observed in both the overall population and in hemodynamically stable patients.

Reduced TAPSE, an increased RV-to-LV diameter ratio, RV hypokinesis, and paradoxical septal motion were the parameters most consistently associated with mortality across analyses. Among patients with multiple RVD parameters available, the presence of only 1 abnormal parameter was not associated with increased mortality. In contrast, the presence of 2 or more abnormal parameters was associated with a higher risk of short-term all-cause death and PE-related death. The strength of the associations was greater for PE-related death than for short-term all-cause death.

The prognostic relevance of RVD on echocardiography is well recognized in international guidelines, which recommend its assessment to diagnose PE-related shock, identify hemodynamically stable patients at increased risk of death, and guide early management [24].

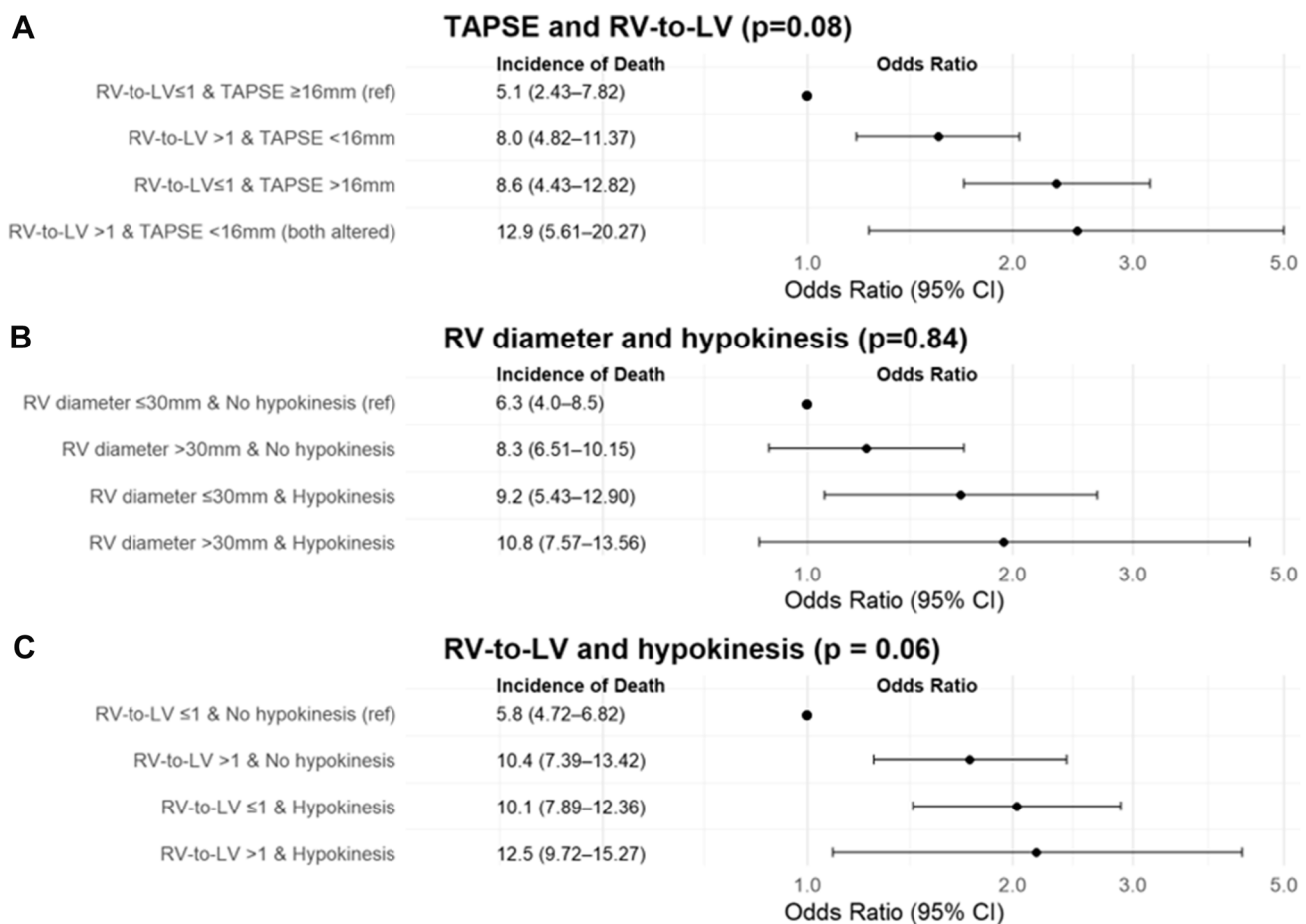


FIGURE 2 Association between the combinations of echocardiographic parameters and short-term all-cause death in all-comers. Incidence of death, weighted incidence; RV, right ventricle; RV-to-LV, right-to-left ventricle diameter ratio; TAPSE, tricuspid annular plane systolic excursion.

Although this association has been repeatedly confirmed in prior studies, some large cohort studies have failed to replicate these findings [25]. Such inconsistencies may be due to heterogeneity across study populations and, importantly, to the lack of standardization in the definition of RVD. Indeed, among 40 studies included in a recent meta-analysis of aggregate data, 16 different definitions of RVD on echocardiography were used, highlighting the urgent need for standardized criteria [4].

All individual RVD parameters were associated with both short-term all-cause death and PE-related death in univariate analyses. Notably, the risk of death increased progressively with the number of abnormal parameters observed. This finding is physiologically plausible: acute PE leads to an abrupt rise in PAP, causing RV dilation and impaired systolic function, often resulting in RV hypokinesis and reduced TAPSE [26]. Increased intracavitary pressure can also lead to tricuspid regurgitation, decreased LV filling, and reduced systemic output. Our findings support defining severe RVD based on the presence of at least 2 abnormal parameters or on specific combinations of parameters (eg, TAPSE < 16 mm plus RV-to-LV diameter ratio > 1.0 , or RV-to-LV diameter ratio plus RV hypokinesis).

Compared with our previous aggregate data meta-analysis [4], which suggested a prognostic role for RV dilatation and hypokinesis, the present IPDMA did not confirm a consistent association between RV diameter > 30 mm and mortality. Conversely, TAPSE < 16 mm and an RV-to-LV diameter ratio > 1.0 remained robustly associated with short-term all-cause death across both aggregate and IPD analyses. These discrepancies likely reflect the added granularity of IPD, which reduces ecological bias and allows for outcome stratification, harmonized definitions, and the exclusion of overlapping predictors.

The PPV of the RVD parameters was higher for PE-related death than for short-term all-cause death. This distinction is important, as a significant proportion of short-term all-cause death in PE patients is attributable to cancer or other comorbidities [27]. While determining PE-related death in clinical practice is challenging, these findings have implications for clinical trials. Patients with severe RVD might be the appropriate candidates for reperfusion strategies [28]. Accordingly, short-term all-cause death may remain the preferred endpoint for trials on anticoagulation and home treatment, whereas PE-related death, if consistently defined, may be more appropriate for trials on reperfusion.

TABLE 4 Risk of death (univariate) based on the number of abnormal right ventricular dysfunction parameters in all-comers and in hemodynamically stable patients. Only patients from studies reporting on 3 or more right ventricular dysfunction parameters were included in this analysis.

	Short-term all-cause death			PE-related death	
No. of abnormal RVD parameters	WMI % (95% CI)	OR (95% CI)	No. of abnormal RVD parameters	WMI % (95% CI)	OR (95% CI)
All-comers					
No abnormal parameter (n = 3438; deaths: 192)	5.6 (4.8-6.8)	Ref	No abnormal parameter (n = 2343; deaths: 40)	1.7 (1.2-2.2)	Ref
One abnormal parameter (n = 2163; deaths: 133)	6.1 (5.1-7.1)	1.17 (0.92-1.47)	One altered parameter (n = 2163; deaths: 60)	3.0 (2.2-3.7)	1.8 (1.2-2.7)
Two abnormal parameters (n = 1447; deaths: 111)	7.7 (6.3-9.0)	1.52 (1.19-1.54)	Two altered parameters (n = 1447; deaths: 48)	3.9 (2.8-5.0)	2.6 (1.7-3.8)
Three or more abnormal parameters (n = 1239; deaths: 146)	11.6 (9.3-13.8)	2.33 (1.79-3.03)	Three or more abnormal parameters (n = 1239; deaths: 70)	7.9 (5.7-10.1)	5.0 (3.2-7.6)
Hemodynamically stable patients					
No abnormal parameter (n = 3384; deaths: 171)	5.0 (4.3-5.8)	Ref	No abnormal parameter (n = 2292; deaths: 29)	1.3 (0.8-1.7)	Ref
One abnormal parameter (n = 2051; deaths: 96)	4.7 (3.8-5.6)	1.15 (0.89-1.49)	One abnormal parameter (n = 2051; deaths: 37)	1.9 (1.3-2.5)	1.9 (1.2-3.1)
Two abnormal parameters (n = 1348; deaths: 81)	6.0 (4.7-7.3)	1.47 (1.12-1.93)	Two abnormal parameters (n = 1348; deaths: 32)	2.8 (1.8-3.7)	2.9 (1.8-4.9)
Three or more abnormal parameters (n = 1078; deaths: 92)	8.1 (6.0-10.1)	1.88 (1.37-2.57)	Three or more abnormal parameters (n = 1078; deaths: 35)	5.2 (3.2-7.2)	5.3 (3.2-8.9)

AR, absolute risk; OR, odds ratio; PE, pulmonary embolism; Ref, reference; RVD, right ventricular dysfunction; WMI, weighted mean incidence.

In the present IPDMA, definitions of PE-related death were retained from each study as reported. While minor wording differences may exist, definitions were largely consistent, generally encompassing objectively confirmed PE-related death, sudden unexplained death without an alternative cause, or death following a clinically severe PE episode.

To be included in the IPDMA, studies should have an echocardiogram performed within 72 hours of PE diagnosis. In 3 studies, the timing of echocardiography could not be precisely determined, and the information was retrieved after direct contact with the authors.

Our study has limitations. As with any meta-analysis, combining data from multiple sources can increase heterogeneity. However, by using IPD, we improved data comparability, minimized bias, and enabled more refined subgroup analyses. Missing values for several variables necessitated multiple imputations, which yielded results consistent with those from complete-case analyses. The timing of echocardiography varied across studies and was not always concurrent with PE diagnosis. We cannot exclude that in some patients, echocardiography was obtained after starting treatment for PE and potentially during recovery of the RV. Indeed, we could not adjust

our analyses for the applied treatment, which may have impacted the primary outcome. The number and type of RVD parameters available varied across studies, and continuous values were reported in about 50% of studies. This reflects clinical practice and supports claims for the standardization of the definition of RVD by echocardiography. As a consequence, multivariable modeling of all individual RVD parameters was not feasible. Echocardiographic measurements were locally assessed without central adjudication, which may have introduced variability due to operator experience, equipment, or patient condition. Although this might have influenced some results, such limitations are common across the literature on acute PE. High-risk patients were underrepresented, limiting the generalizability of our findings to this subgroup. Furthermore, parameters such as RV strain, TAPSE/PAP ratio, and the 60/60 sign were not consistently available and were thus excluded from our analysis, despite their known prognostic value in selected cohorts. Multivariable adjustment for clinical confounders was not feasible due to inconsistent reporting and nonharmonized definitions across studies. Nevertheless, we conducted extensive subgroup analyses based on hemodynamic status and baseline risk profiles (eg, sPESI = 0), which provided clinically meaningful insights.

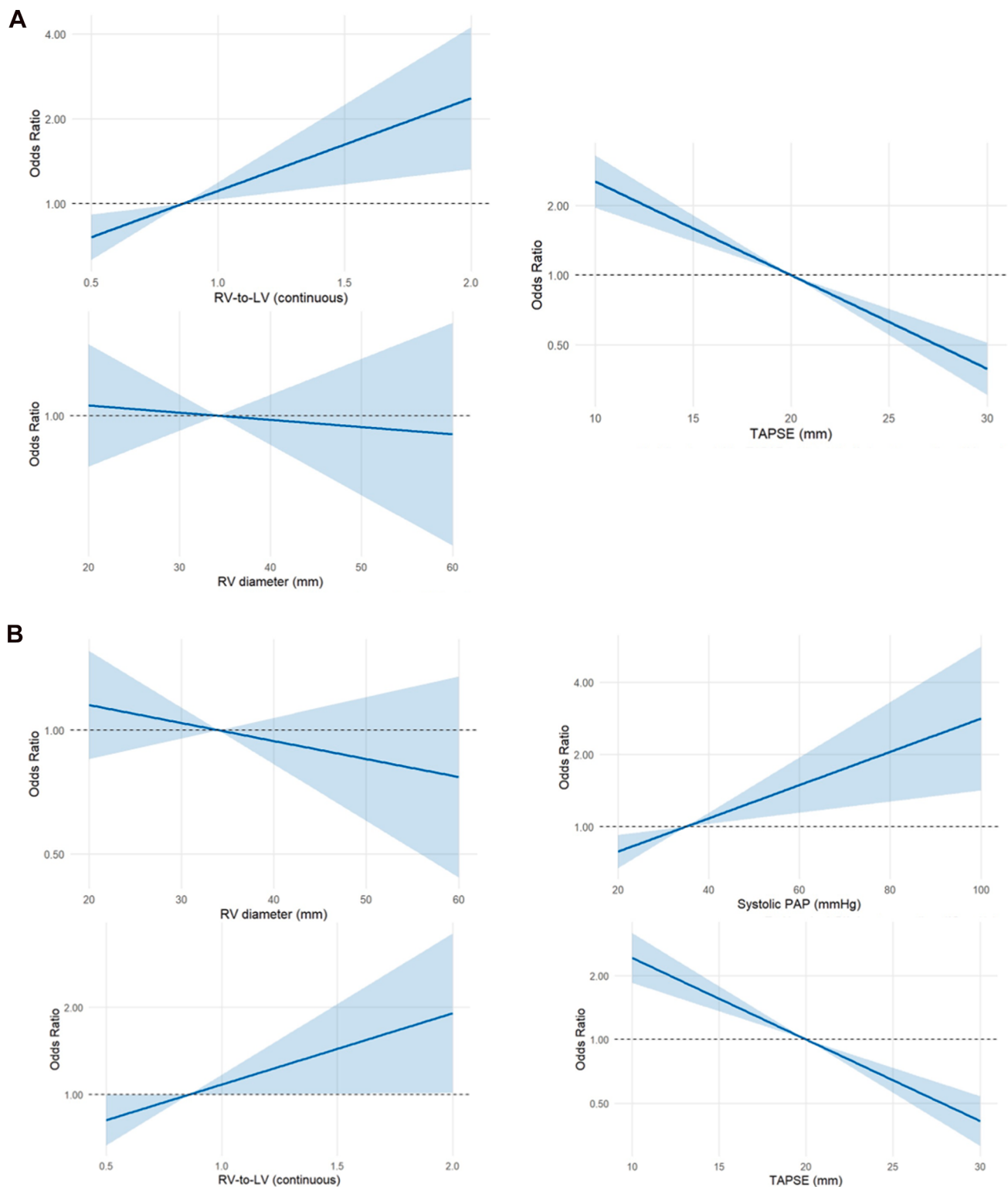


FIGURE 3 Risk of short-term all-cause death by continuous right ventricular dysfunction parameters. The shaded areas represent 95% CIs. (A) Analysis of all-comers and (B) hemodynamically stable patients. Analysis of estimated pulmonary artery pressure (PAP) was not performed because this parameter was available only for hemodynamically stable patients. RV, right ventricle; RV-to-LV, right-to-left ventricle diameter ratio; TAPSE, tricuspid annular plane systolic excursion.

Our study also presents several strengths. With more than 9200 patients, it is the largest study to date assessing the prognostic role of echocardiography in acute PE. The IPDMA approach increased

statistical power, allowed robust subgroup analyses, and provided precise estimates. For most parameters, missing data were below 30%, ensuring reliable estimates.

In conclusion, our IPDMA provides original, clinically relevant findings on the prognostic value of individual and combined echocardiographic markers of RVD in acute PE, with the strongest associations observed when at least 2 parameters are abnormal. These results will potentially lead to the standardization of the definition of RVD in this setting. Future prospective studies adopting standardized RVD definitions are needed to determine how these markers should guide patients' management in clinical practice.

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AUTHOR CONTRIBUTIONS

C.B., P.P., and L.A.C. conceived the study; D.J., A.W., M.Z., S.V., M.C., M.K., D.K., E.Y., M.B., S.R., F.P., M.M., L.A.C., M.V.U., and C.B. conducted systematic searches and selected articles; L.A.C. and M.V.U. performed the bias evaluation; L.A.C., M.V.U., and C.B. managed the data; L.A.C. and C.B. performed the statistical analysis; C.B. was responsible for statistical supervision; C.B. and L.A.C. interpreted the results; L.A.C. and C.B. wrote the first draft of the manuscript, and all authors critically revised the manuscript for important intellectual content. All authors were responsible for the decision to submit the manuscript to the journal.

DECLARATION OF COMPETING INTERESTS

There are no competing interests to disclose.

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SUPPLEMENTARY MATERIAL

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