Original Article

Need for Transthoracic Echocardiogram in Patients with Low-Risk Pulmonary Thromboembolism: A Systematic Review and Meta-Analysis[☆]

Isabel Andrade,[a] Aldara García,[a] Edwin Mercedes,[a] Francisco León,[a] Diurbis Velasco,[a] Carmen Rodríguez,[a] Beatriz Pintado,[a] Andrea Pérez,[a] David Jiménez[a,b,c,*]

[a] *Servicio de Neumología, Hospital Ramón y Cajal, IRYCIS, Madrid, Spain*
[b] *Departamento de Medicina, Universidad de Alcalá, Madrid, Spain*
[c] *CIBER de Enfermedades Respiratorias (CIBERES), Instituto de Salud Carlos III, Madrid, Spain*

ABSTRACT

Introduction: It is unclear whether low-risk patients with acute symptomatic pulmonary embolism (PE) should undergo echocardiogram.
Methods: We performed a meta-analysis of studies that enrolled patients with acute low-risk PE to assess the prognostic value of echocardiographic diagnosis of right ventricular (RV) dysfunction for the primary outcome of short-term all-cause mortality, and the secondary outcome of short-term PE-related mortality. We used a random-effects model to pool study results, a Begg rank correlation method to evaluate for publication bias, and I^2 testing to assess heterogeneity.
Results: The meta-analysis included a total of 11 studies with 1868 low-risk PE patients. Ten of the 447 (2.2%; 1.1%–4.1%) low-risk patients with echocardiographic RV dysfunction died soon after the diagnosis of PE compared with 10 of 1421 (0.7%; 0.3%–1.3%) patients without RV dysfunction. RV dysfunction was not significantly associated with short-term all-cause mortality (odds ratio 2.0; 95% confidence interval, 0.8–5.1, *P*=.14; I^2=8%). RV dysfunction was significantly associated with short-term PE-related mortality (odds ratio 5.2; 95% confidence interval, 1.7–16, *P*<.01; I^2=0%).
Conclusions: In patients with low-risk PE, echocardiographic RV dysfunction is not associated with all-cause mortality, but identifies patients with an increased risk for short-term PE-related mortality.

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Necesidad de una ecocardiografía transtorácica en pacientes con tromboembolia de pulmón de riesgo bajo: revisión sistemática y metanálisis

RESUMEN

Introducción: No se ha aclarado completamente si se debería realizar una ecocardiografía a los pacientes con tromboembolia de pulmón (TEP) de riesgo bajo.
Métodos: Realizamos un metanálisis de estudios observacionales que incluyeron pacientes con TEP de riesgo bajo para determinar el significado pronóstico de la disfunción ecocardiográfica del ventrículo derecho (VD). El evento primario considerado fue la muerte por cualquier causa a corto plazo. El evento secundario fue la muerte por la propia TEP a corto plazo. Utilizamos un modelo de efectos aleatorios para combinar los resultados, la prueba de correlación de rangos de Begg para estimar el sesgo de publicación y la prueba de la I^2 para evaluar la heterogeneidad de los estudios incluidos.

Resultados: Identificamos once estudios observacionales que incluyeron 1.868 pacientes con TEP de riesgo bajo. Diez de los 447 (2,2%) pacientes con TEP de riesgo bajo y disfunción del VD fallecieron, comparado con 10 de los 1.421 (0,7%) pacientes sin disfunción del VD. La presencia de disfunción ecocardiográfica del VD no se asoció con la mortalidad precoz por cualquier causa (odds ratio 2,0; intervalo de confianza del 95%, 0,8-5,1, P = 0,14; I^2 = 8%), pero se asoció de forma significativa con la muerte por la propia TEP (odds ratio 5,2; intervalo de confianza del 95% 1,7-16, P < 0,01; I^2 = 0%).
Conclusiones: En pacientes con TEP de riesgo bajo, la disfunción ecocardiográfica del VD no se asocia significativamente a la muerte por cualquier causa pero se asocia de forma significativa a la muerte por la propia TEP.

Introduction

Pulmonary embolism (PE) is a disease with a wide spectrum of clinical manifestations, prognoses, and treatments.[1] In recent years, various prognostic tools have been validated for patients with acute symptomatic PE, including clinical scales, imaging tests, and cardiac biomarkers.[2]

The prognostic stratification of patients with PE identifies patients with acute symptomatic PE and a low risk of complications in the short term who might benefit from a shorter hospital stay or even home treatment of their disease.[3] Clinical practice guidelines recommend the use of validated prognostic scales (i.e., the Pulmonary Embolism Severity Index[4] scale, the simplified PESI scale[5] or the Hestia criteria[6]) for the identification of low-risk patients.[7] However, some studies suggest that such scales used in isolation are not sufficiently sensitive to safely identify PE patients with a negligible risk of complications in the short term.[8–10]

A recent meta-analysis analyzed the prognostic significance of right ventricular (RV) dysfunction in patients with low-risk PE.[11] However, this systematic review combined studies that had used chest computed tomography (CT) or echocardiography indiscriminately to assess RV size/function. As the concordance between CT angiography and echocardiography is poor,[12,13] the authors were unable to determine whether a transthoracic echocardiography should be requested in patients with low-risk acute PE.

The aim of this meta-analysis was to assess the prognostic significance of RV dysfunction determined by echocardiography in low-risk PE patients according to a well-validated clinical scale.

Method

Study Retrieval

Two investigators (IA and DJ) performed independent literature searches for eligible articles published between October 2010 and May 2019 by way of a systematic review of the PubMed and Web of Science databases. Discrepancies between the two investigators' results were resolved with the help of a third researcher (EM). The searches were made using the following strategy: («pulmonary embolism»[MeSH Terms] OR «pulmonary embolism»[All Fields]) AND («PESI»[All Fields] OR «sPESI»[All Fields] OR «HESTIA»[All Fields] OR «low risk»[All Fields] OR «low-risk»[All Fields] OR «right ventricular dysfunction»[All Fields] OR «echocardiograph*»[All Fields] OR «risk stratification»[All Fields] OR «predict*»[All Fields]) AND («2008/10/30»[PDAT]: «3000/12/31»[PDAT]), with no restriction for languages. The systematic review was completed by a manual search of the literature and the investigators' files.

Selection Criteria and Outcome Measures

The meta-analysis included studies that met the following selection criteria: (1) retrospective or prospective observational studies; (2) population: patients with an objective diagnosis of low-risk acute symptomatic PE according to a validated prognostic scale (i.e., PESI, simplified PESI, Hestia criteria); (3) intervention: transthoracic echocardiography performed during acute phase PE; (4) outcome variables: early all-cause death (i.e., in the first 30 days) as primary variable, and early death due to PE as secondary variable.

Articles that did not include death as an outcome variable or which did not provide accurate data for evaluation of mortality were excluded. For duplicate publications, only the most recent was included.

Data Extraction and Quality Assessment

For each study, 2 investigators (IA and DJ) extracted data referring to the baseline characteristics of the patients, echocardiography results, and number of events for each group. Discrepancies were resolved with the help of a third researcher (EM). The Quality in Prognosis Studies tool was used to evaluate the quality of the studies selected.[14]

Statistical analysis

The meta-analysis was conducted in accordance with Meta-analysis of Observational Studies in Epidemiology (MOOSE) recommendations.[15] Data were analyzed using Review Manager (RevMan) 5.3.5 software (Cochrane Collaboration, Copenhagen), which offers open-source statistical packages for meta-analysis. A random effects model was used for data aggregation, and the odds ratio (OR) and corresponding 95% confidence intervals (95% CI) were used in the summary. Heterogeneity of the original studies was assessed using the I statistic.[2] Significance levels in all analyses were 2-tailed and P values <0.05 were considered significant. Publication bias was addressed using Begg's rank correlation test.

Results

Description of the Studies

Of 2073 articles evaluated, 23 were reviewed in depth and 6 were excluded. Two studies were added after the manual search, so a total of 19 studies met the inclusion criteria (Fig. 1). For 8 of these studies,[16–23] the number of events in each group was obtained by contacting the corresponding authors. Eight studies were excluded because the authors did not provide the necessary data.[24–31] Finally, we included 11 studies with 1868 patients with low-risk acute PE who underwent transthoracic echocardiography.[16–23,32–34]

Eight studies were prospective[16,19,21–23,32–34] and 3 were retrospective.[17,18,20] Age and sex of study patients with a diagnosis of PE were similar in all studies (Table 1). Follow-up ranged from duration of hospital stay[17,18,20,22,23] and 30 days after diagnosis of PE.[16,19,21,32–34] The prevalence of echocardiographic RV dysfunction ranged between 11%[21] and 58%.[20] Echocardiographic criteria for RV dysfunction are shown in Table 2.

Table 1
Description of Studies Included.

Author	Year	Design	Event Evaluated	Clinical Scale	RV Dysfunction	Low-Risk Patients, n (%)	Sex	Age, Mean (SD) or Range, Years	Follow-up	Results
Vanni et al.[22]	2011	Prospective	All-cause death	PESI	48%	145 (28)	56% women	–	In-hospital	4.3% mortality for patients with RV dysfunction vs. 0% for patients without RV dysfunction.
Jimenez et al.[32]	2011	Prospective	PE death	PESI	19%	199 (34)	57% women	74 (65–82)	30 days	0% mortality for patients with RV dysfunction vs. 1.2% for patients without RV dysfunction.
Lankeit et al.[33]	2012	Prospective	All-cause death	Simplified PESI	34%	165 (31)	57% women	74 (61–80)	30 days	0% mortality for patients with RV dysfunction vs. 0% for patients without RV dysfunction.
Sanchez et al.[21]	2013	Prospective	All-cause death, cardiogenic shock, or thrombotic recurrence	PESI	11%	329 (56)	53% women	67 (52–77)	30 days	0% mortality for patients with RV dysfunction vs. 0.7% for patients without RV dysfunction.
Jimenez et al.[34]	2014	Prospective	Complicated clinical course	Simplified PESI	13%	313 (37%)	51% women	72 (59–80)	30 days	2.5% mortality for patients with RV dysfunction vs. 0.7% for patients without RV dysfunction.
Khemasuwan et al.[20]	2015	Retrospective	All-cause death	Simplified PESI	58%	92 (44)	51% women	61 (15)	In-hospital	7.5% mortality for patients with RV dysfunction vs. 10% for patients without RV dysfunction.
Becattini et al.[19]	2016	Prospective	All-cause death	Simplified PESI	34%	186 (21)	54% women	68 (16)	30 days	1.6% mortality for patients with RV dysfunction vs. 0% for patients without RV dysfunction.
Bing et al.[17]	2016	Retrospective	All-cause death	Simplified PESI	22%	221 (15)	56% women	68 (16)	In-hospital	2.1% mortality for patients with RV dysfunction vs. 0% for patients without RV dysfunction.
Weekes et al.[18]	2017	Retrospective	All-cause death	Simplified PESI	23%	43 (35)	49	59 (43–69)	In-hospital	0% mortality for patients with RV dysfunction vs. 0% for patients without RV dysfunction.
Erol et al.[23]	2018	Prospective	All-cause death	Simplified PESI	21%	33 (30)	58% women	47	In-hospital	0% mortality for patients with RV dysfunction vs. 0% for patients without RV dysfunction.
Vanni et al.[16]	2018	Prospective	All-cause death	Simplified PESI	17%	100 (18)	54% women	76 (65–83)	30 days	4.3% mortality for patients with RV dysfunction vs. 0% for patients without RV dysfunction.

PESI: Pulmonary Embolism Severity Index; RV: right ventricle; SD: standard deviation.
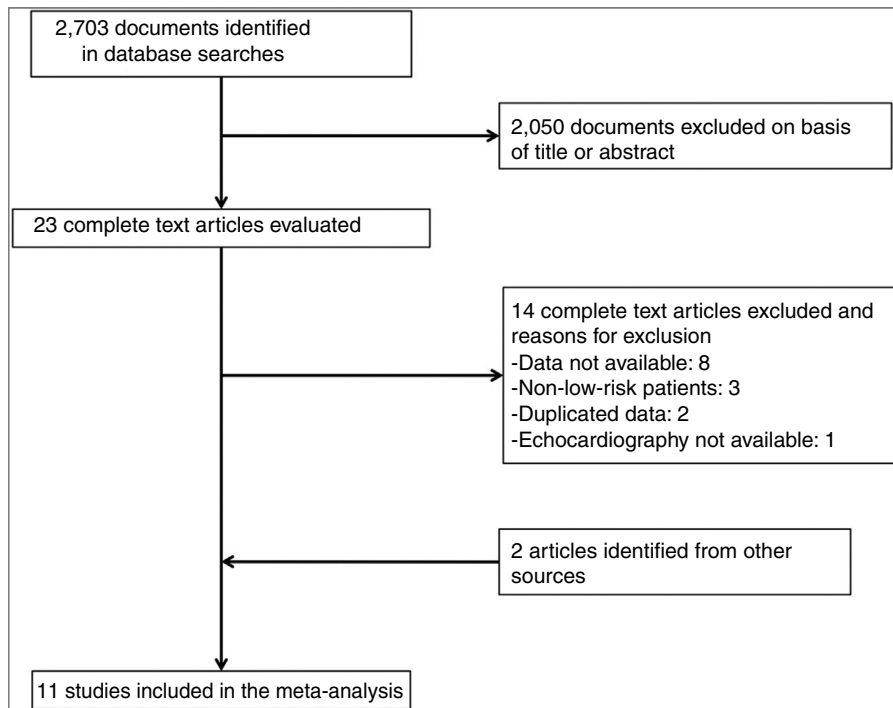
Fig. 1. Flow chart according to MOOSE recommendations.

Table 2
Right Ventricular Dysfunction Criteria.

Study	Right Ventricular Dysfunction Criteria
Vanni et al.[22], 2011	At least one of the following: (1) RVDD/LVDD >1 in 4-chamber apical view, (2) RVDD >30 mm in 4-chamber apical view, (3) paradoxical movement of the interventricular septum, and (4) right ventricle/right atrial pressure gradient >30 mmHg
Jimenez et al.[32], 2011	At least one of the following: (1) RVDD >30 mm in the parasternal view or RV greater than LV in apical or subcostal view, (2) hypokinesis of the RV free wall, and (3) pulmonary systolic pressure >30 mmHg
Lankeit et al.[33], 2012	At least one of the following: (1) RVDD >30 mm in the parasternal view or RV greater than LV in apical or subcostal view, (2) hypokinesis of the right ventricle free wall, and (3) pulmonary systolic pressure >30 mmHg
Sanchez et al.[21], 2013	RV/LV >0.9
Jimenez et al.[34], 2014	At least one of the following: (1) RVDD >30 mm in the parasternal view or RV greater than LV in apical or subcostal view, (2) hypokinesis of the RV free wall, and (3) pulmonary systolic pressure >30 mmHg
Khemasuwan et al.[20], 2015	Not described
Becattini et al.[19], 2016	At least one of the following: (1) RVDD/LVDD >1 in 4-chamber apical view, (2) RVDD/LVDD >0.6 in parasternal long-axis or subcostal 4-chamber view, (3) right ventricle/right atrial pressure gradient >30 mmHg
Bing et al.[17], 2016	Not described
Weekes et al.[18], 2017	Severe RV dilation, or severe RV dysfunction, or interventricular septal flattening or shift toward the LV
Erol et al.[23], 2018	Not described
Vanni et al.[16], 2018	At least one of the following: (1) RVDD/LVDD >0.9 in 4-chamber apical view, (2) hypokinesis of the RV free wall, (3) right ventricle/right atrial pressure gradient >30 mmHg

LV: left ventricle; LVDD: left ventricular end-diastolic diameter; RV: right ventricle; RVDD: right ventricular end-diastolic diameter.

Quality of Studies Included

With regard to the quality of the studies included (Table 3), the participation and baseline characteristics of the patients were described adequately in most of the studies.[16–19,21–23,32–34] All studies provided an adequate description of the RV dysfunction criteria used, with the exception of Khemasuwan et al., Bing et al. and Erol et al. Adjustments were made for potential confounding factors in 7 of the studies included.[17,20–22,32–34] Events were adjudicated by a committee in only 3 of the studies.[16,21,34]

Events

Of the 11 cohorts with 1868 patients with low-risk PE, 447 (24%; 95% CI, 22%–26%) had echocardiographic RV dysfunction, and 1421 did not (76%; 95% CI, 74%–78%). Ten of the 447 patients with low-risk PE and RV dysfunction died (2.2%; 95% CI, 1.1%–4.1%) compared to 10 of the 1421 patients without RV dysfunction (0.7%; 95% CI, 0.3%–1.3%).

Based on the results of the 11 observational studies, it was estimated that the combined OR of all-cause mortality of patients with RV dysfunction was 2.0 (95% CI, 0.8–5.1, P=.14; I^2=8%, P=.37) (Fig. 2A). None of the studies showed statistically significant results. In all studies except for 2, patients with RV dysfunction had a worse, but not statistically significant, prognosis. No publication bias was revealed by Begg's rank correlation test.

All studies provided information on mortality due to PE in the short term. PE mortality was 1.3% (6 of 447 patients; 95% CI, 0.5%–2.9%) and 0.1% (2 of 1421 patients; 95% CI, 0.0%–0.5%) in patients with and without echocardiographic RV dysfunction, respectively. The combined OR of PE mortality of patients with RV dysfunction was 5.2 (95% CI, 1.7–16, P=.01; I^2=0%, P=.93) (Fig. 2B). A transthoracic echocardiography would have to be performed in 83 patients with low-risk acute PE in order to identify 1 patient who will die due to PE in the first 30 days after diagnosis.

Table 3
Quality of Studies Included.

Study	Participation	Follow-up Described and Appropriate	Description of RV Dysfunction	Primary Event Adequately Defined and Described	Control of Confounding Factors[a]	Adequately Described Analysis
Vanni et al.[22], 2011	Appropriate	Yes	Appropriate	Yes	Good	Yes
Jimenez et al.[32], 2011	Appropriate	Yes	Appropriate	Yes	Good	Yes
Lankeit et al.[33], 2012	Appropriate	Yes	Appropriate	Yes	Good	Yes
Sanchez et al.[21], 2013	Appropriate	Yes	Appropriate	Yes	Good	Yes
Jimenez et al.[34], 2014	Appropriate	Yes	Appropriate	Yes	Good	Yes
Khemasuwan et al.[20], 2015	Unclear	Yes	Poor	Yes	Appropriate	Yes
Becattini et al.[19], 2016	Appropriate	Yes	Appropriate	Yes	Poor	Yes
Bing et al.[17], 2016	Appropriate	No	Poor	Yes	Appropriate	Yes
Weekes et al.[18], 2017	Appropriate	Yes	Appropriate	Yes	Poor	Yes
Erol et al.[23], 2018	Appropriate	No	Poor	No	Poor	No
Vanni et al.[16], 2018	Appropriate	Yes	Appropriate	Yes	Poor	Yes

[a] Control of confounding factors was defined as poor, if usual confounding factors were not controlled; appropriate, if controlled for age and comorbidities; and, good, if most confounding factors were controlled.
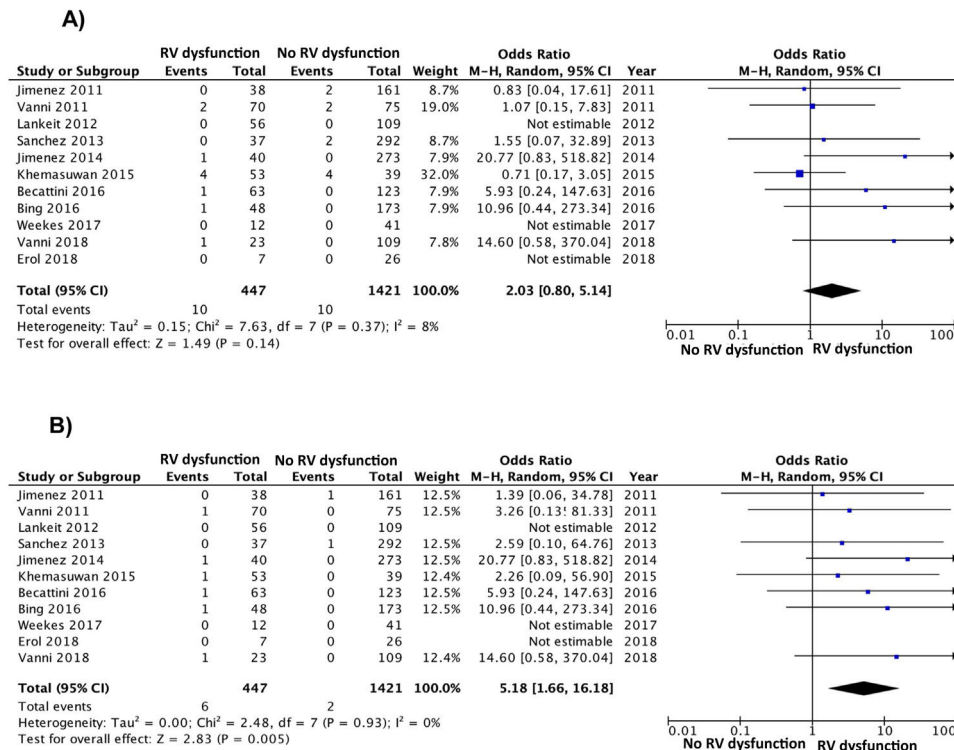RV: right ventricle.

A)

Study or Subgroup	RV dysfunction Events	Total	No RV dysfunction Events	Total	Weight	Odds Ratio M–H, Random, 95% CI	Year
Jimenez 2011	0	38	2	161	8.7%	0.83 [0.04, 17.61]	2011
Vanni 2011	2	70	2	75	19.0%	1.07 [0.15, 7.83]	2011
Lankeit 2012	0	56	0	109		Not estimable	2012
Sanchez 2013	0	37	2	292	8.7%	1.55 [0.07, 32.89]	2013
Jimenez 2014	1	40	0	273	7.9%	20.77 [0.83, 518.82]	2014
Khemasuwan 2015	4	53	4	39	32.0%	0.71 [0.17, 3.05]	2015
Becattini 2016	1	63	0	123	7.9%	5.93 [0.24, 147.63]	2016
Bing 2016	1	48	0	173	7.9%	10.96 [0.44, 273.34]	2016
Weekes 2017	0	12	0	41		Not estimable	2017
Vanni 2018	1	23	0	109	7.8%	14.60 [0.58, 370.04]	2018
Erol 2018	0	7	0	26		Not estimable	2018
Total (95% CI)		**447**		**1421**	**100.0%**	**2.03 [0.80, 5.14]**	
Total events	10		10				

Heterogeneity: Tau² = 0.15; Chi² = 7.63, df = 7 (P = 0.37); I² = 8%
Test for overall effect: Z = 1.49 (P = 0.14)

B)

Study or Subgroup	RV dysfunction Events	Total	No RV dysfunction Events	Total	Weight	Odds Ratio M–H, Random, 95% CI	Year
Jimenez 2011	0	38	1	161	12.5%	1.39 [0.06, 34.78]	2011
Vanni 2011	1	70	0	75	12.5%	3.26 [0.13, 81.33]	2011
Lankeit 2012	0	56	0	109		Not estimable	2012
Sanchez 2013	0	37	1	292	12.5%	2.59 [0.10, 64.76]	2013
Jimenez 2014	1	40	0	273	12.5%	20.77 [0.83, 518.82]	2014
Khemasuwan 2015	1	53	0	39	12.4%	2.26 [0.09, 56.90]	2015
Becattini 2016	1	63	0	123	12.5%	5.93 [0.24, 147.63]	2016
Bing 2016	1	48	0	173	12.5%	10.96 [0.44, 273.34]	2016
Weekes 2017	0	12	0	41		Not estimable	2017
Erol 2018	0	7	0	26		Not estimable	2018
Vanni 2018	1	23	0	109	12.4%	14.60 [0.58, 370.04]	2018
Total (95% CI)		**447**		**1421**	**100.0%**	**5.18 [1.66, 16.18]**	
Total events	6		2				

Heterogeneity: Tau² = 0.00; Chi² = 2.48, df = 7 (P = 0.93); I² = 0%
Test for overall effect: Z = 2.83 (P = 0.005)

Fig. 2. Mortality in low-risk PE patients with right ventricular dysfunction. (A) All-cause death. (B) PE death.
CI: confidence interval; M–H: Mantel–Haenszel; RV, right ventricle.

A)

Study or Subgroup	RV dysfunction Events	Total	No RV dysfunction Events	Total	Weight	Odds Ratio M–H, Random, 95% CI	Year
Jimenez 2011	0	38	2	161	14.2%	0.83 [0.04, 17.61]	2011
Vanni 2011	2	70	2	75	33.5%	1.07 [0.15, 7.83]	2011
Lankeit 2012	0	56	0	109		Not estimable	2012
Sanchez 2013	0	37	2	292	14.2%	1.55 [0.07, 32.89]	2013
Jimenez 2014	1	40	0	273	12.8%	20.77 [0.83, 518.82]	2014
Becattini 2016	1	63	0	123	12.8%	5.93 [0.24, 147.63]	2016
Erol 2018	0	7	0	26		Not estimable	2018
Vanni 2018	1	23	0	109	12.7%	14.60 [0.58, 370.04]	2018
Total (95% CI)		**334**		**1168**	**100.0%**	**2.75 [0.87, 8.70]**	
Total events	5		6				

Heterogeneity: Tau² = 0.00; Chi² = 4.35, df = 5 (P = 0.50); I² = 0%
Test for overall effect: Z = 1.73 (P = 0.08)

B)

Study or Subgroup	RV dysfunction Events	Total	No RV dysfunction Events	Total	Weight	Odds Ratio M–H, Random, 95% CI	Year
Khemasuwan 2015	4	53	4	39	64.3%	0.71 [0.17, 3.05]	2015
Bing 2016	1	48	0	173	35.7%	10.96 [0.44, 273.34]	2016
Weekes 2017	0	12	0	41		Not estimable	2017
Total (95% CI)		**113**		**253**	**100.0%**	**1.89 [0.15, 24.66]**	
Total events	5		4				

Heterogeneity: Tau² = 2.12; Chi² = 2.31, df = 1 (P = 0.13); I² = 57%
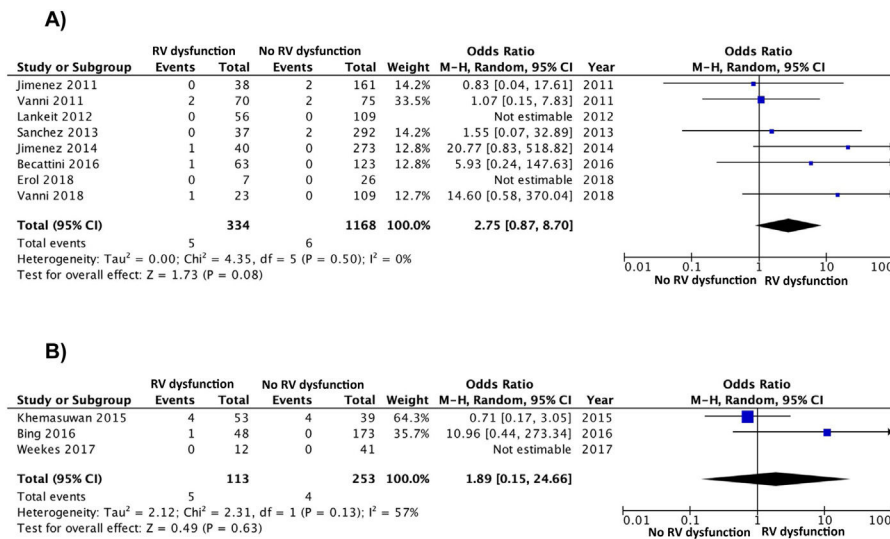Test for overall effect: Z = 0.49 (P = 0.63)

Fig. 3. All-cause mortality in low-risk PE patients with right ventricular dysfunction. (A) Prospective studies. (B) Retrospective studies.
CI: confidence interval; M–H: Mantel–Haenszel; RV, right ventricle.

The results were similar when the analysis was limited to 8 studies (1502 patients) with a prospective design (OR 2.8; 95% CI, 0.9–8.7), with no clear heterogeneity (χ=4.4, df=5, P=.50, I²=0%) (Fig. 3A). The results were similar for the retrospective studies (OR 1.9; 95% CI, 0.2–25; heterogeneity χ=2.3, df=1, P=.13, I²=57%) (Fig. 3B). When the analysis was limited to the 8 studies that used the simplified PESI scale, the combined OR of mortality of patients with RV dysfunction was 4.4 (95% CI, 0.9–21, P=.07; I²=41%, P=.15) For studies that used the PESI scale, the OR was 1.1 (95% CI, 0.3–4.8, P=.90; heterogeneity χ=0.1, df=2, P=.96, I²=0%). A statistically significant association was maintained between RV dysfunction and PE mortality when the analysis was limited to 3 studies that had an adjudication committee of events (OR 9.2; 95% CI, 1.4–59, P=.02; heterogeneity χ=0.9, df=2, P=.63, I²=0%).

Discussion

This study evaluated the prognostic utility of transthoracic echocardiography in patients with low-risk acute symptomatic PE. There were no statistically significant differences in all-cause mortality among low-risk patients with or without echocardiographic

RV dysfunction. However, the presence of echocardiographic RV dysfunction resulted in a 5-fold increase in risk of PE death in the short term.

Risk stratification for clinical events is a basic variable in the management of patients with acute symptomatic pulmonary embolism. Clinical prognostic models were developed to identify PE patients with a low risk of complications, who might benefit from shorter hospital stays or even ambulatory treatment of their disease. The results of previous meta-analyses indicate that, in general, clinical scales reliably identify PE patients with a low risk of mortality in the first 30 days after diagnosis.[35] Even so, it has not been fully clarified whether transthoracic echocardiography should be routinely performed in this subgroup of patients.

What are the implications of these findings in clinical practice? Given that the results of our meta-analysis indicate that echocardiographic RV dysfunction is not associated with all-cause mortality, and that in many centers this procedure is not always available, it seems reasonable not to routinely request this examination in patients with low-risk acute symptomatic PE. However, performing it early (i.e., in the first hours after diagnosis) might be useful for low-risk PE patients seen in centers with short stay programs and/or home treatment of PE, since our results indicate that the risk of PE death is negligible if echocardiographic RV dysfunction can be ruled out.

In a previous meta-analysis, Barco et al. found that RV dysfunction conferred a 4-fold increase in the risk of early all-cause mortality in patients with low-risk PE (according to a validated clinical prognostic scale).[11] There are several reasons for this discrepancy with our study. These authors, unlike us, included data from studies that used angio-CT scan of the chest or echocardiography indistinctly to evaluate RV size/function. Moreover, our systematic review identified 8 studies with 1726 patients who were not included in the meta-analysis.

Our study has some limitations. Firstly, we were not able to adjust the association between RV dysfunction and mortality due to various confounding factors. This type of adjustment could be performed in a meta-analysis of individual data. Secondly, the validity of the results and the conclusions of the meta-analysis depend on the quality of the individual studies, so the combination of biased studies could have exaggerated this bias even further. Thirdly, there is no consensus in the literature for the definition of echocardiographic RV dysfunction. However, the studies included used very similar definitions, and given the fact that most studies found a worse (while not significant) prognosis in patients with RV dysfunction, it seems unlikely that this limitation could have influenced the results of this meta-analysis. Finally, only 3 of the studies had an events adjudication committee, which could explain the difference between the results for the primary variable (all-cause mortality) and the secondary variable (PE mortality). However, similar findings were obtained when the analyses were restricted to these studies, thus reinforcing the validity of our results.

In conclusion, in patients with low-risk PE according to a clinical prognostic scale, echocardiographic RV dysfunction is not associated with an increased risk of premature death from any cause. Since the presence of echocardiographic RV dysfunction was significantly associated with PE death, it seems reasonable to request this procedure only in low-risk patients in whom outpatient treatment of their disease is contemplated. Well-designed studies are required in order to determine if the evaluation of RV using chest angio-CT scan can provide similar information to that of transthoracic echocardiography in this group of patients.

Conflict of Interests

D. Jiménez was the principal investigator of 2 of the studies included in this meta-analysis.

References

1. Goldhaber SZ, Visani L, de Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry. Lancet. 1999;353:1386–9.
2. Jiménez D, Aujesky D, Yusen RD. Risk stratification of normotensive patients with acute pulmonary embolism. Br J Haematol. 2010;151:415–24.
3. Aujesky D, Roy PM, Verschuren F, Righini M, Osterwalder J, Egloff M, et al. Outpatient versus inpatient treatment for patients with acute pulmonary embolism: an international, open-label, randomised, non-inferiority trial. Lancet. 2011;378:41–8.
4. Aujesky D, Obrosky DS, Stone RA, Auble TE, Perrier A, Cornuz J, et al. Derivation and validation of a prognostic model for pulmonary embolism. Am J Respir Crit Care Med. 2005;172:1041–6.
5. Jiménez D, Aujesky D, Moores L, Gomez V, Lobo JL, Uresandi F, et al. Simplification of the Pulmonary Embolism Severity Index for prognosticating patients with acute symptomatic pulmonary embolism. Arch Intern Med. 2010;170: 1383–9.
6. Zondag W, Mos IC, Creemers-Schild D, Hoogerbrugge AD, Dekkers OM, Dolsma J, et al. Hestia Study Investigators Outpatient treatment in patients with acute pulmonary embolism: the Hestia study. J Thromb Haemost. 2011;9: 1500–7.
7. Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galiè N, et al. Authors/Task Force Members 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism: The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC) Endorsed by the European Respiratory Society (ERS). Eur Heart J. 2014;35:3033–73.
8. Otero R, Uresandi F, Jimenez D, Cabezudo MA, Oribe M, Nauffal D, et al. Home treatment in pulmonary embolism. Thromb Res. 2010;126:e1–5.
9. Hellenkamp K, Kaeberich A, Schwung J, Konstantinides S, Lankeit M. Risk stratification of normotensive pulmonary embolism based on the sPESI-does it work for all patients? Int J Cardiol. 2015;197:162–3.
10. Cote B, Jimenez D, Planquette B, Roche A, Marey J, Pastre J, et al. Prognostic value of right ventricular dilatation in patients with low-risk pulmonary embolism. Eur Respir J. 2017;50, pii:1701611.
11. Barco S, Mahmoudpour SH, Planquette B, Sanchez O, Konstantinides SV, Meyer G. Prognostic value of right ventricular dysfunction or elevated cardiac biomarkers in patients with low-risk pulmonary embolism: a systematic review and meta-analysis. Eur Heart J. 2019;40:902–10.
12. Barrios D, Morillo R, Lobo JL, Nieto R, Jaureguizar A, Portillo AK, et al., PROTECT Investigators. Assessment of right ventricular function in acute pulmonary embolism. Am Heart J. 2017;185:123–9.
13. Dudzinski DM, Hariharan P, Parry BA, Chang Y, Kabrhel C. Assessment of right ventricular strain by computed tomography versus echocardiography in acute pulmonary embolism. Acad Emerg Med. 2017;24:337–43.
14. Hayden JA, Côté P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. Ann Intern Med. 2006;144:427–37.
15. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology. JAMA. 2000;283:2008–12.
16. Vanni S, Becattini C, Nazerian P, Bova C, Stefanone VT, Cimini LA, et al. Early discharge of patients with pulmonary embolism in daily clinical practice: a prospective observational study comparing clinical gestalt and clinical rules. Thromb Res. 2018;167:37–43.
17. Bing R, Chow V, Lau JK, Thomas L, Kritharides L, Ng AC. Prevalence of echocardiography use in patients hospitalized with confirmed acute pulmonary embolism: a real-world observational multicenter study. PLoS ONE. 2016;11: e0168554.
18. Weekes AJ, Johnson AK, Troha D, Thacker G, Chanler-Berat J, Runyon M. Prognostic value of right ventricular dysfunction markers for serious adverse events in acute normotensive pulmonary embolism. J Emerg Med. 2017;52: 137–50.

19. Becattini C, Agnelli G, Lankeit M, Masotti L, Pruszczyk P, Casazza F, et al. Acute pulmonary embolism: mortality prediction by the 2014 European Society of Cardiology risk stratification model. Eur Respir J. 2016;48:780–6.
20. Khemasuwan D, Yingchoncharoen T, Tunsupon P, Kusunose K, Moghekar A, Klein A, et al. Right ventricular echocardiographic parameters are associated with mortality after acute pulmonary embolism. J Am Soc Echocardiogr. 2015;28:355–62.
21. Sanchez O, Trinquart L, Planquette B, Couturaud F, Verschuren F, Caille V, et al. Echocardiography and pulmonary embolism severity index have independent prognostic roles in pulmonary embolism. Eur Respir J. 2013;42:681–8.
22. Vanni S, Nazerian P, Pepe G, Baioni M, Risso M, Grifoni G, et al. Comparison of two prognostic models for acute pulmonary embolism: clinical vs. right ventricular dysfunction-guided approach. J Thromb Haemost. 2011;9:1916–23.
23. Erol S, Batum O, Yilmaz U. Is advanced risk stratification unnecessary in patients with simplified Pulmonary Embolism Severity Index (sPESI) of 0? Arastırma Makalesi. 2018;71:55–9.
24. Yamashita Y, Morimoto T, Amano H, Takase T, Hiramori S, Kim K, et al., COMMAND VTE Registry Investigators. Validation of simplified PESI score for identification of low-risk patients with pulmonary embolism: from the COMMAND VTE Registry. Eur Heart J Acute Cardiovasc Care. 2018;11, http://dx.doi.org/10.1177/2048872618799993, 2048872618799993.
25. Osman AM, Abdeldayem EH. Value of CT pulmonary angiography to predict short-term outcome in patients with pulmonary embolism. Int J Cardiovasc Imaging. 2018;34:975–83.
26. Şahan E, Karamanlıoğlu M, Şahan S, Gül M, Korkmaz A, Tüfekçioğlu O. The relationship between right ventricular outflow tract fractional shortening and Pulmonary Embolism Severity Index in acute pulmonary embolism. Turk Kardiyol Dern Ars. 2017;45:709–14.
27. Vamsidhar A, Rajasekhar D, Vanajakshamma V, Lakshmi AY, Latheef K, Siva Sankara C, et al. Comparison of PESI, echocardiogram, CTPA, and NT-proBNP as risk stratification tools in patients with acute pulmonary embolism. Indian Heart J. 2017;69:68–74.
28. Hofmann E, Limacher A, Méan M, Kucher N, Righini M, Frauchiger B, et al. Echocardiography does not predict mortality in hemodynamically stable elderly patients with acute pulmonary embolism. Thromb Res. 2016;145:67–71.
29. Cordeanu M, Gaertner S, Faller A, Mirea C, Le Ray I, Stephan D. Prognostic value of the simplified PESI score in comparison with the 2014 ESC risk model in pulmonary embolism. Int J Cardiol. 2016;220:623–4.
30. Kilic T, Gunen H, Gulbas G, Hacievliyagil SS, Ozer A. Prognostic role of simplified Pulmonary Embolism Severity Index and the European Society of Cardiology Prognostic Model in short- and long-term risk stratification in pulmonary embolism. Pak J Med Sci. 2014;30:1259–64.
31. Ozsu S, Abul Y, Orem A, Oztuna F, Bulbul Y, Yaman H, et al. Predictive value of troponins and simplified pulmonary embolism severity index in patients with normotensive pulmonary embolism. Multidiscip Respir Med. 2013;8:34.
32. Jiménez D, Aujesky D, Moores L, Gómez V, Martí D, Briongos S, et al. Combinations of prognostic tools for identification of high-risk normotensive patients with acute symptomatic pulmonary embolism. Thorax. 2011;66:75–81.
33. Lankeit M, Gómez V, Wagner C, Aujesky D, Recio M, Briongos S, et al., Instituto Ramón y Cajal de Investigación Sanitaria Pulmonary Embolism Study Group. A strategy combining imaging and laboratory biomarkers in comparison with a simplified clinical score for risk stratification of patients with acute pulmonary embolism. Chest. 2012;141:916–22.
34. Jiménez D, Kopecna D, Tapson V, Briese B, Schreiber D, Lobo JL, et al., On Behalf Of The Protect Investigators. Derivation and validation of multimarker prognostication for normotensive patients with acute symptomatic pulmonary embolism. Am J Respir Crit Care Med. 2014;189:718–26.
35. Kohn CG, Mearns ES, Parker MW, Hernandez AV, Coleman CI. Prognostic accuracy of clinical prediction rules for early post-pulmonary embolism all-cause mortality: a bivariate meta-analysis. Chest. 2015;147:1043–62.