Computed tomography to assess risk of death in acute pulmonary embolism: a meta-analysis

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ABSTRACT   The aim of this study was to evaluate whether right ventricle dilation at computed tomography (CT) angiography can be used to assess the risk of death in patients with acute pulmonary embolism.

Medline and EMBASE were searched up to April 30, 2013. Studies reporting on the association between right ventricle dilation (right-to-left ventricle diameter) or dysfunction (inter-ventricular septal bowing) at CT angiography and death at 30 days, as well as at 3 months in patients with acute pulmonary embolism, were included in a systematic review and meta-analysis.

CT-detected right ventricle dilation was associated with an increased 30 day-mortality in all-comers with pulmonary embolism (OR 2.08 (95% CI 1.63–2.66); p<0.00001) and in haemodynamically stable patients (OR 1.64 (95% CI 1.06–2.52); p=0.03), as well as with death due to pulmonary embolism (OR 7.35 (95% CI 3.59–15.09); p<0.00001). An association between right ventricle dilation and 3-month mortality was also observed (OR 4.65 (95% CI 1.79–12.07); p=0.002).

Right-to-left ventricle dilation as assessed by CT angiography can be used to evaluate risk of death in all-comers with pulmonary embolism and in haemodynamically stable patients.

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Introduction

Recent guidelines recommend tailoring the clinical management of patients with acute pulmonary embolism to the estimated risk of death [1, 2]. In these patients, models for risk stratification integrate patient haemodynamic status (mainly presence of shock or hypotension) with markers of myocardial dysfunction or injury [3]. In patients with shock or hypotension, mortality is high and early reperfusion by thrombolysis or embolectomy is recommended without any further risk stratification [1, 2]. In haemodynamically stable patients, mortality ranges from <1% to 10% [4–6]; this wide range makes risk stratification crucial to drive clinical management. Right ventricle dysfunction or injury are associated with increased mortality in patients with acute pulmonary embolism and have been claimed to be useful to stratify haemodynamically stable patients for the risk of death [7–9].

The assessment of right ventricle dysfunction (echocardiography or brain natriuretic peptide levels) or injury (troponin levels) requires time, is expensive and is not readily available around the clock in several hospitals. Nowadays, computed tomography (CT) angiography is by far the most commonly used method for the diagnosis of acute pulmonary embolism. The development of multi-slice scanners allows accurate visualisation of the heart chambers and pulmonary vessels. Two different methods have been proposed to assess right ventricle dilation on CT angiography. One option is to obtain multiplanar-reconstructed CT images with the aim of recreating the apical 4-chamber view of echocardiography [10]. The second option is to measure heart chambers in the same axial transverse images used to diagnose pulmonary embolism, without reconstructions [11]. The right-to-left ventricle dimension ratio obtained by these methods is by far the most commonly used marker for the assessment of right ventricle dilation at CT angiography in acute pulmonary embolism. Right ventricle dilation at CT angiography has been shown to be associated with an increased risk of death in patients with acute pulmonary embolism [7, 11]. Using these approaches, diagnosis and risk stratification could merge into a single procedure.

We performed a systematic review and a meta-analysis to assess the value of right ventricle dilation or dysfunction at CT angiography to stratify patients with acute pulmonary embolism for risk of death.

Material and methods

Right-to-left ventricle dimension ratio and inter-ventricular septal (IVS) bowing toward the left ventricle were selected as the markers of right ventricle dilation and right ventricle dysfunction, respectively. We assessed the risk of death associated with these markers in patients with acute pulmonary embolism. The outcomes of the study were death at 30 days and death within 3 months from the index pulmonary embolism. We followed the guidelines and the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) checklist [12].

Search strategy

We performed an unrestricted search in Medline and EMBASE up to April 30, 2013. Search criteria included the terms "acute pulmonary embolism AND computed tomography". No language restrictions were applied. Reference lists of retrieved articles and review articles were manually searched for other relevant studies. Two authors independently performed the searches and reviewed all identified publications and abstracts for inclusion, using predetermined criteria.

Inclusion criteria

Studies were included in this review if they reported on patients with: 1) an objective diagnosis of pulmonary embolism; 2) assessment of right ventricle dilation or dysfunction at CT angiography; 3) death at 30 days from diagnosis of pulmonary embolism and/or death within 3 months. Disagreement was solved by consensus with a third investigator and by discussion.

For duplicate publications, the most recent was considered. To assess agreement between reviewers for study selection, we used the κ statistic, which measures agreement beyond chance [13].

Data extraction

For each study, the following data were extracted independently by two authors: general data (study design and year of publication); patients (number, mean age, sex, comorbidities, haemodynamic status and number who received thrombolysis); features of the CT scanner (single or multidetector); markers evaluated at CT angiography (methods for assessment of right ventricle dilation or dysfunction); and clinical outcome (death). The quality of the studies was evaluated using the Newcastle-Ottawa quality assessment scale [14].

Selection of studies for meta-analysis

To be considered for a meta-analysis, a CT-assessed sign of right ventricular dilation or dysfunction had to be reported in at least five studies. Studies were included in the meta-analysis if the following data were available: 1) numbers of patients with/without study outcome in patients with/without a CT feature of right ventricle dilation or dysfunction; or 2) risk measures for death calculated for CT markers of right ventricle dilation or dysfunction. Study authors were contacted to ask for data allowing inclusion in the meta-analysis.

Statistical analysis

We determined pooled odds ratios (ORs) and 95% confidence intervals (CI) for death in patients with right ventricle dilation or dysfunction as assessed at CT angiography. We planned separate analyses for: 1) death at 30 days; 2) haemodynamically stable patients; 3) death due to pulmonary embolism; 4) different methods for assessment of right ventricle dilation at CT angiography and different cut-offs; 5) studies reporting on death occurring beyond the hospital stay and between 3 months; and 6) right ventricle dysfunction.

Data were pooled using the Mantel–Haenszel method [15]; we reported results according to a fixed-effects model in the absence of significant heterogeneity and to a random-effects model in the presence of significant heterogeneity [16]. We used the random effects model because it accounts for variations between studies, in addition to sampling error within studies. For studies presenting zero cells, 0.5 was added for a correct estimation of risk measures. For markers of right ventricle dilation or dysfunction that were significantly associated with death, the negative predictive value and the positive predictive value were calculated by meta-analysis of predictive values [17]. The appropriateness of pooling data across studies was assessed using the Cochran's Chi-squared test and the I^2 test for heterogeneity. The I^2 test measures inconsistency across the study results and describes the proportion of total variation in study estimates that is due to heterogeneity rather than sampling error [16, 18]. Statistically significant heterogeneity was considered to be present in cases with $p < 0.10$ and $I^2 > 50\%$. Funnel plots were used to assess for publication bias [15].

The statistical analyses, forest plots and publication bias analyses were produced with RevMan 5.1 (Cochrane Collaboration, Oxford, UK) and STATA/SE 10.1 (StataCorp, College Station, TX, USA). To be included in the quantitative analysis, studies had to provide sufficient data for calculation of an effect size measure. We calculated the summary ORs with 95% CI from study-specific ORs taken directly from the study or estimated as crude ORs from cell counts. We also took study specific CIs directly from the study if they were reported or calculated using the corresponding standard error. The study was performed without any external support.

Results

Overall, 1504 papers were found of which 36 met the inclusion criteria. The flow diagram of literature search and study selection is shown in figure S1. The agreement between reviewers for study selection was good (κ statistic 0.85). The main features of the studies are shown in table 1. Eight studies had a prospective design and 27 studies were retrospective. A minimum of 39 and a maximum of 1596 patients were included in the individual studies. Patients were followed for the in-hospital period in seven studies, up to 30 days in 17 studies and from 30 days up to 3 months in 12 studies. Two studies reported on different signs of right ventricle dilation assessed in the same study population. These studies have been included in the meta-analysis, but only one of them has been included in each individual analysis.

Markers of right ventricle dilation at CT-angiography

Methods for the assessment of right ventricle dilation at CT, features of the scanners and use of image reconstruction [47] are shown in table 2.

In the majority of the studies, right ventricle dilation was assessed as the right-to-left ventricle ratio. 34 studies reported on right-to-left ventricle short-axis diameter ratio, four studies on the right-to-left ventricle volume ratio and one study on the right-to-left ventricle area ratio. Right-to-left ventricle short-axis diameter ratio was assessed in transverse bi-dimensional images in 28 studies and in reconstructed 4-chamber images in 16 studies. Cut-off values for the right-to-left ventricle ratios were different among studies and are reported in table 2.

Meta-analysis of CT assessed right ventricle dilation

The 36 studies reporting on the prognostic value of right ventricle dilation at CT angiography were further evaluated for inclusion in the meta-analysis. 15 studies were initially excluded [10, 19, 20, 22, 26, 31, 33, 35, 38, 39, 41, 43, 46, 50, 52]. For six of them, the inclusion in the analysis was possible following contact with the authors [22, 35, 38, 39, 43, 52]. Among the eight excluded studies, an association between right ventricle dilation at CT and adverse outcome was observed in five studies.

TABLE 1 Main features of studies reporting on the prognostic value of right ventricle dilation or dysfunction at computed tomography angiography

First author [ref.]	Year	Study design	Included patients	Age years	Male	Hypotension at admission	Study outcome	Follow-up duration
Apfaltrer [19]	2012	Retrospective	60	65±14.4	47 [78]	NA	Death or adverse clinical events§	2 months
Araoz [20]	2003	Retrospective	173	60±17	106 [61]	NA	Death and adverse clinical events§	In hospital
Araoz [21]	2007	Retrospective	1193	63±16	552 [46]	64+	Death	3 months
Aviram [22]	2008	Retrospective	145	67±19	50 [35.5]	NA	All-cause mortality	1 month
Baptista [23]	2013	Retrospective	39	59.1±19.6	18 [46.2]	NA	All-cause mortality	40 days, 33 months
Bazeed [24]	2010	Retrospective	48	54±22	26 [54]	NA	All-cause mortality	In hospital
Becattini [11]	2011	Prospective	457	67±16.2	209 [45.7]	46	All-cause mortality or clinical deterioration§	In hospital
Cai [25]#	2013	Retrospective	1596	M: 60.8±13.9 NM: 54.5±18.8	M: 378 [45.3] NM: 336 [44.2]	NA	All-cause mortality	1 month
Ceylan [26]	2011	Retrospective	122	65±15	61 [50]	NA	All-cause mortality	In hospital
Díaz [27]	2007	Retrospective	89	60.2 [27–89]	35 [39]	NA	Death	3 months
Furlan [28]	2012	Retrospective	635	58 [18–94]	304 [48]	NA	Death	1 month
Ghaye [29]	2006	Retrospective	82	61±15	40 [49]	32+	All-cause mortality	In hospital
Gul [30]	2012	Prospective	61	62±17	23 [37.7]	0	Death	1 month
Henzler [31]	2010	Retrospective	100	NA	NA	NA	Death or adverse clinical events§	1 month
Jimenéz [32]	2013	Prospective	848	72 [59–80]	416 [49]	34	All-cause mortality	1 month
Jeebun [33]	2010	Retrospective	137	65±16 [20–90]	57 [42]	41	Death	In hospital
Kang [34]	2011	Retrospective	260	55±18	139 [53.5]	0	All-cause mortality or adverse outcome§	1 month
Klok [35]¶	2010	Prospective	113	56±17	60 [53]	0	Death or adverse clinical events§	6 weeks
Kumamaru [36, 37]	2012	Retrospective	200	60±16	87 [43.5]	NA	PE-related death or clinical deterioration§	1 month
Lu [38]	2008	Retrospective	50	60±13 [23–82]	19 [38]	NA	Death [all-cause and PE-related]	1 month
Lu [39]	2012	Retrospective	674	58±17	302 [44.8]	NA	Death [all-cause and PE-related]	1 month
Mansencal [40]	2005	Prospective	46	54±16	30 [65]	5	All-cause mortality	3 months
Meyer [41]	2012	Prospective	83	Male: 61±13 Female: 64±18	46 [55]	0	All-cause mortality and clinical deterioration	2 months
Moroni [42]	2011	Retrospective	226	67±17	114 [50.4]	0	All-cause mortality	3 months
Nural [43]	2009	Retrospective	53	61 [22–85]	26 [49]	20	All-cause mortality	1 month
Ozsu [44]	2010	Prospective	108	70 [21–90]	61 [56]	0	All-cause mortality	1 month
Ozsu [45]	2012	Retrospective	99	67±15	34 [34]	0	All-cause mortality	3 months
Park [46]	2011	Retrospective	56	63.5 [52–71]	28 [50]	9	PE-related death or clinical deterioration§	1 month
Quiroz [10]	2004	Retrospective	63	58±15	27 [43]	13	Death or adverse clinical events§	1 month
Schoepf [47]	2004	Retrospective	431	59±16	192 [45]	27	All-cause mortality	1 month
Soares [48]	2013	Retrospective	96	54±20	45 [47]	2	All-cause mortality	3 months
Stein [49]	2008	Retrospective	157	57±17	65 [41]	NA	Death [all-cause and PE-related]	In hospital
van der Bijl [50]¶	2011	Prospective	113	57±16	60 [53]	0	Death or adverse clinical events§	6 weeks
van der Meer [51]	2005	Retrospective	120	59±18 [18–89]	55 [46]	0	Death [all-cause and PE-related]	3 months
Venkatesh [52]	2010	Retrospective	125	60 [16–94]	47 [38]	NA	PE-related death	1 month
Zondag [53]	2013	Post hoc analysis	496	58±17	268 [54]	26	All-cause mortality	1 month

Data are presented as n, mean±SD, mean [range], mean±SD [range] or n [%]. M: malignancy; NM: no malignancy; NA: not available; PE: pulmonary embolism. #: data are reported separately for the two study groups; ¶: studies reporting on the same study population; +: systolic blood pressure defined as <100 mmHg; §: adverse clinical events usually included: cardiopulmonary resuscitation, mechanical ventilation, vasopressor therapy for systemic arterial hypotension, thrombolysis, catheter intervention, surgical embolectomy or subsequent admission to the intensive care unit.

TABLE 2 Features of the scanners and assessment methods of right ventricle dilation or dysfunction

Firth author [ref.]	CT		Parameters for right ventricle dilation/dysfunction		
	CT scanner	Reconstructed image	Right-to-left ventricle ratio		Others
			Methods	Cut-off	
Apfaltrer [19]	64	Both	Transverse diameter 4-chamber diameters Volumes	Not reported	
Araoz [20]	Single or 4	Both	Transverse diameters 4-chamber diameters	Not reported	IVS bowing
Araoz [21]	Single, 4, 8, 16	No	Transverse diameters	Not reported	IVS bowing
Aviram [22]	10, 16, 40, 64	Yes	4-chamber diameters	>0.9	RV short axis IVC reflux IVS bowing
Baptista [23]	4, 64	No	Transverse diameters	>1	RV short axis LV short axis
Bazeed [24]	64	Yes	Transverse diameters	>1	RV short axis
Becattini [11]	4, 16	No	Transverse diameters	≥0.9	
Cai [25]	4, 16, 64	Yes	4-chamber diameters	>1	
Ceylan [26]	16	Both	Transverse diameters 4-chamber diameters	Not reported	SVC diameter IVS bowing IVC reflux
Díaz [27]	2	No	Transverse diameters	≥1	
Furlan [28]	16–64	Yes	Transverse diameters	≥1	RV short axis LV short axis SVC diameter IVC reflux IVS bowing
Ghaye [29]	Single	Yes	Transverse diameters	>1	RV short axis SVC diameter IVC reflux IVS bowing
Gul [30]	64	No	Transverse diameters	>1	PA diameter
Henzler [31]	16, 64	Both	Transverse diameters 4-chamber diameters Volumes	Not reported	
Jimenéz [32]	NA	No	Transverse diameters	>0.9	
Jeebun [33]	4	No	Transverse diameters	Not reported	
Kang [34]	64	Both	Transverse diameters 4-chamber diameters Volumes	>1 >1 >1.2	IVS bowing IVC reflux
Klok [35]#	Multi	Yes	Transverse diameters 4-chamber diameters	>1	
Kumamaru [36, 37]	16, 64	Both	Transverse diameters 4-chamber diameters	>0.9¶ >1	
Lu [38]	4–64	Yes	4-chamber diameters	>1	
Lu [39]	4, 16, 64	Both	Transverse diameters 4-chamber diameters	>0.9 >0.9	
Mansencal [40]	2	No	Areas	>1	
Meyer [41]	16, 64	Yes	Transverse diameters 4-chamber diameters Volumes	Not pre-specified	
Moroni [42]	4, 16	Yes	Transverse diameters	>1	IVS bowing SVC diameter
Nural [43]	Single or 16	No	4-chamber diameters	Not reported	RV diameter SVC diameter IVS bowing IVC reflux
Ozsu [44]	4, 16	No	Transverse diameters	≥1.1	
Ozsu [45]	4, 16	No	Transverse diameters	≥1.3	
Park [46]	8	No	Transverse diameters	>1	IVS bowing
Quiroz [10]	4	Both	Transverse diameters 4-chamber diameters	>0.9 >0.9	
Schoepf [47]	4, 16	Yes	4-chamber diameters	>0.9	
Soares [48]	64	Yes	4-chamber diameters	≥0.9	
Stein [49]	Multi	No	Transverse diameters	>1	IVS bowing
van der Bijl [50]#	16, 64	Both	Transverse diameters 4-chamber diameters Volumes	>1 >1 >1.2	RVEF
van der Meer [51]	Single	No	Transverse diameters	>1	IVS bowing
Venkatesh [52]	4	No	Transverse diameters	>0.9+	IVS bowing RV diameter
Zondag [53]	4, 16, 64	No	Transverse diameters	>1	

CT: computed tomography; IVS: inter-ventricular septum; RV: right ventricle; IVC: inferior vena cava; LV: left ventricle; SVC: superior vena cava; PA: pulmonary artery; RVEF: right ventricular ejection fraction; NA: not available. #: studies reporting on the same study population; ¶: data on the same study population have been reported in two publications; +: unpublished data.

First author [ref.]	logOR	SE	Weight %	OR (95% CI) IV, Random	OR (95% CI) IV, Random
Prospective					
BECATTINI [11]	1.026	0.5551	3.9	2.79 (0.94–8.28)	
GUL [30]	0.5306	1.5594	0.7	1.70 (0.08–36.12)	
JIMÉNEZ [32]	0.1339	0.3496	6.3	1.14 (0.58–2.27)	
KLOK [35]	1.8116	1.099	1.4	6.12 (0.71–52.75)	
MANSENCAL [40]	2.3418	1.1797	1.2	10.40 (1.03–105.00)	
OZSU [44]	0.6931	0.5894	3.6	2.00 (0.63–6.35)	
Subtotal (95% CI)			**17.1**	**1.99 (1.13–3.50)**	

Heterogeneity: τ^2=0.07; Chi-squared=5.79, df=5 (p=0.33); I^2=14%
Test for overall effect: Z=2.38 (p=0.02)

	logOR	SE	Weight %	OR (95% CI)	
Retrospective					
ARAOZ [21]	0.0953	0.3222	6.7	1.10 (0.58–2.07)	
AVIRAM [22]	-0.1863	0.4406	5.1	0.83 (0.35–1.97)	
BAPTISTA [23]	2.5649	1.1908	1.2	13.00 (1.26–134.13)	
BAZEED [24]	2.7942	1.4851	0.8	16.35 (0.89–300.35)	
CAI (malignancy) [25]	0.2062	0.1757	9.0	1.23 (0.87–1.73)	
CAI (no malignancy) [25]	1.4061	0.4555	4.9	4.08 (1.67–9.96)	
DÍAZ [27]	3.653	1.4638	0.8	38.59 (2.19–679.93)	
FURLAN [28]	1.3801	0.3415	6.4	3.98 (2.04–7.76)	
GHAYE [29]	0.0953	0.3222	6.7	1.10 (0.58–2.07)	
KANG [34]	0.8796	0.5317	4.1	2.41 (0.85–6.83)	
KUMAMARU [36]	2.4952	1.4412	0.8	12.12 (0.72–204.36)	
LU [38]	1.0116	0.6981	2.9	2.75 (0.70–10.80)	
LU [39]	0.802	0.2714	7.5	2.23 (1.31–3.80)	
MORONI [42]	0.5128	0.4364	5.1	1.67 (0.71–3.93)	
NURAL [43]	0.47	1.5285	0.8	1.60 (0.08–32.00)	
OZSU [45]	1.8132	0.6281	3.3	6.13 (1.79–20.99)	
SCHOEPF [47]	0.7885	0.3445	6.4	2.20 (1.12–4.32)	
SOARES [48]	0.6931	0.8913	2.0	2.00 (0.35–11.47)	
STEIN [49]	0.01	1.0082	1.6	1.01 (0.14–7.29)	
VAN DER MEER [51]	3.6109	1.4471	0.8	37.00 (2.17–630.91)	
VENKATESH [52]	0.2151	0.6754	3.0	1.24 (0.33–4.66)	
ZONDAG [53]	0.5248	0.6774	3.0	1.69 (0.45–6.38)	
Subtotal (95% CI)			**82.9**	**2.13 (1.56–2.91)**	

Heterogeneity: τ^2=0.22; Chi-squared=42.67, df=21 (p=0.003); I^2=51%
Test for overall effect: Z=4.76 (p<0.00001)

| **Total (95% CI)** | | | **100.0** | **2.11 (1.61–2.76)** | |

Heterogeneity: τ^2=0.18; Chi-squared=48.47, df=27 (p=0.007); I^2=44%
Test for overall effect: Z=5.39 (p<0.00001)
Test for subgroup differences: Chi-squared=0.04, df=1 (p=0.84), I^2=0%

0.001   0.1   1   10   1000
Favours experimental   Favours control

FIGURE 1 Forest plots for death within 3 months. Risk of death in patients with increased or normal right-to-left ventricle ratio. SE: standard error; IV: inverse variance.

Thus, 27 studies (4767 patients) were eligible for inclusion in the meta-analysis of right-to-left ventricle ratio (diameters, areas or volumes) and death within 3 months [11, 21–25, 27–30, 32, 34–36, 38–40, 42–45, 47–49, 51–53]. An association was found between an increase of right-to-left ventricle ratio and death; the summary OR calculated by random effects model was 2.11 (95% CI 1.61–2.76, p<0.00001), with an I^2 of 44% (fig. 1). The association was confirmed in the subgroups of the retrospective (21 studies; OR 2.13 (95% CI 1.56–2.91); I^2 51%) and prospective studies (six studies; OR 1.99 (95% CI 1.13–3.50); I^2 14%) (fig. 1). The funnel plot is presented in figure S2.

The strength of the association was similar in studies conducted with CT scanners of different technical development (mean detector number ⩾16 or <16).

Death at 30 days
Among 15 studies reporting on death at 30 days (4661 patients), an association was found between death and right ventricle dilation measured as right-to-left ventricle diameter ratio (OR 2.08 (95% CI 1.63–2.66);

First author [ref.]	CT-RVC +ve		CT-RVD -ve		Weight %	OR (95% CI) M–H, Fixed	OR (95% CI) M–H, Fixed
	Events	Total	Events	Total			
Transverse							
BAZEED [24]	9	30	0	18	0.4	16.35 (0.89–300.40)	
BECATTINI [11]	21	303	4	154	5.1	2.79 (0.94–8.28)	
FURLAN [28]	17	114	22	521	7.0	3.98 (2.04–7.76)	
JIMÉNEZ [32]	25	533	13	315	16.2	1.14 (0.58–2.27)	
KANG [34]	15	148	5	112	5.3	2.41 (0.85–6.85)	
KUMAMURU [36]	23	164	0	36	0.7	12.12 (0.72–204.35)	
LU [39]	78	452	19	222	21.9	2.23 (1.31–3.78)	
OZSU [44]	8	48	6	60	4.6	1.80 (0.58–5.60)	
STEIN [49]	2	78	2	79	2.0	1.01 (0.14–7.38)	
VENKATESH [52]	20	106	3	19	4.3	1.24 (0.33–4.67)	
ZONDAG [53]	5	201	4	269	3.5	1.69 (0.45–6.38)	
Subtotal (95% CI)		**2177**		**1805**	**71.2**	**2.25 (1.69–3.00)**	
Total events	**223**		**78**				

Heterogeneity: Chi-squared=11.57, df=10 (p=0.31); I^2=14%
Test for overall effect: Z=5.53 (p<0.00001)

Chamber reconstruction							
AVIRAM [22]	16	91	11	54	11.8	0.83 (0.35–1.96)	
LU [38]	8	24	4	26	2.7	2.75 (0.70–10.74)	
NURAL [43]	3	44	0	9	0.8	1.60 (0.08–33.70)	
SCHOEPF [47]	43	276	12	155	13.5	2.20 (1.12–4.31)	
Subtotal (95% CI)		**435**		**244**	**28.8**	**1.67 (1.04–2.70)**	
Total events	**70**		**27**				

Heterogeneity: Chi-squared=3.70, df=3 (p=0.30); I^2=19%
Test for overall effect: Z=2.11 (p=0.04)

Total (95% CI)		**2612**		**2049**	**100.0**	**2.08 (1.63–2.66)**	
Total events	**293**		**105**				

Heterogeneity: Chi-squared=16.24, df=14 (p=0.30); I^2=14%
Test for overall effect: Z=5.85 (p<0.00001)
Test for subgroup differences: Chi-squared=1.08, df=1 (p=0.30), I^2=7.8%

FIGURE 2 Forest plots for death at 30 days. Risk of death in patients with increased right-to-left ventricle ratio. CT-RVD +ve: computed tomography (CT)-detected right ventricle dysfunction (RVD) present; CT-RVD -ve: CT-detected RVD absent.

p<0.00001, I^2 14%) (fig. 2) [11, 22, 24, 28, 32, 34, 36, 38–39, 43–44, 47, 49, 52, 53]. The funnel plot is presented in figure S3.

The pooled estimated negative predictive value for right-to-left ventricle diameter ratio measured in transverse images was 95% (95% CI 93–97%) and the positive predictive value was 10% (95% CI 6–15%). The association between death at 30 days and right ventricle dilation was confirmed in a separate analyses for right-to-left ventricle diameter ratio assessed either in transverse images (11 studies, 3982 patients; OR 2.25 (95% CI 1.69–3.00); p<0.00001, I^2 14%) or reconstructed 4-chamber views (four studies, 679 patients; OR 1.67 (95% CI 1.04–2.70); p<0.04, I^2 19%). Results related to different cut-offs are reported in figures 3 and 4.

Six studies (2254 patients) reported on right-to-left ventricle diameter ratio (all measuring transverse images) in haemodynamically stable patients [11, 32, 34, 44, 49, 53]. The meta-analysis of these studies revealed an increased risk of death at 30 days in patients with right-to-left ventricle diameter ratio, the OR was 1.64 (95% CI 1.06–2.52; p=0.03, I^2 0%) (fig. 5). The funnel plot is presented in figure S4.

Eight studies (2925 patients) reported on death due to pulmonary embolism at 30 days [11, 32, 36, 38, 39, 44, 49, 53]. Analysing these studies an association was found between right-to-left ventricle ratio and death due to pulmonary embolism (OR 7.35 (95% CI 3.59–15.09); p<0.00001, I^2 16%) (fig. S5). The funnel plot is presented in figure S6. The negative predictive value of right-to-left ventricle ratio for death due to pulmonary embolism at 30 days was 99% (95% CI 98–100%) and the positive predictive value was 5% (95% CI 2–12%). Association was confirmed when the analysis was restricted to the seven studies reporting on right-to-left ventricle ratio measured in transverse images (OR 7.78 (95% CI 3.53–17.14); I^2 28%)

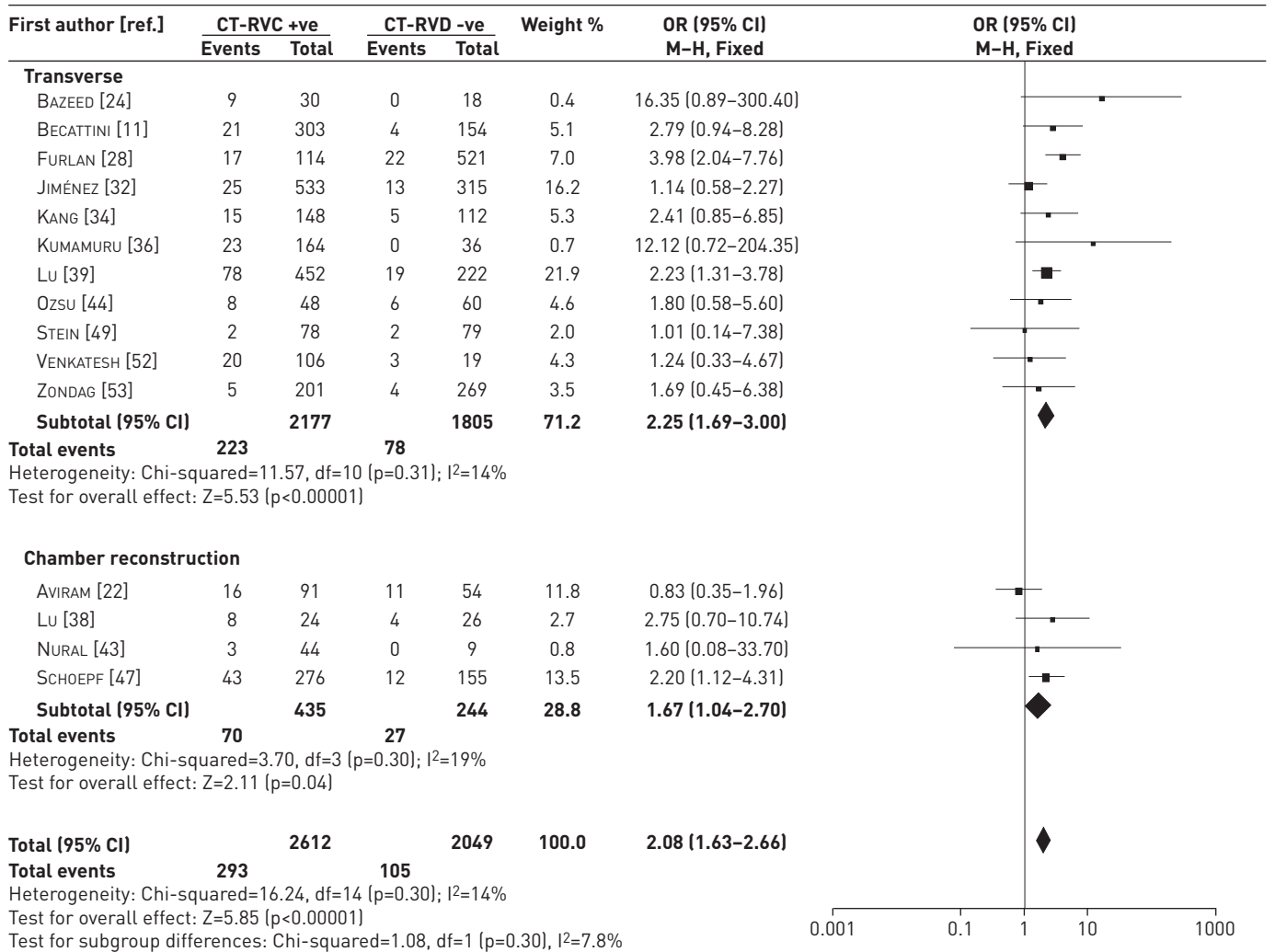| First author [ref.]	CT-RVD +ve		CT-RVD -ve		Weight %	OR (95% CI) M–H, Fixed	OR (95% CI) M–H, Fixed
	Events	Total	Events	Total			
Cut-off 0.9							
BECATTINI [11]	21	303	4	154	7.2	2.79 (0.94–8.28)	
JIMÉNEZ [32]	25	533	13	315	22.8	1.14 (0.58–2.27)	
KUMAMURU [36]	23	164	0	36	1.0	12.12 (0.72–204.35)	
LU [39]	78	452	19	222	30.8	2.23 (1.31–3.78)	
VENKATESH [52]	20	106	3	19	6.0	1.24 (0.33–4.67)	
Subtotal (95% CI)		1558		746	67.9	1.99 (1.38–2.86)	
Total events	167		39				
Heterogeneity: Chi-squared=5.11, df=4 (p=0.28); I²=22%							
Test for overall effect: Z=3.68 (p=0.0002)							
Cut-off 1 or 1.01							
BAZEED [24]	9	30	0	18	0.6	16.35 (0.89–300.40)	
FURLAN [28]	17	114	22	521	9.8	3.98 (2.04–7.76)	
KANG [34]	15	148	5	112	7.5	2.41 (0.85–6.85)	
OZSU [44]	8	48	6	60	6.5	1.80 (0.58–5.60)	
STEIN [49]	2	78	2	79	2.8	1.01 (0.14–7.38)	
ZONDAG [53]	5	201	4	269	4.9	1.69 (0.45–6.38)	
Subtotal (95% CI)		619		1059	32.1	2.81 (1.78–4.42)	
Total events	56		39				
Heterogeneity: Chi-squared=4.69, df=5 (p=0.46); I²=0%							
Test for overall effect: Z=4.45 (p<0.00001)							
Total (95% CI)		2177		1805	100.0	2.25 (1.69–3.00)	
Total events	223		78				
Heterogeneity: Chi-squared=11.57, df=10 (p=0.31); I²=14%							
Test for overall effect: Z=5.53 (p<0.00001)							
Test for subgroup differences: Chi-squared=1.35, df=1 (p=0.25), I²=25.9%							

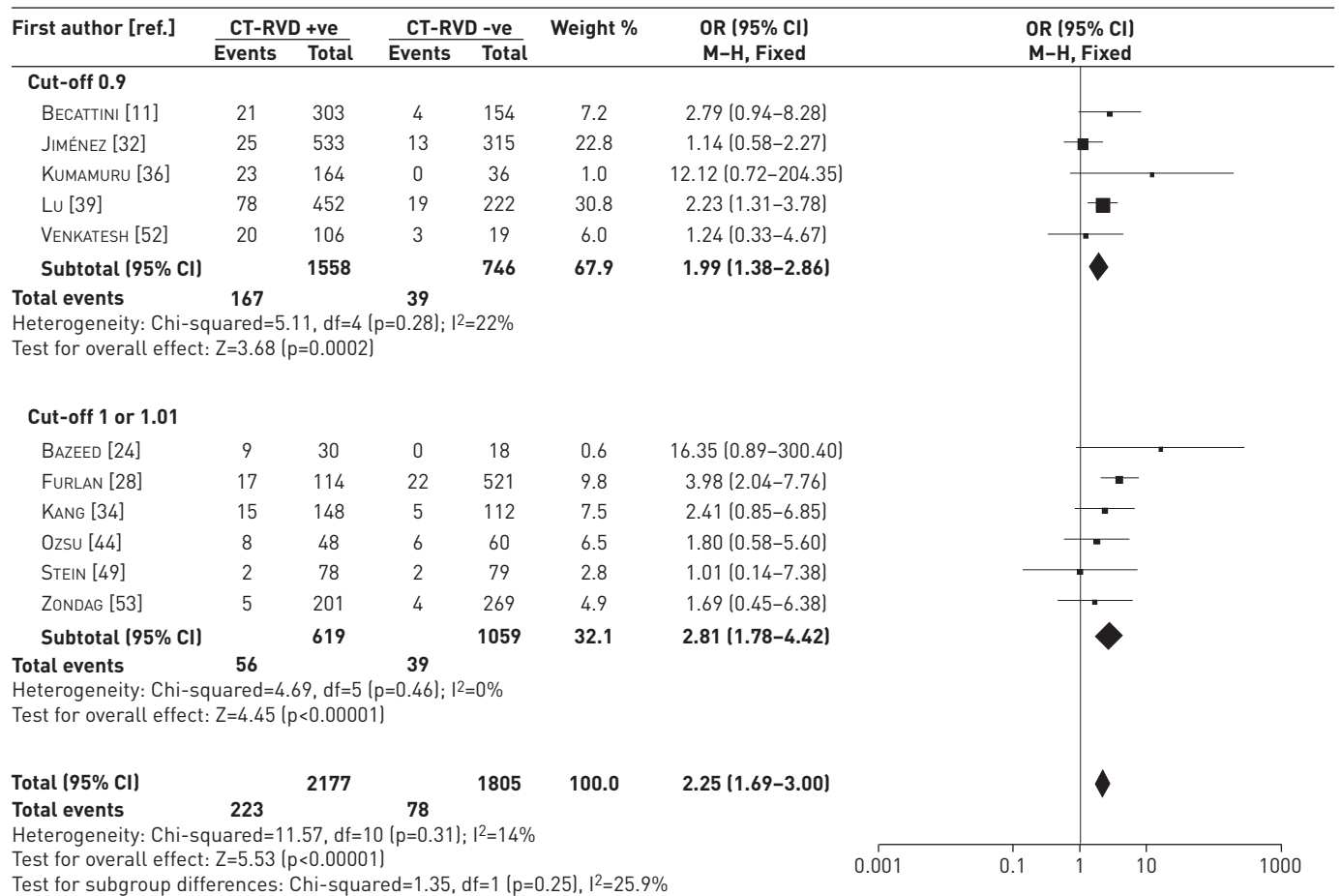OR (95% CI) M–H, Fixed axis: 0.001   0.1   1   10   1000

FIGURE 3 Forest plots for death at 30 days. Risk of death in patients with increased right-to-left ventricle ratio as assessed in transverse images. CT-RVD +ve: computed tomography (CT)-detected right ventricle dysfunction (RVD) present; CT-RVD -ve: CT-detected RVD absent.

(fig. S7) and to the five studies specifically reporting on hemodynamically stable patients (1994 patients; OR 3.48 (95% CI 1.36–8.91); I² 0%) (fig. S8).

Death within 3 months

Seven studies (782 patients) reported on right-to-left ventricle diameter ratio and mortality within 3 months from index pulmonary embolism. All but one study reported right-to-left ventricle diameter ratio measured in transverse images [23, 27, 35, 42, 44, 51]. The analysis of these studies showed a significant association between right-to-left ventricle diameter ratio and death; the OR measured by random effects model was 4.65 (95% CI 1.79–12.07; p=0.002) with significant heterogeneity (I² 51%). Five of these studies (647 patients) reported separate data for patients who were haemodynamically stable at presentation [27, 35, 41, 44, 50]. The analysis of these studies showed a statistically significant association between right-to-left ventricle diameter ratio and death with an OR of 5.14 measured by a random effects model (95% CI 1.45–18.19, p=0.01), with significant heterogeneity (I² 63%). The funnel plots did not reveal publication bias in any of the above analyses. Data on the prognostic value of IVS bowing and other CT features are presented in the supplementary material.

Discussion

This meta-analysis shows that right ventricle dilation at pulmonary CT angiography is associated with an increased risk of death at 30 days in the general population of patients with acute pulmonary embolism, and in those who are haemodynamically stable at diagnosis. The increased risk is confirmed for death due to pulmonary embolism.

The optimal management of haemodynamically stable patients remains one the most controversial issues in patients with acute pulmonary embolism. In these patients, stratification for the risk of death is required to tailor the clinical management. Right ventricle dysfunction, usually assessed by echocardiography, is

First author [ref.]	CT-RVD +ve		CT-RVD -ve		Weight %	OR (95% CI) M–H, Fixed	OR (95% CI) M–H, Fixed
	Events	Total	Events	Total			
Cut-off 0.9							
Aviram [22]	16	91	11	54	19.3	0.83 (0.35–1.96)	
Lu [39]	75	436	22	238	39.9	2.04 (1.23–3.38)	
Nural [43]	3	44	0	9	1.3	1.60 (0.08–33.70)	
Schoepf [47]	43	276	12	155	22.0	2.20 (1.12–4.31)	
Subtotal (95% CI)		**847**		**456**	**82.5**	**1.79 (1.25–2.57)**	
Total events	**137**		**45**				

Heterogeneity: Chi-squared=3.69, df=3 (p=0.30); I^2=19%
Test for overall effect: Z=3.20 (p=0.001)

Cut-off 1							
Kang [34]	17	162	3	98	5.7	3.71 (1.06–13.01)	
Kumamaru [36]	18	107	5	93	7.5	3.56 (1.27–10.01)	
Lu [38]	8	24	4	26	4.3	2.75 (0.70–10.74)	
Subtotal (95% CI)		**293**		**217**	**17.5**	**3.41 (1.71–6.78)**	
Total events	**43**		**12**				

Heterogeneity: Chi-squared=0.12, df=2 (p=0.94); I^2=0%
Test for overall effect: Z=3.49 (p=0.0005)

Total (95% CI)		**1140**		**673**	**100.0**	**2.08 (1.51–2.85)**	
Total events	**180**		**57**				

Heterogeneity: Chi-squared=6.47, df=6 (p=0.37); I^2=7%
Test for overall effect: Z=4.53 (p<0.00001)
Test for subgroup differences: Chi-squared=2.63, df=1 (p=0.10), I^2=62.0%
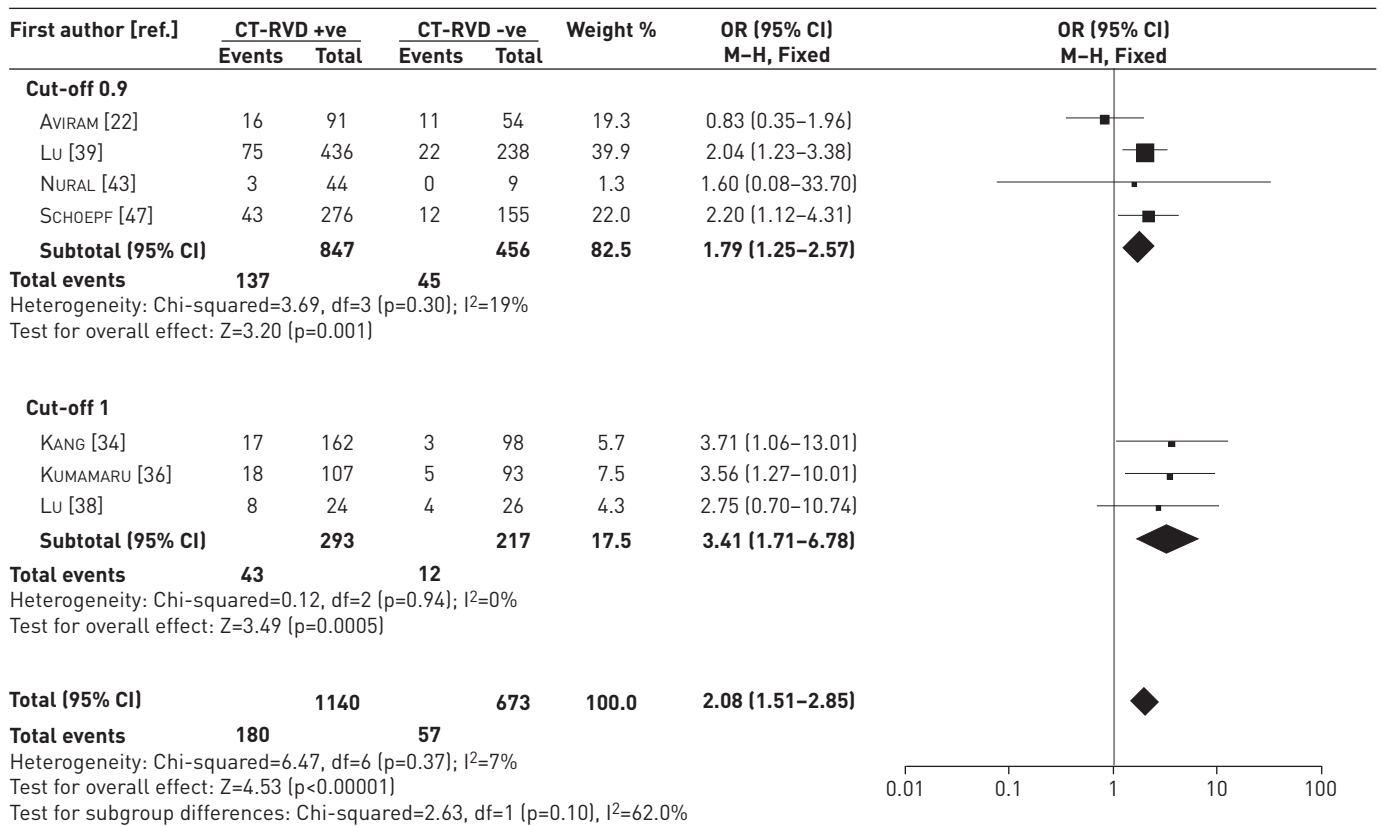
0.01   0.1   1   10   100

FIGURE 4 Forest plots for death at 30 days. Risk of death in patients with increased right-to-left ventricle ratio as assessed in reconstructed images. CT-RVD +ve: computed tomography (CT)-detected right ventricle dysfunction (RVD) present; CT-RVD -ve: CT-detected RVD absent.

associated with an increased risk of in-hospital death. More recently, a role has been identified for CT angiography in the assessment of right ventricle dilation and, if confirmed, could make risk stratification simpler and rapidly available in an urgent setting. A recently published meta-analysis showed an increased risk of death in patients with sub-massive pulmonary embolism [54]. By confirming this association in both the real "short-term" phase (up to 30 days) and up to 3 months for different CT measurement (transverse and 4-chamber images, and IVS bowing), and in a large population (almost 4000 patients), our study sets the stage for the role of CT angiography in risk stratification in patients with pulmonary embolism. More specifically, our findings support the use of a single test to diagnose pulmonary embolism and to assess the risk of death.

The negative predictive value for death of right ventricle dilation at CT angiography is as high as 95%. However, the 99% negative predictive value for death due to pulmonary embolism at 30 days allows the identification of haemodynamically stable patients with acute pulmonary embolism who could be managed during a short hospital stay or even as outpatients. The use of the cut-off with high sensitivity for death (right-to-left ventricle ratio $\geqslant 0.9$) could improve the safety of this management approach. At present, only one randomised controlled trial has compared home treatment with hospitalisation in patients with acute pulmonary embolism at low risk for death [55]. In this study, low-risk patients were identified using the pulmonary embolism severity index. The accuracy of the HESTIA prediction rule in identifying patients with acute pulmonary embolism who could be candidates for outpatient management was evaluated in a prospective study, and reported promising results [56]. The evaluation of right ventricle dilation at CT angiography could potentially improve the accuracy of clinical prediction rules in the identification of low-risk patients for outpatient management.

The positive predictive value of right ventricle dilation at CT angiography for death is low (~10–15%). This finding is similar to those obtained with echocardiography and biomarkers. Thus, the idea of using one of these markers for treatment upgrading in an individual patient is probably inappropriate. It is conceivable that in patients with right ventricle dilation at CT angiography further risk stratification would improve clinical management. Whether echocardiography or troponin could improve the positive predictive value of

First author [ref.]	CT-RVD +ve		CT-RVD -ve		Weight %	OR (95% CI) M−H, Fixed	OR (95% CI) M−H, Fixed
	Events	Total	Events	Total			
Cut-off 0.9							
BECATTINI [11]	14	262	3	149	10.6	2.75 (0.78–9.72)	
JIMÉNEZ [32]	25	533	13	315	45.8	1.14 (0.58–2.27)	
Subtotal (95% CI)		**795**		**464**	**56.4**	**1.45 (0.80–2.62)**	
Total events	**39**		**16**				

Heterogeneity: Chi-squared=1.44, df=1 (p=0.23); I^2=31%
Test for overall effect: Z=1.22 (p=0.22)

Cut-off 1 or 1.1							
KANG [34]	15	148	5	112	15.0	2.41 (0.85–6.85)	
OZSU [44]	8	48	6	60	13.1	1.80 (0.58–5.60)	
STEIN [49]	2	78	2	79	5.7	1.01 (0.14–7.38)	
ZONDAG [53]	5	201	4	269	9.8	1.69 (0.45–6.38)	
Subtotal (95% CI)		**475**		**520**	**43.6**	**1.88 (1.01–3.52)**	
Total events	**30**		**17**				

Heterogeneity: Chi-squared=0.62, df=3 (p=0.89); I^2=0%
Test for overall effect: Z=1.99 (p=0.05)

Total (95% CI)		**1270**		**984**	**100.0**	**1.64 (1.06–2.52)**	
Total events	**69**		**33**				

Heterogeneity: Chi-squared=2.48, df=5 (p=0.78); I^2=0%
Test for overall effect: Z=2.24 (p=0.03)
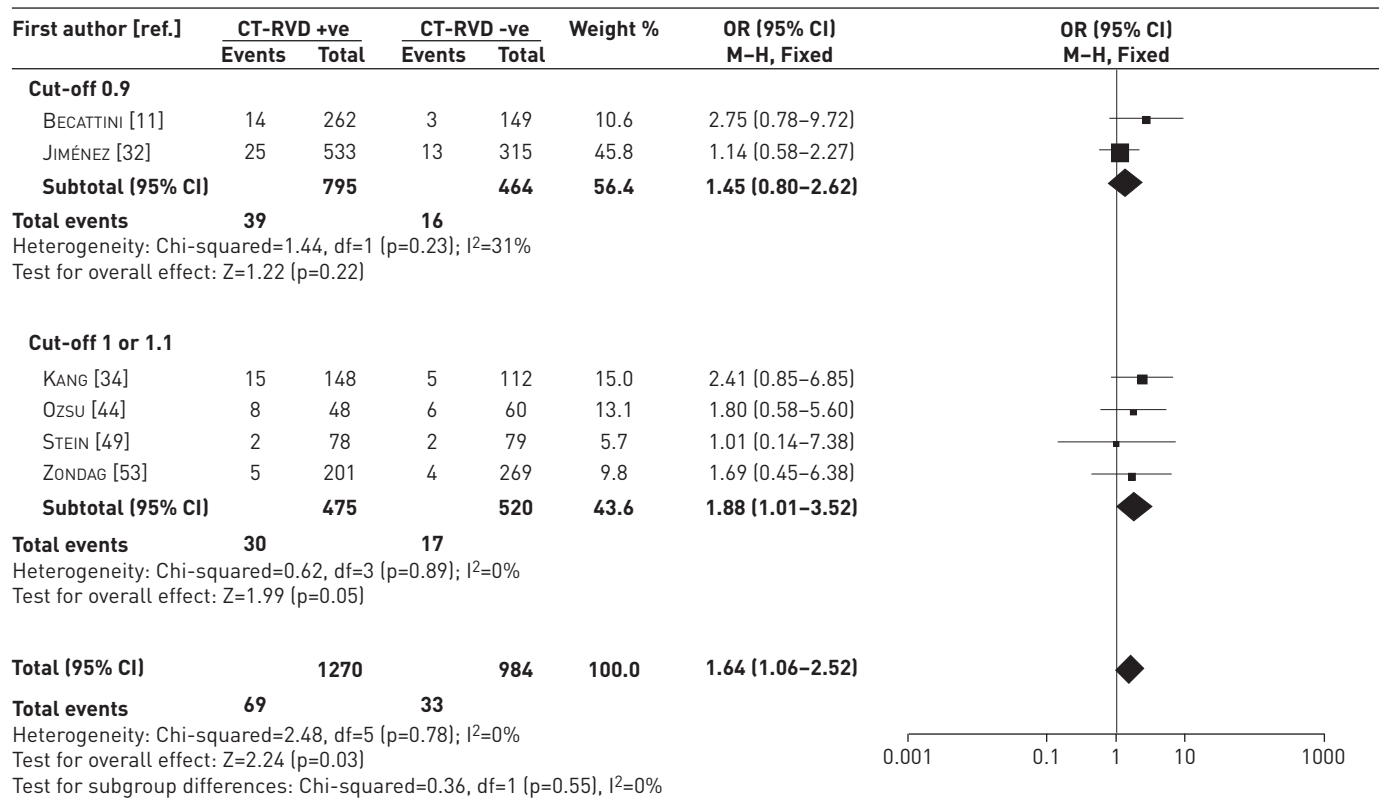Test for subgroup differences: Chi-squared=0.36, df=1 (p=0.55), I^2=0%

FIGURE 5 Forest plots for death at 30 days in haemodynamically stable patients. Risk of death in haemodynamically stable patients with increased right-to-left ventricle ratio. CT-RVD +ve: computed tomography (CT)-detected right ventricle dysfunction (RVD) present; CT-RVD -ve: CT-detected RVD absent.

CT angiography for death is currently undefined. One prospective study suggested that the combination of right ventricle dilation at CT plus increased troponin could add prognostic value [57]. Currently, no management study aimed at validating a CT-guided approach in patients with acute pulmonary embolism is available. The Pulmonary Embolism Thrombolysis (PEITHO) study aimed at assessing the clinical benefit of thrombolytic therapy compared to placebo in haemodynamically stable patients with right ventricle dysfunction and increased troponin [58]. As a proportion of patients had right ventricle dysfunction diagnosed at CT angiography, this study could provide evidence on a CT angiography-based management strategy in these patients.

Several methods have been proposed for the assessment of right ventricle dilation at CT angiography in patients with acute pulmonary embolism. The right-to-left ventricle diameter ratio is more commonly used to measure right ventricle dilation because it is simple to calculate and mirrors the concept of right ventricle dilation at echocardiography. We found an association between higher cut-offs of right-to-left ventricle diameter ratio and higher risk of death. Different methods were used to assess right-to-left ventricle ratio at CT angiography through the studies included in our critical review. The meta-analyses show that, whatever method is used (diameter ratio, volume ratio or area ratio), right ventricle dilation at CT can be used to stratify patients with acute pulmonary embolism. Indeed, separate analyses showed similar results for transverse or reconstructed images. The evaluation of right ventricle dilation by reconstructed images requires time for reconstruction and measurement. Measurements in transverse images are obtained in the same images used for the diagnosis of pulmonary embolism, which are immediately available at the end of image acquisition with no need for post-processing.

As an additional finding of our analysis, improving scanner technology (number of detectors) does not seem to be associated with an improved prediction of the risk of death associated with right ventricle dilation. It is conceivable that improved technology results in an improved accuracy in the assessment of small lung structures (segmental or sub-segmental arteries).

Our study also shows an association between IVS bowing toward the left ventricle and mortality. Given the limited number of studies reporting on IVS bowing, a separate analysis in haemodynamically stable patients

was not possible. None of the studies included in our study used an ECG-gated procedure and this could be a limitation for the specific aim of evaluating IVS bowing.

A limitation of the CT approach is it does not allow functional assessments of the right ventricle concerning pulmonary hypertension, right ventricle hypokinesis and tricuspid motion, which are all evaluated by echocardiography.

There are several limitations of our study in addition to those intrinsic to the meta-analysis approach (combining heterogeneous datasets). For example, differences were noted regarding the definition of haemodynamic stability across the studies. In this meta-analysis it was not possible to evaluate interobserver agreement in the assessment of right ventricle dilation or dysfunction at CT. However, interobserver agreement was shown to be good for the evaluation of right-to-left ventricle diameter ratio [11]. Significant heterogeneity was found in the analyses of death occurring beyond 30 days and within 3 months. However, the main clinical implications of risk stratification concern in-hospital management. Thus, the prognostic value at 30 days is of most interest for clinicians.

In conclusion, we found that right ventricle dilation as assessed by CT angiography can be used to identify haemodynamically stable patients with acute pulmonary embolism who are at high and low risk of death and death due to pulmonary embolism. Different management strategies (including home treatment and early discharge) in patients with pulmonary embolism with and without right ventricle dilation at CT angiography should be evaluated in prospective studies.

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