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META-ANALYSIS
Thrombosis and antithrombotic treatment

Right ventricle assessment in patients with pulmonary embolism at low risk for death based on clinical models: an individual patient data meta-analysis

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Aims Patients with acute pulmonary embolism (PE) at low risk for short-term death are candidates for home treatment or short-hospital stay. We aimed at determining whether the assessment of right ventricle dysfunction (RVD) or elevated troponin improves identification of low-risk patients over clinical models alone.

Methods and results Individual patient data meta-analysis of studies assessing the relationship between RVD or elevated troponin and short-term mortality in patients with acute PE at low risk for death based on clinical models (Pulmonary Embolism Severity Index, simplified Pulmonary Embolism Severity Index or Hestia). The primary study outcome was short-term death defined as death occurring in hospital or within 30 days. Individual data of 5010 low-risk patients from 18 studies were pooled. Short-term mortality was 0.7% [95% confidence interval (CI) 0.4–1.3]. RVD at echocardiography, computed tomography or B-type natriuretic peptide (BNP)/N-terminal pro BNP (NT-proBNP) was associated with increased risk for short-term death (1.5 vs. 0.3%; OR 4.81, 95% CI 1.98–11.68), death within 3 months (1.6 vs. 0.4%; OR 4.03, 95% CI 2.01–8.08), and PE-related death (1.1 vs. 0.04%; OR 22.9, 95% CI 2.89–181). Elevated troponin was associated with short-term death (OR 2.78, 95% CI 1.06–7.26) and death within 3 months (OR 3.68, 95% CI 1.75–7.74).

Conclusion RVD assessed by echocardiography, computed tomography, or elevated BNP/NT-proBNP levels and increased troponin are associated with short-term death in patients with acute PE at low risk based on clinical models. RVD assessment, mainly by BNP/NT-proBNP or echocardiography, should be considered to improve identification of low-risk patients that may be candidates for outpatient management or short hospital stay.

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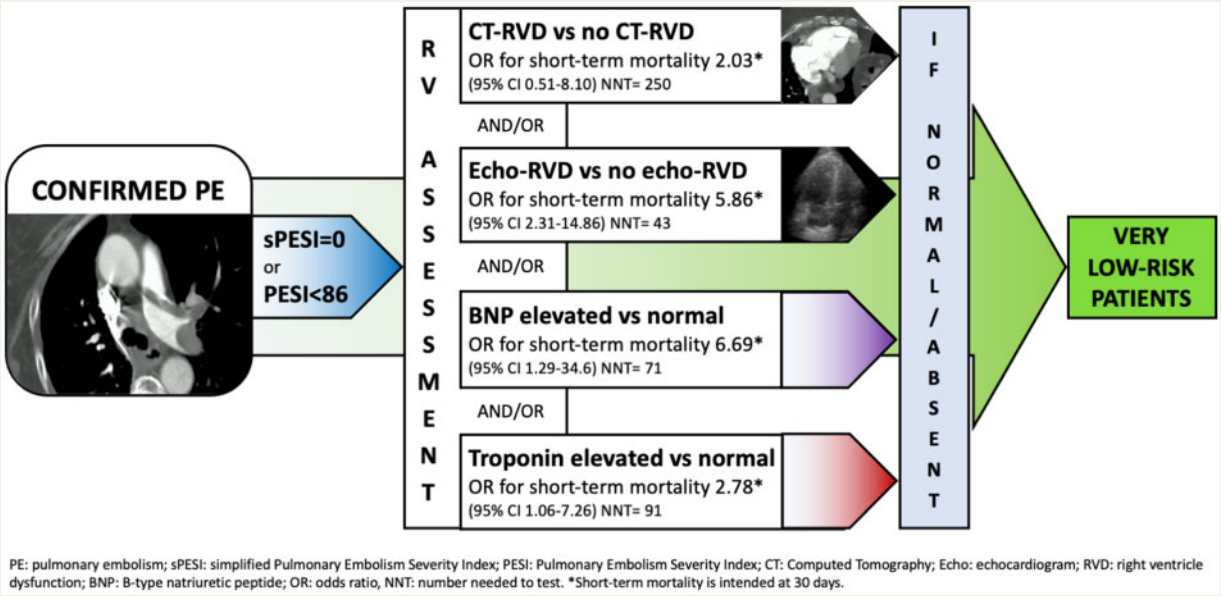
Graphical Abstract



The Association of Right Ventricle Assessment with Short-term Mortality in Patients with Pulmonary Embolism at Low Risk for Death.

Keywords Pulmonary embolism • Home treatment • Low risk • Mortality • Outpatient • Right ventricular dysfunction

Introduction

Pulmonary embolism (PE) is a potentially life-threatening disease.[1] The presentation of acute PE varies from acute shock or cardiac arrest (about 5–10% of patients) to a stable condition with mild symptoms and absence of relevant comorbidities (about 30–40% of patients), through hemodynamically stable disease with some evidence of right ventricle dysfunction (RVD) or elevated troponin (about 50–60% of patients).[2,3] Current guidelines from the European Society of Cardiology classify these three groups as patients with acute PE at high, low, or intermediate risk for short-term death.[4]

In recent years, several efforts were made to identify PE patients at low risk of death, also to inform decisions on home treatment or short hospital stay and on acute treatment strategies. Several clinical prognostic models, mostly based on clinical variables, were developed to identify PE patients at low risk of death.[5,6] The Pulmonary Embolism Severity Index (PESI) and its simplified version (sPESI) are the most validated and currently used models (Supplementary material online, *Table S1*). The expected 30-day mortality in patients classified as low risk according to the PESI or sPESI is about 1% (upper 95% confidence limit 1.6% for PESI class I and 3.5% for PESI class II; upper 95% confidence limit 2.1% for sPESI).[5] In recent years, a more pragmatic approach using the Hestia criteria has been proposed and validated in prospective studies on home treatment in patients with acute PE (Supplementary material online, *Table S2*).[7] In patients with none of the Hestia criteria who were managed as outpatients, the 90-day mortality was 1% (upper confidence limit 2.9%).

More than 30% of patients at low risk for death according to clinical models have RVD or myocardial injury.[8] However, it has been debated whether right ventricle assessment improves risk stratification in these patients. A study-level meta-analysis in patients with acute PE at low risk according to clinical models has shown that RVD is associated with a four-fold increased risk for death, with an absolute death rate of 1.8% (upper confidence limit 3.5%).[9]

We conducted an individual patient data meta-analysis (IPDMA) to determine whether the assessment of RVD or elevated troponin in patients with acute PE at low risk for death as determined by clinical models improves identification of low-risk patients over clinical models alone.

Methods

The present study was designed as an IPDMA of observational studies and followed the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) convention and PRISMA-IPD for study selection, collation of data, and analysis.[10,11] We also followed the related methodological standard statements from the American Heart Association.[12]

Data sources and searches

We conducted a systematic search of the literature for publications in PubMed and Embase between October 2008 (after the derivation and prospective validation of the PESI score) and September 2019. No

language restrictions were applied. Conference proceedings of international meetings were searched from 2007 to 2019 for additional studies. The full search strategy is provided in the Supplementary material online.

Study selection

Two investigators (G.M. and C.B.) independently screened all titles and abstracts of identified records, according to the inclusion criteria. Subsequently, the two authors independently assessed full-text publications of selected articles. Reference lists of eligible articles were handsearched. Disagreement was resolved by discussion or by consulting a third author (D.J.) when necessary. For duplicate publications, the most recent was considered.

The study protocol was registered in PROSPERO 2020 (CRD42020197900).

Studies were considered eligible for this analysis if they fulfilled all the following criteria: (i) inclusion of patients with confirmed acute PE categorized as at 'low risk' by means of clinical models (PESI class I or II, sPESI <1 or absence of Hestia criteria) regardless of the presence/absence of RVD at imaging [echocardiography or computed tomography (CT) angiography] or elevated biomarkers [N-terminal pro B-type natriuretic peptide (NT-proBNP), B-type natriuretic peptide (BNP)], or troponin; (ii) assessment of RVD at imaging (echocardiography or CT angiography) or NT-proBNP, BNP or troponin; and (iii) reporting on death (either all-cause or PE-related) occurring during the hospital stay, at 30 or 90 days in patients with or without RVD and/or elevated or normal troponin.

Studies were excluded from the analysis in case of: (i) inclusion of <30 patients and (ii) unavailability of individual patient data after a request was made to the authors.

RVD at presentation was defined according to the criteria used in the original studies either at echocardiography or CT angiography. Elevated plasma levels of NT-proBNP or BNP or cardiac troponins [troponin I (TnI) or T (TnT), by standard or high-sensitivity (hs) assays] were defined according to assays and cut-off levels adopted in the original studies.

Study outcomes

The primary study outcome is the point incidence of short-term all-cause mortality. Short term is defined as death occurring in hospital or within 30 days following the diagnosis of acute PE, as reported in the individual studies. The secondary outcomes are the point incidence of death and of PE-related death occurring up to 3 months.

Data extraction and quality assessment

Corresponding authors or first author of eligible studies were invited to participate in this collaborative project. Study-level information was sought on: setting of patients' accrual (emergency department vs. hospitalized patients), strategy for definition of low risk for death (PESI, sPESI, or Hestia criteria), prospective or retrospective design, observational or management study, strategy for right ventricle assessment (imaging or biomarkers), duration of follow-up (in-hospital, 30 days, or 90 days), and study outcome (all-cause death or PE-related death). For studies reporting mortality occurring both during in-hospital stay and at 30 days, 30-day mortality was considered for the primary outcome analysis.

The following patient-level data were requested: demographics (age in years, sex); clinical features at presentation [systolic blood pressure (sBP) in mmHg, heart rate (HR) in b.p.m., respiratory rate (RR) in breaths/min, oxygen saturation, temperature in °C, altered mental status (defined as disorientation, lethargy, stupor, or coma)]; comorbidities (cancer, heart failure, chronic lung disease); results of assessment by PESI, sPESI, or Hestia criteria, imaging of the right ventricle (performed or not performed, performed by CT and/or echocardiography, RVD present or absent); biomarkers (tested or not tested, elevated or normal); and clinical outcome (dead or alive, PE-related death).

Individual databases were merged in a pooled electronic database that was housed at the University of Perugia. PESI and sPESI assessments were recalculated for each patient. Variables were identified, measurements verified, and comparisons with individual reports were made. Discrepancies with the published data were resolved by contacting the principal investigators.

All studies had been approved by the institutional review boards of participating centres.

Risk of bias was assessed by the use of the QUIPS tool.[13]

Data synthesis and analysis

IPDMA was carried out preserving the clustering of individual participant data of patients within studies. Summary probability estimates were calculated by one-stage meta-analysis using a generalized linear mixed-effects model, in which a study-specific random effect was included to account for the clustering of patients within studies.[14] The overall effect estimate of presence vs. absence of RVD or elevated troponin was calculated.

Subgroup differences were analysed with an indicator variable as a fixed effect.

To illustrate heterogeneity across the studies, 95% prediction intervals were calculated around the point estimates on the basis of the standard error of the fixed effect and the variance of the random effect. Forest plots were generated to visualize potential heterogeneity. The *I*-squared statistic and Chi-square test were used to assess heterogeneity among individual odds ratios (ORs) for each included study.

We performed predefined sensitivity analyses for the primary study outcome and the secondary study outcomes in order to assess the effect of:

(1) Study characteristics: timing of short-term death (in-hospital or 30 days), prospective vs. retrospective design;
(2) Patient characteristics: (i) age either as a continuous variable and by groups (<50, 50–70, and >70 years), (ii) cancer, (iii) HR either as a continuous variable and by groups (<100, 100–110, and ≥110 b.p.m.), (iv) sBP either as a continuous variable and by groups (<100 and ≥100 mmHg), (v) RR either as a continuous variable and by groups (<20 and 20–30 breaths/min);
(3) Tests characteristics: PESI, sPESI, Hestia, CT angiography, echocardiography, troponin, and natriuretic peptides.

A confirmatory analysis of the study outcomes was also carried out via a two-stage IPDMA and results are reported in the Supplementary material online.

All analyses were performed in SPSS (version 25.0) and R [version 3.3.2 (R Foundation for Statistical Computing), by using the lme4 package, version 1.1-23, meta (version 4.11-0), and metafor (version 2.4-0) packages].

Results

Our search identified 5370 papers. After study selection, 36 studies were identified as fulfilling the inclusion criteria (*Figure 1*). After direct contact with authors, individual patient data from 18 studies (8948 patients) were made available, merged in a pooled database, and included in the study.[8,15–31] Eighteen eligible studies were not included because the data were not made available,[32–49] leading to the inclusion in the analysis of about 70% of the potentially eligible patients.

The main characteristics and RVD definitions of the 18 included studies are described in Supplementary material online, *Table S3*. The main features of studies included or not included in the IPDMA are reported in Supplementary material online, *Table S4*.

Among the 18 included studies, PESI, sPESI and Hestia were used to identify low-risk patients in seven, nine and one studies, respectively. In one study, assessment of low risk was based on either PESI, sPESI, or Hestia.[30] RVD assessment was reported by imaging in 15 studies (by echocardiography in seven, by CT angiography in two and either echocardiography or CT angiography in six).[8,15–18,20–23,25–31] BNP or NT-proBNP was determined in seven studies[18,23–25,27,29,31] and troponin in 12 studies.[8,15,16,18–20,22,23,25,27,29,31] Funnel plot inspection revealed no publication bias.

Among 8948 patients from 18 studies,[8,15–31] 5010 patients were classified at low risk for death according to the recalculated sPESI (3830 patients) or PESI (3483 patients) scores and were included in the IPDMA. The main features of the included patients are reported in *Table 1*. Main patient features by study are reported in Supplementary material online, *Table S5*. Notably, the mean age was 55 ± 16 years and the prevalence of comorbidities was low.

RVD assessment was available in 3795 patients and troponin in 2249 patients. RVD at echocardiography or CT angiography was observed in 25% and in 38% of the evaluated patients, respectively. Elevated BNP/NT-proBNP levels were found in 22% and elevated levels of troponin in 19% of patients.

Characteristics of patients with sPESI score of 0 or PESI class I or II by study are reported in Supplementary material online, *Table S5*.

Short-term mortality in low-risk patients according to PESI or sPESI

Fifteen studies (4444 patients) reported on death occurring during the hospital stay or within 30 days of diagnosis of acute PE.[8,15,16,18–21,23,25–31] The point estimate for death occurring during the hospital stay or within 30 days was 0.7% [95% confidence interval (CI) 0.4–1.3].

A significant association was observed between RVD at echocardiography, CT or BNP/NT-proBNP and death occurring during the hospital stay or within 30 days of diagnosis of acute PE (1.5 vs. 0.3%; OR 4.81, 95% CI 1.98–11.68) (*Table 2* and *Figure 2*). The number needed to test to identify one patient that will die during the hospital stay or within 30 days of diagnosis was 83 (*Table 2*). RVD at echocardiography (OR 5.86, 95% CI 2.31–14.86), increased levels of BNP/NT-proBNP (OR 6.69, 95% CI 1.29–34.6) and elevated levels of troponin (OR 2.78, 95% CI 1.06–7.26) were associated with death occurring during the hospital stay or up to 30 days from diagnosis of acute PE. RVD at CT angiography was not associated with death occurring during the hospital stay or within 30 days of diagnosis of acute PE (OR 2.03, 95% CI 0.51–8.10). Similar strength of association was observed by using different cut-off levels for definition of RVD at

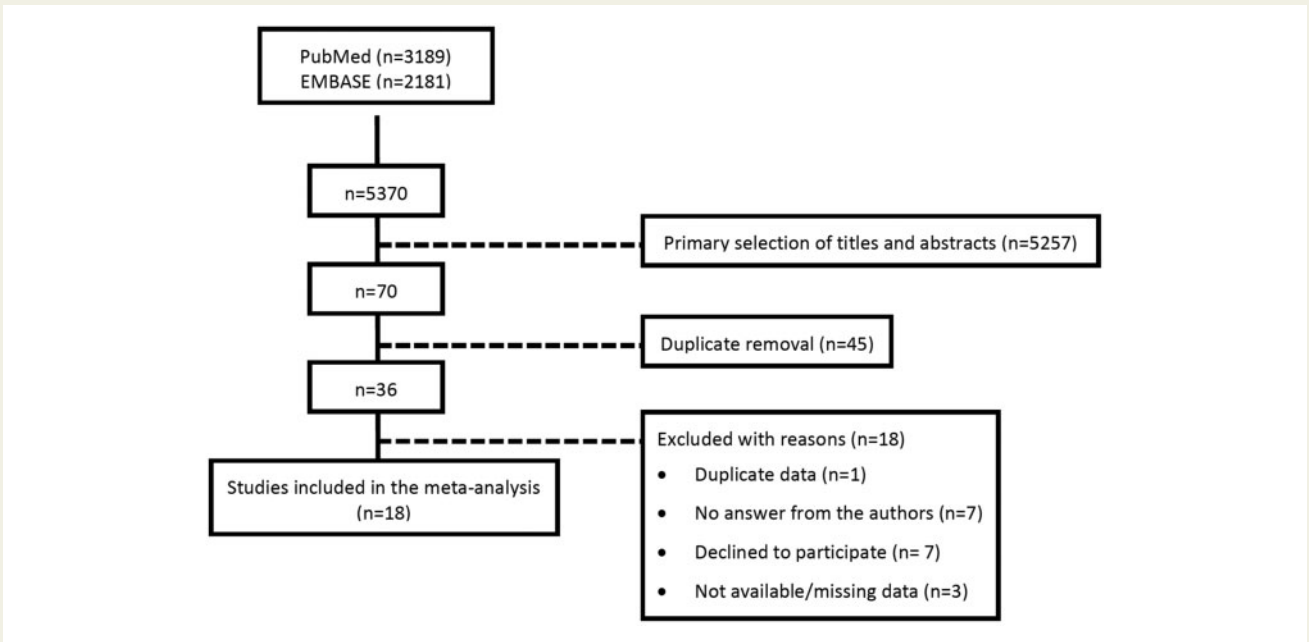


Figure 1 Study flow.

Table 1 Characteristics of study patients

Clinical feature	
Patients, *n*	5010
Age (years)	
Range	16-89
Mean ± SD	55 ± 16
Male sex, *n/N* (%)	2403/5010 (48)
Cancer, *n/N* (%)	77/5010 (1.5)
Heart failure, *n/N* (%)	88/4756 (1.8)
Chronic lung disease, *n/N* (%)	361/4952 (7.3)
Systolic BP, mean ± SD	130 ± 20
Heart rate, mean ± SD	89 ± 17
Oxygen saturation, mean ± SD	96 ± 3
Respiratory rate, mean ± SD	21 ± 4
Clinical assessment	
sPESI score available, *n* (%)	4965 (99)
sPESI = 0, *n* (%)	3830 (77)
PESI score available, *n* (%)	3652 (73)
Class I, *n* (%)	1571 (43)
Class II, *n* (%)	1912 (52)
Class >II, *n* (%)	169 (5)
RVD or injury	
RVD at echocardiography, *n/N* (%)	474/1904 (25)
RVD at CT angiography, *n/N* (%)	589/1546 (38)
Elevated BNP/NT-proBNP, *n/N* (%)	354/1573 (22)
Elevated troponin, *n/N* (%)	422/2249 (19)

SD: standard deviation; BP: blood pressure; sPESI: simplified Pulmonary Embolism Severity Index; PESI: Pulmonary Embolism Severity Index; RVD: right ventricle dysfunction; CT: Computed Tomography; BNP: B-type natriuretic peptide; NT-pro BNP: N-terminal pro B-type natriuretic peptide.

CT, with the limit of small groups and small number of outcome events.

Clinical course within 3 months in patients at low risk according to PESI or sPESI

Point estimate for all-cause mortality up to 3 months was 0.8% (95% CI 0.4–1.8).

Presence of RVD at echocardiography, CT, or BNP/NT-proBNP was associated with increased risk for death occurring within 3 months (1.6% vs. 0.4%; OR 4.03, 95% CI 2.01–8.08).

The analyses of association between individual methods for RVD assessment and death within 3 months are reported in *Table 3* and *Figure 2*. A significant association between RVD and death within 3 months was confirmed for all methods except for CT angiography assessment.

Assessment of troponin levels was reported in 12 studies.[8,15,16,18–20,22,23,25,27,29,31] A significant association was observed between elevated troponin levels and mortality (*Table 3*).

PE-related mortality within 3 months was reported in 13 studies (3638 patients) and occurred in 0.4% of patients (95% CI 0.1–1.5).[8,15,16,18,21–23,26–31] RVD assessment by imaging or BNP/NT-proBNP was associated with PE-related death (1.1 vs. 0.04%; OR 22.9, 95% CI 2.89–181), and this finding was mainly driven by RVD at echocardiography (OR 26.9, 95% CI 3.39–212) (*Table 3*). None of the patients with normal BNP/NT-proBNP levels died due to PE. The number needed to test to identify one patient that will die within 3 months was 45 for echocardiography and 77 for BNP/NT-proBNP.

Results were confirmed by a two-stage method (Supplemental *Figure 1*).

Table 2 Association between different methods for assessment of right ventricle dysfunction and injury and short-term death (occurring in hospital or within 30 days)

Parameter for RVD/myocardial injury (sPESI = 0 or PESI <86)	In-hospital/30-day all-cause mortality			
	Yes vs. no	OR (95% CI)	*P*-value	*N*. needed to test
Imaging or biochemical RVD (14 studies; 3266 patients)	1.5% (0.8–3.0) vs. 0.3% (0.1–0.7)	**4.81 (1.98–11.68)**	**<0.001**	83
RVD at imaging (14 studies; 2892 patients)	1.4% (0.6–3.1) vs. 0.3% (0.1–0.8)	**4.49 (1.80–11.18)**	**0.001**	91
RVD at echocardiography (12 studies; 1843 patients)	2.8% (1.5–5.2) vs. 0.5% (0.2–1.1)	**5.86 (2.31–14.86)**	**<0.001**	43
RV enlargement at CT (8 studies; 1479 patients)	0.7% (0.2–2.7) vs. 0.3% (0.08–1.5)	2.03 (0.51–8.10)	0.316	250
Elevated BNP or NT-proBNP (6 studies; 1172 patients)	1.6% (0.6–3.7) vs. 0.2% (0.06–0.9)	**6.69 (1.29–34.6)**	**0.024**	71
Elevated troponin (11 studies; 2183 patients)	1.8% (0.8–4.1) vs. 0.7% (0.3–1.3)	**2.78 (1.06–7.26)**	**0.036**	91

RVD: right ventricle dysfunction; RV: right ventricle; sPESI: simplified Pulmonary Embolism Severity Index; PESI: Pulmonary Embolism Severity Index; OR: odds ratio; CI: confidence interval; CT: Computed Tomography; BNP: B-type natriuretic peptide; NT-pro BNP: N-terminal pro B-type natriuretic peptide; N.= number.
For imaging RVD, results at echocardiography or computed tomography are intended.
For biochemical RVD, results at BNP/NT-pro BNP are intended.
All results have been obtained by univariate analysis. Numbers in bold indicate statistically significant differences.

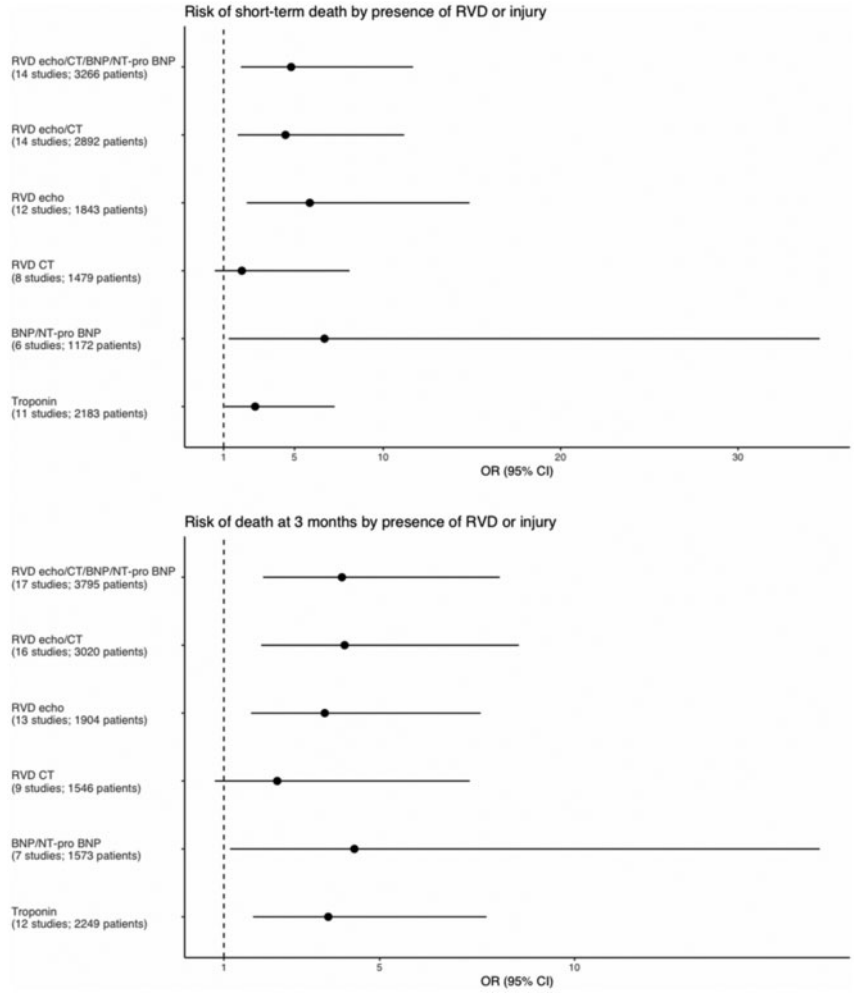


Figure 2 Risk of short-term or 3-month death by presence of right ventricle dysfunction or injury. BNP, B-type natriuretic peptide; CI, confidence interval; CT, computed tomography; NT-proBNP, N-terminal pro B-type natriuretic peptide; OR, odds ratio.

Sensitivity analyses

The role of sequential test for RV assessment is reported in *Table 4*. No improvement in risk stratification for short-term death was observed by the assessment of BNP/NT-proBNP in patients without RVD on echocardiography. BNP/NT-proBNP assessment seems to improve identification of low-risk patients when used with CT angiography or troponin. Similarly, echocardiography seems to improve risk stratification when used in patients with no RVD at CT angiography or normal troponin levels.

The associations between RVD assessments and death occurring within 3 months either in patients at low risk according to sPESI or in patients at low risk according to PESI are reported in *Table 5*. Presence of RVD at echocardiography, CT or BNP/NT-proBNP was associated with increased risk for death in both patients at low risk according to PESI and patients at low risk according to sPESI (Supplementary material online, *Table S6*). RVD at CT angiography was not associated with death occurring within 3 months in either group.

Further sensitivity analyses in patients with RVD assessment available either by imaging or biomarkers are reported in *Table 5*. The prospective or retrospective design did not influence the associations between RVD or elevated troponin and death. The association between RVD and death was confirmed after exclusion of studies with <50 patients.

No association was found between patient characteristics such as age, gender, heart rate below or above 110 b.p.m. or respiratory rate below or above 30 breaths/min, and short-term death.

Discussion

Our IPDMA, which included >5000 patients with acute PE at low risk for death as determined by clinical scores, showed a short-term mortality of <1% (with an upper limit of the 95% CI of 1.3%) and a PE-related mortality of 0.4% (upper limit of the 95% CI of 1.5%). In these patients, both all-cause mortality and PE-related mortality were

Table 3 Association between different parameters of right ventricle dysfunction or injury and death or PE-related death occurring up to 3 months in patients at low risk by either simplified Pulmonary Embolism Severity Index or Pulmonary Embolism Severity Index"

Parameter for RVD/myocardial injury	All-cause mortality within 3 months			
	Yes vs. No	OR (95% CI)	*P*-value	*N.* needed to test
Imaging or biochemical RVD (17 studies; 3795 patients)	1.6% (0.7–3.3) vs. 0.4% (0.2–0.9)	**4.03 (2.01–8.08)**	**<0.0001**	83
RVD at imaging (16 studies; 3020 patients)	1.4% (0.6–3.6) vs. 0.3% (0.1–0.9)	**4.10 (1.96–8.57)**	**<0.001**	91
RVD at echocardiography (13 studies; 1904 patients)	2.4% (1.0–5.6) vs. 0.7% (0.3–1.7)	**3.59 (1.70–7.59)**	**<0.0001**	59
RV enlargement at CT (9 studies; 1546 patients)	0.5% (0.1–3.4) vs. 0.2% (0.0–1.6)	2.37 (0.77–7.31)	0.132	333
Elevated BNP or NT-proBNP (7 studies; 1573 patients)	1.4% (0.6–3.3) vs. 0.3% (0.1–0.9)	**4.35 (1.16–16.29)**	**0.029**	91
Elevated troponin (12 studies; 2249 patients)	2.9% (1.1–7.4) vs. 0.8% (0.3–2.0)	**3.68 (1.75–7.74)**	**<0.001**	48
Parameter for RVD/myocardial injury	**PE-related mortality within 3 months**			
	Yes vs. No	**OR (95% CI)**	***P*-value**	***N.* needed to test**
Imaging or biochemical RVD (13 studies; 2868 patients)	1.1% (0.05–2.4) vs. 0.04% (0–0.4)	**22.9 (2.89–181)**	**0.001**	94
RVD at imaging (13 studies; 2494 patients)	1.0% (0.03–2.6) vs. 0.05% (0–0.4)	**19.4 (2.36–159)**	**0.001**	105
RVD at echocardiography (11 studies; 1513 patients)	2.3% (1.2–4.4) vs. 0.09% (0.01–0.6)	**26.9 (3.39–212)**	**0.002**	45
RV enlargement at CT (6 studies; 1243 patients)	0.4% (0.1–1.5) vs. 0.3% (0.07–1.1)	1.43 (0.20–10.21)	0.719	1000
Elevated BNP or NT-proBNP (5 studies; 1106 patients)	1.3% (0.5–3.5) vs. 0%	n.v.	–	77
Elevated troponin (9 studies; 1982 patients)	0.5% (0.1–2.9) vs. 0.2% (0.06–1.0)	2.08 (0.49–8.82)	0.323	333

*Simplified Pulmonary Embolism Severity Index = 0 or Pulmonary Embolism Severity Index < 86.
RVD: right ventricle dysfunction; RV: right ventricle; sPESI: simplified Pulmonary Embolism Severity Index; PESI: Pulmonary Embolism Severity Index; OR: odds ratio; CI: confidence interval; CT: Computed Tomography; BNP: B-type natriuretic peptide; NT-pro BNP: N-terminal pro B-type natriuretic peptide; PE: pulmonary embolism; N.= number; n.v.= not valuable.
For imaging RVD, results at echocardiography or computed tomography are intended.
For biochemical RVD, results at BNP/NT-pro BNP are intended.
All results have been obtained by univariate analysis. Numbers in bold indicate statistically significant differences.

associated with the presence of RVD assessed either at imaging or by elevated BNP/NT-proBNP; mortality either at short term or within 3 months was also associated with elevated troponin. When RVD was absent on echocardiography, or CT or elevated BNP or NT-proBNP levels, the short-term mortality was as low as 0.3–0.5% (*Graphical Abstract*).

Identification of patients with acute PE at very low risk for death has several clinical implications and among these are the options for home treatment directly from the emergency department or after a short hospital stay. In fact, our IPDMA did not assess the issue of home treatment or short hospital stay, rather the accuracy of different methods for RV assessment in identifying a very low-risk population of patients with acute PE. By reinforcing the evidence on optimal methods for identification of a group of patients with acute PE and very low risk for death, and providing rates of short-term deaths and PE-related deaths, our study can help clinicians on decision making concerning patient disposition and drive further studies on home treatment/short hospital stay. Indeed, recent studies have shown that home treatment or short-term hospital stay are feasible in patients with acute PE at low risk for death.[7,50] However, home treatment is underused in clinical practice as concerns still remain among physicians regarding the risk of adverse outcomes in the short course after discharge. In this view, increased accuracy of risk stratification and increased safety of the clinical course of patients may lessen concerns about home treatment or short hospital stay.

Risk stratification, based on RVD by imaging or cardiac biomarkers and troponin assessment, was consistently proven to be effective in the general population of patients with PE,[51–54] but its value in patients with acute PE at low risk for death based on PESI or sPESI remains unclear. Based on our IPDMA, it appears that identification of patients with acute PE at low risk based on current clinical risk scores could be further refined by RVD or troponin assessment. In

Table 4 Role of sequential tools for right ventricle assessment in the prediction of death occurring in-hospital or within 30 days

	No RVD on echocardiography		No RVD on CT angiography		Normal BNP or NT-proBNP		Normal troponin	
BNP or NT-proBNP	**Elevated**	**Normal**	**Elevated**	**Normal**	–	–	**Elevated**	**Normal**
Death in-hospital or at 30 d	0.8% (1/123)	0.3% (1/357)	1.8% (1/55)	0.4% (1/225)	–	–	1.1% (2/179)	0.3% (2/598)
Troponin	**Elevated**	**Normal**	**Elevated**	**Normal**	**Elevated**	**Normal**	–	–
Death in-hospital or at 30 d	2.0% (3/152)	0.4% (3/766)	2.3% (2/88)	0.5% (2/415)	– (0/38)	0.3% (2/598)	–	–
Echocardiography	–	–	**RVD**	**No RVD**	**RVD**	**No RVD**	**RVD**	**No RVD**
Death in hospital or at 30 d	–	–	4.2% (2/48)	0.5% (2/421)	– (0/47)	0.3% (1/357)	2.9% (5/170)	0.4% (3/766)
CT Angiography	**RVD**	**No RVD**	–	–	**RVD**	**No RVD**	**RVD**	**No RVD**
Death in hospital or at 30 d	0.4% (1/223)	0.5% (2/421)	–	–	– (0/159)	0.4% (1/225)	0.3% (1/282)	0.5% (2/415)

RVD: right ventricle dysfunction; CT: Computed Tomography; BNP: B–type natriuretic peptide; NT–pro BNP: N–terminal pro B–type natriuretic peptide.

Table 5 Sensitivity analysis for short-term death in patients with right ventricle dysfunction at imaging or B-type natriuretic peptide/N-terminal pro B-type natriuretic peptide available

	Death at 30 days		Death at 3 months	
	***N* studies; *N* patients**	**OR (95% CI)**	***N* studies; *N* patients**	**OR (95% CI)**
RVD by Imaging or BNP/NT-proBNP	14; 3265	4.46 (1.81–11.00)	17; 3794	3.68 (1.82–7.47)
Age 50–70 years		0.67 (0.25–1.81)		1.25 (0.55–2.88)
Age >70 years		1.07 (0.39–2.94)		1.90 (0.75–4.80)
RVD by Imaging or BNP/NT-proBNP	14; 3266	4.81 (1.98–11.69)	17; 3795	4.02 (2.00–8.07)
Female sex		1.07 (0.48–2.39)		1.10 (0.57–2.10)
RVD by Imaging or BNP/NT-proBNP	14; 3240	4.37 (1.78–10.71)	17; 3754	3.90 (1.95–7.84)
sPESI >0		2.29 (0.96–5.49)		1.64 (0.79–3.40)
RVD by Imaging or BNP/NT-proBNP	13; 3029	3.59 (1.42–9.10)	16; 3557	3.36 (1.63–6.94)
HR 100–110 b.p.m.		2.49 (0.96–6.44)		1.13 (0.49–2.62)
HR >110 b.p.m.		2.87 (0.86–9.62)		1.88 (0.71–5.02)
RVD by Imaging or BNP/NT-proBNP	9; 2258	8.73 (2.57–29.63)	11; 2363	5.64 (2.42–13.18)
RR 20–30 breaths/min		0.44 (0.14–1.31)		0.90 (0.39–2.05)
RR >30 breaths/min		0.78 (0.08–7.16)		0.66 (0.08–5.82)
RVD by Imaging or BNP/NT-proBNP	14; 3265	4.49 (1.82–11.05)	17; 3794	3.84 (1.90–7.76)
Prospective design		0.83 (0.25–2.71)		0.63 (0.16–2.48)
RVD by Imaging or BNP/NT-proBNP after exclusion of studies with <50 patients	13; 3233	4.84 (1.99–11.75)	16; 3762	4.04 (2.01–8.11)

OR: odds ratio; CI: confidence interval; RVD: right ventricle dysfunction; CT: Computed Tomography; BNP: B–type natriuretic peptide; NT-pro BNP: N–terminal pro B–type natriuretic peptide; sP ESI: simplified Pulmonary Embolism Severity Index, HR: heart rate; RR: respiratory rate. For RVD by imaging, results at echocardiography or computed tomography are intended.

the present analysis of low-risk patients, those without RVD or with normal troponin had a risk for death that was <0.5%. This risk appears to be lower than that derived in low-risk patients by clinical models based on clinical evaluation alone (~1%).

In our IPDMA in low-risk PE patients based on clinical models, we found a non-negligible prevalence of RVD of ~30% if assessed by echocardiography, CT angiography, or BNP/NT-proBNP and a prevalence of elevated troponin of ~20%. These prevalences translate to a proportion of >65% of patients without RVD that can still safe candidates for management by home treatment or short hospital stay. In the remaining patients with RVD or elevated troponin such management strategies should probably be avoided or used with caution. In fact, in our study in patients with low-risk PE according to clinical models, short-term mortality in the presence of RVD or elevated troponin may reach 5%. Based on these results, RVD assessment in patients at low risk according to clinical models is able to identify a subgroup of patients that, despite an apparent low risk for death, may require attention and a subgroup at very low risk for death.[50]

As death in patients with acute PE is related to acute RV overload, it is clinically plausible that the assessment of RVD could have a role in the risk stratification of these patients.

In terms of resource utilization, the issue remains whether a population with an expected all-cause mortality <1% requires further risk stratification taking into account that use of clinical models such as PESI or sPESI makes risk assessment rapid and feasible around the clock. The number needed to test could be informative in this specific issue and would lead to select echocardiography or BNP/NT-proBNP for clinical practice. However, these numbers may have been affected by differences among populations assessed with different tools for RVD.

Mortality was shown to be low in all groups of patients without RVD, whatever the strategy used for the assessment. However, differences were found between different methodologies for RVD assessment. While CT angiography allows assessment only of RV dilatation, echocardiography also allows functional assessments and estimate of pulmonary artery pressure. BNP and NT-proBNP offer indirect estimate of functional overload.

In our study, RVD at echocardiography and BNP or NT-proBNP levels were the most reliable predictors of death. Although the definition of RVD at echocardiography varied across studies—and probably across individual patients in each study—the association with death was consistent across all the analyses and no heterogeneity was shown. Similarly, we pooled BNP and NT-proBNP to avoid small groups' effect and almost all the analyses revealed an association between these biomarkers and death with no evidence for heterogeneity. The non-significant association observed for CT-assessed RVD and death might be due to less defined criteria for RVD at CT angiography as well as the limited number of patients included in the analysis and their particularly low death rates. In fact, the prognostic value of CT-assessed RVD is based on studies in the overall population of patients with acute PE or in those haemodynamically stable. This is the first study specifically assessing the prognostic role of CT-assessed RVD in a large sample of patients with acute PE at low risk for death. It should be considered that a good correlation has been shown between CT and echo assessment of RVD.[55,56] It is conceivable that the low mortality rates reported in the low-risk population according to clinical models reduce the power of CT-assessed RVD.

The results on the predictive value of RVD at echocardiography are reassuring. In fact, in our era of portable point-of-care ultrasound, the feasibility of RVD assessment has much improved, also thanks to the improved skill of physicians in emergency departments, critical care, and intensive care units that are trained and familiar with the use of this technology.[57–59]

PESI and sPESI have shown a high accuracy in identifying patients at low risk for death. Limited data are currently available on comparison between clinical scores or clinical gestalt for risk assessment in patients with acute PE. By including assessment of vital parameters, clinical scores represent a snapshot of the patient's situation in a specific time point that may completely change over time. It is coinceivable that RV assessment by echo or biomarkers is a more stable parameter. In this view, PESI and sPESI should not be intended as substitutes for reasonable clinical judgement that is mandatory to make any decision on patient management.

Sensitivity analyses showed no association between patients' features and short-term death. These results could be related to the low number of study outcome events. In fact, no deaths were observed in some of the predefined subgroups. Moreover, these results suggest that most of the clinical prognostic information is already captured by clinical prognostic scores. Whether risk stratification of low-risk patients can be further improved by better clinical evaluation remains undefined. Concerning the potential role of sequential combination of tests for RV assessment, the association of echocardiography or BNP/NT-proBNP can be useful in combination with CT angiography or troponin; in this view, troponin seems to improve risk stratification obtained by echocardiography and vice versa. However, absolute mortality rates seem quite low in almost all subgroups with a first negative test.

Our study had death as primary and secondary study outcomes. Several recent studies also assessed clinical deterioration or treatment upgrading as undesirable clinical events. However, the definition of clinical deterioration varies across studies and probably across physicians. In this view, death is the hardest clinical event with no chance for overestimation.

Recently, a study-level meta-analysis reported an association between RVD in patients with acute PE at low risk for death.[9] In this context, the IPDMA design used in our study allows adjustments for confounding factors in observational studies.[60] In our study, availability of individual patient data allowed the use of consistent criteria for the definition of PE patients at low risk for death. Moreover, PESI and sPESI were recalculated for each patient and disagreements with the original assessment were resolved with the corresponding authors. Missing data were accounted for at the individual level. IPDMA also allows adjustment of estimates for baseline (prognostic) factors in subgroup analyses. Finally, the IPDMA approach increases the power of analyses in populations with low rates of study outcome events. Our IPDMA was performed according to a one-stage method and results were confirmed by a two-stage method. One-stage is by far the most recommended methodology for IPDMA as it allows the use of individual patient data while the two-stage method is still based on aggregate comparisons.

Our study has some limitations. We were not able to obtain all the available data for our IPDMA. Although this can be an issue in IPDMA, the main features of included and excluded studies and their results were comparable. More specifically, as reported in Supplementary material online, *Table S4*, the provision of studies' individual patient data was unlikely to be associated with the significance of its results. Moreover, the rates of events in unavailable studies seem to be comparable to those of the included studies (Supplementary material online, *Table S3*). This could reduce the possibility of an availability bias. In regard to the prognostic assessment of some individual methods for RV assessment, the low prevalence of abnormal findings together with low rates of mortality would have limited the power of the analyses to identify robust associations. This limit is also reflected by the wideness of some CIs of individual estimates. However, as our IPDMA deals with patients at low risk for death, our results largely improve estimates from individual studies. Moreover, the relative sensitivity and specificity of echocardiography and CT parameters of RV dysfunction, and of cut-off levels (e.g. 1.0 for the RV/LV ratio) are still controversial. Similarly, assays for troponin assessment varied across studies, some reporting on hs and some on standard troponin. The observational nature of the included studies is an additional limit. However, observational cohorts are the

usual setting for identification of outcome predictors. Finally, timing of assessment may impact on findings of RVD. Unfortunately, we do not have timing of examinations in the individual patients.

Our study has also some strengths. By including >5000 patients, ours is by far the largest study on risk assessment of patients with PE at low risk for death based on clinical models. As in all IPDMAs, it increases the precision of study results by increasing the sample size, and enables the development of more robust subgroup analyses.[61] Our IPDMA offered the possibility of standardizing the assessment of low-risk groups by recalculating clinical models (PESI and sPESI) and establishing uniform outcome definitions.

In conclusion, our study shows that echocardiography and cardiac biomarkers can improve the selection of patients with acute PE at low risk for death based on clinical models. RVD assessment, mainly by BNP/NT-proBNP or echocardiography, should be considered to improve identification of low-risk patients that may be candidates for outpatient management or short hospital stay, thus reducing the burden on the health systems and harm to patients.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Data availability

The data underlying this article will be shared on request to the corresponding author after agreement with each individual contributing author.

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