Prognostic value of right ventricular dysfunction or elevated cardiac biomarkers in patients with low-risk pulmonary embolism: a systematic review and meta-analysis

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Aims	Patients with acute pulmonary embolism (PE) classified as low risk by the Pulmonary Embolism Severity Index (PESI), its simplified version (sPESI), or the Hestia criteria may be considered for early discharge. We investigated whether the presence of right ventricular (RV) dysfunction may aggravate the early prognosis of these patients.
Methods and results	We did a systematic review and meta-analysis of studies including low-risk patients with acute PE to investigate the prognostic value of RV dysfunction. Diagnosis of RV dysfunction was based on echocardiography or computed tomography pulmonary angiography. In addition, we investigated the prognostic value of elevated troponin or natriuretic peptide levels. The primary outcome was all-cause mortality at 30 days or during hospitalization. We included 22 studies (*N* = 3295 low-risk patients) in the systematic review: 21 were selected for quantitative analysis. Early all-cause mortality rates in patients with vs. without RV dysfunction on imaging were 1.8% [95% confidence interval (CI) 0.9–3.5%] vs. 0.2% (95% CI 0.03–1.7%), respectively, [odds ratio (OR) 4.19, 95% CI 1.39–12.58]. For troponins, rates were 3.8% (95% CI 2.1–6.8%) vs. 0.5% (95% CI 0.2–1.3%), (OR 6.25, 95% CI 1.95–20.05). For natriuretic peptides, only data on early PE-related mortality were available: rates were 1.7% (95% CI 0.4–6.9%) vs. 0.4% (95% CI 0.1–1.1%), (OR 3.71, 95% CI 0.81–17.02).
Conclusions	In low-risk patients with acute PE, the presence of RV dysfunction on admission was associated with early mortality. Our results may have implications for the management of patients who appear at low risk based on clinical criteria alone, but present with RV dysfunction as indicated by imaging findings or laboratory markers.
Keywords	Pulmonary embolism • Home treatment • Risk stratification • Right ventricular dysfunction • Mortality • Anticoagulation

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Introduction

Acute pulmonary embolism (PE) contributes to the global burden of cardiovascular disease in terms of morbidity, mortality, and financial impact on healthcare systems.[1,2] Current management strategies are tailored to the patient's risk of early death or other serious early complications. In the 2014 European Society of Cardiology (ESC) Guidelines, risk stratification of patients with acute PE is based on three sets of criteria: (i) haemodynamic status and clinical characteristics at baseline, (ii) findings of right ventricular (RV) dysfunction on imaging, notably echocardiography or computed tomography pulmonary angiography (CTPA), and (iii) elevation of cardiac biomarkers, particularly cardiac troponins and natriuretic peptides, indicating myocardial injury and (right) heart failure, respectively.[1]

A reliable risk classification of PE has immediate clinical implications, notably with regard to the decision on whether to hospitalize the patient or discharge him/her to ambulatory treatment. Home treatment may improve satisfaction with treatment and more generally the quality of life of patients with acute PE; in addition, it may help to reduce costs as well as potential health risks related to unnecessary hospitalization. This is particularly important in view of the fact that, in many countries, patients with acute PE are still hospitalized for several days.[3–5] Cohort studies and randomized controlled trials, which investigated the efficacy and safety of ambulatory PE treatment in the vitamin K antagonist (VKA) era, used mainly clinical severity scores for patient selection.[6–9] These include the Pulmonary Embolism Severity Index (PESI), its simplified version (sPESI), and the Hestia criteria. In the years to come, non-VKA oral anticoagulants may facilitate early discharge and outpatient treatment for selected patients with acute PE. Consequently, the 2014 ESC Guidelines on the management of acute PE proposed an algorithm, in which a low clinical risk based on the PESI (or sPESI) alone could justify early discharge without the need for further testing.[1] However, caution is warranted and maximum safety is imperative when judging a patient to be at sufficiently low risk to be released from medical attention. In this context, accumulating reports appear to suggest that standardized clinical severity scores alone might be insufficient to exclude subclinical RV dysfunction and thus an intermediate risk of early complications.[8,10,11] Therefore, we conducted the present systematic review and study-level meta-analysis to determine the prognostic relevance of RV dysfunction resulting from RV pressure overload, detected on echocardiography or CTPA, or of elevated cardiac biomarkers, in patients with acute PE classified into the low-risk category according to current clinical severity scores.

Methods

Literature search and study selection

We conducted a systematic search of the literature for publications in *PubMed* or *Web of Science* between October 2008 and May 2018, that is after the derivation and validation of the PESI[12] and the publication of the 2008 ESC guidelines on acute PE,[13] in which an advanced concept of risk stratification was first introduced. We performed an additional manual search of potentially eligible studies within references of the included studies, international guidelines, relevant (systematic) reviews, and derivation/validation studies of prognostic scores. The literature search strategy is available as Supplementary material online.

Search results were screened independently by two reviewers for the relevance of titles/abstracts and full-texts of the studies fulfilling the inclusion criteria. Potential disagreements were solved by a third reviewer. The authors of publications with missing data were contacted at least twice within a 2-week period. The present work was performed in accordance with the PRISMA and MOOSE guidelines.[14,15] We registered the study protocol in PROSPERO (CRD42018103926).

Eligibility criteria

Studies were considered eligible if they fulfilled all the following criteria:

i. They included normotensive patients (or provided subgroup data for this category of patients) not selected based on the presence/absence of RV dysfunction, with an objectively confirmed diagnosis of acute PE, and categorized as being at low risk according to either the (s)PESI (PESI Classes I or II, PESI < 86 points, or sPESI = 0) or Hestia (all criteria absent);

ii. The study evaluated the prognostic role of RV dysfunction on admission, here primarily defined as the presence of signs of RV pressure overload on imaging tests (echocardiography or CTPA) among low-risk patients, or, alternatively, as myocardial injury based on elevated cardiac troponins or natriuretic peptides.

iii. At least one of the outcomes of interest was assessed during short-term (either at 30 days or, if not available, in-hospital) or 90-day follow-up.

The description of the items that are part of the clinical scores are summarized in the Supplementary material online. Two authors independently assessed the quality of studies focusing on clinical outcomes in accordance with the Newcastle–Ottawa Scale for cohort studies.[16]

Right ventricular dysfunction and elevated cardiac biomarkers

Visualization of RV dysfunction (due to pressure overload) at presentation was based on echocardiography or CTPA. Since the definition of the parameters of RV dysfunction, and the cut-off values that were used, varied over time, we included studies requiring at least one of the following criteria: dilatation of the right ventricle (e.g. diastolic diameter ≥30 mm in the parasternal short-axis view) on echocardiography or an elevated RV/left ventricular end-diastolic diameter ratio (cut-off of 0.9 or 1.0) on echocardiography, or CTPA; hypokinesis of the RV free wall or abnormal motion of the interventricular septum on echocardiography; tricuspid valve regurgitation velocity (cut-off 2.7 or 2.8 m/s) on echocardiography.[1,17]

We further defined myocardial injury and (right) heart failure based on elevated circulating levels of cardiac troponins [troponin I (TnI) or T (TnT), by standard or high-sensitivity (hs) assays] and natriuretic peptides [B-type natriuretic peptide (BNP), N-terminal pro B-type natriuretic peptide (NT-proBNP)], respectively. Since current ESC guidelines do not recommend specific assays or cut-offs, we based our classification on the cut-offs reported in the selected studies.[1]

Study outcomes

We defined early all-cause mortality, i.e. death during the hospital stay or within the first 30 days following diagnosis of acute PE, as the primary outcome of our meta-analysis. The secondary outcomes were (i) early PE-related adverse outcome, defined as (PE-related) mortality, haemodynamic collapse (with need for cardiopulmonary resuscitation, mechanical ventilation, or catecholamine administration), or recurrent venous thromboembolism (VTE); (ii) early PE-related mortality; and (iii) long-term all-cause mortality.
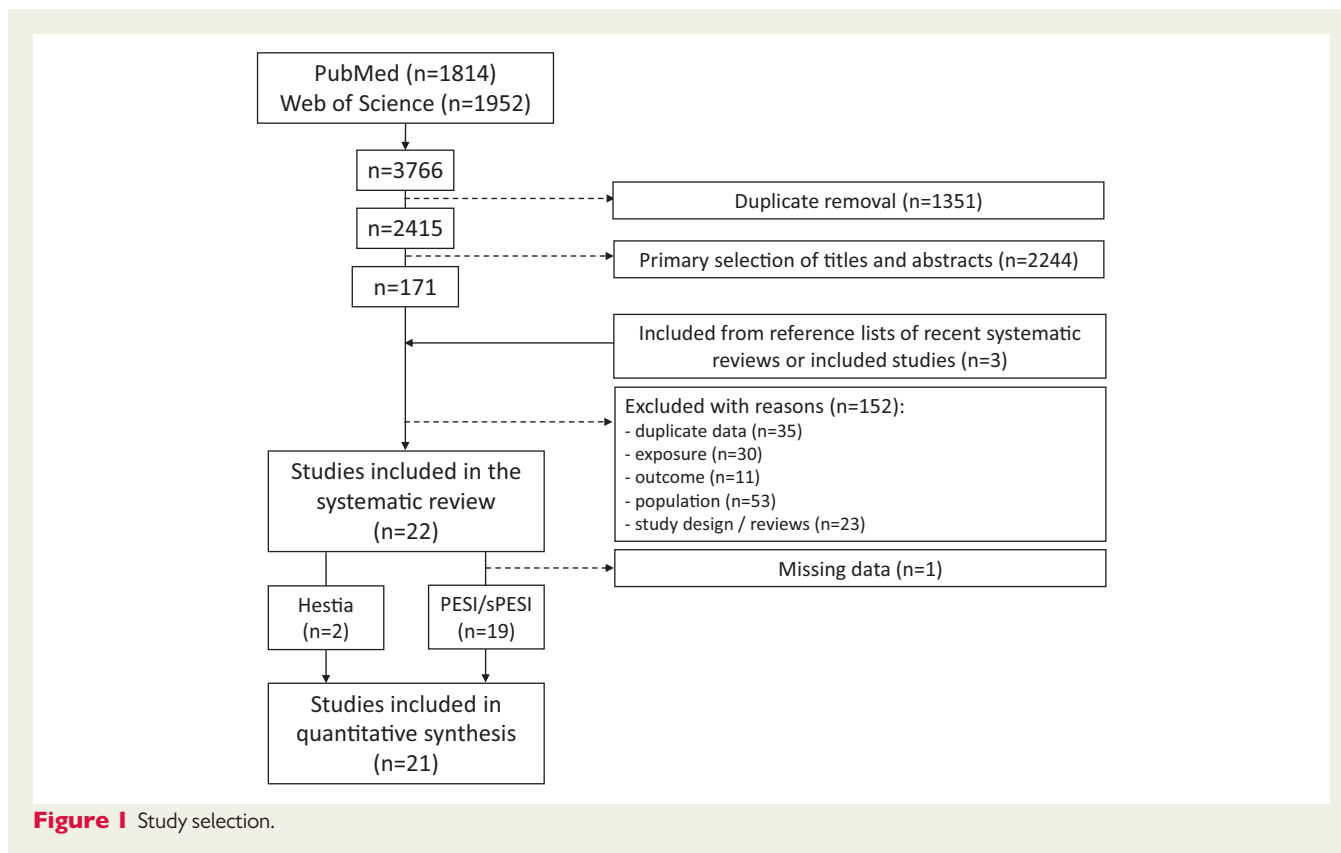
Figure 1 Study selection.

Statistical analysis

We calculated pooled odds ratios (ORs), weighed rates, and absolute risk differences between groups of patients with vs. without RV dysfunction applying a random-effect model [95% confidence interval (CI)]. An exact binomial approach was preferred since the proportions were expected to be close to the low boundary. We assessed (statistical) heterogeneity of exposure effects by calculating the I^2 statistic, which summarizes the amount of variance among studies beyond chance. Heterogeneity was defined as low ($I^2 < 25\%$), moderate ($I^2 = 25$–75%), or high ($I^2 > 75\%$). The presence of publication bias was evaluated by visually inspecting funnel plots if >10 studies were analysed. We performed predefined subgroup analyses investigating the prognostic value of different cut-offs and tests, the rate of complications in inpatient vs. outpatient, and differences between studies grouped by study design (prospective or management studies vs. *post hoc* analyses). RevMan 5.3 (Cochrane Collaboration) and R 3.4.3 (*mada*, *metafor*) served for data analysis.

Results

Systematic review of the literature

The literature search identified 1814 records in *PubMed* and 1952 in *Web of Science*, leaving 2415 records after duplicate removing. The process of study selection is summarized in *Figure 1*. We identified three additional studies not retrieved by our initial search.[18–20] Eventually, we included 22 studies in the systematic review for a total of 7536 patients diagnosed with acute PE (*Table 1*). Of these patients, 3295 were classified as being at low risk according to the PESI [1516/3265 (46%)], the sPESI [932/2639 (35%)], or the Hestia criteria [847/

1632 (52%)]. Additional information on the individual studies included in the systematic review of the literature is shown in the Supplementary material online, *Tables S1 and S2*. The study outcomes and quality assessment are summarized in the Supplementary material online, *Tables S3 and S4*.

Twenty cohort studies adopted PESI[19–26] or sPESI[11,18,27–36] for risk stratification of the patients, while two adopted the Hestia criteria.[37,38] One study did not provide complete information on outcomes, and it was therefore excluded from the meta-analysis.[26] Eventually, a total of 21 studies were selected for the quantitative analysis.[11,18–25,27–36]

Early all-cause mortality

Among patients classified as being at low risk by the PESI, sPESI, or the Hestia criteria, 34% (95% CI 30–39%) were reported to have signs of RV dysfunction on echocardiography or CTPA ($n = 9$ studies, $n = 1987$ patients). Of these, seven studies ($n = 1597$ patients) provided data on early all-cause mortality. As shown in *Table 2* and *Figure 2*, early all-cause mortality rates of this 'low-risk' population were 1.8% (95% CI 0.9–3.5%) and 0.2% (0.03–1.7%) in the presence and absence of RV dysfunction, respectively, corresponding to an OR of 4.19 (95% CI 1.39–12.58; I^2 0%; *Figure 3*).

Among low-risk PE patients based on the PESI or sPESI, 26% (95% CI 17–39%) tested positive for cardiac troponin I or T ($n = 13$ studies, $n = 1458$ patients). Of these, eleven studies ($n = 1176$ patients) provided data on early all-cause mortality. Early all-cause mortality rates were 3.8% (95% CI 2.1–6.8%) and 0.5% (95% CI 0.2–1.3%) in patients with and without elevated troponin levels, respectively,

Table 1 Characteristics of the studies included after systematic review of the literature

Study	N	Low risk, n (%)	Men, n (%)	Age (standard deviation or interquartile range)	Early discharge, n (%)	Exposure	Study population
Erol et al.[18]	110	34 (31), sPESI	14 (42)	47 (range 21–79)	0	RV dysfunction (echo), TnI, NT-proBNP	Pneumology Department
Singanayagam et al.[20]	585	288 (49), PESI	251 (43)[a]	55% >65 years[a]	—	RV dysfunction (CTPA)	Without known thrombophilia, haematological malignancy, or ongoing anticoagulation (Emergency Room)
Palmieri et al.[19]	89	27 (30), PESI	6 (22)	24 (18) PESI I, 57 (21) PESI II	—	RV dysfunction (echo), Troponin	Acute central without renal failure, recent acute coronary syndrome, or haemodynamic instability on admission (Emergency Room)
PROTECT[27,28]	848	313 (37), sPESI	416 (49)[a]	72 (59–80)[a]	—	RV dysfunction (echo and CTPA), BNP	Without haemodynamic instability, life expectancy <3 months, pregnancy, geographic inaccessibility
PREP[21]	529	329 (62), PESI	247 (47)[a]	67 (52–77)[a]	—	RV dysfunction (echo), TnI, BNP	Patients not anticoagulated for >24 h or with cardiogenic shock at admission
Côté et al.[11]	779	779 (100), sPESI	347 (45)[a]	61 (44–72)[a]	—	RV dysfunction (CTPA)	Patients from PREP study, PROTECT study, and consecutive patients from a single-centre prospective registry
Hakemi et al.[22]	298	173 (58), PESI	151 (51)[a]	56 (13)[a]	—	hsTnI	Patients admitted for acute PE
Lankeit et al.[29]	526	198 (37), sPESI	266 (51)[a]	71 (55–79)[a]	—	TnI	Normotensive patients at presentation; PERGO, PROTECT, and Polish cohorts
Lankeit et al.[30]	688	258 (38), sPESI	326 (47)[a]	70 (54–78)[a]	—	NT-proBNP	
Vanni et al.[23]	540	145 (31), PESI	65 (45)	73% >65 years	—	RV dysfunction (echo)	Emergency Room
Kartal et al.[31]	68	30 (44), sPESI	30 (44)[a]	60 (18)[a]	23 (34)	TnI	Without prior pulmonary hypertension, suboptimal imaging tests, and pregnancy (Emergency Room)
Moores et al.[24]	567	191 (34), PESI	245 (43)[a]	74% >65 years[a]	191 (100)	TnI	Outpatients (Emergency Room)
Ozsu et al.[32]	121	45 (38), sPESI	52 (43)[a]	70 (55–76)[a]	—	hsTnT, TnT	Emergency Room
Ozsu et al.[33]	206	59 (29), sPESI	82 (40)[a]	71 (58–80)	31 (15)	TnT	Emergency Room
SWIVTER[34]	369	106 (29), sPESI	66 (62)	72 (13)	49 (46)	TnI, TnT, hsTnT	With available troponin measurement
Polo Friz et al.[35]	106	34 (32), sPESI	35 (33)[a]	74 (14)[a]	—	hsTNT	Emergency Department
Weekes et al.[36]	123	53 (43), sPESI	63 (51)[a]	59 (43–69)[a]	—	RV dysfunction (CTPA), TnI, BNP	Emergency Room
Choi et al.[25]	657	363 (64), PESI	295 (45)	68	—	RV dysfunction (echo), TnI, NT-proBNP	Hospitalized because of acute PE
HESTIA[38]	530	297 (56), Hestia	159 (58)	55 (16)	275 (100)	RV dysfunction (echo)	Selected for anticoagulant treatment at home
VESTA[37]	1102	550 (50), Hestia	297 (54)	54 (15)	275 (100)	NT-proBNP	Selected for anticoagulant treatment at home, life expectancy >3 months
Systematic review only							
Singanayagam et al.[26]	411	214 (52), PESI	177 (43)[a]	55% >65 years[a]	—	TnI	First PE; without thrombophilia, haematological malignancy, or ongoing anticoagulation (Emergency Room)

BNP, B-type natriuretic peptide; CTPA, computed tomography pulmonary angiography; hsTnI, (high sensitivity) troponin I; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PE, pulmonary embolism; RV, right ventricular; (s)PESI, (simplified) pulmonary embolism severity index; TnT, troponin T.
[a]Baseline characteristics referring to the overall study population.

Table 2 Rates of short-term adverse events in low-risk patients with or without imaging and laboratory indicators of right ventricular dysfunction or myocardial injury

	RV dysfunction (exposure)	Study population (n studies)	With RV dysfunction, % (95% CI)	Without RV dysfunction, % (95% CI)
Early all-cause mortality	RV pressure overload (echo/CTPA)	1597 (7)	1.8 (0.9–3.5)	0.2 (0.03–1.7)
	Troponin	1176 (11)	3.8 (2.1–6.8)	0.5 (0.2–1.3)
	BNP/NT-proBNP	—	—	—
Early PE-related adverse outcome	RV pressure overload (echo/CTPA)	1488 (6)	3.7 (0.9–14.4)	0.7 (0.06–6.4)
	Troponin	1137 (8)	10.2 (7.2–14.3)	0.6 (0.1–5.6)
	BNP/NT-proBNP	1405 (6)	5.4 (1.8–14.6)	1.3 (0.6–2.6)

The PE-related adverse outcome includes PE-related mortality, haemodynamic collapse, and/or recurrent venous thromboembolism.
BNP, B-type natriuretic peptide; CTPA, computed tomography pulmonary angiography; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PE, pulmonary embolism; RV, right ventricular.
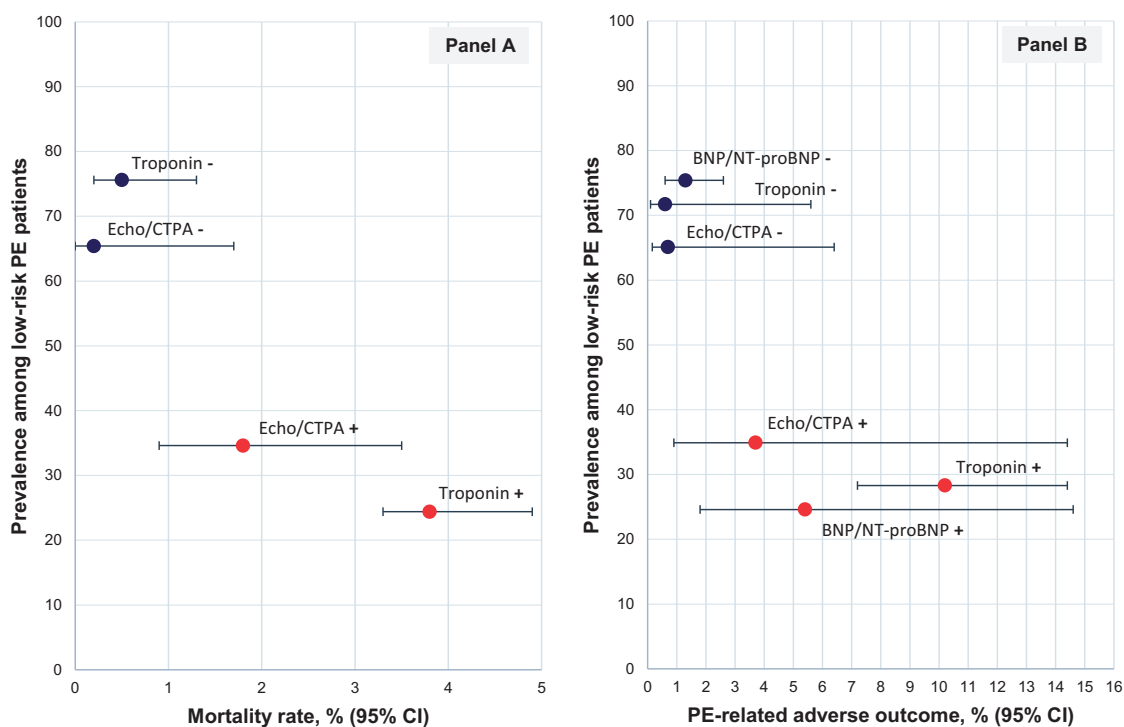

Figure 2 (A) Early mortality and early pulmonary embolism-related adverse outcome rates in patients with vs. without right ventricular dysfunction. An early pulmonary embolism-related adverse outcome (B) was defined as early death, haemodynamic collapse, and/or recurrent venous thromboembolism. Red dots (with corresponding confidence intervals) represent estimates in the presence of right ventricular dysfunction; blue dots, in its absence. BNP, B-type natriuretic peptide; CTPA, computed tomography pulmonary angiography; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PE, pulmonary embolism; 95% CI, 95% confidence interval.

corresponding to an OR of 6.25 (95% CI 1.95–20.05; I^2 0%). The corresponding proportions of low-risk patients testing positive for BNP and NT-proBNP were 30% (95% CI 26–33%) and 23% (95% CI 12–40%) of tested (n = 7 studies, n = 1663 patients). No data on all-cause mortality were reported in these latter studies.

Early pulmonary embolism-related outcome

As shown in *Table 2* and *Figure 2*, the rates of an early adverse outcome (PE-related mortality, haemodynamic collapse, or recurrent VTE) were 3.7% (95% CI 0.9–14.4%) and 0.7% (95% CI 0.06–6.4%) in
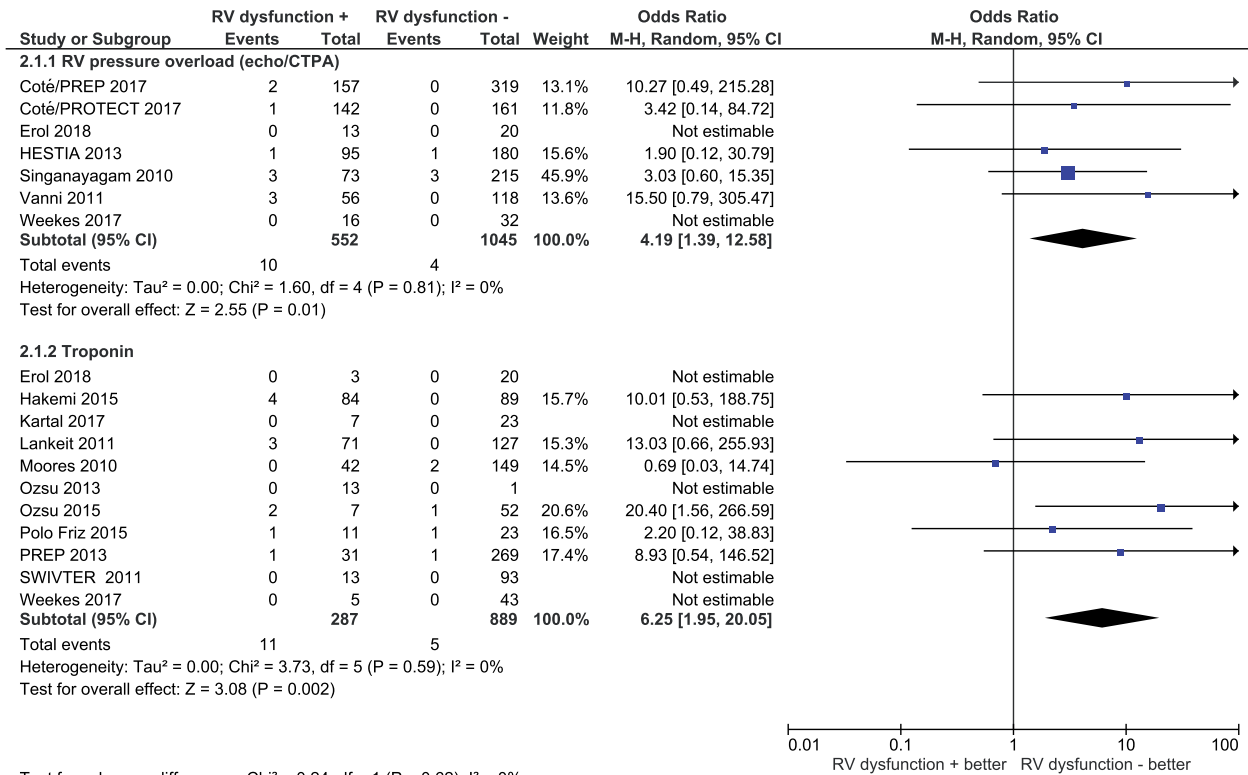
Figure 3 Prognostic value of imaging and laboratory indicators of right ventricular dysfunction or myocardial injury for early all-cause mortality in low-risk patients. CTPA, computed tomography pulmonary angiography; RV, right ventricular; 95% CI, 95% confidence interval.

patients with vs. without RV dysfunction on echocardiography or CTPA ($n = 6$ studies, $n = 1488$ patients), respectively, corresponding to an OR of 3.37 (95% CI 1.73–6.57; I^2 0%; *Figure 4*).

In patients with a positive vs. negative cardiac troponin test ($n = 8$ studies, $n = 1137$ patients), the corresponding rates were 10.2% (95% CI 7.2–14.3%) vs. 0.6% (95% CI 0.1–5.6%), for an OR of 5.14 (95% CI 2.65–9.97; I^2 0%). Finally, for those with BNP/NT-proBNP values above and below the cut-off used ($n = 6$ studies, $n = 1405$ patients), the rates were 5.4% (95% CI 1.8–14.6%) and 1.3% (95% CI 0.6–2.6%), respectively, resulting in an OR of 3.63 (95% CI 1.69–7.80; I^2 0%).

We calculated separately the pooled rates of early PE-related mortality. These rates were 1.3% (95% CI 0.5–3.1%) vs. 0.02% (95% CI 0.01–21.4%) in patients with and without RV dysfunction on imaging ($n = 8$ studies, $n = 1699$ patients), respectively; 1.3% (95% CI 0.3–5.4%) vs. 0.4% (95% CI 0.1–2.0%) in those with and without elevated troponin levels ($n = 10$ studies, $n = 1199$ patients); and 1.7% (95% CI 0.4–6.9%) vs. 0.4% (95% CI 0.1–1.1%) in patients with vs. without elevated BNP or NT-proBNP levels ($n = 5$ studies, $n = 1092$ patients). Of note, pooled ORs for RV dysfunction on imaging (OR 2.95, 95% CI 1.00–8.65; I^2 0%), elevated troponin (OR 1.71, 95% CI 0.50–5.86; I^2 0%), and elevated BNP/NT-proBNP (OR 3.71, 95% CI 0.81–17.02; I^2 0%) were based on only four, three, and three studies, respectively, since the other studies recorded no events.

Three-month mortality in patients with low-risk pulmonary embolism

A total of three studies provided data on all-cause mortality at 90 days. Mortality rates in low-risk patients by PESI or sPESI with a positive vs. negative cardiac troponin test were 28.6% (95% CI 13.4–50.8%) and 5.3% (95% CI 2.2–12.0%), respectively, (OR 8.72, 95% CI 2.05–37.05; I^2 0%); *Figure 5*.

Publication bias and subgroup analyses

We did not identify publication bias for all-cause mortality, whereas this cannot be excluded for the PE-related adverse outcome (Supplementary material online, *Figure S1*).

We found no differences in the additive prognostic value of RV dysfunction on imaging vs. that of laboratory biomarkers (*P*-values for subgroup differences reported in *Figures 2* and *3*). This was also the case if only studies comparing multiple markers within the same study population were analysed (data not shown). The results after exclusion of the two Hestia studies are provided in the Supplementary material online, *Table S5* and *Figures S2–S3*.

Low-risk patients classified using standardized troponin cut-off levels or high sensitivity assays had a mortality rate similar to that of patients classified by different cut-off levels and assays [absolute risk difference -1.0% (95% CI -3.3% to +0.3%)]. The absolute risk
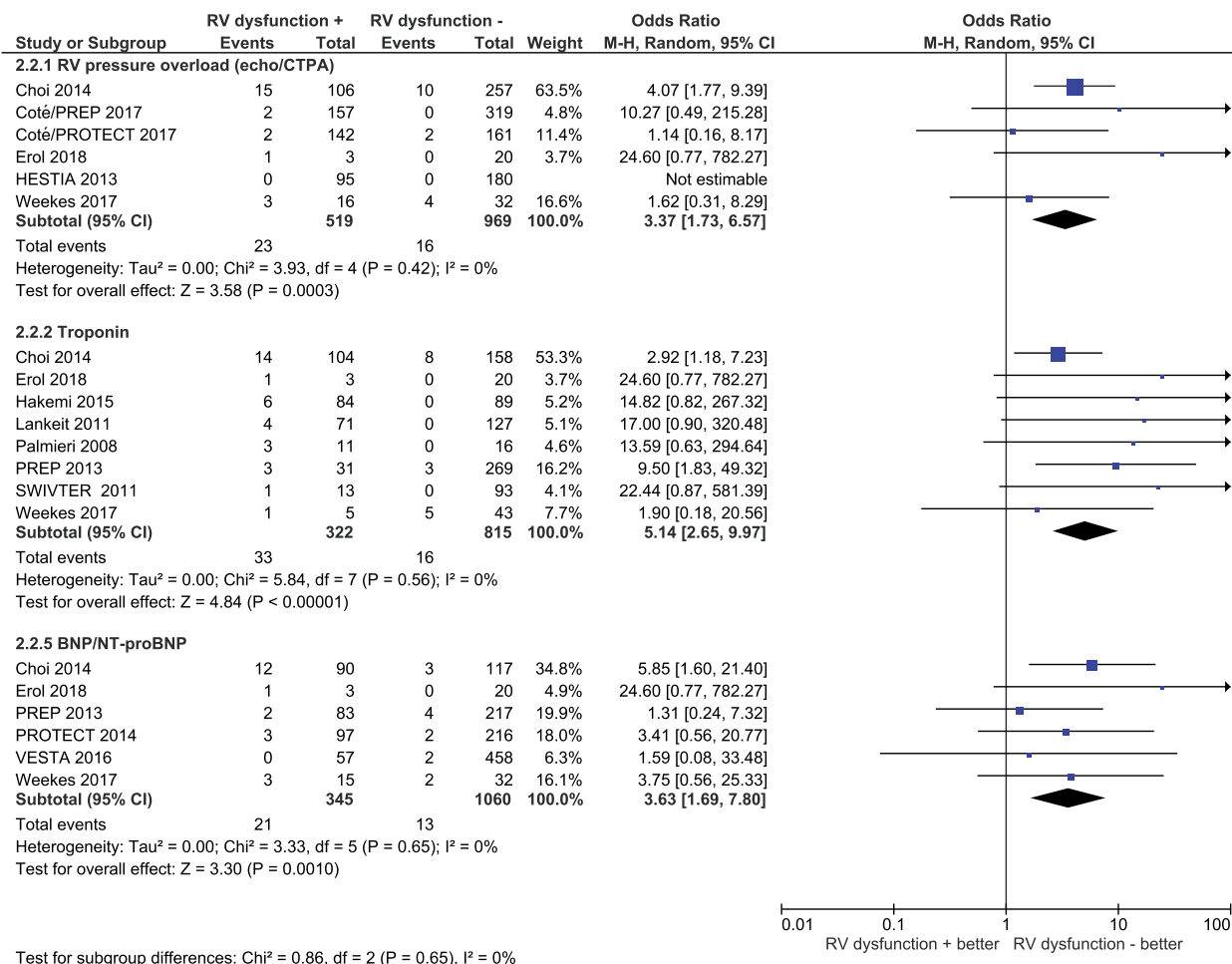
Study or Subgroup	RV dysfunction + Events	Total	RV dysfunction - Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
2.2.1 RV pressure overload (echo/CTPA)							
Choi 2014	15	106	10	257	63.5%	4.07 [1.77, 9.39]	
Coté/PREP 2017	2	157	0	319	4.8%	10.27 [0.49, 215.28]	
Coté/PROTECT 2017	2	142	2	161	11.4%	1.14 [0.16, 8.17]	
Erol 2018	1	3	0	20	3.7%	24.60 [0.77, 782.27]	
HESTIA 2013	0	95	0	180		Not estimable	
Weekes 2017	3	16	4	32	16.6%	1.62 [0.31, 8.29]	
Subtotal (95% CI)		**519**		**969**	**100.0%**	**3.37 [1.73, 6.57]**	
Total events	23		16				
Heterogeneity: Tau² = 0.00; Chi² = 3.93, df = 4 (P = 0.42); I² = 0%							
Test for overall effect: Z = 3.58 (P = 0.0003)							
2.2.2 Troponin							
Choi 2014	14	104	8	158	53.3%	2.92 [1.18, 7.23]	
Erol 2018	1	3	0	20	3.7%	24.60 [0.77, 782.27]	
Hakemi 2015	6	84	0	89	5.2%	14.82 [0.82, 267.32]	
Lankeit 2011	4	71	0	127	5.1%	17.00 [0.90, 320.48]	
Palmieri 2008	3	11	0	16	4.6%	13.59 [0.63, 294.64]	
PREP 2013	3	31	3	269	16.2%	9.50 [1.83, 49.32]	
SWIVTER 2011	1	13	0	93	4.1%	22.44 [0.87, 581.39]	
Weekes 2017	1	5	5	43	7.7%	1.90 [0.18, 20.56]	
Subtotal (95% CI)		**322**		**815**	**100.0%**	**5.14 [2.65, 9.97]**	
Total events	33		16				
Heterogeneity: Tau² = 0.00; Chi² = 5.84, df = 7 (P = 0.56); I² = 0%							
Test for overall effect: Z = 4.84 (P < 0.00001)							
2.2.5 BNP/NT-proBNP							
Choi 2014	12	90	3	117	34.8%	5.85 [1.60, 21.40]	
Erol 2018	1	3	0	20	4.9%	24.60 [0.77, 782.27]	
PREP 2013	2	83	4	217	19.9%	1.31 [0.24, 7.32]	
PROTECT 2014	3	97	2	216	18.0%	3.41 [0.56, 20.77]	
VESTA 2016	0	57	2	458	6.3%	1.59 [0.08, 33.48]	
Weekes 2017	3	15	2	32	16.1%	3.75 [0.56, 25.33]	
Subtotal (95% CI)		**345**		**1060**	**100.0%**	**3.63 [1.69, 7.80]**	
Total events	21		13				
Heterogeneity: Tau² = 0.00; Chi² = 3.33, df = 5 (P = 0.65); I² = 0%							
Test for overall effect: Z = 3.30 (P = 0.0010)							

Test for subgroup differences: Chi² = 0.86, df = 2 (P = 0.65), I² = 0%

0.01   0.1   1   10   100
RV dysfunction + better   RV dysfunction - better

Figure 4 Prognostic value of imaging and laboratory indicators of right ventricular dysfunction or myocardial injury for early pulmonary embolism-related adverse outcome in low-risk patients. The outcome includes mortality, haemodynamic collapse, and/or recurrent venous thromboembolism. BNP, B-type natriuretic peptide; CTPA, computed tomography pulmonary angiography; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RV, right ventricular; 95% CI, 95% confidence interval.

difference of mortality rates for NT-proBNP (cut-off 600 pg/mL) vs. BNP (cut-off 100 pg/mL) was -0.3% (95% CI -1.6% to +1.2%).

Discussion

The results of the present systematic review of the literature and meta-analysis indicate that RV dysfunction, primarily defined by RV pressure overload assessed on imaging tests, may have a significant impact on the early prognosis of patients classified as being at low risk based on the PESI, sPESI, or the Hestia criteria. Similar findings were obtained when the elevation of laboratory cardiac biomarkers, notably cardiac troponin or natriuretic peptides, served as a parameter of myocardial injury and (subclinical) RV dysfunction, respectively. Our results may have implications for the acute-phase management of patients who appear to be at a low risk of early death or severe complications based on clinical criteria alone. These

findings also support the concept that optimal risk stratification of acute PE should include the assessment of RV status on admission.

The spectrum of PE severity largely varies and early mortality rates can range from <1% among stable patients to over 50% in the presence of haemodynamic instability.[39] Consequently, the management of acute PE is tailored to the patient's early risk and may include early discharge and home treatment for low-risk patients.[17] Risk assessment models are practical and helpful for clinicians, permitting a standardized categorization of patients with acute PE into risk classes.[1] In particular, the PESI and sPESI have been extensively validated for the identification of low-risk PE. In a randomized trial, 344 patients with acute PE and a PESI low-risk risk Class of I–II were assigned to outpatient or inpatient treatment; all patients received subcutaneous enoxaparin followed by oral VKA anticoagulation.[40] In this study, outpatient care appeared to be non-inferior when compared with standard inpatient treatment. Based on these and other findings, the 2014 guidelines of the ESC proposed that patients with a low PESI or a negative sPESI be considered for home treatment.[1]
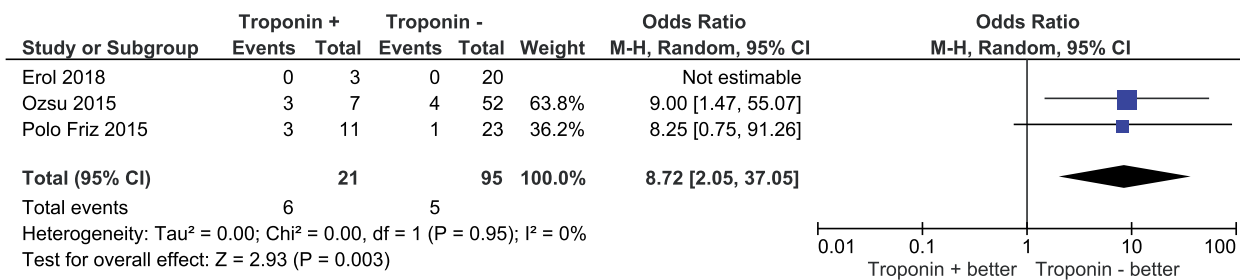
Study or Subgroup	Troponin + Events	Total	Troponin - Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Erol 2018	0	3	0	20		Not estimable
Ozsu 2015	3	7	4	52	63.8%	9.00 [1.47, 55.07]
Polo Friz 2015	3	11	1	23	36.2%	8.25 [0.75, 91.26]
Total (95% CI)		21		95	100.0%	8.72 [2.05, 37.05]
Total events	6		5			

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.95); I² = 0%
Test for overall effect: Z = 2.93 (P = 0.003)

Figure 5 Prognostic value of troponin for 3-month all-cause mortality in patients classified to the low risk category according to the pulmonary embolism severity index (PESI) or (simplified) pulmonary embolism severity index (sPESI).

However, the use of clinical scores does not directly take into account the functional status of the right ventricle, which has repeatedly been shown to be a key determinant of PE prognosis.[11,41,42] Consequently, it cannot be excluded that patients initially classified into the low-risk category, based on the parameters and cut-off values of a formal clinical severity score calculated on admission, may deteriorate few hours later due to the decompensation of previously unnoticed RV dysfunction.

The results of the present meta-analysis indicate that low-risk patients are at higher risk of early mortality if RV dysfunction is present. Due to the low absolute rate of events in this population, this question could not be adequately addressed by single studies.[11,21,24,26,27] Of note, the early death risk of 'low-risk' patients with RV dysfunction appears similar to that previously reported for intermediate-risk PE[39] The mortality rates yielded by our meta-analysis are clearly higher than those reported for low-risk PE patients in studies that validated the PESI or sPESI,[43] and raise doubts on whether such patients could be sent home safely. The paucity of data in the literature regarding event rates after early discharge and home treatment (as opposed to standard in-hospital management), or of data reported in prospective management trials (vs. *post hoc* analyses) did not allow us to perform additional subgroup analyses. Finally, it must be noted that the association between RV dysfunction and the outcomes was consistent across the studies, at least in terms of statistical heterogeneity (I^2 = 0%). However, I^2 may have been underestimated due to the imprecision of single studies.

The Hestia criteria have been proposed as an alternative tool for selecting low-risk patients.[7] Although some of these criteria are less standardized than the items included in the (s)PESI, this set of questions integrates familial, social, and broad medical factors. In light of this fact, the Hestia criteria and PESI are not directly comparable. In our meta-analysis, we could not provide pooled estimates only for the Hestia criteria due to the paucity of data in the literature. The ongoing Hospitalization or Out-treatment ManagEment of Pulmonary Embolism (HOME-PE) trial (NCT02811237) aspires to directly compare these two strategies.

Limitations

The present meta-analysis has a number of limitations that need to be discussed. First, several of the included studies were *post hoc* analyses of existing cohorts, having adopted heterogeneous criteria of RV dysfunction as well as non-prespecified cut-off values. On the other hand, it can also be argued that previous cohort studies which validated the value of the PESI, sPESI, or other criteria for defining low risk, may have included pre-selected 'lower-risk' populations with PE and were thus able to show such favourable results for clinical assessment alone. Second, we acknowledge that the CIs of our estimates remain wide, despite statistical significance, due to the low absolute rates of early adverse events encountered in this patient population. It is also important to mention that the present study was not designed to test if there is a single optimal biomarker or imaging parameter to quantify the early risk in patients with a low clinical score. Therefore, our results suggesting that RV pressure overload on imaging possesses prognostic value similar to the elevation of cardiac biomarkers must be considered as hypothesis-generating. An ongoing prospective management trial is investigating whether early discharge and home treatment is feasible, effective, and safe in patients who are classified into the low-risk category using the combination of clinical (modified Hestia) criteria and the absence of RV dysfunction or free-floating thrombi on an imaging test.[44]

Conclusion

In conclusion, in patients with acute PE classified into the low-risk category according to clinical criteria alone, the presence of RV dysfunction was associated with an increased risk of early complications including all-cause death and PE-related serious adverse events. The estimated risk was in the lower range of that previously reported for patients with intermediate-risk PE. Right ventricular pressure overload and dysfunction on imaging appeared to possess a prognostic value comparable to the elevation of cardiac troponins or natriuretic peptides. Our results reinforce the concept of integrating the functional status of the right ventricle into the risk stratification of acute PE.

Supplementary material

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

Acknowledgements

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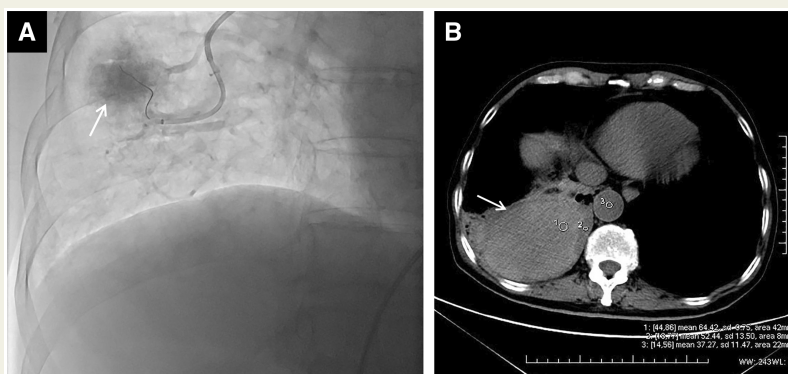
CARDIOVASCULAR FLASHLIGHT

Pulmonary haematoma caused by percutaneous transluminal pulmonary angioplasty

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A 77-year-old man was diagnosed with chronic thromboembolic pulmonary hypertension (CTEPH) in our hospital due to exertional dyspnoea. After evaluation of multidisciplinary team for CTEPH including cardiac surgeon, percutaneous transluminal pulmonary angioplasty (PTPA) was performed to restore pulmonary perfusion. However, during PTPA, perivascular exudation (*Panel A*, white arrow) was found when we dilated the stenosed right dorsal segment artery of lower lobe with balloon (Sprinter 2.0 * 20 mm) and repeated angiography revealed that the exudation disappeared. Chest computed tomography scan after PTPA showed pulmonary haematoma formation (*Panel B*, white arrow), which has not been reported before.