Prognostic value of right ventricular dysfunction in patients with haemodynamically stable pulmonary embolism: a systematic review

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Aims
To determine the prognostic value of right ventricular (RV) dysfunction assessed by echocardiography or spiral computed tomography (CT), or by increased levels of cardiac biomarkers [troponin, brain natriuretic peptide (BNP) and pro-BNP] in patients with haemodynamically stable pulmonary embolism (PE).

Methods and results
We included all studies published between January 1985 and October 2007 estimating the relationship between echocardiography, CT or cardiac biomarkers and the risk of death in patients with haemodynamically stable PE. Twelve of 722 potentially relevant studies met inclusion criteria. The unadjusted risk ratio of RV dysfunction as assessed by echocardiography (five studies) or by CT (two studies) for predicting death was 2.4 [95% confidence interval (CI) 1.3–4.4]. The unadjusted risk ratio for predicting death was 9.5 (95% CI 3.2–28.6) for BNP (five studies), 5.7 (95% CI 2.2–15.1) for pro-BNP (two studies) and 8.3 (95% CI 3.6–19.3) for cardiac troponin (three studies). Threshold values differed substantially between studies for all markers.

Conclusion
RV dysfunction assessed by CT, echocardiography, or by cardiac biomarkers are all associated with an increased risk of mortality in patients with haemodynamically stable PE. These findings should be interpreted with caution because of the clinical and methodological diversity of studies.

Keywords
Pulmonary embolism • Prognosis • Right ventricular dysfunction • BNP • Echocardiography

Introduction
The short-term prognosis of pulmonary embolism (PE) depends on haemodynamic status and underlying disease.1,2 It has been suggested that patients with PE should be classified into two groups: those with massive PE presenting with hypotension or shock, for whom the risk of death is high, and patients with non-massive PE who present with normal blood pressure and have a low risk of death.3 The debate has recently focused on a subgroup of normotensive patients with subclinical haemodynamic impairment detected by echocardiography, cardiac biomarkers or spiral computed tomography (CT). This subgroup of patients has been shown to have a higher mortality rate in some studies but not all case series.4,5 We carried out a meta-analysis to assess the prognostic value of right ventricular (RV) dysfunction as evaluated by echocardiography or spiral CT, and the prognostic value of increased levels of brain natriuretic peptide (BNP), pro-BNP and troponin in patients with non-massive PE with a view to identifying this subgroup more accurately.

Methods
Search strategy
We searched for eligible studies published between January 1985 and October 2007 using two strategies. In Medline, we used the following strategy based on a Pubmed sensitive query to identify
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<th>Study reference</th>
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NR, not reported; RVEDD/LVEDD, right to left end-diastolic diameter ratio; RVEDA/LVEDA, right to left ventricular end-diastolic area ratio; RV–RA gradient, right ventricular–right atrial gradient; PAT, pulmonary arterial flow acceleration time; TVPG, tricuspid valve pressure gradient; SBP, systolic blood pressure; HR/SBP, ratio of heart rate to systolic blood pressure; IFA, immunofluorescence assay; IRMA, immunoradiometric assay; CIA, chemiluminescence immunoassay; ECIA, electrochemiluminescence immunoassay.

\(^{a}\)Multicenter study (all others are single-centre studies).

\(^{b}\)Cardiopathy and chronic respiratory insufficiency.

\(^{c}\)ROC curve cut-off value.

\(^{d}\)Laboratory cut-off value.

\(^{e}\)Highest tertile cut-off value.
prognostic studies:5-7 'Pulmonary Embolism'[MeSH] AND (Ventricular Dysfunction, Right'[MeSH] OR 'Natriuretic Peptide, Brain'[MeSH] OR 'Troponin'[MeSH] OR 'Echocardiography'[MeSH] OR 'Tomography, Spiral Computed'[MeSH]) AND (incidence[MeSH:noexp] OR mortality[MeSH Terms] OR follow-up studies[MeSH:noexp]) OR prognosis*[Text Word] OR predict*[Text Word] OR course*[Text Word]. We restricted our searches to databases dealing with humans. We applied no language restriction. We also searched the references of the primary articles selected to identify other relevant publications.

Study identification and eligibility

We included studies in which: (i) patients had an acute PE confirmed by either a high PIOPED probability lung scan8 or by thrombus visualization in at least segmental arteries by contrast-enhanced spiral CT or pulmonary angiography; (ii) all patients were haemodynamically stable according to the definition of each study (Table 1); (iii) patients underwent at least one of the following tests at baseline – echocardiography or spiral CT to assess RV dysfunction, cardiac troponin I or T, BNP, or N-terminal pro-BNP determination; (iv) all-cause in-hospital or up to 90-day mortality was reported; and (v) consecutive patients were included (i.e. an inception cohort or a retrospective identification of consecutive patients).

Study selection and data extraction

Two reviewers (O.S., G.M.) reviewed independently the lists of titles and abstracts and used the inclusion criteria to mark potentially relevant articles for full review. Each study that was selected as potentially relevant in the search process was read and abstracted independently by four reviewers (O.S., G.M., I.C., P.D.). Reviewers were not blinded to authors. We also contacted authors of the primary studies for clarifications when necessary.

For each study, information was collected on: (i) characteristics of the study population (mean age, percentage of patients with cancer, cardiac disease and respiratory disease); (ii) design of the study (prospective or retrospective, single-centre or multi-centre); (iii) methodological quality of the study (discussed later); (iv) treatment (number of patients who received thrombolytic therapy or underwent pulmonary embolectomy); (v) mortality; and (vi) full description of the prognostic factor – brand name and manufacturer, method and cut-off value for assays of biological markers; criteria for RV dysfunction on echocardiography or spiral CT.

Disagreements between reviewers on study selection and abstraction results were resolved by a formal discussion process (O.S., L.T., I.C., P.D., G.M.) to achieve consensus. The reasons for excluding particular studies are presented in Figure 1.

Assessment of study validity

We adapted published frameworks for assessing the methodological quality of the selected studies.10,11 Methodological quality was evaluated based on four sets of criteria: homogeneity of the study population; outcome measures; definition and measurement of prognostic variables; method of analysis.

The study population was considered homogenous if consecutive patients were recruited and the objective confirmation of PE was used as an inclusion criterion. The homogeneity of the study population was also checked by assessing potential confounding factors (i.e. age, cancer, heart failure, thrombolytic treatment or embolectomy).

We evaluated the quality of outcome measurement by checking for the complete follow-up of subjects (outcome measure obtained from 100% of subjects).

We considered biological prognostic variables to have been fully described if the name of the kit and manufacturer, the method of measurement, the threshold used to define abnormal results and its method of determination (laboratory threshold or ROC curve analysis) were reported. We considered imaging prognostic variables to have been fully described if RV dysfunction was defined and the threshold value defining RV dilatation was reported. Quality of the measure of prognostic factors was assessed by the time to measurement from inclusion and the blindness of assessment for both biological and imaging prognostic variables.

The quality of analysis was evaluated based on adjustment for potential confounding factors.

Statistical analysis

To assess the prognostic value of the variables of interest, we calculated unadjusted relative risks and confidence intervals (CIs) for individual studies. We present the results of individual studies using forest plots for each prognostic factor. As a small number of studies met the criteria for being included in the review for each prognostic factor, we assessed statistical heterogeneity using the I^2 coefficient.12 It describes the percentage of total variation across studies that are attributable to heterogeneity rather than chance and it does not inherently depend upon the number of studies considered. In absence of statistical heterogeneity (I^2 < 25%), we calculated a pooled unadjusted effect size using a fixed effect model of the relative risk. We further explored heterogeneity by describing the clinical and methodological characteristics of studies in terms of the study population, prognostic factors and confounding factors. Finally, some studies that met the eligibility criteria for our review reported positive predictive values (PPV). For comparative purposes, we calculated the corresponding pooled diagnostic indexes: pooled sensitivity, specificity, and unconditional positive and negative predictive values were estimated. Analyses were carried out with STATA v8.0 and RevMan 4.2.

Results

Twelve studies from a list of 722 potentially relevant studies met the criteria for being included in the review (Figure 1). Five studies (including 475 patients) evaluated RV dysfunction on echocardiography,5,13-16 two studies (including 191 patients) analysed RV dysfunction on spiral CT17,18 five studies (including 272 patients) evaluated BNP16,19-22 two studies (including 170 patients) assessed pro-BNP14,23 and three studies (including 187 patients) evaluated cardiac troponin levels.14,15,22 Four studies evaluated multiple prognostic factors of interest.18-16,22 (Table 1).

The proportion of patients receiving thrombolysis or embolectomy ranged from 7 to 33%.

Biological and imaging prognostic factors were well defined as assessed by their complete description in all studies. But their measurement is questionable. The physicians treating the patients were blind to the test result in only four studies.14,18,20,22 The physicians had access to the test result in three studies16,21,23 and in the remaining five studies, this information was not reported.5,13,15,17,19
Outcome was obtained from 100% of patients in all studies. Eight studies reported in-hospital mortality,10–17,19,21,23 One study reported 40-day mortality,14 and three reported 90-day mortality.18,20,22 Overall mortality varied between 0 and 16%.

Potential confounders were fully reported in only four out of 12 identified studies (Table 1).13,14,16,18 Statistical analysis was adjusted for confounding variables in only three studies for all-cause mortality.14,20,23 The other criteria used to assess the methodological quality of the 12 studies are reported in Table 1.

Right ventricular dysfunction as assessed by echocardiography or spiral computed tomography

Table 1 and Figure 2 summarize the characteristics of the seven studies reporting on RV dysfunction and the pooled unadjusted relative risk for mortality. All but one of the studies were single-centre studies. Four studies involved emergency department patients, one involved intensive-care patients and two involved patients admitted to a cardiology department. Potential confounding factors were described in detail in four of seven studies (Table 1).13,14,16,18

Five studies evaluated the prognostic role of RV dysfunction assessed on echocardiography.5,13–16 RV dysfunction was defined as RV hypokinesia in one study15 and using a composite criteria in the remaining four studies.5,13,14,16 This composite criteria included a quantitative index for RV dilatation with a threshold for RV end-diastolic diameter/left ventricular (LV) end-diastolic diameter ratio (RVd/LVd) of 0.6–1.

Two studies evaluated the prognostic role of RV dysfunction assessed on spiral CT. In those studies, RV dysfunction was defined as RV dilatation with two different thresholds of RVd/LVd (Table 1).17,18

The pooled unadjusted relative risk of RV dysfunction for predicting death was 2.4 [95% CI 1.3–4.4] when the seven echocardiography and spiral CT studies were combined, with no significant statistical heterogeneity. When the five echocardiography studies were analysed separately, the unadjusted relative risk
of RV dysfunction for predicting death was 2.5 (95% CI 1.2–5.5) with no heterogeneity. The pooled unadjusted relative risk for the two spiral CT studies was 2.3 (95% CI 0.9–5.98).

For echocardiography and spiral CT, the pooled sensitivity, specificity, positive and negative predictive values are summarized in Table 2.

**Cardiac biomarkers**

Table 1 and Figure 3 summarize the characteristics of the eight studies evaluating one or several cardiac biomarkers and the pooled unadjusted relative risk for mortality. Six studies assessed one biomarker15,16,19–21,23 and two studies assessed two different biomarkers in the same patients.14,22 BNP was evaluated in five studies16,19–22 and pro-BNP in two studies.14,23 Cardiac troponin-T was evaluated in three studies.19,22,23 Two studies described potential confounding factors in detail.14,16 The patients were recruited in the emergency department in one study,15 and were admitted to cardiology departments in the other seven studies.14,16,19–23 All studies provided the method for biomarker determination, the manufacturer, the name of the kit and time to measurement which ranged from 0 to 4 h after admission. The threshold used for the biological dosage was reported for seven of the 10 evaluations (Table 1). The threshold value was defined according to ROC curve analysis in five studies.15,16,19,20,23 The threshold values varied from 0.08 to 0.49 ng/mL for BNP, from 0.6 to 7.6 ng/mL for pro-BNP and from 0.01 to 0.07 ng/mL for troponin-T. The pooled unadjusted relative risk for predicting in-hospital or 30-day death was 9.5 (95% CI 3.1–28.6) for BNP, 5.7 (95% CI 2.2–15.1) for pro-BNP and 8.3 (95% CI 3.6–19.3) for troponin-T. No statistical heterogeneity was observed for any of these biomarkers ($I^2 = 0$). Some adjustment for confounders was reported in three studies for all-cause mortality.14,20,23 In one study, the prognostic value of pro-BNP on in-hospital mortality was still statistically significant after adjustment for pulse, oximetry, age, blood pressure, RV/LV ratio, and tricuspid valve pressure gradient (OR (odds ratio) for...
log NT-pro-BNP 1.9, 95% CI 1.1–3.2. In another study, the association between a BNP level 21.7 pmol/L and 90-day mortality was still statistically significant after adjustment for age and cancer (OR 9.4, 95% CI 1.8–49.2). Finally another study reported a significant increase in 40-day mortality risk when cardiac troponin was 0.07 mg/L after adjustment for age [HR (heart rate) 6.5, 95% CI 3.3–18.9].

For BNP, pro-BNP, and cardiac troponin, the pooled sensitivity, specificity, positive and negative predictive values are summarized in Table 2.

### Discussion

This systematic review suggests that RV dysfunction as assessed by echocardiography and spiral CT, or by increased levels of BNP, pro-BNP or troponin-T is associated with a higher risk of mortality in clinically stable patients with PE. However, studies that met the eligibility criteria showed clinical and methodological diversity because of various criteria and thresholds used to define RV dysfunction. Although all risk ratios associated with cardiac biomarkers were higher than those associated with cardiac imaging, one must not conclude that elevated biomarkers are associated with higher mortality risk than RV dysfunction on echocardiography. Moreover, all these markers do not measure RV dysfunction in the same way: while CT provides information on RV dilatation only, echocardiography also gives some information on contractility, i.e. septal or RV hypo- or dyskinesia; cardiac troponin is a marker of myocardial injury. BNP or pro-BNP are two specific markers of wall ventricular stress but there are other reasons for increased BNP or pro-BNP levels such as neurohumoral stimulation, inflammation, cytokines or ischaemia.

Besides, those elevated risk ratios should be interpreted cautiously, having regard to the low PPV. The large 95% CI of each value of PPV underlines the degree of uncertainty of these results even when all potentially eligible studies are included in the analysis.

The in-hospital mortality of patients with so-called massive PE, defined on the basis of systemic hypotension or cardiogenic shock ranges from 25 to 50%. Most experts recommend the use of aggressive treatments, including thrombolytic treatment, in these patients. BNP and troponin levels are usually high in these patients, but are not particularly useful in this context because the presence of cardiogenic shock per se is a major risk factor for death in patients with PE. Recently, Becattini et al. performed a meta-analysis of studies in patients with acute PE to assess the prognostic value of elevated cardiac troponins for short-term death. The unadjusted OR associated with elevated troponin levels was 5.2 (95% CI 3.3–8.4). However, the study eligibility criteria were less stringent. In particular, studies assessing troponin in patients with haemodynamic instability were eligible in that analysis. We focused our analysis on clinically stable patients because a risk stratification tool that accurately predicts the prognosis of these patients may be useful for clinicians. The in-hospital mortality of patients with PE and normal blood pressure has been reported to vary from 3 to 15%. Patients estimated to be at low risk could be discharged early or managed entirely at home whereas high-risk patients may benefit from a more careful in-hospital follow-up. However, the use of these markers for

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**Figure 3** Prognostic value of cardiac biomarkers for mortality in patients with pulmonary embolism without shock. The outcome was in-hospital mortality for all studies, except two: (•) 40-day mortality and (†) 90-day mortality.
guiding initial treatment, i.e. thrombolytic treatment, seems premature because of several limitations.

Combination of imaging modalities with cardiac biomarkers may further optimize risk stratification. In our review, only three studies evaluated the prognostic value of RV dysfunction and cardiac biomarkers in the same population. We could extract the 2 × 2 table crossing echocardiography and BNP results in one study and those crossing echocardiography and pro-BNP or cardiac troponin results in another study. In the first study, the unadjusted risk ratio for combination of a positive echocardiography and elevated BNP value was 18.0, 95% CI 1.0–318.9 vs. 6.8, 95% CI 0.4–120.1 for echocardiography alone. In the second study, the unadjusted risk ratio for combination of a positive echocardiography and elevated pro-BNP value was 2.7, 95% CI 0.9–8.6; that of combination of both positive echocardiography and cardiac troponin was 1.7, 95% CI 0.6–4.5 vs. 2.1, 95% CI 0.6–7.2 for echocardiography alone. Because of the small number of patients included, we cannot draw any definitive conclusion concerning the incremental value of cardiac biomarkers in patients with positive imaging.

Limitations

We encountered several methodological limitations, some of which are inherent to any systematic review of prognostic studies, whereas others were related to the fact that few studies were specifically designed to answer our research question.

First, we cannot entirely exclude the possibility of a publication bias. We attempted to minimize it by reviewing abstracts of major scientific meetings. Tests for asymmetry of the funnel plots were not significant but are not useful because of the small number of studies. It is possible that our findings are partly affected by publication bias, and that the prognostic value of biomarkers and RV dysfunction might be lower than reported in this review since failure to publish studies with negative or null findings contributes to publication bias. Secondly, we could only include a small number of studies because most studies assessing prognostic factors for PE included both stable and unstable patients and the results were rarely reported separately for these two groups of patients. Thirdly, we were faced with clinical and methodological diversity in the studies in terms of study populations, prognostic variables, confounding variables, and outcome definition. The study setting was either emergency department or a specialty department. Unclear reporting made it difficult to determine whether consecutive patients had been recruited in several studies. Differences in the definition of cardiogenic shock used in eligible studies may have resulted in additional diversity in the study population as reflected by the wide range of in-hospital mortality across studies.

The methods used for the measurement and interpretation of prognostic factors differed considerably between studies. Different techniques and thresholds were used in studies evaluating cardiac biomarkers. In all studies, continuous data were handled by categorization; the choice of threshold was data-dependent in four studies. We were not able to perform analysis using the biomarkers on their original continuous scale nor using a common threshold value for all studies. This is a limitation to the study since categorizing continuous variables discards important quantitative information and makes the results difficult to compare between studies. Moreover, different definitions were also used for echocardiography and spiral CT in studies evaluating RV dysfunction. Heterogeneous reporting of confounding factors was also noted, and the possible effect of such factors was not analysed in all studies. Even when these factors were summarized for the study population, no universally acknowledged method can be used to take them into account when pooling results.

We chose to study mortality as the primary outcome summarizing studies. Unlike composite clinical outcomes, in-hospital mortality is an objective unbiased outcome (i.e. low censored bias) and pertinent for evaluations of the prognosis of PE. We chose to include four studies reporting 40-day and 90-day mortality, assuming that the death rate following PE peaks within 30 days. This was confirmed by the consistency in death rates and individual relative risks between each of these four studies and other studies evaluating the same prognostic factor.

Surprisingly, whatever the prognosis factor considered, we found no statistical heterogeneity. This may be because we were unable to pool relative risks adjusted for confounding factors. Further statistical exploration of heterogeneity was not possible because of the small number of studies and the non-availability of data for individual patients.

Conclusion

This systematic review suggests that elevated cardiac biomarkers and RV dysfunction, demonstrated by echocardiography or spiral CT, are associated with increased risk of mortality in patients with non-massive PE. These findings should be interpreted with caution because of the clinical and methodological diversity of studies. Well-designed prospective studies, with pre-specified definitions of RV dysfunction assessed by echocardiography and spiral CT as well as plasma-levels of cardiac biomarkers, are required to tackle this research question specifically. Limitations of available studies preclude the use of these markers for selecting the appropriate candidates to thrombolytic therapy among clinically stable patients with PE.

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References