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D-Dimer for risk stratification in patients with acute pulmonary embolism

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Abstract Background: Risk stratification is currently recommended for the initial management of patients with acute pulmonary embolism (PE). Methods: We performed a meta-analysis of studies in patients with acute PE to assess the prognostic value of elevated D-dimer levels for short-term (within 30 days) and 3-month mortality. The association between D-dimer levels and markers of PE severity was also reviewed. Unrestricted searches were performed using the terms D-dimer and pulmonary embolism. Studies reporting on D-dimer levels and mortality and/or markers of PE severity were included in the review. A random-effects model was used to pool study results, funnel-plot inspection to evaluate publication bias and I squared testing to test for heterogeneity. Results: Five studies (2,885 patients) reported on D-dimer levels and short-term mortality. D-dimer levels above a prognostic cut-off were significantly associated with short-term mortality in the overall population (OR: 2.76; 95% CI: 1.83–4.14; $I^2 = 0\%$) and in hemodynamically stable patients (three studies, 874 patients; OR: 4.28; 95% CI: 1.88–9.71; $I^2 = 0\%$). Four studies (1,254 patients) reported on D-dimer levels and 3-month mortality. D-dimer levels above a prognostic cut-off were associated with 3-month mortality (OR: 4.29; 95% IC: 1.70–10.79; $I^2 = 0\%$). Overall, 14 studies assessed the association between D-dimer and markers of PE severity. An association has been observed between D-dimer levels and the degree of pulmonary artery obstruction. Conclusion: In patients with acute PE elevated D-dimer is associated with increased short-term and 3-month mortality, suggesting the potential of using this test for both diagnosis and risk stratification.

Keywords D-Dimer · Pulmonary embolism · Prognosis

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Introduction

Acute pulmonary embolism (PE) remains associated with a substantial risk of death during the hospital stay, outcomes varying depending on patient characteristics [1]. In-hospital mortality ranges from 5.4 to 15% in recent studies in patients with acute PE [2, 3]. Current guidelines recommend that patients with acute PE should be stratified according to the risk of in-hospital death [4]. Combinations of clinical features and signs of right ventricular dysfunction or injury (right ventricle assessment at echocardiography or at computed tomography, BNP and troponins) allow prognostic stratification and could drive the early management of patients with PE [1, 4, 5]. The need for rapid and around-the-clock available tools for prognostic stratification derives from the observation that the majority of deaths for acute PE occurs during the first hours after hospital admission [6].

D-Dimer, a product of fibrin degradation, has been widely recognized to be useful in the diagnostic work-up of PE [7]. High-sensitive D-dimer tests have been proved to have a high negative predictive value in ruling out PE in patients with non-high clinical probability [7–9]. The

potential role of D-dimer in risk stratification in patients with acute PE has been assessed in several studies with a particular attention to intermediate risk patients.

The aim of this paper is to report on a meta-analysis on the prognostic value of D-dimer for short-term and 3-month mortality and on a systematic review on the association between D-dimer levels and markers of PE severity.

Materials and methods

Study objectives

The objectives of this meta-analysis and review in patients with acute PE were: (1) to assess the prognostic value of elevated D-dimer levels for short-term and 3-month mortality, (2) to assess the correlation between D-dimer levels and currently accepted prognostic factors (clinical scores, right ventricular dysfunction and degree of pulmonary artery obstruction at CT scan).

For the purpose of this study, short-term death was defined as death occurring within 30 days from diagnosis, as reported in the individual studies.

Study identification

An unrestricted electronic search was performed in MedLine and Embase. Search criteria included the terms "pulmonary embolism and D-dimer". Studies were included in this study if they had reported on: (1) patients with an objective diagnosis of PE, (2) D-dimer sampling at diagnosis of PE and (3) short-term or 3-month death and/or results of prognostic stratification. Only those studies enrolling five or more patients were considered. Studies reporting data allowing the creation of a 2×2 table were also included in a formal meta-analysis.

One author (A. Lignani) initially performed study selection by reviewing titles and abstracts. Candidate abstracts were then reviewed and selected for data retrieval. Only full articles were considered for analysis. Two authors (A. Lignani and M. B. Forte) reviewed each study for quality assessment and extracted data on studies and patient characteristics as well as outcomes, using standardized extraction forms. Disagreements were resolved by consensus and through revision by an additional reviewer (C. Becattini).

Because no standardized quality scoring system is available for quality assessment of observational studies, the components of the quality review were derived largely from the Egger's quality checklist for prognostic studies [10].

Studies were assessed for the presence of eight features: description of patient characteristics, description of inclusion and exclusion criteria, potential selection bias (e.g. consecutiveness), completeness of follow-up, a priori definition of study outcomes, objectivity of outcomes, and definition and measurement of prognostic variables and treatment.

For each study, the following individual data were extracted: general data (study design, duration of follow up), patients (number of included patients, inclusion and exclusion criteria), type of patients (in-patients or out-patients), D-dimer assays (type of test, cut-off level, and overall D-dimer-positive/negative patients), number of patients who died among D-dimer-positive or -negative patients; methods for prognostic stratification (e.g. clinical score, troponin, degree of embolic obstruction at computed tomography (CT), RVD at echocardiography); study outcome: correlation between D-dimer and markers of prognosis; clinical outcome: death.

Statistical analysis

Meta-analyses of all outcomes are reported using random-effects models because fixed- and random-effects results were similar. Cochran's Chi-square test and the I^2 test for heterogeneity were used to assess between-study heterogeneity. Statistically significant heterogeneity was considered present at $P < 0.10$ and $I^2 > 50\%$. Pooled odds ratios (ORs) were reported with 95% confidence intervals (CIs). Publication bias was assessed visually by the use of funnel plot analysis and by Duval and Tweedie's Trim and Fill statistics as well as Begg and Mazumdar rank correlation test when funnel plot could not definitively rule out publication bias. Analyses were performed with Review Manager 5 (The Cochrane Collaboration, Oxford, England) and Comprehensive Meta-analysis V2.

Results

Overall, 1,010 articles were found by searching "pulmonary embolism and D-dimer". Seven-hundred-sixty-four articles were excluded by review of the title and abstracts as they were studies on diagnosis of venous thromboembolism ($n = 334$), review articles or editorials ($n = 195$), studies on laboratory or animal research ($n = 82$), epidemiology ($n = 57$), therapy ($n = 37$), pathophysiological value of D-dimer ($n = 17$) or case reports ($n = 21$), evaluation of D-dimer in patients without PE ($n = 16$) or pediatric patients ($n = 5$) (Fig. 1). Two-hundred-forty-six studies were reviewed as a full text version and 22 studies were retained for inclusion in the systematic review (Table 1).

In four studies [11–14] the numbers of patients with normal/elevated D-dimer who had died were not reported.

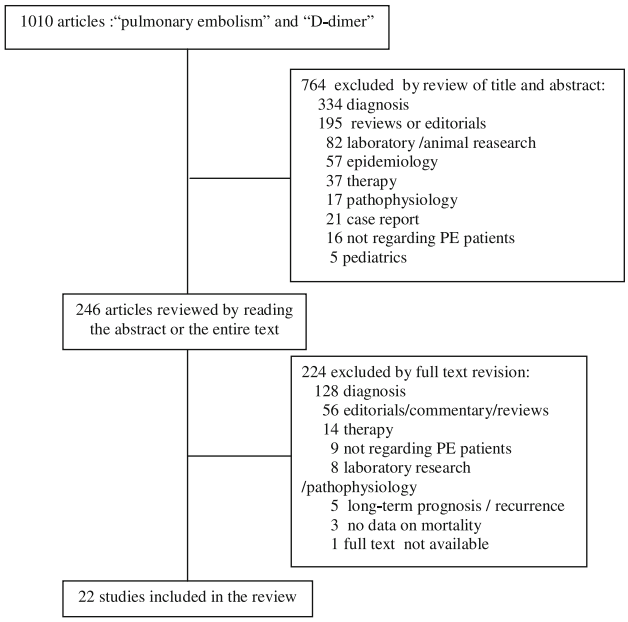

Fig. 1 Flow diagram for study selection

For two of these studies, these numbers were obtained by contacting the authors [12, 13].

Eight different assays for D-dimer assessment were used across the considered studies (Table 2). In 11 studies an 'ad hoc' D-dimer cut-off for prognostic assessment was used different from the diagnostic cut-off.

D-dimer and mortality

The association between D-dimer levels and clinical outcome was reported in 11 studies [11–21] (Table 3). In nine of these studies a prognostic cut off level of D-dimer, generally higher than the diagnostic one, was identified [11–15, 17, 18, 20, 21]. These prognostic cut offs varied between studies.

Seven studies reported on the correlation between D-dimer levels and short-term outcome [11–14, 20–22]. Short-term was intended as in-hospital (two studies), 10 or 15 days (three studies), 30 days and 6 weeks (one study each). Four studies assessed the correlation between D-dimer levels and short-term adverse outcome events while specific data on death and D-dimer levels were not reported [11–14]. Data on short term mortality adequate for meta-analysis were obtained by directly contacting the authors for two of the selected studies [12, 13].

Eight studies assessed the correlation between D-dimer levels and 3-month mortality [11, 12, 15–19, 21]. All these studies reported a higher mortality in patients with elevated levels of D-dimer. D-Dimer resulted to be an independent predictor of mortality at 3 months in two of these studies [12, 18]. In two of these studies the numbers of patients with elevated/normal D-dimer levels who died/survived were not available [14, 19].

Short-term mortality

Five of the studies (2,885 patients) evaluating the correlation between short-term mortality (in four studies in hospital or 15 days and in one study at 30 days) and D-dimer levels were included in a meta-analysis [12, 13, 18, 20, 21]. A correlation was found between D-dimer levels and short-term mortality in four studies. In one study this correlation with mortality was not observed during the hospital stay but at 3 months [21].

D-Dimer was above or below the prognostic cut-off in 890 and 2,027 patients, respectively. Death occurred within 30 days from diagnosis of PE in 56 and 57 patients with D-dimer levels above and below the prognostic cut-off. D-Dimer levels above the prognostic cut-offs were associated with high risk of short-term mortality (OR: 2.76; 95% CI: 1.83–4.14) with no evidence of between-studies heterogeneity ($I^2 = 0\%$) (Fig. 2a). As funnel plot inspection could not rule out definitely publication bias, further analyses were performed. Although the impact of bias probably is not trivial, the major finding of the association between elevated D-dimer and short term mortality is still valid (adjusted OR: 2.50; 95% CI: 1.69–3.68) (see Supplementary material). The association between elevated D-dimer and short term mortality was confirmed after excluding the study with the larger sample size that could dominate the analysis (OR: 4.66; 95% CI: 2.18–9.98; $I^2 = 0\%$) (Supplementary material). The association between D-dimer levels above the prognostic cut-offs and short-term mortality was confirmed in the analysis of studies only including hemodynamically stable patients (three studies, 874 patients; OR: 4.28; 95% CI: 1.88–9.71; $I^2 = 0\%$) (Fig. 2b).

Mortality at 3 months

Four studies (1,254 patients) evaluated the correlation between 3-month mortality and D-dimer levels and were included in the meta-analysis [15–17, 21]. D-Dimer was above or below the prognostic cut-off in 961 and 293 patients, respectively. Death occurred within 3 months in 96 and seven of these patients, respectively. D-Dimer levels above the prognostic cut-off were associated with increased mortality at 3 months (OR: 4.29; 95% IC: 1.70–10.79) with no evidence of between-studies heterogeneity ($I^2 = 0\%$) (Fig. 3). Given the small number of studies, publication bias could not be rule out by funnel plot inspection (see Supplementary material). Thus, further analyses were performed showing that the association

Table 1 Features of studies on the role of D-dimer in patients with acute PE included in the review

Author	Study design	Patients (*n*)	Inclusion criteria	End point	Follow up	Overall mortality
Gallè et al. [23]	Prospective	104	Hemodynamically stable out-patients with acute PE	Correlation between D-dimer levels and the extent of PE at ventilation-perfusion lung scan	In hospital	NR
De Monyé et al. [24]	Prospective	100	Out- or in-patients with suspected PE	Correlation between D-dimer levels and embolus location	In hospital	NR
Kline et al. [11]	Prospective	200	Normotensive out- or in-patients with PE	Prognostic accuracy of several markers of adverse outcome	In-hospital and 6 months	1% in-hospital 8.9% at 6 months
Aujesky et al. [15]	Retrospective	366	Hemodynamically stable, consecutive out-patients	Overall mortality	3 months	5.2%
Ghanima et al. [16]	Retrospective	99	Consecutive out-patients	1. Severity of PE (radiological markers and troponin) 2. Overall mortality	30 days 3 months	5%
Hochuli et al. [22]	Retrospective	88	Out- or in-patients with suspected PE	1. Diagnostic yield of CT at different levels of D-dimer and clinical probability 2. Correlation between D-dimer and the degree of pulmonary arteries obstruction at CT	In hospital	NR
Masotti et al. [25]	Retrospective	60	Out-patients with proven PE	Relationship between D-dimer and the extension of emboli and right ventricle dysfunction	In hospital	8.3%
Grau et al. [17]	Retrospective	588	Stable and unstable patients with PE	Overall mortality	3 months	10.5%
Klok et al. [18]	Retrospective	262	Patients with low clinical probability and PE confirmed by CT	Overall mortality	15 days 3 months	1.9%[a]
Goldin et al. [26]	Retrospective	75	Out-patients with D-dimer levels and CT performed ≤48 h from presentation	Correlation between D-dimer levels and the degree of pulmonary vascular obstruction at CT	In hospital	NR
Kabbara et al. [19]	Retrospective	497	Consecutive patients with clinical suspicion of PE	Overall mortality	3 months	NR
Vuillemier et al. [33]	Prospective	146	Non massive PE	Death at any time during follow-up, or PE-related hospitalization	3 months	7.3%
Agterof et al. [12]	Retrospective	440	Out-patients with suspected PE	Correlation between D-dimer levels and serious adverse events (death, recurrent VTE, major bleeding)	10 days, 90 days	11.6% overall (3.9% at 10 days 8% between 11 and 90 days
Lobo et al. [20]	Retrospective	1,707	Stable and unstable patients with PE	1. Overall mortality 2. Mortality related to PE, major bleeding	15 days	4.2%
Bova et al. [21]	Prospective	201	Stable, out- or in-hospital patients	1. In hospital adverse event related to PE 2. Overall mortality at 3 month	In hospital 3 months	2% (in hospital) 9% (3 month)
Sen et al. [27]	Retrospective	172	Patients with PE diagnosed by CT angiography	Relationship between localization of emboli and clinical and laboratory parameters	In hospital	NR
Jeebun et al. [28]	Retrospective	137	Stable and unstable, out- or in-hospital patients with PE	1. Correlation between the degree of pulmonary vascular obstruction at CT and hemodynamic parameters 2. Overall mortality	In hospital	21%

Table 1 continued

Author	Study design	Patients (*n*)	Inclusion criteria	End point	Follow up	Overall mortality
Nakada et al. [29]	Retrospective	48	Out- or in-hospital patients with PE	Correlation between embolus size and clinical features	2 months	2.4%
Turedi et al. [30]	Prospective	47	Outpatients	Relationship between D-dimer and the degree of pulmonary vascular obstruction and RV/LV ratio at CT	In hospital	NR
Gutte et al. [31]	Prospective	71	Patients with acute PE diagnosed at CT	Correlation between D-dimer levels and RV dysfunction at CT	6 months	NR
Singanayagam et al. [13]	Retrospective	411	Normotensive outpatients with PE	Compare biomarkers and PESI score for predicting 30-day mortality	30-day	5.1%
Klok et al. [14]	Prospective	113	Normotensive outpatients with likely probability (Wells) or positive D-dimer	To compare the predictive value of CT derived right ventricle dysfunction to cardiac biomarkers	6 weeks	6.2%

RV Right ventricle, *LV* left ventricle, *PE* pulmonary embolism, *CT* computed tomography

[a] Death due to PE

Table 2 Features of D-dimer assays used in studies included in the review

Author	D-dimer assay	Manufacturer	Test cut off	Study cut off
Galle et al. [23]	ELISA Asserachrom D-Di	Diagnostica Stago	NR	4,000 mcg/l
De Monyè et al. [24]	Immunoturbidimetric Tinaquant latex test	Roche diagnostic	0.5 mcg/ml	NA
Kline et al. [11]	MDA assay	Biomérieux	NR	8 mcg/ml
Aujesky et al. [15]	VIDAS	Biomérieux	500 ng/ml	<1,500 ng/ml 5,500 ng/ml
Ghanima et al. [16]	Immuno-turbidimetric STA LIA test	Diagnostica Stago	500 ng/ml	NA
Hochuli et al. [22]	Immunoturbidimetric Tinaquant latex test	Roche diagnostic	0.5 mcg/ml	NA
Masotti et al. [25]	ELISA, VIDAS	Biomérieux	500 mcg/L	NA
Grau et al. [17]	Latex agglutination Turbimetric immunoassay	IL	500 ng/ml	5,000 ng/ml
Klok et al. [18]	VIDAS and Immunoturbidimetric Tinaquant latex test	Roche diagnostic	500 ng/ml	3,000 ng/ml
Goldin et al. [26]	Immunoturbidimetric, LATEX enhanced	Dade Behring	221 ng/ml	NA
Kabbara et al. [19]	NR	NR	NR	NR
Vuillemier et al. [33]	VIDAS	Biomérieux	500 ng/ml	2,000 ng/ml
Agterof et al. [12]	Immunoturbidimetric Tinaquant latex test	Roche diagnostic	0.5 mcg/ml	3,000 mcg/ml
Lobo et al. [20]	Latex agglutination Turbimetric immunoassay	IL	500 ng/ml	4,200 ng/ml
Bova et al. [21]	VIDAS or Immunoturbidimetric	Biomérieux and Roche diagnostic	< 0.5 mg/l 250 mcg/ml	3,000 ng/ml 1,200 mcg/ml
Sen et al. [27]	Latex turbidimetric assay	NR	500 mcg/ml	500 mcg/ml
Jeebun et al. [28]	ELISA	NR	300 ng/ml	NA
Nakada et al. [29]	Immunofotometric LPIA – ACE	Mitsubishi chemical medience	1.0 mcg/ml	NA
Turedi et al. [30]	Colorimetrical STA-liatest	Diagnostica Stago	500 ng/ml	NR
Gutte et al. [31]	Immunoturbidimetric Tinaquant latex test	Roche diagnostic	>0.5 mg/l	NA
Singanayagam et al. [13]	VIDAS	Biomérieux	500 mcg/l	>4,000 mcg/l[a]
Klok et al. [14]	Quantitative immunoassay, STA LIA Roche	NR	NR	3,000 ng/ml

[a] Quartiles defined as D-dimer concentration <1,000 mcg/l; 1,001–2,000 mcg/l; 2,001–4,000 mcg/l; >4,001 mcg/l

Table 3 Correlation between D-dimer and mortality

Author	Follow up	Overall mortality *n* (%)	Mortality related to PE *n* (%)	Correlation D-dimer- mortality	D-dimer > cut-off		D-dimer < cut-off	
					Died	Survived	Died	Survived
Kline et al. [11]	In hospital 6 month	2 (1)	2	D-dimer > 8,000 mcg/l is related to in hospital adverse outcomes	na 17[a]	na 17[a]	na 34[a]	na 113[a]
Aujesky et al. [15]	3 months	19 (5.2)	7 (1.9)	D-dimer is not a predictor of 3-month mortality	18	257	1	90
Ghanima et al. [16]	3 months	5 (5)	Na	Non significant association between D-dimer levels and mortality	1	25	3	70
Grau et al. [17]	3 months	62 (10.5)	18 (3)	D-dimer ≥ 5,000 ng/ml correlated with mortality due to PE	62	492	0	34
Klok et al. [18]	15 days, 3 months	55 (8.2) at 3 months	5 (1.9) at 15 days	D-dimer > 3,000 ng/ml is an independent predictor of mortality	4[c] na	101 na	1[c] na	156 na
Kabbara et al. [19]	3 months	Na	Na	Correlation between D-dimer and mortality in patients with or without PE	na	na	na	na
Lobo et al. [20]	15 days	72 (4.2)	39 (2.3)	Correlation between D-dimer and overall mortality or mortality related to PE.	30[b] 17[c]	396[b] 409[c]	42[b] 22[c]	1239[b] 1,259[c]
Bova et al. [21]	In hospital 3 months	4 (2) 18 (9)	1 (0.9) Na	D-dimer not associated to in-hospital mortality D-dimer associated to 3-month mortality	4 15	102 91	0 3	95 92
Agterof et al. [12]	10 days 3 months	51 (11.6)	23	D-Dimer > 3,000 is a predictor of 10-day mortality	10[d]	180[d]	1[d]	145[d]
Singanayagam et al. [13]	30-days	5.1%	Na	Patients who died had higher D-dimer levels compared to survivors	8[e]	55[e]	13[e]	335[e]
Klok et al. [14]	6 weeks	7 (6.2)	4	Elevated D-dimer is associated with increased risk of adverse events at univariate analysis	4	na	3	na

na not available

[a] Adverse outcome events

[b] Overall mortality

[c] Mortality due to PE

[d] Death at 10 days

[e] Data are reported for D-dimer > 4,000 mcg/l

between elevated D-dimer and short term mortality is valid (adjusted OR: 3.93; 95% CI: 1.64–9.44) (see Supplementary material).

D-dimer and determinants of prognosis

The correlation between D-dimer levels and tests for risk stratification in patients with acute PE was reported in 14 studies [11, 15, 16, 18, 22–31]. Different tools were used across the considered studies for prognostic assessment (Table 4).

In one observational study an association was found between PESI risk class and D-dimer levels [12].

The association between D-dimer levels and the presence of right ventricle dysfunction at CT angiography was evaluated in four studies [16, 28, 30, 31] (Table 3). In all these studies the criterion for right ventricle dysfunction at CT was the right to left ventricle diameter ratio. In two of these studies [16, 31] a positive correlation was found between right ventricle dysfunction at CT angiography and D-dimer levels while in the remaining two studies this correlation was not confirmed [28, 30]. A positive association was found in one study between D-dimer levels and right ventricle dysfunction at echocardiography [25].

The correlation between D-dimer levels and the burden of PE as assessed by CT angiography was evaluated in nine studies [16, 18, 22, 24, 26–30]. The burden of PE was evaluated by quantitative or qualitative methods in different studies (Table 4). In five studies [16, 18, 24, 27, 28] a correlation was found between a proximal location of emboli within the pulmonary vessels and D-dimer levels. Similarly, in five studies a direct correlation was observed between D-dimer levels and a quantitative measure of the burden of emboli according to the Qanadli score [32] in four studies [16, 22, 28, 30] and different scores in one [26].

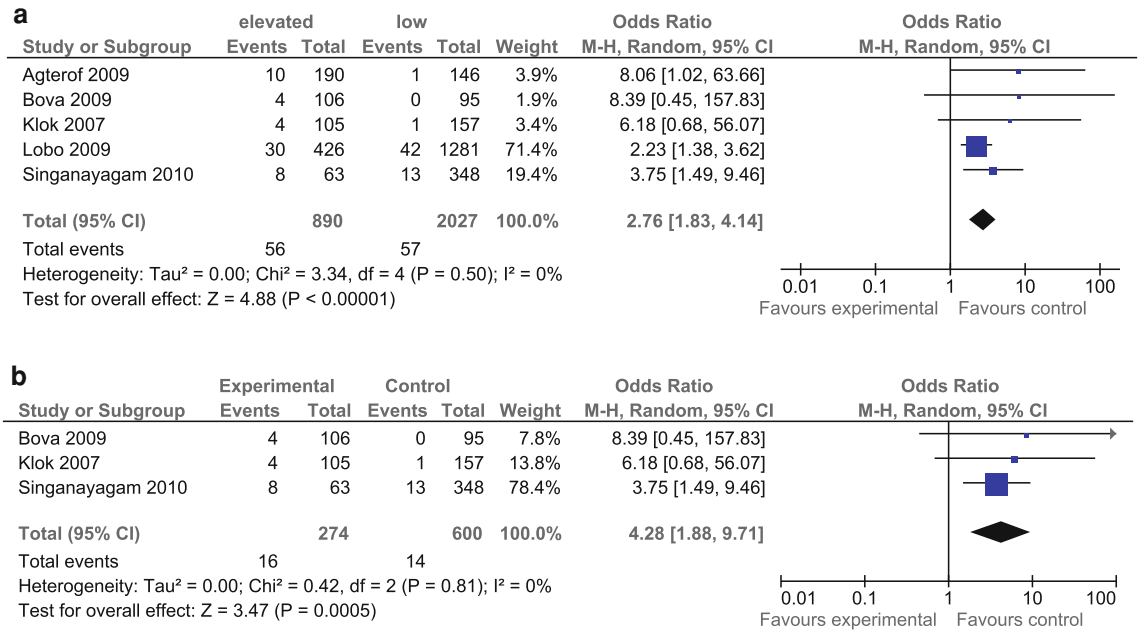

Fig. 2 Mortality at 15 days in patients with PE and D-dimer levels above and below the prognostic cut-off level

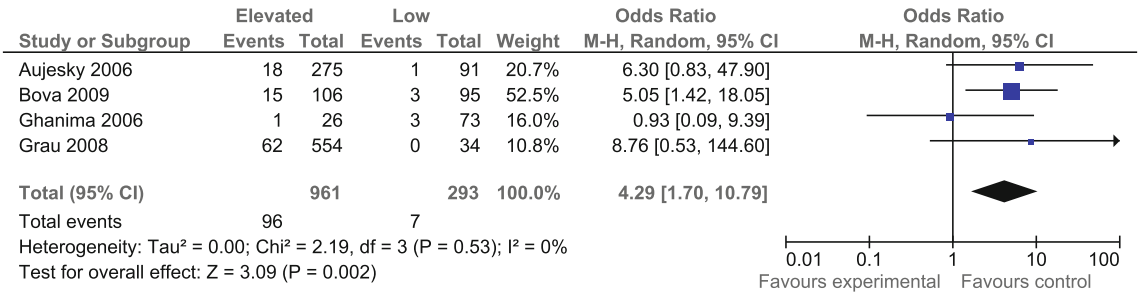

Fig. 3 Mortality at 3 month in patients with PE and D-dimer levels above and below the prognostic cut-off level

Two studies evaluated the association between troponin and D-dimer levels in patients with acute PE [16, 28]. In one of these studies an association was found between D-dimer and troponin levels [16] that was not confirmed in the other study [28].

A meta-analysis of these studies was not possible, because of differences in study methodology for the assessment of severity of PE and because of absence of data, allowing the creation of a 2 × 2 table and for the different methods employed in the studies for risk stratification.

Discussion

This meta-analysis suggests that high D-dimer levels are associated with short-term and 3-month mortality in patients with acute PE. This is particularly the case when D-dimer levels are above a prognostic cut-off value. The association is confirmed in studies only including hemodynamically stable patients.

Indeed, risk stratification remains a critical point in the acute management of patients with acute PE to tailor medical and interventional therapies to appropriate patients [1]. Recent guidelines recommend risk stratification to drive admission and treatment [4]. Patients at high risk of mortality should receive thrombolytic treatment. High risk is defined based on hemodynamic status. In non-high risk patients risk stratification according to markers of right ventricle dysfunction and injury could influence decision making on in-hospital or home-treatment as well as on the need for monitoring and even on treatment upgrading. Numerous clinical predictors are available for risk stratification in these patients including biomarkers, imaging tests, ECG and clinical decision rules. Based on our results, D-dimer could have a role in risk stratification and this seems to be the case also for hemodynamically stable patients. Indeed, a definite prognostic cut-off value can not

Table 4 Correlation between D-dimer and prognostic stratification tests

Author	Parameters						Correlation with D-dimer
	Troponin	PESI	V/Q lung scan	CT parameters			
				PAOI	RV/LV	Location of emboli	
Galle et al. [23]	NA	NA	Yes	NA	NA	NA	D-Dimer concentration is associated with larger perfusion defects on hight probability lung scan
De Monyè et al. [24]	NA	NA	NA	NA	NA	Yes	Significant correlation between D-dimer concentration and proximal embolus location
Kline et al. [11]	NA	NA	NA	NA	NA	NA	D-Dimer not associated with RV hypokinesis on echocardiography
Aujeski et al. [15]	NA	Yes	NA	NA	NA	NA	Significant association between PESI risk class and D-dimer levels
Ghanima et al. [16]	Yes	NA	NA	Yes	Yes	Yes	Significant association between: D-dimer and RV/LV, PAOI, extension of emboli and troponin levels
Hochuli et al. [22]	NA	NA	NA	Yes[a]	NA	NA	Association between high D-dimer and PAOI
Masotti et al. [25]	NA	NA	NA	NA	Yes[b]	NA	Correlation between: D-dimer levels and RV dysfunction at echocardiography; right ventricle dysfunction and location of emboli;
Klok et al. [18]	NA	NA	NA	NA	NA	Yes	Significant association between proximal embolus location and D-dimer levels
Goldin et al. [26]	NA	NA	NA	Yes	NA	NA	Significant correlation between D-dimer levels and PAOI
Sen et al. [27]	NA	NA	NA	NA	NA	Yes	D-Dimer level significantly higher in patients with central PE
Jeebun et al. [28]	Yes	NA	NA	Yes	Yes	Yes	Weakly positive correlation between PAOI and D-dimer levels; correlation between location of emboli and D-dimer levels; no correlation between RV/LV ratio or troponin levels and D-dimer levels
Nakada et al. [29]		NA	NA	NA	NA	Yes	Positive correlation between pulmonary embolus volume and D-dimer levels
Turedi et al. [30]	NA	NA	NA	NA	Yes	Yes	Positive correlation between levels of D-dimer and PAOI, no correlation between levels of D-dimer and RV/LV ratio
Gutte et al. [31]	NA	NA	NA	NA	Yes	NA	D-Dimer is predictor for increased RV/LV ratio

NA Not assessed

[a] QUANADLI COLLOMB simplified

[b] RVD assessed at echocardiography

be identified as both, the D-dimer assay and the cut-off levels, vary among the studies and because the cut-offs were often defined post hoc. Thus, although our analyses show an association between D-dimer levels and mortality, this association should be interpreted as hypothesis-generating and is not ready for clinical use. More specifically, the association between high D-dimer levels and mortality needs confirmation in prospectively designed management studies with pre-defined prognostic cut-off before clinical use. The accuracy of elevated levels of D-dimer for the assessment of prognosis was compared to that of other predictors in three studies (13, 31–32). In these studies the accuracy of D-dimer compared with that of the other predictors (mainly troponin levels, echocardiography and PESI score) varied based on the selected cut-off value. Thus, a direct comparison results difficult. Moreover, as D-dimer can be influenced by several conditions (age, cancer, pregnancy, infections, etc.) we believe that its use as a single predictor of prognosis could be seen as inappropriate for its low specificity. In alternative, the clinical value of integrating D-dimer levels into clinical scores should be defined. This strategy could be of value as it

offers the opportunity of using the same test for diagnosis and risk stratification, this resulting in reduction of time and costs.

The association between D-dimer levels and short-term mortality could be related to a potential link between D-dimer and PE severity. As an hypothesis, D-dimer levels could be related to the extent of thrombotic load. This hypothesis seems to be supported by the data described on Table 3 on the association between the embolic load as assessed by CT angiography and D-dimer levels. The systematic review shows that a correlation was found between D-dimer levels and markers of adverse outcome in patients with acute PE in several studies. Indeed, while conflicting results were obtained on the correlation between D-dimer levels and right ventricle dysfunction or elevated troponin, consensus exists regarding the association between elevated D-dimer and the burden of PE as assessed at CT angiography.

An association has also been suggested between D-dimer levels and PESI score.

Particularly elevated D-dimer levels in patients with acute PE could even be the result of both, the acute thromboembolic event and comorbidities. In this view, D-dimer could be very high as a result of concomitant cancer or COPD. These conditions are known predictors of outcome in patients with acute PE.

Currently, the main role of D-Dimer in the acute management of PE is in ruling out the diagnosis in patients with non high pre test clinical probability. A role has been suggested in making decision on whether discontinuing or not the long-term treatment after the first episode of unprovoked PE. Our systematic review suggests that when diagnosis of PE is performed, D-dimer values could have a role in prognostic assessment.

Our study has some limitations. A meta-analysis has the intrinsic limit of combining heterogeneous datasets. The studies included in this analysis differ for number of included patients, for duration of follow-up and, in some cases, for the main features of patients (in and out patients, inclusion of hemodynamically unstable patients, etc.). Regarding D-dimer measurements, it should be taken into account that a number of different assays have been used across the considered studies. Moreover, all the studies that evaluated the prognostic value of D-dimer used 'ad hoc' arbitrary prognostic cut-off. Finally, funnel plots inspection could not definitively rule out publication bias. This may be due to the limited number of available studies. However, after further specific tests were performed, publication bias could be confidently ruled out.

In conclusion, a relationship has been shown between elevated D-dimer levels and short-term and 3 months mortality in patients with acute PE. Further studies are needed to assess whether D-dimer, alone or combined with other prognostic tools for PE, may be useful to identify low-risk patients with PE who are potential candidates for outpatient treatment or an abbreviated hospital stay.

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