Effects of impaired renal function on levels and performance of D-dimer in patients with suspected pulmonary embolism

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Summary

Clinical probability and D-dimer measurement play an essential role in the non-invasive diagnostic strategies for pulmonary embolism (PE). PE can be ruled out without further imaging in patients with non-high clinical probability and negative D-dimer. D-dimer level is increased in patients with renal impairment. Whether its diagnostic usefulness is maintained in these patients is not well determined. We aimed to evaluate the effects of renal impairment on diagnostic performances of D-dimer in patients with suspected PE. A retrospective analysis of 1,625 patients with suspected PE included in a multicentre prospective study was performed. D-dimer levels and percentages of patients with a negative D-dimer were compared between three subgroups according to glomerular filtration rate (GFR) estimated by the MDRD formula: ≥90 ml/min (normal renal function), 60–89 ml/min (mild renal impairment), 30–59 ml/min (moderate renal impairment). D-dimer levels increased and the proportion of negative D-dimer decreased significantly according to renal status: 46% negative D-dimer in patients with normal GFR, 31% in patients with mild renal impairment, 11% in those with moderate renal impairment, corresponding to number of patients needed to test to obtain one negative test of 2.2, 3.2 and 9, respectively. In conclusion, the clinical usefulness of D-dimer decreases with renal impairment. However, PE can still be ruled out by negative D-dimer in a substantial proportion of patients with non-high clinical probability, avoiding exposure to contrast media.

Keywords

Creatinine, glomerular filtration rate, D-dimer, pulmonary embolism, renal insufficiency

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Introduction

Over the last two decades, the assessment of pre-test clinical probability in conjunction with the measurement of plasma D-dimer concentration have been shown to allow a completely non-invasive diagnostic work-up for the exclusion of PE in about one third of outpatients presenting with suspected pulmonary embolism (PE) to the emergency room (1–3). Indeed, in patients with an "unlikely" or a "non-high" clinical probability as assessed by either of the two largely validated clinical rules (the Geneva score or the Wells rule), a D-dimer concentration below a certain assay-dependent cut-off (hereafter referred to as "negative") safely allows to rule out the diagnosis of PE (3, 4). The diagnostic usefulness of D-dimer tests thus lies in their high sensitivity, the assays with the highest sensitivity being those performed by the ELISA technique (median sensitivity 99%) (5). D-dimers are fibrin degradation products and their level increases in the presence of a clot, but also in other clinical situations where the coagulation system is activated. D-dimers are therefore not a specific marker of thrombosis: specificity of the test varies from 40–70% depending on the laboratory method used (2). The clinical usefulness of D-dimer measurement is reduced in several clinical situations associated with increased D-dimer levels (6), such as post-operative periods, pregnancy and post-partum period, or in hospitalised patients as well as in elderly patients and those suffering from malignancy or with previous venous thromboembolism (VTE) (7–12). In other words, the number of patients needed to test (NNT) to exclude one PE without further investigations is increased. Indeed, in patients presenting to the emergency department with suspected PE, the diagnosis can be ruled out by negative D-dimer in one out of three patients (1) whereas it can only be ruled out in 1/9 cancer patients (13) and in 1/20 patients older than 80 years (9).

Previous data suggest that renal failure may be another condition associated with increased D-dimer levels, not simply due to reduced elimination of D-dimers by the kidneys, but also due to an activation of coagulation in patients with renal diseases (14–18).

Indeed, decreasing renal function has also been shown to be associated with increasing levels of other haemostatic markers, such as soluble thrombomodulin, soluble tissue factor, von Willebrand factor, factor VIII levels, fibrinogen and thrombin-antithrombin complex (TAT) (18–20), even after adjusting for potential confounding factors in studies including multivariate analysis. The specificity and clinical usefulness of D-dimer measurement could thus be reduced in patients with renal impairment. We therefore analysed the effect of impaired renal function on the diagnostic performances of D-dimer in a large database including 1,693 patients with suspected PE.

Methods

We retrospectively analysed data from a multicenter randomised prospective management outcome study with a non-inferiority design comparing two strategies for the diagnosis of PE. All consecutive outpatients admitted to the emergency department were included if they had a clinical suspicion of PE defined as acute onset of new or worsening shortness of breath or chest pain without any other obvious etiology. Written informed consent was obtained from all patients. Patients with severe renal impairment defined as GFR <30 ml/minute (min) were excluded from the study because of the potential need to perform CT using iodine contrast media (4). After assessment of the clinical probability of PE using the Revised Geneva score (13), eligible patients were randomly assigned to one of two diagnostic strategies: 1) D-dimer measurement and computed tomography (DD-CT strategy) or 2) D-dimer measurement, lower limb vein compression ultrasonography and computed tomography (DD-CUS-CT strategy). D-dimer measurement was performed only in patients with a low or intermediate clinical probability, using an ELISA assay (VIDAS, BioMérieux, Marcy-l'Etoile, France) with a cut-off of 500 ng/ml. In those patients, PE was ruled out by a negative D-dimer without further testing. When clinical probability was high or D-dimer level was above 500 ng/ml, the diagnostic strategy was as follows: in the DD-CUS-CT arm, the next performed test was CUS and patients with a proximal deep-vein thrombosis (DVT) were treated without further testing. Patients without proximal DVT proceeded to multidetector CT (MDCT) and were treated if MDCT was positive for PE. Patients with a negative MDCT were not treated; in the DD-CT arm, the strategy was similar to the DD-CUS-CT strategy except for the omission of CUS (4).

Treatment consisted of therapeutic anticoagulation in patients with confirmed PE, and the rate of thromboembolic events was assessed at three months in all patients. The study had been conducted in Belgium, France and Switzerland between January 2005 and August 2006.

Statistical analysis

First, we analysed the difference in D-dimer levels between subgroups of patients with increasing renal impairment. Creatinine level was measured on admission and glomerular filtration rate (GFR) was estimated according to the MDRD (Modification of Diet in Renal Disease) formula (22). Patients were separated in three different categories of GFR according to the Kidney Disease Outcomes Quality Initiative (K-DOQI) guidelines: GFR ≥ 90 ml/min (normal renal function), GFR 60–89 ml/min (mild renal impairment), GFR 30–59 ml/min (moderate renal impairment) (23).

Then, PE prevalence was defined in the three categories of renal function. D-dimer levels' geometric means were compared between renal function categories in patients with PE and in patients without PE.

A multivariate analysis was conducted to assess the association between D-dimer levels and renal function categories with adjustment on variables known to be associated with increased D-dimer levels, namely age, cancer, personal history of venous thromboembolism (VTE) and recent surgery. The variations in D-dimer levels' geometric means according to each of these factors are reported in patients with PE and in patients without PE.

The sensitivity and specificity of D-dimer for the diagnosis of PE were assessed for patients with normal GFR, mild and moderate renal impairment and compared between these categories of patients. Changes in the diagnostic performance of D-dimer for PE according to renal function or age were analysed by comparing the area under the curves (AUC) across different renal function and age categories.

The diagnostic usefulness of D-dimer in patients with renal failure was further assessed by identifying the percentage of patients with negative D-dimer in each renal function category, and the number of patients needed to test to obtain one negative result

Table 1: General characteristics.

Total (n)	1625
Age (years)	59.9 (+/- 18)
Male / Female	735 (45.2%) / 890 (54.8%)
Patients with negative D-dimers <500 ng/ml	544 (33.5%)
Distribution of patients according to GFR (MDRD) -GFR > 90 ml/min	 596 (36.7%)
-GFR 60–89 ml/min	774 (47.6%)
-GFR 30–59 ml/min	255 (15.7%)
Distribution of patients according to GFR (Cockcroft)* -GFR > 90 ml/min	 678 (41.9%)
-GFR 60–89 ml/min	528 (32.6%)
-GFR 30–59 ml/min	413 (25.5%)
Personal history of VTE	268 (16.5%)
Active malignancy or in remission for < 1 year	119 (7.3%)
Surgery within 1 month	84 (5.2%)
PE confirmed PE excluded	314 (19.3%) 1311 (80.4%)

Data are number (%) or mean (1 SD). *N=6 patients with missing data (weight not available).

Table 2: Patients' characteristics, D-dimer levels, and diagnostic performances of D-dimer according to renal status (MDRD).

Renal status	All	GFR >90mL/min	GFR 60–89mL/min	GFR 30–59 mL/min	p-values*
N	1625 (100.0%)	596 (36.7%)	774 (47.6%)	255 (15.7%)	
D-dimer levels, geometric mean (CI 95%)	806 (764 to 850)	593 (544 to 645)	841 (780 to 907)	1493 (1324 to 1684)	<0.0001
Age, mean (SD)	59.9 (18.0)	50.4 (17.3)	62.6 (17.2)	73.8 (11.6)	<0.0001
PE prevalence, N (%)	314 (19.3%)	77 (12.9%)	158 (20.4%)	79 (31.0%)	0.0001
Active malignancy or in remission for < 1 year, N (%)	119 (7.3%)	35 (5.9%)	61 (7.9%)	23 (9.0%)	0.002
Personal history of VTE, N (%)	268 (16.5%)	76 (12.8%)	134 (17.3%)	58 (22.7%)	0.001
Surgery within 1 month, N (%)	84 (5.2%)	35 (5.9%)	40 (5.2%)	9 (3.5%)	0.42
Negative D-dimer <500 ng/ml, N (%)	541 (33.4%)	273 (45.8%)	243 (31.4%)	28 (11.0%)	<0.0001
Negative D-dimer (Age-adjusted cut-off)**	646 (41.9%)	296 (52.1%)	300 (40.8%)	53 (22.7%)	<0.0001
Number needed to test <500 ng/ml	3.0 (2.8–3.2)	2.2 (2.0–2.4)	3.2 (2.9–3.6)	9.1 (6.5–13.5)	
(Age-adjusted cut-off)**	2.4 (2.2–2.5)	1.9 (1.8–2.1)	2.3 (2.1–2.5)	4.3 (3.6–5.2)	
Sensitivity	100% (98.8–100.0)	100% (95.3–100.0)	100% (97.7–100.0)	100% (95.4–100.0)	NA
(Age-adjusted cut-off)**	99.3% (97.4–99.9)	100.0% (94.5–100.0)	98.6% (95.0–99.8)	100.0% (94.5–100.0)	0.27
Specificity	41.9% (38.8–44.2)	52.6% (48.2–57.0)	39.4% (35.6–43.4)	15.9% (10.8–22.2)	<0.0001
(Age-adjusted cut-off)*	51.2% (48.4–54.0)	58.8% (54.4–63.2)	50.3% (46.2–54.4)	31.5% (24.6–39.2)	<0.0001

* comparison between sub-groups of renal function. ** cut-off determining positivity of D-dimer levels is 500ng/mL for patients ≤ 50 years and 10xage in years for patients >50 years.

was compared between patients with normal renal function and patients with mild and moderate renal failure.

All the analyses were performed with the GFR calculated with the MDRD formula and a sensitivity analysis was conducted by performing the same statistical analyses with the GFR calculated with the Cockcroft-Gault formula (24).

Statistical analysis was carried out with S-plus 8.0 for Windows (Insightful Corp., Seattle, WA, USA) and STATA 10.1 software (StataCorp, College Station, TX, USA).

Results

A total of 1,693 patients were included in the original management outcome study (4). Patients with high clinical probability (N=50) were excluded from the present analysis, as D-dimer measurement was not part of the diagnostic strategy in these patients (insufficient negative predictive value). Of the 1,643 patients with low or intermediate clinical probability, creatinine level was unavailable for 17 patients, and one patient had severe renal insufficiency on haemodialysis. The total number of patients for the present analysis was therefore 1,625. Clinical characteristics of the patients are presented in ▶Table 1. PE was confirmed in 19% of suspected patients.

D-dimer levels increased significantly with decreasing renal function (▶Table 2). PE prevalence was also significantly higher in patients with renal impairment ranging from 13% in patients with normal renal function to 20% and 31% in patients with mild and moderate renal impairment, respectively (▶Table 2). Besides D-dimer levels and PE prevalence, several other clinical characteristics were significantly associated with renal function (▶Table 2): as renal function (MDRD-based) decreased, patients' age and the proportion of patients with cancer or previous VTE increased.

The association between D-dimer levels and renal function was found both in patients with and without PE (▶Figure 1) but was more pronounced in patients without PE. Indeed, in patients without PE, the geometric mean of D-dimer levels was increased by 28.4% (95% CI: 15.0 to 43.3, p<0.0001) for patients with mild renal impairment and 119.7% (95% CI: 86.8 to 158.4, p<0.0001) for patients with moderate renal impairment, compared to patients with normal renal function. In patients with PE, the increases were smaller: 16.9% (95% confidence interval [CI]: –2.9 to 40.7, p=0.10) and 49.4% (95% CI: 20.2 to 85.7, p=0.0004), respectively. Similar

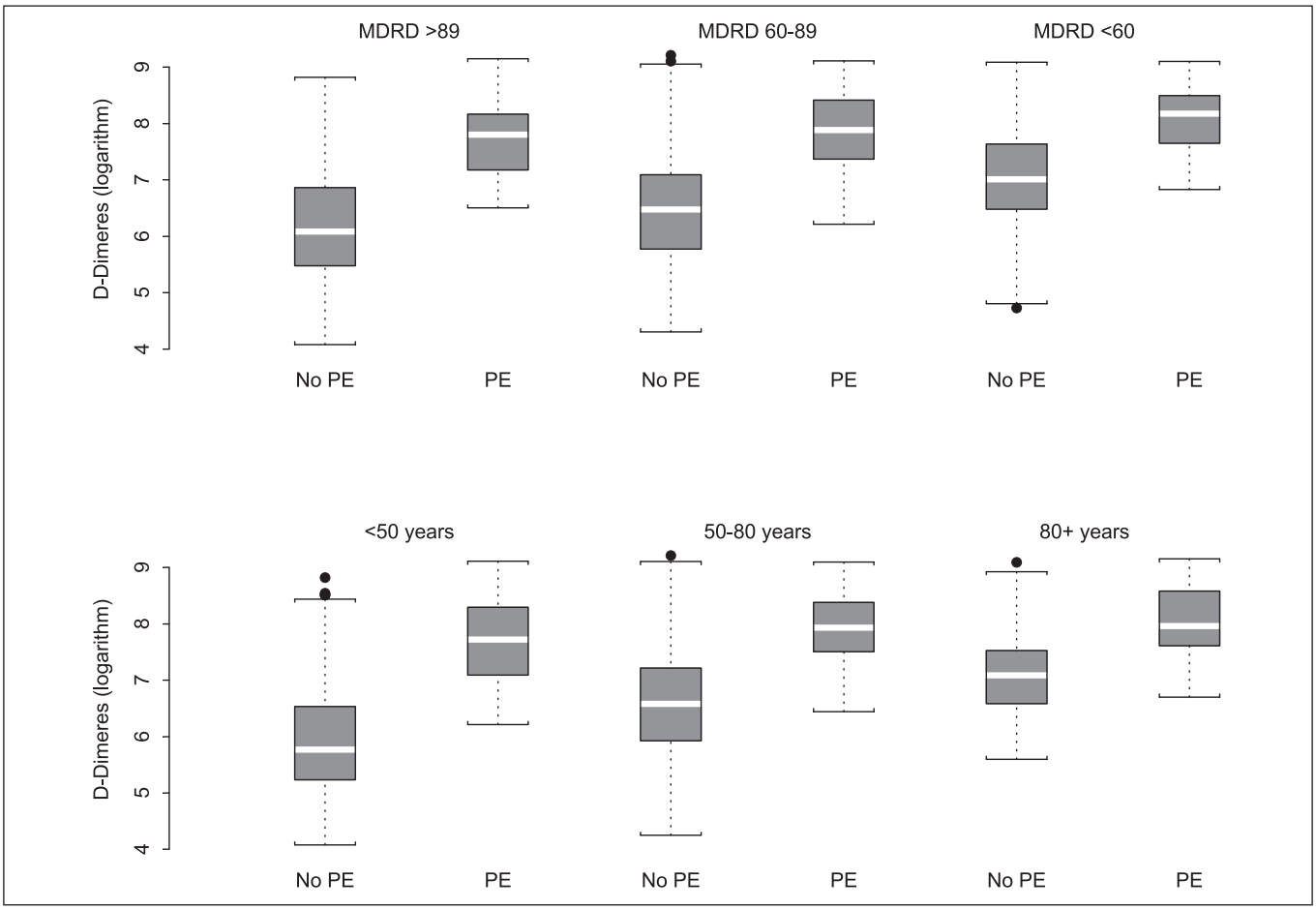

Figure 1: D-dimer levels according to creatinine clearance and age in patients with and without PE.

findings were observed for the association between age and D-dimer levels (►Figure 1).

After adjustment for the main potential confounding factors (age, presence of cancer, surgery and previous VTE) however, the magnitude of the association between D-dimer levels and renal function was markedly reduced (►Table 3). Indeed, compared to normal renal function, mild renal impairment had no significant impact on the geometric mean of D-dimer, and moderate renal impairment was associated with an increase of only 30% (in both patients with and without PE). The increase in D-dimer associated with increasing age was much more pronounced: the geometric mean was multiplied by 3 in patients >80 years compared to patients <40 years (►Table 3).

As none of the patients in whom PE was ruled out based on a non-high clinical probability and negative D-dimer (defined as a level <500 ng/ml for the VIDAS test) experienced VTE within the three-month follow-up, the sensitivity of D-dimer was considered of 100% (95% CI: 98–100) in this study. However, specificity of D-dimer for the diagnosis of PE was dramatically reduced with increasing renal impairment: 52.6% (95% CI: 48.2–57.0) in patients with normal renal function, 39.4% (95 % CI: 35.6-43.4) in case of mild renal impairment and 15.9% (95% CI: 10.8-22.2) in case of moderate renal impairment (►Table 2).

As shown in ►Table 4, the AUC of the D-dimer receiver operating characteristic (ROC) curve decreased significantly across age subgroups (p=0.003) but not across renal function subgroups (p=0.15). The performance of D-dimer in the diagnosis of PE was good regardless of age and renal function: in crossed strata, the AUCs ranged from 0.825 (patients >80 years and mild renal impairment) to 0.930 (patients <50 years with normal renal function). In each age subgroup, the AUCs did not significantly vary between renal function categories (p=0.08 for age <50 years, p=0.27 for age 50-80 and p=0.45 for age >80 years) (►Table 4).

The proportion of negative D-dimer ranged from 45.8% in patients with normal renal function to 31% in patients with mild renal impairment and 11% in patients with moderate renal impairment. Thus the number of patients needed to test to exclude one PE ranged from 2.2 to 9.1. When the effect of age on the positivity threshold of D-dimer was accounted for by using new age-adjusted cut-offs (25) that are ongoing prospective validation, the proportion of patients with negative D-dimer was still significantly different across sub-groups of renal function but to a much lesser extent (►Table 2). Indeed, the number needed to test (NNT) decreased from 9 to 4.3 in patients with moderate renal impairment for instance when age-adjusted cut-offs were used.

		Patients with PE		Patients without PE	
		Geometric mean increase % (CI95%)	p-value	Geometric mean increase % (CI95%)	p-value
MDRD	>90	Ref	0.12*	Ref	0.001*
	60–89	7.4 (-12.3 to 31.4)	0.50	-0.9 (-10.7 to 10.0)	0.87
	30–59	27.9 (-0.7 to 64.7)	0.06	29.8 (10.8 to 52.2)	0.001
Cancer	No	Ref		Ref	
	Yes	30.7 (-1.6 to 73.7)	0.07	38.1 (14.9 to 66.1)	0.0006
Age (years)	<40	Ref	0.09*	Ref	<0.0001*
	40 – 50	8.0 (-22.6 to 50.7)	0.65	10.2 (-5.6 to 28.6)	0.22
	>50 – 60	-8.5 (-33.3 to 25.4)	0.58	41.5 (20.2 to 66.5)	<0.0001
	>60 – 70	22.0 (-11.7 to 68.6)	0.23	98.6 (69.1 to 133.2)	<0.0001
	>70 – 80	30.5 (-3.9 to 77.1)	0.09	157.8 (119.1 to 203.3)	<0.0001
	>80	31.3 (-4.3 to 80.0)	0.09	219.3 (168.2 to 280.2)	<0.0001
Surgery	No	Ref		Ref	
	Yes	12.4 (-16.5 to 51.4)	0.44	92.7 (51.1 to 145.7)	<0.0001
Previous VTE	No	Ref		Ref	
	Yes	0.1 (-15.4 to 18.5)	0.99	0.3 (-12.6 to 15.1)	0.96

* global p-value.

Table 3: Increases in geometric mean in D-dimer levels in patients with and without PE. Estimates were obtained from multivariate regression analyses.

		Renal status			
		Normal renal function	Mild renal failure	Moderate renal failure	All
Age	<50 years	0.930 [0.889;0.971] 1.8/1.8	0.862 [0.797;0.928] 1.8/1.7	- * 1.3/1.1	0.925 [0.897;0.952] 1.8/1.7
	50–80 years	0.896 [0.852;0.940] 2.5/2.0	0.847 [0.804;0.889] 3.8/2.7	0.856 [0.797;0.915] 9.2/4.6	0.875 [0.850;0.900] 3.6/2.6
	>80 years	- * 9.0/3.5	0.825 [0.746;0.904] 8.7/4.0	0.875 [0.772;0.978] 40.0/6.0	0.834 [0.778;0.890] 11.6/4.3
	All	0.896 [0.864;0.928] 2.2/1.9	0.852 [0.820;0.883] 3.2/2.5	0.875 [0.832;0.917] 9.1/4.4	0.886 [0.868;0.904] 3.0/2.4

*AUC was not assessed because of the low number of patients.

Table 4: AUC of D-dimers in the diagnosis of PE (1st line), number needed to test with a D-dimer cut-off of 500 ng/ml and age-adjusted cut-off (2nd line): cross strata of age and renal insufficiency.

Finally, to check the robustness of the results according to the definition of creatinine clearance, the same statistical analyses were conducted using GFR values estimated by the Cockcroft-Gault formula. A total of 413 patients (25.5%) had moderate renal impairment, 528 (32.6%) a mild renal impairment and 678 (41.9%) a normal renal function (►Table 1). In crossed strata of age and renal function, the AUCs ranged from 0.826 to 0.958, and the number of patients needed to test to obtain one negative result ranged from 2.2 (2.0–2.3) to 2.9 (2.6–3.3) and 9.3 (7.1–12.7) in patients with normal renal function, mild and moderate renal impairment respectively, figures that favourably compare to those obtained when using the MDRD formula.

Discussion

Our data confirm in a large database that impaired renal function has a significant effect on the diagnostic performances of D-dimer for PE diagnosis. The specificity of D-dimer decreases significantly with increasing renal failure. Therefore, a patient with suspected PE and mild or moderate renal impairment is less likely to have negative D-dimer results than a patient with normal renal function, and the NNT to obtain a negative result rises from 2.2 to 9 with declining renal function (►Table 2). Nevertheless, considering the low cost of D-dimer, its measurement seems acceptable even in patients with moderate renal impairment (GFR 30–59 ml/

min) as it may avoid in 11% of these patients an unnecessary CT scan, which is associated with potential adverse renal consequences in this category of patients at particularly high risk of contrast-induced nephropathy (CIN) (26, 27). One of the most important risk markers for developing CIN is indeed preexisting renal impairment, with an exponential increase in CIN rate as GFR decreases below 60 ml/min, a risk which is even amplified in case of associated diabetes (28). Moreover, although there is no scientific proof to define an "NNT cut-off" above which D-dimer measurement would be considered completely useless in the diagnostic strategy of PE, the NNT of 9 in patients with moderate renal impairment is very similar to the ones reported in other clinical situations well known to be associated with decreased clinical usefulness of D-dimer testing. Nonetheless, despite NNTs varying between 6.3 and 9 reported in patients with previous VTE (12) or cancer (8), D-dimer measurement is quite well accepted in these subgroups of patients with suspected VTE and used in everyday practice. Finally, integrating D-dimer measurement in PE diagnostic strategies is cost-effective even when the NNT is high. Indeed, the cost-sparing effect of D-dimer was shown to be reduced but not abolished in patients >80 years (in whom the percentage of negative D-dimer was 5% and the NNT 20) (11).

To our knowledge, only one previous study published to date has analysed the impact of renal insufficiency on the performance of D-dimer in patients with suspected PE. In a post-hoc analysis of a cohort of 385 patients (of whom >90% were outpatients) included in a multicentre prospective study evaluating a diagnostic algorithm using clinical decision rule, D-dimer and CT in patients with suspected PE (Christopher study) (3), Karami-Djurabi et al. have also shown a reduced specificity of the VIDAS D-dimer assay (BioMérieux) in patients with renal impairment (29). In their study, the NNTs were however lower, ranging from 1.7 in patients with GFR >90 ml/min to 3.6 in patients with GFR 30–59 ml/min. This might be at least partly due to the fact that patients were significantly younger than in our study (mean age 48 ± 16 years vs 59 ± 18 years in our study) and to the difference between the clinical prediction rules used. Indeed, the dichotomised Wells rule used in the Christopher study (3) resulted in a proportion of patients in whom PE was unlikely of 67%, whereas the proportion of patients with a non-high probability using the revised Geneva score in our study was more than 90% (4). This means that according to the PE diagnostic strategy, a significantly higher proportion of patients were tested for D-dimer in our study, which could contribute to the higher number of patients needed to test to obtain one negative result. Moreover, the sample size of the study by Karami-Djurabi et al. (29), was rather limited.

The main limitations of our study are the absence of data on patients with severe renal impairment (GFR <30 ml/min) and the presence of several potential confounding factors influencing D-dimer levels. First, the higher proportion of patients with confirmed PE among the subgroups of patients with renal impairment compared to those with normal renal function could have partly influenced some of the results. However, when analyses are performed in patients *without* PE, thus excluding the effect of increased D-dimer related to VTE, significant differences in D-dimer levels were found according to renal status as described in detail in the results.

Second, increasing age is known to be associated with progressively decreasing renal function but also increasing D-dimer levels and represents another major confounding factor. However, the multivariate analysis including some of the main potential confounding factors, and performed separately in patients with PE and in patients without PE, allows estimating the strength of effect of each of these factors. Indeed, our data highlight the impact of age whose effect on D-dimer levels is much stronger than the effect of renal function as shown in the results above. Age-adjusted D-dimer cut-offs for patients >50 years (age x10) have been suggested and shown to be safe in retrospective studies (25). Prospective validation of these new cut-offs has been performed in a large multicentre outcome study whose results are pending. If the safety of age-adjusted D-dimer cut-offs for excluding PE without further imaging is confirmed, their use could be generalised and would overcome a great part of the effect of declining renal function on D-dimer levels. Indeed, using age-adjusted cut-offs could allow to reduce the number of patients needed to test to obtain one negative result from 9 to 4.3 in patients with GFR 30–59 ml/min. The effect of decreasing renal function on D-dimer levels in patients <50 years is less of a concern because of the much lower prevalence of renal failure in this age category.

Concerning patients with severe renal impairment (GFR <30 ml/min), there are no available data in the literature that could allow any recommendation on D-dimer use in case of suspected PE in these patients. Based on our results showing a gradual and statistically significant increase in D-dimer levels' geometric mean values associated with decreasing levels of renal function (▶Table 2), we can only hypothesise that the percentage of negative

What is known about this topic?

- Pulmonary embolism (PE) can be ruled out without the need for thoracic imaging in suspected patients with non-high clinical probability and negative D-dimer. This represents one out of three outpatients presenting to the emergency room with suspected PE.
- Renal insufficiency is associated with increased D-dimer levels, potentially reducing the clinical usefulness of D-dimer in this setting.

What does this paper add?

- The proportion of negative D-dimer tests and hence the clinical usefulness of D-dimer in the diagnostic strategy of PE decreases with renal impairment.
- The number of patients needed to test to obtain one negative result remains however interesting (9 in patients with moderate renal failure) considering that negative D-dimer avoids exposure to nephrotoxic contrast media.
- The potential use of age-adjusted D-dimer cut-offs in the future could allow to overcome a large part of the effect of renal function on the performance of D-dimer in the diagnosis of PE.

D-dimer results would probably be lower in patients with severe renal impairment than in patients with moderate renal impairment, thus leading to a higher NNT, so as to potentially render D-dimer measurement in the diagnostic strategy of PE less useful in these patients. The magnitude of the difference between patients with moderate renal impairment and severe renal impairment is however impossible to infer from available data.

Our study has some strength. Initial data arose from a large number of patients included in a randomised multicentric study including consecutive unselected patients with suspected PE. The same, well validated D-dimer test (rapid ELISA assay, Vidas DD, BioMérieux) was used in all institutions. Three independent experts blinded to the allocation group adjudicated all the outcome events.

In conclusion, our data confirm and extend in a large population of patients with suspected PE that the clinical usefulness of D-dimer measurement decreases in patients with renal impairment. Even though the number of patients needed to test to obtain one negative result is higher in patients with renal impairment, D-dimer testing remains justified in all patients with a non-high clinical probability regardless of renal status, as a negative test excludes PE without further imaging and avoids exposure to the potential adverse effects of contrast media. Furthermore, increasing age seems to play a major role in reducing the specificity of D-dimer in patients with renal failure. The potential implementation of age-adjusted D-dimer cut-offs could probably allow to overcome a large part of the effect of renal function on the performance of D-dimer in the diagnosis of PE in the future.

Conflicts of interest

None declared.

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