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Prognostic value of D-dimer in elderly patients with Pulmonary Embolism

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Abstract In a general population with acute Pulmonary Embolism (PE) elevated D-dimer concentrations associate with increased mortality. The aim of the study was to assess the ability of D-dimer to predict 30 and 90-days mortality in elderly patients with acute PE. Hemodynamically stable patients aged ≥65 years old with confirmed PE were included in this retrospective cohort study. A pulmonary computerized tomography angiography scan, D-dimer concentrations, simplified Pulmonary Embolism Severity Index (sPESI) variables and vital status were available for all patients. The study included 154 confirmed cases of PE (23.5 % of suspected), median age 79.1 years. D-dimer was higher in patients dead than in those alive at 30 (median 14,547 vs. 8340 ng/mL, p = 0.05) and 90 days (13,604 vs. 7973 ng/mL, p = 0.013). When adding D-dimer to sPESI, the discriminant capacity to predict mortality within 30 and 90 days was increased by 0.080 and 0.089, respectively. The contribution of D-dimer to the discriminating ability was NRI = 0.286 (95 % CI −0.198 to 0.770, p value: 0.247) at 30 days and NRI = 0.605 (95 % CI 0.223–0.988, p-value: 0.002) at 90 days.D-dimer concentration was associated with 30 and 90-days mortality and showed a higher discriminant capacity than sPESI alone to predict 90-days mortality. Adding D-dimer concentrations to sPESI score seems to improve its prognostic ability, supporting multivariable risk models as the best approach to estimate prognosis in elderly patients with PE.

Keywords Pulmonary Embolism · Mortality · Prognosis · Aged · Aged, 80 and over

Introduction

Acute Pulmonary Embolism (PE) is a common, life-threatening disease, occurring in 0.5–2 per 1000 adults each year [1]. Reported all-causes 30 days mortality rate ranges from 5 to 10 % [1–4] but figures are even higher in elderly (≥65 years old) and very elderly (≥80 years old) subjects [5].

D-dimer has been widely recognized to be useful in the diagnostic work-up of hemodynamically stable patients with PE [6] and showed a high Negative Predictive Value to rule out PE in subjects with non-high clinical probability, allowing a reduction in the number of ordered imaging test [7–9].

Recent guidelines recommend risk stratification to drive admission, management and treatment [10, 11] of patients with PE. In subjects at high risk of mortality because of hemodynamic instability, thrombolytic treatment should be considered. In non-high risk, hemodynamically stable patients, risk stratification should influence decision making

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on in-hospital or outpatient management. Different studies suggest that truly low-risk patients with acute PE can be safely treated as outpatients or be considered candidates for an abbreviated hospital stay, thus reducing health care costs associated with hospitalization and possibly improving patients' quality of life [12, 13]. The introduction of direct oral anticoagulants as an alternative to vitamin-K antagonists may simplify outpatient management in this setting.

Several clinical predictors are available for risk stratification in patients with PE, including clinical decision rules (CDR), biomarkers, imaging tests and echocardiography. Presently, the most used CDRs include risk scores like Pulmonary Embolism Severity Index (PESI) [14] and its simplified version (sPESI) [15].

Different studies showed that in general population with acute PE an elevated D-dimer was associated with an increased short-term and 90-days mortality, suggesting the potential of this biomarker also for risk stratification [16]. Using D-dimer as a prognostic marker could be an interesting strategy as it would allow using the same test for diagnosis and risk stratification, resulting in a reduction of time and costs. However, since elderly population was under-represented in most studies on risk stratification in acute PE [16], data on the prognostic value of D-dimer in these patients are lacking.

We designed the present study to assess the ability of D-dimer to predict 30 and 90-days mortality in elderly patients with PE.

Materials and methods

This retrospective cohort study was designed to explore the prognostic role of D-dimer in elderly patients, including all patients aged $\geq$65 years old evaluated in the Emergency Department (ED) of Vimercate Hospital for clinically suspected PE since January 1, 2010 through December 31, 2014. The standard praxis in the ED of our hospital considers performing a pulmonary computerized tomography angiography (CTA) scan based on an emergency physician's gestalt approach or evidence based algorithms, to exclude PE if suspected in hemodynamically stable subjects, whereas data on D-dimer, Wells score and sPESI variables are recorded and available for all patients with suspected PE. Helical computerized tomography scans were performed on a Brilliance Philips CT scanner (Philips, Cleveland, OH) which included 64-detector row capability. D-dimer was measured with particle enhanced immunoturbidimetric assay Innovance DDIMER on the Behring Coagulation System (BCS) analyzer (Siemens Medical Solutions Diagnostics, Deerfield, IL; normal value declared by the producer:<490 ng/mL). The reported Innovance DDIMER assay correlation coefficient for linear regression analysis comparing measured and expected D-dimer concentrations was $r^2 = 0.995$, with a regression line $y = 0.949x + 0.068$, and concordance between Innovance D-DIMER assay and VIDAS D-Dimer assay results was observed in 96.5 % of samples with results above the cut-off value and in 97.8 % of samples below the cut-off value, with a $k = 0.860$ (95 % confidence interval [95 % CI]: 0.811–0.908) [17].

PE was ruled out or confirmed on the basis of the absence or presence of a filling defect in one or more pulmonary arteries up to sub-segmental arteries in pulmonary CTA, as stated at the time of the acquisition of images by certified radiologists belonging to the hospital team. Patients with confirmed PE were treated according to international guidelines [11].

The sPESI score was calculated giving one point for the presence of every of the following parameters: (1) age >80 years; (2) history of cancer; (3) history of chronic cardiac or pulmonary disease (heart failure or chronic lung disease); (4) pulse rate >110 beats/min; (5) systolic blood pressure <100 mmHg; and (6) arterial oxyhemoglobin saturation <90 % measured at the time of PE diagnosis. Patients with none of the variables (0 points) were categorized as low-risk; and those with one to six the variables (1–6 points) as high-risk [15].

Vital status within 30 and 90 days was recorded for all patients. Unique personal identifiers were checked for the follow-up concerning mortality using the regional demographic register updated at 31st August 2015.

Because of the retrospective design, informed consent was not obtained from individual patients, but permission for data analysis and to perform the study was asked to the Institutional Research Ethics Committee.

To compare the distribution of the variables in patients died and alive at 30 and 90 days Chi squared test was performed for the categorical variables and Wilcoxon rank sum test for quantitative variables The distributions of D-dimer in patients with different sPESI score were compared by Kruskal–Wallis test and the distributions of D-dimer in patients with sPESI score $= 0$ and ≥ 1 by Wilcoxon rank sum test.

Firstly the contribution of D-dimer to discriminate between people died and alive at 30 or 90 days was evaluated. Logistic models with sPESI score only and with d-dimer in addition to sPESI score were fitted [18]. Using the two model predictors ROC curves were plotted and the corresponding area under the curve (AUC) with 95 %CI were computed. To better evaluate the prognostic contribution of D-dimer the interaction between sPESI score and D-dimer was taken into account because it was considered clinically plausible. Thus, it was included into logistic regression model irrespectively to its statistically significance. The improvement in the discriminative ability of

D-dimer was then evaluated by continuous Net Reclassification Improvement (NRI) [19].

Subsequently, the possibility of identifying cut-offs for prognostic classification of D-dimer was explored. Due to the strong impact of the study outcome (death), a minimum sensitivity of 75 % was considered. Because of the relationship between D-dimer and sPESI, the ROC curve were separately computed in patients with sPESI = 0 and in patients with sPESI ≥1, and partial AUC and 95 % CI were reported [20]. In both sPESI = 0 and sPESI ≥1 groups the optimal cut-off was then obtained as the D-dimer value which maximizes the specificity [21], given a sensitivity of at least 0.75. Given these cut-offs, the corresponding values of sensitivity and specificity, Positive Predictive Value and Negative Predictive Value were computed with pertinent 95 % CI. Bootstrap was used to evaluate an approximate 95 % CI of cut-off values, by bootstrapping 5000 samples for dead and alive patients.

Results

A total of 655 patients aged ≥65 years old were evaluated in the ED with suspected PE since 2010 through 2014, with an overall prevalence of confirmed PE of 23.5 % (154 cases). Among patients with confirmed PE, 48 (31.1 %) were female, the median age was 79.1 years, 73 (47.4 %) were aged ≥80 years and the overall mortality within 30 and 90 days was 11.7 % (95 % CI 7.1–17.8) and 19.5 % (95 % CI 13.6–26.6), respectively. D-dimer was higher in patients dead than in those alive at 30 days (median 14,547 ng/mL vs. 8340 ng/mL, p = 0.05) and 90 days (13,604 ng/mL vs. 7973, p = 0,013). Tables 1 and 2 show demographic and sPESI variables according 30 and 90-days mortality in patients with confirmed PE.

Considering logistic regression model including only sPESI, estimated OR for mortality at 30 days was 1.33 for a unit increase of sPESI score (wald statistic = 1.211 p value = 0.226) and estimated OR for mortality at 90 days model was 1.55 for a unit increase of sPESI score (wald statistics = 2.250, p value = 0.0245). Concerning the model predictive ability, AUCs (95 %CI) for mortality at 30 and 90 days were 0.582 (0.501–0.664) and 0.619 (0.572–0.667).

When the model included D-dimer in addition to sPESI, its estimated OR for mortality at 30 days was 1.037 for every 1000 ng/mL of increase in D-dimer concentration (Wald statistic = 1.612, p value = 0.107) and for mortality at 90 days 1.040 for every 1000 ng/mL of increase in D-dimer concentration (Wald statistic = 2.030, p value = 0.042).

When D-dimer was included into the logistic regression model considering also the interaction between D-dimer and sPESI), the AUC increased to 0.662 (95 % CI 0.516–0.809) and to 0.708 (95 % CI 0.599–0.818), for mortality at 30–90 days, respectively. Thus, when adding D-dimer to sPESI, the discriminant capacity to predict mortality within 30 and 90 days was increased by 0.080 and 0.089, respectively, against the model including only sPESI. The contribution of D-dimer to the discriminating ability was NRI = 0.286 (95 % CI −0.198 to 0.770, p value: 0.247) at 30 days and NRI = 0.605 (95 % CI 0.223–0.988, p value: 0.002) at 90 days. Figure 1 depicts the ROC curves for predicting mortality at 30 and 90 days obtained from the previously described logistic models.

The difference between the distributions of D-dimer in patients with sPESI = 0 and in patients with sPESI ≥1 was statistically significant (median 7065 ng/mL vs. median 10,058 ng/mL respectively, p = 0.023). Thus, two different optimal cut-offs values were computed separately for patients with sPESI = 0 and for those with sPESI ≥1 starting from a minimum value of sensitivity of 0.75. Figure 2 plots ROC curve of D-dimer values and survival within 30 (2a) and 90 days (2b), for elderly patients with PE with sPESI = 0 and sPESI ≥1. For patients with sPESI = 0, five patients died within 30 days with a corresponding cut-off value of 2026 ng/mL and eight patients died within 90 days with a corresponding cut-off value of 3548 ng/mL. For patients with sPESI ≥1, 13 patients died within 30 days with a corresponding cut-off value of 10,351 ng/mL and 22 patients died within 90 days with a corresponding cut-off value of 9520 ng/mL. Table 3 shows the ability of these D-dimer cut-off values to predict mortality at 30 and 90 days in elderly patients with sPESI = 0 and sPESI ≥1.

Discussion

As stated by recent guidelines, risk stratification remains a critical point to drive admission and treatment in hemodynamically stable patients with PE [10, 11]. Even though different studies showed an association between D-dimer concentration and mortality in general population [16], data on the potential of D-dimer for risk stratification in the elderly are lacking. Thus, this study explored the performance of D-dimer at diagnosis as a risk stratification tool in elderly patients with PE.

We found that D-dimer concentration at diagnosis was associated with 30 days and 3 months overall mortality in patients ≥65 years old with hemodynamically stable acute PE, with an statistically significant higher discriminant capacity than sPESI alone to predict mortality at 90 days. The optimal D-dimer thresholds we identified to discriminate low and high risk of mortality showed good Negative Predictive Values, but cut-offs markedly differed when

Table 1 Main characteristics of the patients with confirmed PE, according to mortality at 30 days

	All patients with PE	Patients alive at 30 days	Patients dead within 30 days	p value (alive vs dead)
n (%)	154 (100.0)	136 (88.3)	18 (11.7)	
Female n (%)	48 (31.1)	41 (30.2)	7 (38.9)	0.433
Age median (range)	79.1 (65–98)	79 (65–98)	79.76 (66–97)	0.557
D-dimer ng/mL median (range)	9477 (709–36,640)	8341 (709–36,640)	14,547 (1285–36,000)	0.05
sPESI variables				
Age ≥80 years, n (%)	73 (47.4)	64 (47.1)	9 (50.0)	1
Cancer, n (%)	23 (14.9)	19 (13.8)	4 (22.2)	0.478
Chronic cardiopulmonary disease, n (%)	10 (6.5)	9 (6.6)	1 (5.6)	1
Pulse ≥110 per min, n (%)	40 (25.8)	38 (27.9)	2 (11.1)	0.241
Systolic blood pressure <100 mmHg, n (%)	10 (6.5)	9 (6.6)	1 (5.6)	1
Arterial oxygen saturation <90 %, n (%)	40 (25.9)	31 (22.8)	9 (50.0)	0.021
sPESI Score median (range)	0 (1–4)	1 (0–4)	2 (0–4)	0.239
sPESI Score ≥1	111 (72.1)	98 (72.1)	13 (72.2)	1

Table 2 Main characteristics of the patients with confirmed PE, according to mortality at 90 days

	All patients with PE	Patients alive at 90 days	Patients dead within 90 days	p value (alive vs dead)
n (%)	154 (100.0)	124 (80.5)	30 (19.5)	
Female n (%)	48 (31.2)	35 (28.2)	13 (43.3)	0.126
Age median (range)	79.1 (65–98)	78.87 (65–99)	80.9 (66–97)	0.170
D-dimer ng/mL median (range)	9477 (709–36,640)	7973 (709–36,640)	13,604 (1285–36,000)	0.013
sPESI variables				
Age ≥80 years, n (%)	73 (47.4)	57 (45.9)	16 (53.3)	0.543
Cancer, n (%)	23 (14.9)	15 (12.1)	8 (26.7)	0.082
Chronic cardiopulmonary disease, n (%)	10 (6.5)	5 (4.0)	5 (16.7)	0.025
Pulse ≥110 per min, n (%)	40 (25.9)	36 (29.1)	4 (13.3)	0.103
Systolic blood pressure <100 mmHg, n (%)	10 (6.5)	7 (5.7)	3 (10)	0.410
Arterial oxygen saturation <90 %, n (%)	40 (25.9)	26 (20.9)	14 (46.7)	0.009
sPESI Score median (range)	0 (1–4)	1 (0–4)	2 (0–4)	0.035
sPESI Score ≥1	111 (72.1)	89 (71.8)	22 (73.3)	1

PE Pulmonary embolism, 95 %CI 95 % Confidence Interval, *sPESI* simplified Pulmonary Embolism Severity Index

considered patients at low and medium-high risk using sPESI score.

Some points are worthy of mention. First, elderly patients with PE presented mortality rates markedly higher than younger subjects. This finding is consistent with available data [5, 22]. Other authors' reported overall 90-days mortality were 9 % [23], 10.5 % [24], 20.8 % [5], depending upon the studied population age and comorbidities. For example, Maestre et al. using data from the RIETE registry, found a 90-days all-cause mortality of 5.6–27 % according the presence of absence of cancer [25].

Second, in elderly patients with PE D-dimer values were associated with 30 and 90-days all-cause mortality. Furthermore, when the model included D-dimer in addition to sPESI, its estimated OR for mortality at 30 and 90 days was 1.037 and 1.040 for every 1000 ng/mL of increase in D-dimer concentration (Wald statistic = 1.612, p value = 0.107 and 2.030, p value = 0.042, respectively). That is, D-dimer concentration increase significantly the ability of sPESI to predict mortality at 90 days. Grau et al. showed that a high D-dimer concentration was a predictive factor associated with overall and PE-related mortality, in a large general population cohort [24]. In another study Bova et al.

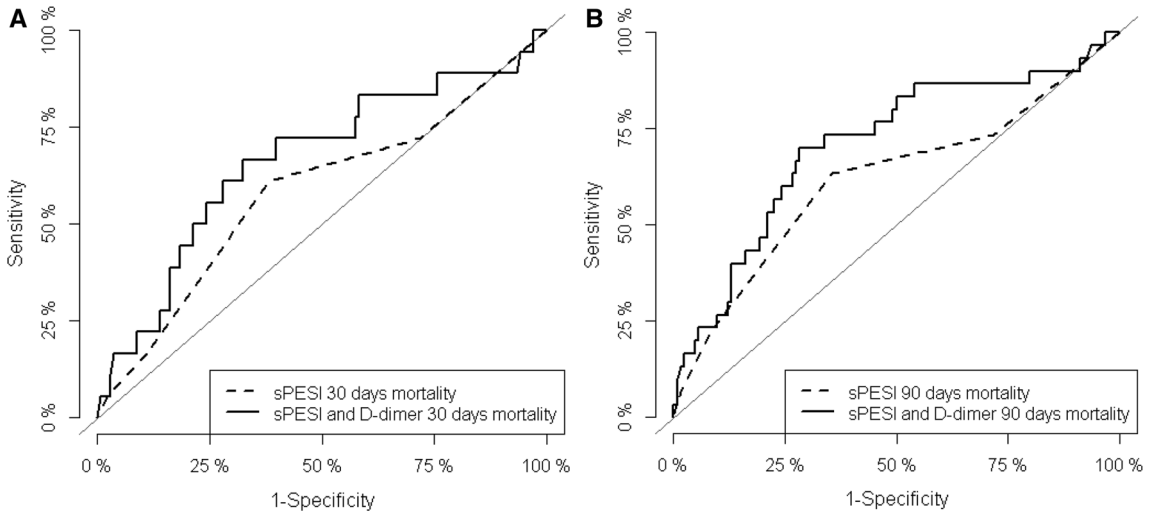

Fig. 1 ROC curve analysis of the ability of a model with sPESI score alone (*dashed lines*) and a model with sPESI score and D-dimer (*continuous lines*) to predict mortality within 30 days (*panel A*) and within 90 days (*panel B*) in elderly patients with PE *ROC* receiver operating characteristic, *sPESI* simplified Pulmonary Embolism Severity Index, *PE* Pulmonary Embolism

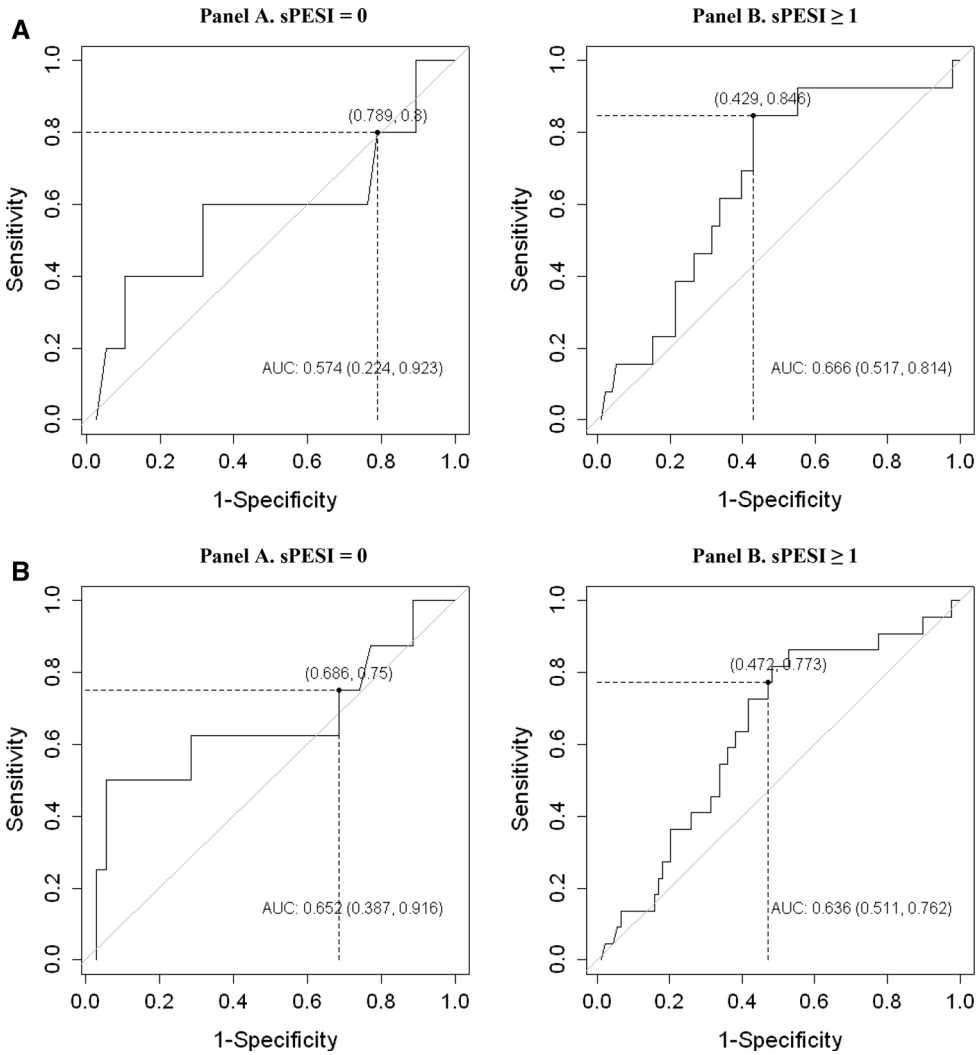

Fig. 2 **a** ROC curve plot of D-dimer values and survival at 30 days, for elderly patients with PE with sPESI = 0 (*panel A*) and sPESI $\geq$1 (Panel B) **b** ROC curve plot of D-dimer values and survival at 90 days, for elderly patients with PE with sPESI = 0 (*panel A*) and sPESI $\geq$ 1 (*panel B*) *ROC*: Receiver operating characteristic. *PE* Pulmonary Embolism, *sPESI*: simplified Pulmonary Embolism Severity Index, *AUC* area under the curve

Table 3 Performance of different D-dimer cut-off values to predict mortality at 30 and 90 days in elderly patients with sPESI = 0 and sPESI $\geq$ 1

	sPESI = 0 (n = 43)	sPESI $\geq$1 (n = 111)
30 days		
Cut-off mg/dL (bootstrap 95 % CI)	2026 (1399–19718)	10351 (8153–16778)
Sensitivity (95 % CI)	0.800 (95 % CI 0.284–0.995)	0.846 (95 % CI 0.546–0.981)
Specificity (95 % CI)	0.211 (95 % CI 0.096–0.373)	0.571 (95 % CI 0.467–0.671)
Positive predictive value (95 % CI)	0.118 (95 % CI 0.05–0.868)	0.208 (95 % CI 0.147–0.709)
Negative predictive value (95 % CI)	0.889 (95 % CI 0.442–0.947)	0.966 (95 % CI 0.859–0.977)
AUC	0.574 (95 % CI 0.224–0.923)	0.666 (95 % CI 0.517–0.814)
Partial AUC (Sensitivity >0.75)	0.032 (95 % CI 0.011–0.191)	0.091 (95 % CI 0.011–0.16)
90 days		
Cut-off (mg/dL (bootstrap 95 % CI)	3548 (1399–21715)	9520 (3463–13380)
Sensitivity (95 % CI)	0.750 (95 % CI 0.349–0.968)	0.773 (95 % CI 0.546–0.922)
Specificity (95 % CI)	0.314 (95 % CI 0.169–0.493)	0.528 (95 % CI 0.419–0.635)
Positive Predictive Value (95 % CI)	0.200 (95 % CI 0.100–0.717)	0.288 (95 % CI 0.207–0.584)
Negative Predictive Value (95 % CI)	0.846 (95 % CI 0.496–0.921)	0.904 (95 % CI 0.769–0.936)
AUC	0.652 (95 % CI 0.387–0.916)	0.636 (95 % CI 0.511–0.762)
Partial AUC (Sensitivity >0.75)	0.045 (95 % CI 0.007–0.157)	0.073 (95 % CI 0.019–0.135)

sPESI simplified Pulmonary Embolism Severity Index, *AUC* area under the curve

found that D-dimer associated with 3 month all-cause mortality [23]. However, these studies included general population, with a lower mean age, and results cannot be applicable to elderly subjects. To our knowledge, the present study represents the first observation on the prognostic ability of D-dimer in elderly and very elderly subjects.

Third, the value of D-dimer in clinical practice is likely to be very limited without a threshold that allows its use in individual patients. The optimal D-dimer thresholds we identify, by maximizing sensitivity to avoid false negative results, showed, with the limits of an small simple size, good Negative Predictive Values. Other study reported that a D-dimer cut-off of six fold the upper normal limit [23] associated to 3 months all-cause mortality on univariate analysis, Hazard Ratio: 4.7 (95 % CI 1.4–16.3), and in the previously mentioned study by Grau et al. a D-dimer values higher than 5000 ng/mL was associated with a 2.9-fold increased risk of overall mortality if compared with PE patients with D-dimer concentrations between 500 and 2499 ng/mL. In both cases cut-off values were chosen arbitrarily [23, 24]. The different distribution of the D-dimer we observed in PE patients with sPESI = 0 and sPESI $\geq$1 and the different prognostic implication of belonging to one or the other stratification group led us to determine two different cut-off of D-dimer, showing good Negative Predictive Values but markedly different thresholds between both groups. The difficult we found to identify a unique prognostic cut-off probably depends on the influence on D-dimer concentrations of other conditions like cancer, infections or aging.

Finally, in the present study D-dimer increased the discriminant capacity of sPESI score to predict 90-days mortality but, as mentioned, cut-offs markedly differed when considered patients at low and medium–high risk using sPESI score, thus reducing the utility of D-dimer in clinical practice if used as an stand alone prognostic biomarker. Therefore, adding D-dimer into risk models that include other variables seems to be an interesting research field, to better understand its prognostic utility. Supporting this kind of approach, in the PROTECT study Jimenez et al. validated a multimarker model to predict 30 days all cause mortality, hemodynamic collapse and/or recurrent PE [26], even though D-dimer was not assessed as risk factor of complicated course.

The main limitations of the present study are small sample size and retrospective design. Small simple size with wide 95 % CI and low number of events make it difficult to obtain robust estimates for the models. Therefore, we prudently propose these results as an explorative study. Further multicenter, prospective, larger cohort studies with age comparison are needed to confirm our findings and to determine D-dimer prognostic utility. By including all consecutive patients we tried to obtain a real world representative sample of elderly patients evaluated in the ED with confirmed PE. Even though the use of the same commercial assay to test D-dimer in our monocentric study guarantee an homogenous analysis of the results, other reagents should be tested.

In conclusion, D-dimer concentration at diagnosis was associated with 30 and 90-days overall mortality and showed an higher discriminant capacity than sPESI alone to predict mortality at 90 days in patients $\geq$65 years old with acute, hemodynamically stable PE. The optimal D-dimer thresholds we identified by maximizing sensitivity showed

good Negative Predictive Values, but cut-offs markedly differed when considered patients at low and medium–high risk using sPESI score. Adding D-dimer concentrations to sPESI score seems to improve its prognostic ability, supporting multivariable risk models as the best approach to estimate prognosis in elderly patients with PE.

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