



Original Contribution

Comorbidity burden conditions the prognostic performance of D-dimer in elderly patients with acute pulmonary embolism



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ABSTRACT

Introduction: The prognostic accuracy of D-dimer for risk assessment in acute Pulmonary Embolism (APE) patients may be hampered by comorbidities. We investigated the impact of comorbidity burden (CB) by using the Charlson Comorbidity Index (CCI), on the prognostic ability of D-dimer to predict 30 and 90-day mortality in hemodynamically stable elderly patients with APE.

Methods: All patients aged >65 years with normotensive APE, consecutively evaluated in the Emergency Department since 2010 through 2014 were included in this retrospective cohort study. Area under the curve (AUC) and ½ Net Reclassification Improvement (NRI) were calculated.

Results: Study population: 162 patients, median age: 79.2 years. The optimal cut-off value of CCI score for predicting mortality was ≤1 (Low CB) and >1 (High CB), AUC = 0.786.

Higher levels of D-dimer were associated with an increased risk death at 30 (HR = 1.039, 95%CI:1.000–1.080, p = 0.049) and 90 days (HR = 1.039, 95%CI:1.009–1.070, p = 0.012). When added to simplified Pulmonary Embolism Severity Index (sPESI) score, D-dimer increased significantly the AUC for predicting 30-day mortality in Low CB (AUC = 0.778, 95%CI:0.620–0.937, ½NRI = 0.535, p = 0.015), but not in High CB patients (AUC = 0.634, 95%CI:0.460–0.807, ½ NRI = 0.248, p = 0.294). Similarly, for 90-day mortality D-dimer increased significantly the AUC in Low CB (AUC = 0.786, 95%CI:0.643–0.929, ½NRI = 0.424, p-value = 0.025), but not in High CB patients (AUC = 0.659, 95%CI:0.541–0.778, ½NRI = 0.354, p-value = 0.165).

Conclusion: In elderly patients with normotensive APE, comorbidities condition the prognostic performance of D-dimer, which was found to be a better predictor of death in subjects with low CB. These results support multimarker strategies for risk assessment in this population.

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1. Introduction

Acute pulmonary embolism (APE) is a common cardiovascular emergency associated with increased morbidity and mortality rates [1]. Short-term mortality after APE depends on patient characteristics [1–3], with elderly having a higher incidence of APE and higher APE-related mortality than younger subjects [4,5].

Current guidelines recommend risk stratification of patients with APE and several clinical predictors tools have been proposed, including clinical decision rules like Pulmonary Embolism Severity Index (PESI) and its simplified version (sPESI), echocardiography and biomarkers [1,3,6,7].

D-dimer is measured as part of the diagnostic work-up of hemodynamically stable patients, with a low/intermediate clinical probability of APE [1,8]. The association between increased D-dimer levels and short term mortality after APE was shown in several studies and meta-analysis [9–13] and some authors have proposed using the test as a risk stratification marker in this clinical setting [9,12]. However, different limitations of the prognostic ability of D-dimer have been pointed out, especially in elderly populations [13].

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Comorbidities increase with age and may condition the prognosis [14,15]. A wide variety of diseases, such as cancer, infections, and inflammatory and vascular diseases can lead to an increase on D-dimer levels [1], acting as confounding variables which may condition D-dimer prognostic performance in APE patients. Thus, comorbidity burden may explain some of the limitations of D-dimer to predict mortality after APE.

The Charlson Comorbidity Index (CCI) is a summation score of the burden of comorbidities [17, 18] which has been shown to be a predictor of mortality in different conditions like sepsis, heart failure, prostate cancer and APE [14–18]. Few data are currently available on the relationship of comorbidity burden with D-dimer prognostic performance, in APE patients.

The objective of the present study was to investigate the impact of comorbidity assessment, by using the CCI score, on the prognostic ability of D-dimer to predict 30 and 90-day mortality in hemodynamically stable elderly patients with APE.

2. Materials and methods

A retrospective cohort study was designed, including all consecutive outpatients aged >65 years old evaluated in the Emergency Department (ED) of Vimercate Hospital since 2010 through 2014, with a hemodynamically stable APE, confirmed by pulmonary computed tomography angiography (CTA).

According to the standard praxis of the ED, in hemodynamically stable subjects a CTA scan was performed to exclude APE if suspected, based on an emergency physician's gestalt approach or evidence based algorithms, and D-dimer values were available for all patients (i.e. even patients with high clinical probability of APE). Variables to calculate sPESI score are available for all patients with PE and were extracted from the electronic medical charts. Helical computerized tomography scans were performed on a Brilliance Philips CT scanner (Philips, Cleveland, OH, USA) which included 64-detector row capability. Pulmonary embolism 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. CTA scans were read by hospital staff board-certified radiologists at the time of the acquisition of images. Patients with confirmed PE were treated according to international guidelines [1].

D-dimer was measured with particle enhanced immunoturbidimetric assay Innovance DDIMER on the Behring Coagulation System (BCS) analyzer (Siemens Medical Solutions Diagnostics, Deerfield, IL, USA; normal value declared by the producer: <490 ng/mL) [19].

The CCI score was used to measure comorbid status [17]. CCI is a summation score based on 17 medical conditions with varying assigned weights (non-age adjusted). A score of 1 is given whether 1 of the following conditions is present: myocardial infarction, cardiac failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, peptic ulcer disease, mild liver disease, and diabetes (without organ damage); a score of 2 is given for hemiplegia, moderate to severe renal disease, any tumor (within last 5 years), lymphoma, leukemia, and diabetes with organ damage; a score of 3 for moderate to severe liver disease; and a score of 6 for metastatic solid tumor and acquired immunodeficiency syndrome. A value of 0 indicates no comorbidity, while higher values represent an increasing burden of comorbid illnesses. 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 mm Hg; and (6) arterial oxyhemoglobin saturation < 90% measured at the time of APE 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 [8].

Vital status at the end of follow-up was recorded for all patients. Unique personal identifiers were checked for the follow-up concerning mortality using the regional demographic register.

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.

2.1. Statistical methods

Demographic and clinical variables were summarized in the whole sample by absolute numbers and percentages, for categorical variables, and by median value and range, for continuous variables. The correlation structure among variables was evaluated by the multivariate analysis of Principal Components. The pairwise correlation between variables was computed by Pearson linear correlation coefficient.

Median follow-up was evaluated by reverse Kaplan Meier method. Survival probability curves were estimated by Kaplan Meier method. The same method was used to estimate the mortality probability at 30 days, 90 days and corresponding 95% Confidence Intervals (CI). Univariate analysis for survival at 30 days, 90 days for the main demographic and clinical relevant variables was performed by Cox regression model [20]. The assumption of proportional hazard was tested according to the procedure proposed by Grambsch and Thernau [21]. Results are reported as hazard ratios (HR) with 95% CI. It is suggested that for reliable results of Cox regression model, the ratio of number of events to number of variables included in the model should be at least five [22]. Thus, when few events occur, only results obtained from univariate analysis can be provided.

A time-dependent ROC curve from censored survival data was computed to find the best cut-off of CCI for predicting 90-day mortality. Kaplan–Meier survival estimate at 90 days was used. Subsequently two analysis subgroups were considered: patients with a value of CCI less or equal to the best cut-off and patients with value of CCI greater than the best cut-off.

Hazard ratios obtained by the univariate Cox regression models including only D-dimer were provided. Given the asymmetric distribution of D-dimer, a logarithmic transformation (base 10) was considered.

Cox regression models were fitted on the two subgroups and the Harrel C indexes were computed [23] to evaluate the contribution of D-dimer alone and of D-dimer together with sPESI score to discriminate between people died and alive within 30 days or 90 days. Furthermore, to evaluate the synergism between D-dimer and sPESI in the Cox model the interaction term was included. Harrel C index was used because it corresponds to the area under the curve (AUC), the area under the ROC curve obtained from the Cox model predictor. The value of C index (AUC) obtained from data used for model estimating provides an optimistic measure of discriminant ability, thus values of C index (AUC) corrected for the optimism by bootstrap method were also reported [23].

Finally, the improvement in the discriminative ability of D-dimer score in addition to sPESI score was evaluated by Net Reclassification Improvement (NRI) for survival analysis. Results were reported as ½ NRI, being interpreted as an average improvement in classification [24]. Confidence interval and p-value of ½ NRI were obtained by bootstrap method.

3. Results

Study population was represented by 162 patients aged ≥65 years old with a confirmed diagnosis of hemodynamically stable APE consecutively evaluated in the ED of our hospital from 2010 through 2014 (out of 657 suspected cases, prevalence of confirmed APE: 24.7%). Fifty-two patients (32.1%) were female, the median age of the cohort was 79.2 years, and the median follow-up was 2.6 (IQR 1.67–3.6) years. Only 1 patient was lost to follow-up before 30 days, all other patients

Table 1
Baseline clinical characteristics of elderly patients with pulmonary embolism.

	All patients N = 162
Female n (%)	52 (32.1%)
Age median (range)	79.2 (65.5–98.5)
Age > 80 years, n (%)	78 (48.1%)
D-dimer, ng/mL median (range)	8427.5 (709–36,640)
Cancer, n (%)	26 (16%)
Chronic cardiopulmonary disease, n (%)	13 (8%)
Pulse ≥ 110 per minute, n (%)	42 (25.9%)
Systolic blood pressure < 100 mm Hg, n (%)	10 (6.2%)
Arterial oxygen saturation < 90%, n (%)	42 (25.9%)
sPESI Score median (range)	1 (0–4)
sPESI Score > 0, n (%)	120 (74.1%)
CCI score median (range)	1 (0–12)
CCI score > 0, n (%)	99 (61.1%)
CCI score > 1, n (%)	63 (38.9%)
CCI score > 2, n (%)	39 (24.1%)

sPESI: Simplified Pulmonary Embolism Severity Index. CCI: Charlson Comorbidity Index.

have complete follow-up till 90 days, corresponding to 99.3% of complete follow-up.

Within 30 days 19 deaths occurred, corresponding to an overall mortality rate of 11.7% (95% CI: 6.6–16.6) and within 90 days 32 deaths occurred, with an overall mortality rate of 19.8% (95% CI 13.4–25.7).

Baseline clinical characteristics of the study population are shown in Table 1.

Correlation among CCI and the other covariates was low (CCI and age $r = 0.05$, CCI and D-dimer $r = 0.04$, CCI and sPESI $r = 0.32$), sPESI was mainly correlated with D-dimer ($r = 0.45$) and the correlation between D-dimer and age was $r = 0.14$.

3.1. Univariate analysis

In univariate analysis there was no evidence of violation of proportional hazard. Univariate analysis showed that D-dimer, sPESI score, CCI score, know cancer, chronic cardiopulmonary disease, and an arterial oxygen saturation < 90%, were associated with a higher mortality. Table 2 shows univariate Cox regression analysis of the effect of different variables on mortality.

The HR for death at 30 and 90 days was statistically significant higher for each increase of 1000 ng/mL in D-dimer levels, and the HR of log10 increasing D-dimer was 3.057 (95%CI:0.952–9.814, $p = 0.060$) for mortality at 30 days and 3.151 (95%CI:1.286–7.725, $p = 0.012$) for mortality at 90 days, Table 2.

Table 2
Univariate Cox regression analysis of the effect of different variables on mortality at 30 and 90 days in elderly patients with pulmonary embolism.

	Mortality at 30 days		Mortality at 90 days	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value
Sex (female vs male)	1.271 (0.500–3.229)	0.614	1.746 (0.868–3.51)	0.118
Age (>80 vs ≤80 years)	1.223 (0.497–3.009)	0.662	1.41 (0.701–2.834)	0.335
D-dimer, for each increase of 1000 ng/mL	1.039 (1.000–1.080)	0.049	1.039 (1.009–1.070)	0.012
log10 D-dimer	3.057 (0.952–9.814)	0.060	3.151 (1.286–7.725)	0.012
Cancer (yes vs no)	2.520 (0.957–6.635)	0.061	2.724 (1.288–5.762)	0.009
Chronic cardiopulmonary disease (yes vs no)	4.875 (1.753–13.554)	0.002	4.255 (1.837–9.857)	0.001
Pulse (≥110 vs <110 per minute)	0.660 (0.228–1.910)	0.443	0.562 (0.238–1.328)	0.189
Systolic blood pressure (<100 vs ≥100 mm Hg)	0.881 (0.118–6.600)	0.902	1.608 (0.49–5.279)	0.434
Arterial oxygen saturation (< 90 vs ≥90%)	3.516 (1.428–8.656)	0.006	2.993 (1.494–5.998)	0.002
sPESI Score, for each increase of 1 point	1.592 (1.047–2.420)	0.030	1.626 (1.182–2.236)	0.003
CCI score, for each increase of 1 point	1.250 (1.098–1.424)	0.001	1.307 (1.19–1.435)	<0.001

sPESI: Simplified Pulmonary Embolism Severity Index. CCI: Charlson Comorbidity Index.

3.2. CCI score: optimal cut-off value for predicting mortality

The optimal cut-off value of CCI score for predicting mortality was ≤1 (low comorbidity burden) and >1 (high comorbidity burden), with Sensitivity = 0.725, Specificity = 0.694 and AUC = 0.786, Fig. 1.

Mortality after APE was higher in patients with high comorbidity burden (mortality within 30 days was 8% and 18% in patients with CCI ≤ 1 and CCI > 1; and mortality within 90 days was 9% and 37%, respectively). The difference between Kaplan Meier's survival curves for low (CCI < 1) and high (CCI > 1) comorbidity burden patients was statistically significant only for mortality at 90 days. HR was 2.197, 95% CI: 0.883–5.462, p -value = 0.090 for mortality at 30 days and HR = 4.484, 95%CI: 2.072–9.702, p -value < 0.001 for mortality at 90 days, Fig. 2.

Difference between median values of D-dimer in patients with low (CCI ≤ 1) and high (CCI > 1) comorbidity burden was not statistically significant (9757 ng/mL and 8153 ng/mL, respectively, p -value Wilcoxon test: 0.409). Patients with CCI ≤ 1 have lower values of sPESI score (p -value of Fisher exact test is <0.001), and the percentage of female was greater in patients with CCI > 1 (p -value of Fisher exact test: 0.025). This and other demographic and clinical characteristics, according to low (CCI ≤ 1) and high (CCI > 1) comorbidity burden, are shown in Table 3.

3.3. Performance of D-dimer to predict 30-day mortality

For mortality at 30 days, the HR of D-dimer (considered as the log10 increasing values) was 6.16 (95%CI: 0.76–49.72, p -value = 0.088) for patients with low comorbidity burden (CCI ≤ 1), and 2.15 (95%CI: 0.55–8.45, p -value = 0.272) for patients with high comorbidity burden (CCI > 1).

In a Cox regression model including only sPESI AUCs were 0.651 (95%CI: 0.452–0.849) and 0.572 (95% CI: 0.401–0.744) for patients with low and high comorbidity burden. When the model included only D-dimer AUCs were 0.705 (95%CI: 0.528–0.882) and 0.605 (95% CI: 0.427–0.784), respectively.

When both D-dimer and sPESI were included into the model (considering also the interaction between D-dimer and sPESI), the AUC increased in patients with low comorbidity burden (0.778, 95%CI: 0.62–0.937, value corrected for optimism: 0.707) with a ½NRI = 0.535 (95%CI: 0.108–0.697, p -value = 0.015), whereas the increment in the AUC in patients with high comorbidity burden was smaller, with a ½ NRI not statistically significant (AUC = 0.634, 95%CI: 0.46–0.807, value corrected for optimism: 0.520; ½NRI = 0.248, 95%CI: –0.202–0.572, p -value = 0.294). Fig. 3A shows HRs for different levels of D-dimer among low (CCI ≤ 1) and high (CCI > 1) comorbidity burden patients, for mortality at 30 days.

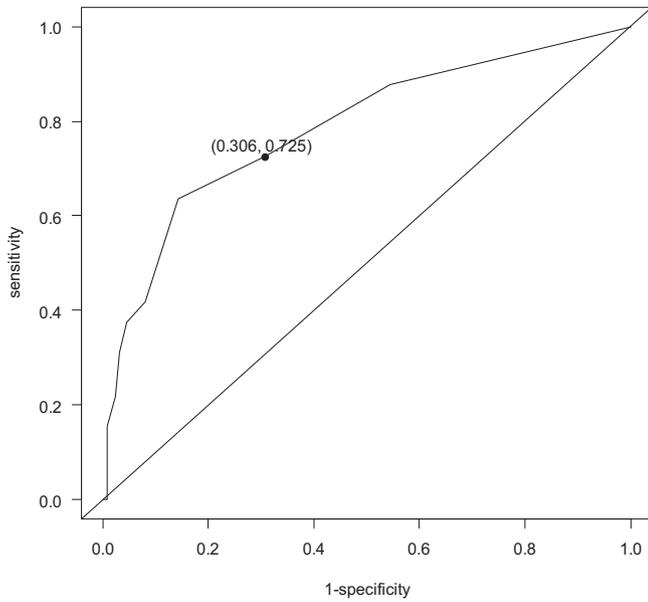


Fig. 1. ROC curve to estimate the optimal cut-off value of CCI score for predicting mortality at 90 days. CCI: Charlson Comorbidity.

3.4. Performance of D-dimer to predict 90-day mortality

For mortality at 90 days, HR of D-dimer (considered as the log10 increasing values) was 7.74 (95%CI: 1.01–59.35, p-value = 0.049) for patients with low comorbidity burden (CCI ≤ 1), and 2.68 (95%CI: 1.04–6.91, p-value = 0.042) for patients with high comorbidity burden (CCI > 1).

AUCs were 0.639 (95%CI: 0.461–0.818) and 0.551 (95%CI: 0.432–0.669) for patients with low and high comorbidity burden, respectively, when the model included only sPESI alone, and 0.723 (95%CI: 0.561–0.885) and 0.633 (95%CI: 0.512–0.754) when the model included only D-dimer.

When both D-dimer and sPESI and the interaction between these variables were included into the model, the AUC increased in patients with low comorbidity burden (0.786, 95%CI: 0.643–0.929, value corrected by optimism: 0.716) with a ½NRI = 0.424 (95%CI:

0.119–0.69, p-value = 0.025), whereas the increment in AUC in patients with high comorbidity burden was smaller and the corresponding ½NRI was not statistically significant (AUC = 0.659, 95%CI: 0.541–0.778, value corrected by optimism: 0.608, ½NRI = 0.354, 95%CI: –0.136–0.602, p-value = 0.165), Fig. 3B.

4. Discussion

In the present study we investigated the impact of comorbidity assessment on the prognostic ability of D-dimer to predict mortality in hemodynamically stable elderly patients with APE.

We found that, together with sPESI and CCI scores, higher values of D-dimer were associated with an increased HR for death at 30 and 90 days. HRs of D-dimer for predicting mortality were higher for patients with low comorbidity burden, and D-dimer increased significantly the ability of sPESI for predicting 30 and 90-day mortality in patients with low comorbidity burden, but not in patients with high comorbidity burden. That is, in elderly patients with hemodynamically stable APE, comorbidities condition the prognostic performance of D-dimer, which, when added to sPESI, appears to be a better predictor of death in subjects with low comorbidity burden when compared with high comorbidity burden patients.

Risk stratification remains a critical point in the management of patients with normotensive APE and a potential role of D-dimer in risk assessment has been proposed. To our best knowledge this is the first study assessing specifically the impact of the comorbidity burden on the ability of D-dimer to predict mortality in elderly patients with acute normotensive APE, and some comments are worth mentioning.

D-dimer is often measured as part of the diagnostic workup of patients with low clinical probability of APE. Therefore, it would be interesting to also use this marker for risk stratification. However, mixed study results regarding the prognostic ability of D-dimer have been pointed out [12,13,25]. Comorbidities may influence D-dimer levels, explaining, at least in part, the limited performance of D-dimer. In our study, the HR of D-dimer for 30-day mortality was 6.16 for patients with low comorbidity burden (CCI ≤ 1), and 2.15 for patients with high comorbidity burden (CCI > 1). For 90-day mortality, figures were 7.74 and 2.68, respectively. Although only HRs for 90-day mortality were statistically significant (probably due to the limited number of deaths within 30 days), these data seem to support the suggestion that D-dimer weakly associates with mortality in patients with

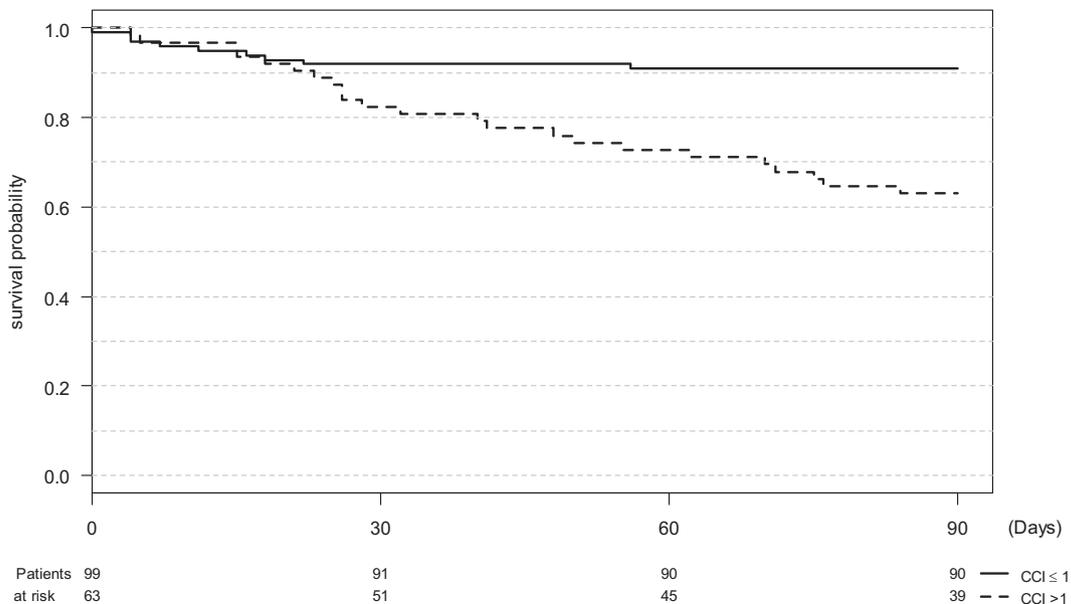


Fig. 2. Kaplan Meier 90 days survival curves for low (CCI ≤ 1) and high (CCI > 1) comorbidity burden patients. CCI: Charlson Comorbidity.

Table 3

Demographic and clinical characteristics of elderly patients with pulmonary embolism, according to low (CCI ≤ 1) and high (CCI > 1) comorbidity burden.

	Patients with low comorbidity burden (CCI ≤ 1) N = 99	Patients with high comorbidity burden (CCI > 1) N = 63	p-Value*
Female n (%)	25 (25.3%)	27 (42.9%)	0.025
Age median (range)	78.8 (65.5–98.5)	81.2 (66.4–93.2)	0.193
D-dimer, ng/mL median (range)	9757 (709–36,640)	8153 (755–35,854)	0.409
sPESI Score = 0, n (%)	32 (33.0%)	10 (16.1%)	<0.001
sPESI Score = 1, n (%)	41 (42.3%)	12 (19.4%)	
sPESI Score = 2, n (%)	20 (20.6%)	25 (40.3%)	
sPESI Score = 3, n (%)	4 (4.1%)	11 (17.7%)	
sPESI Score = 4, n (%)	0 (0%)	4 (6.5%)	

CCI: Charlson Comorbidity Index. sPESI: Simplified Pulmonary Embolism Severity Index.

* p-Value of Fisher exact test for Sex and sPESI score. p-Value of Wilcoxon test for age and D-dimer value.

comorbidities, because of the confounding effect of increased levels of D-dimer due to other conditions different than APE. Instead, in patients with low comorbidity burden, D-dimer association with mortality is stronger.

The finding that D-dimer increased significantly the ability of sPESI (one of the most used validated prognostic assessment tools) for predicting 30 and 90-day mortality only in patients with low comorbidity burden, further supports the hypothesis that D-dimer presents a better ability to predict death in these subjects.

Only a few published studies assessed the discriminatory power of CCI for predicting outcomes following APE [26,27]. Klok et al., in a study aimed to investigate whether high D-dimer levels and centrally located clots in the pulmonary artery directly increase mortality in patients with APE, found that active malignancy, COPD, older age and developing APE while being inpatient were significantly related to death after APE. However, not data on the prognostic performance of D-dimer in patients with and without comorbidities were presented [28]. In another clinical setting, after a first episode of unprovoked VTE in patients enrolled in the PROLONG study, D-dimer levels in combination with comorbidity assessment have not been confirmed as risk factors for recurrence [29].

Our data confirm the ability to predict short term mortality of sPESI, a score validated in general population [7], even in elderly patients. Moreover, in the present study, also the CCI score predicted 30 and 90-day mortality. Although publications on the prognostic utility of CCI in subjects with APE are scarce [26,27], these data confirm the

importance of comorbidity as a prognostic factor even in these patients. The optimal cut-off value of CCI score for predicting mortality we found was 1, with an AUC = 0.786 for identify low (CCI ≤ 1) and high (CCI > 1) comorbidity burden. We estimated that cut-off by plotting a ROC curve using censored survival data. In other studies the considered cut-off was 0 and ≥1, but authors acknowledged the this threshold was determined arbitrarily [26,27]. Moreover, from the Principal Component Analysis it emerged that the multivariate correlation structure is mainly characterized by d-dimer, sPESI and CCI, with a small contribution of age.

Even considering the limitations of this retrospective small-sized study, our study show that comorbidity burden may influence the prognostic performance of a proposed tool for risk stratification of patients with APE (D-dimer), thus providing new evidence to the current debate on the approach to risk assessment in this clinical setting. These results highlight the limits of a single test strategy, and support the use of multimarker models, as proposed by some authors [30].

Main limitations of the present study are, as mentioned, small simple size and retrospective cohort design. Moreover, we did not perform an external validation of the best cut-off of CCI for predicting mortality. Therefore, further larger and prospective studies are required to confirm our findings. On the other hand, our study population may be proposed as representative of real world elderly patients consecutively evaluated in the ED with a confirmed diagnosis of APE.

Another limitation may lie in the potential collinearity between CCI and PESI score, since some items (e.g. chronic cardiac and pulmonary disease) are present in both scores. However, apart from the more

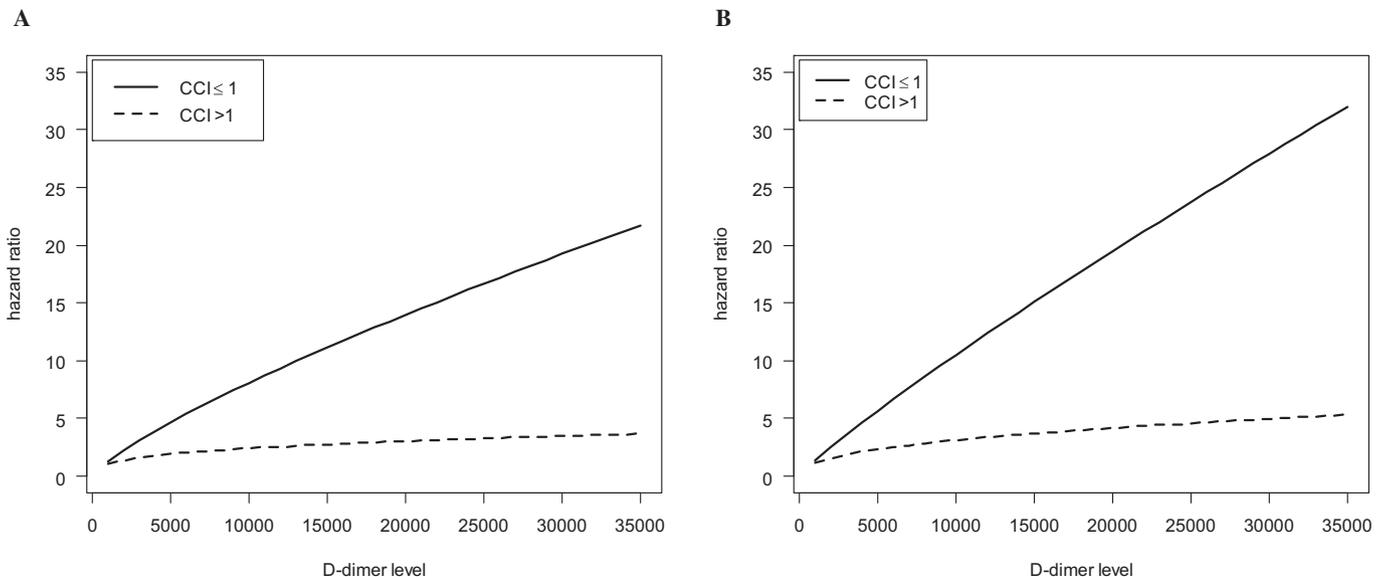


Fig. 3. Hazard ratio for mortality at 30 days (A) and 90 days (B) for different levels of D-dimer (ng/mL), in patients with low (CCI < 1) and high (CCI > 1) comorbidity burden. CCI: Charlson Comorbidity Index. Reference value for hazard ratio: D-dimer = 709 ng/mL, corresponding to the lower observed value in this study.

substantial relationship between sPESI and D dimer we observed, no other strong correlation between CCI and the remaining covariates was found, probably due to the reduced sample size and, for D dimer and age, to the role of thrombotic burden that influences its values much more than age [12].

5. Conclusions

In hemodynamically stable elderly patients with APE, higher values of D-dimer, sPESI score and CCI score were associated with an increased HR for death at 30 and 90 days. The optimal cut-off value of CCI score for predicting mortality was ≤ 1 (low comorbidity burden) and >1 (high comorbidity burden). HRs of D-dimer for predicting mortality were higher for patients with low comorbidity burden, and D-dimer increased significantly the ability of sPESI for predicting 30 and 90-day mortality in patients with low comorbidity burden, but not in patients with high comorbidity burden.

In elderly patients with hemodynamically stable APE, comorbidities condition significantly the prognostic performance of D-dimer, which was found to be a better predictor of death in subjects with low comorbidity burden than among those with high comorbidity burden. These results support the use of multimarker instead of single test strategies to approach the risk assessment in this clinical setting.

Contribution of authors to the article

All authors, namely HPF, VP, AO, AC, VC, CC, FP, MPF, VP, DT, LCO, CG, GV, CC, PB, certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, and revision of the manuscript.

All authors have read and approved the submission of the manuscript. The manuscript has not been published and is not being considered for publication elsewhere, in whole or in part, in any language.

Conflict of interest

None to declare.

Writing assistance

None to declare.

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