Acute pulmonary embolism in acutely ill COVID-19 patients admitted to internal medicine wards.

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Research Article

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Abstract

INTRODUCTION. Emerging evidence linking COVID-19 to an increased risk of acute pulmonary embolism (APE). The aim of the present study was to assess the prevalence of APE in acutely ill COVID-19 patients admitted to internal medicine department wards and to investigate the association of clinical and biochemical variables with a confirmed diagnosis of APE.

METHODS. All consecutive patients admitted to the internal medicine department wards of a general hospital with a diagnosis of severe COVID-19, who performed a Computer Tomography Pulmonary Angiography(CTPA) for respiratory deterioration in April 2020, were included.

RESULTS. Study populations: 41 subjects, median(IRQ) age: 71.7(63-76) years, CPTA confirmed APE=8(19.51%,CI95%:8.82%-34.87%). Among patients with and without APE, no significant differences were found with regards symptoms, comorbidities, treatment, Wells score and outcomes. The optimal cut-off value of D-dimer for predicting APE was 2454 ng/mL, sensitivity(CI95%):63(24-91), specificity:73(54-87), Positive Predictive Value:36(13-65), Negative Predictive Value: 89(71-98) and AUC:0.62(0.38-0.85). The standard and age-adjusted D-dimer cut-offs, and the Wells score $\geq$ 2 did not associate with confirmed APE, albeit a cut-off value of D-dimer=2454 ng/mL showed an RR:3.21;CI95%:0.92-13.97;p = 0.073.

CONCLUSION. In acutely ill COVID-19 patients admitted to internal medicine department wards who performed CTPA for respiratory deterioration, the prevalence of APE was high, and the traditional diagnostic tools to identify high APE pre-test probability patients did not show to be clinically useful. These results support the use of a lower threshold of suspicion to perform CTPA for excluding or confirming APE as the most appropriate approach in this clinical setting.

Introduction

Coronavirus disease (COVID-19) is an illness caused by severe acute respiratory syndrome coronavirus – *2* (SARS-CoV-2). The first cases of COVID-19 were reported in the city of Wuhan, China, in December 2019, and in the following weeks the infection spread across China and in other countries, leading to the declaration of pandemic by the World Health Organization [1-2].

The clinical presentation of COVID-19 can be very varied, and encompasses asymptomatic infection, mild illness affecting the upper respiratory tract, and severe pneumonia, which may cause life-threatening respiratory failure [3]. The severity of COVID-19 cases has been classified as mild, moderate, severe, and critical [1,4].

Emerging evidence suggest that COVID-19 can be complicated by acute pulmonary embolism (APE) [5-7]. Moreover, D-dimer values have been linked to a higher risk of death in patients with COVID-19 [5], and

some data suggests that heparin prophylaxis may be associated with better prognosis in COVID-19 patients with severe disease or with markedly elevated D-dimer [8].

Although data from different studies indicate that the incidence of venous thromboembolism (VTE) in COVID- 19 patients is higher than that seen in similarly ill hospitalized non COVID-19 subjects, the exact prevalence of APE in COVID-19 patients is not known, and the diagnostic value of D-dimer in subjects with acute SARS-CoV-2 infection is not clear [5]. In effect, the increase in mortality associated with elevated D-dimer values in these patients may reflect an increased rate of APE, but it also could be a manifestation of disseminated intravascular coagulation or simply a higher level of systemic inflammation [9]. Therefore, data on the value of D-dimer and other clinical and biochemical markers for the diagnosis of VTE in subjects hospitalized for COVID-19 may improve the diagnostic and therapeutic approach to this disease. In addition, most of the few published studies evaluating thrombotic complications of COVID-19 included intensive care unit (ICU) critical ill patients [8,10-15], and less is known on acutely ill severe – not critical – subjects admitted to internal medicine department general wards.

The present study aimed to assess the prevalence of APE in acutely ill - not critical - patients hospitalized for COVID-19 in internal medicine department wards, as well as to investigate the association of D-dimer and other clinical and biochemical variables with a confirmed diagnosis of APE in these subjects.

Materials And Methods

The study was conducted at the Vimercate Hospital, a 500 bed General Hospital located in Lombardy, northern Italy. From February to May 2020, 712 patients with a confirmed diagnosis of COVID-19 were hospitalized in our institution.

All acutely ill patients admitted to the internal medicine department (sub intensive and acute general beds of the internal medicine department wards) with severe COVID-19 who had CTPA examinations performed from April 1st to April 31st for respiratory deterioration after admission, defined by a reduction of $\geq$ 30% of the PaO2/FiO2 ratio, were included in this retrospective cohort study. Exclusion criteria: subjects with a story of bleeding diathesis and/or current use of anticoagulant therapy before hospitalization; age < 18, and critical COVID19 infection, defined by any of the following criteria a. respiratory failure needing mechanical assistance, b. shock c. “extra pulmonary” organ failure needing intensive care unit. Electronic charts of all included patients were retrieved for evaluation. Trained study personnel retrospectively recorded relevant clinical, laboratory and treatment data. The diagnosis of COVID-19 was confirmed by RNA detection of the SARS-CoV-2. According to previously published criteria, COVID-19 was defined as severe whether presenting at least one of following items: respiratory rate ≥30 breaths /min; Arterial oxygen saturation≤93% at rest; PaO2/FiO2 ratio $\leq$ 300mmHg (1mmHg=0.133kPa) [1,4].

Data of the following laboratory test performed upon admission have been collected: D-dimer, international normalized ratio (INR), c-reactive protein (CRP), white blood cell count (WBCC), lactate dehydrogenase (LDH), alanine transaminase (ALT), aspartate transaminase (ALT), Creatinine (Cr), arterial partial pressure of carbon dioxide (PaCO2), arterial oxygen partial pressure (PaO2), fraction of inspired oxygen (FiO2). Albumin, Interleukin 6, and Antithrombin III were measured within 24 hours of performing CTPA. D-dimer was measured by using HemosIL D-Dimer HS, a latex- enhanced turbidimetric immunoassay from Instrumentation Laboratory, on the fully automated coagulometer ACL TOP analyzer [16]. The normal value declared by the producer is less than 243 ng/mL [16].

Based on a retrospective chart review of clinical symptoms and patient history factors Wells score simplified version was calculated for each patient giving one point for the presence of each of the following items: (1) Previous PE or DVT; (2) Heart rate ≥100 b.p.m.; (3) Surgery or immobilization within the past four weeks; (4) Haemoptysis; (5) Active cancer (6); Clinical signs of DVT ; (7) Alternative diagnosis less likely than PE. Patients with < 2 point were categorized as PE unlikely and those with ≥ 2 points PE likely [1,17]. Since CTPA was performed in subjects suspected by presenting APE in addition to COVID-19 as causing respiratory deterioration, the last item of Wells score (alternative diagnosis less likely than PE) was considered present (1 point) in all cases.

Pulmonary embolism was confirmed on the basis of the presence of a filling defect in one or more pulmonary arteries up to sub-segmental arteries in CTPA, as stated by certified radiologists belonging to the hospital team, at the time of the acquisition of images. Helical CTPA scans were performed on a Brilliance Philips CT scanner (Philips, Cleveland, OH, USA) which included 64-detector row capability.

This study was conducted in accordance with the amended Declaration of Helsinki. The protocol was approved by to the Local institutional review board, i.e. the Comitato Etico della Provincia Monza e Brianza. Waiver of written informed consent was granted due to the retrospective, observational design.

Statistical methods

Clinical characteristics and laboratory data were summarized by number and percentage for categorical variables and by median and interquartile range for numerical variables, in the whole study group and according to APE. To compare the different characteristics among patients with APE confirmed and APE excluded, Fisher exact test was used for categorical variables and Wilcoxon rank rum test was used for numerical variables.

To evaluate the diagnostic accuracy of D-dimer to predict APE, a ROC curve was fitted and the Area Under the ROC Curve (AUC) with pertinent 95% confidence interval (CI95%) was estimated. Optimal cut-off was obtained as the D-dimer value which maximizes both the specificity and the sensitivity. The diagnostic performance of different D- dimer cut-offs (standard cut-off: > 243 ng/mL, age adjusted cut off: patients' age x 5, ROC curve best discriminating value: 2454 ng/mL) and Wells score (standard cut off: >2) was evaluated by computing the corresponding values of sensitivity and specificity, positive predictive value,

negative predictive value with pertinent CI95%. Furthermore, four generalized linear regression models with binomial error and link log were fitted: the response was APE and the explanatory variable was a dichotomous variable discriminating patients with D-dimer value over the different cut offs or Wells score over 2. Results were reported as Relative Risk (RR) with corresponding CI95% and p-values.

All analyses were performed using R software version 4.0.0, with packages OptimalCutpoints, pROC and epiR added.

Results

From the 1st to 30th April 2020, 41 acutely ill patients admitted to internal medicine department wards underwent a CTPA because respiratory deterioration after admission, and represent the study population. The median (IRQ) age of the cohort was 71.7 (63-76) years, 30 (73%) were females, the median days (IRQ) since onset of symptoms to hospitalization was 8 (4-12) and the median days (IRQ) since onset of symptoms to CTPA was 11 (7-17). By the end of May 2020 in-hospital mortality of the cohort was 4.88%, with 2 patients still hospitalized and 90% already discharged. Clinical characteristics, treatment and outcomes of the study population are shown in Table 1.

The most frequent symptoms were fever (98%), dyspnea (73%) and cough (63%), and more than 70% of subjects were hypertensive (29 cases). Most patients have been treated empirically with hydroxychloroquine (95%) and steroids (80%), more than 70% with full anticoagulant doses of heparin before performing CTPA, and 61% with continuous positive airway pressure.

Eight out of 41 patients (19.51%, CI95%: 8.82% - 34.87%) presented a confirmed APE after performing CTPA. Except for a trend to a higher prevalence of chest pain among subjects with APE, (37% vs. 9%, p = 0.077), no statistically significant differences in patients with and without APE were found, with regards symptoms, comorbidities, treatment, Wells score and outcomes, Table 1. Among patients with confirmed APE a higher median value of white blood cell count (12. 4 vs 8.4 *10^9/L, p = 0.007), and a trend for a lower value of alanine aminotransferase were found. The results of laboratory test in patients with APE confirmed and excluded are shown in Table 2.

The median values of D-dimer in patients with APE confirmed and excluded were 3236 and 1056 ug/mL, p = 0.316. The discriminant ability of D-dimer upon admission to identify confirmed vs. non confirmed APE showed an Area Under ROC Curve (AUC) of 0.62 (CI95%: 0.38 - 0.85), Figure 1. The optimal cut-off obtained by the ROC curve was 2454 ng/mL, with values of sensitivity: 63% (CI95%: 24-91%), specificity: 73% (CI95%: 54-87%), Positive Predictive Value: 36% (CI95%: 13-65%), Negative Predictive Value: 89% (CI95%: 71-98%). The standard D-dimer cut-off (243 ng/mL) showed, for a confirmed diagnosis of APE, values of sensitivity (CI95%): 88% (47-99%), specificity: 12% (3-28%), Positive Predictive Value: 1 % (8-36%), and Predictive Negative Value: 80% (28-99%). Figures for the age-adjusted D- dimer cut-off (patients' age x 5) and Wells score $\geq$ 2 (likely) were 88% (47-99%), 18% (7-35%), 21% (9-38%), 86% (42-99%), and 13% (0.3-53%), 85% (68-95%), 17% (0.42-64%), and 80% (63-92%), respectively. The RRs of the

optimal D- dimer cut-off (2454 ng/mL) for confirmed APE was 3.31, p-value=0.073, whereas the standard and age adjusted D- dimer cut-offs and Wells score presented RRs (CI95%) of 0.97 (0.23-16.22, p = 0.977; 1.44 (0.32-24.77, p = 0.711) and 0.83 (0.05-3.67, p = 0.851), respectively, Table 3.

Discussion

Although emerging data suggest that acutely ill patients with COVID-19 have an increased risk for APE, the actual prevalence of APE in this clinical setting is not well known. Most information on the thrombotic complications of COVID-19 derives from studies including critical ill patients admitted to ICUs [8,10-15], and data on severe – not critical – acutely ill subjects are lacking.

In the present study we found that among acutely ill patients admitted to internal medicine department wards with a diagnosis of severe – not critical – COVID-19, in whom a CTPA was performed because of respiratory deterioration after admission, near 20% presented a confirmed APE. The best discriminating cut-off value of D-dimer for predicting APE was approximately 10 fold the standard threshold (2454 ng/mL), showing a trend to be associated with confirmed APE, albeit not statistically significant (RR: 3.21; CI95%: 0.92-13.97; p = 0.073). The values of D-dimer, when the standard and the age adjusted cut-offs were applied, the simplified Wells score, and other laboratory test did not appear to be clinically useful to identify patients with confirmed APE.

Our study aimed to investigate the prevalence of APE specifically performed in acutely ill patients with severe COVID-19 admitted to internal medicine department wards, and some points are worth discussing.

Firstly, the prevalence of APE we found in this clinical setting was markedly high, and similar to the figures found in critical ICU patients. This finding is even more noticeable when considering that most patients were receiving heparin at anticoagulant doses. As mentioned, most data on prevalence of APE and thrombotic events in general, are from COVID-19 ICU critical patients [8,10-15]. COVID- 19 patients admitted to the ICUs of 3 Dutch hospitals, Klok and colleagues found a cumulative incidence of the composite thromboembolic outcome of 31% (CI95%: 20-41%) with APE representing 81% of all these thrombotic complication (n = 25) [10]. The rate of thromboembolic complications, mainly APE, was higher (11.7%) in COVID-19 patients referred to ICU from a French hospital, than that observed in a historical control group of non-COVID-19 ARDS patients (2.1%) [14]. Among patients with severe COVID-19 infection examined with CTPA in another study [15], 23% [CI95%, 15-33%] presented APE and were more likely to require mechanical ventilation than those without APE. These figures are much higher than the rates of APE observed in non COVID-19 ICU patients with sepsis or shock receiving guideline-recommended thromboprophylaxis [18,19]. In one of the very few studies which describing thromboembolic events in non ICU COVID-19 patients, Mestre-Gomez et al found that 29 out of 91 subjects (31.9%) who underwent CTPA presented APE, after admission to the internal medicine department [20]. Our results confirm the finding of a high incidence of APE in internal medicine department non-critical COVID-19 patients.

Second, the tools currently used in non COVID-19 patients to estimate the pre-test probability of APE as part of the diagnostic workup (Wells score and standard or age adjusted D-dimer values) seem not to be useful for predicting APE in COVID-19 patients. This was also true for other laboratory test, such as arterial blood gas analysis, interleukin- 6, antithrombin III, AST, ALT, LDH, and serum creatinine. Our results suggest that a very high D-dimer cut-off (approximately 10 fold the standard threshold) may be associated to confirmed APE. A recent study reported that a D- dimer threshold of 2660 µg/L detected all subject with APE among hospitalized COVID-19 patients [21], and in the formerly mentioned study by Mestre-Gomez et al., the best cut-off point was 5000 ug/dL [20]. These cut-off values are much higher than those used to exclude pulmonary embolus in non-ICU patients [22-23]. Even though a diagnostic strategy for APE suspicion based on a single variable (D-dimer) showed evident limitations and guidelines recommend multivariable predicting algorithms [22], the diagnostic value of a sharp increase of D-dimer as marker of increased risk of APE in COVID-19 patients remains to be establish. Some authors have proposed using age-adjusted D-dimer cut-off levels to rule out venous thromboembolism in COVID-19 patients [24]. Yet, in our study the so adjusted threshold did not show to be clinically useful.

Third, in our study most acutely ill patients admitted to the internal medicine department wards with a diagnosis of COVID-19 and presenting respiratory deterioration after admission, were under treatment with full anticoagulant doses of heparin before performing CTAP. The fact that these patients have certainly been considered at a very high risk of having APE [25] probably lead physicians to prescribe full anticoagulation instead of prophylaxis with heparin. Interestingly, also in the study by Klok et al [10] it was described as heparin regimes differed between hospitals and the doses increased over time, presumably reflecting an increasing concern on the risk of developing APE in COVID-19 patients. However, empirical use of anticoagulant doses of heparin may not only be ineffective but deleterious since it has been well established that high-dose LMWH administration may be associated with increased incidence of major and fatal bleeding [26]. In fact, pending the results of randomized clinical trials, in patients without a confirmed diagnosis of APE, most authors recommend thromboprophylaxis with LMWH for non-ICU COVID-19 patients [5,27].

Finally, in COVID-19 patients, given the high prevalence of APE, the unavailability of satisfactory tools for estimating pretest probability and the potential high risk of complications associated with the use of empirical anticoagulation, a low threshold for obtaining CTPA should be strongly recommended. Main contraindications for CTPA are an impaired renal function and hemodynamic instability to undergo the test. Our results show that these conditions are relatively rare among non-ICU COVID-19 patients.

The main limitations of our study are retrospective and monocentric design and small sample size, with large CI95% limiting the precision of estimates and the generalizability of results. Yet, we included all consecutive subjects fulfilling the inclusion criteria, to reduce selection bias. Thus, our study population would represent a real world sample severe COVID-19 patients admitted to internal medicine department wards in whom a CTPA was performed due to respiratory deterioration. Nevertheless, to confirm our findings, larger and multicenter studies are needed.

Conclusions

Among acutely ill patients admitted to internal medicine department wards with a diagnosis of severe COVID- 19, in whom a CTPA was performed because of respiratory deterioration after admission, the prevalence of confirmed APE was high (20%) and similar to the figures found in critical ICU patients.

Some validated tools used in the APE diagnostic workup of non COVID-19 patients, such as D-dimer (standard and age-adjusted cutoffs) and Wells score, along with other commonly used laboratory test, did not show to be clinically useful to identify high pre-test probability patients.

Most subjects have been treated empirically with full anticoagulant doses of heparin before performing CTPA, even though in many cases CTPA did not confirmed the diagnosis of APE.

While awaiting additional evidence and the development of new diagnostic and therapeutic algorithms, our results support the use of a lower threshold of APE suspicion to perform CTPA for excluding or confirming APE, as the most appropriate approach in this clinical setting.

Declarations

Conflict of interest/funding disclosure/authorship

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All authors approve the final version to be published.

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Tables

TABLE 1. Clinical characteristics of the study population, treatment during hospitalization and outcomes.

Characteristics	Total (n=41)	APE confirmed (n=8)	APE excluded (n=33)	p value (APE confirmed vs excluded)
Age, median (IQR)	71.7 (63 - 76.2)	67 (57.3 - 74.4)	72.1 (63.1 - 76.2)	0.459
Female, n (%)	30 (73.17%)	6 (75%)	24 (72.73%)	1.000
Time since onset of symptoms to hospitalization, median days (IQR)	8 (4 - 12)	8.5 (3.5 - 14.8)	8 (4 - 12)	0.830
Time since hospitalization to CTPA, median days (IQR)	11 (7 - 17)	11 (1.2 - 13.5)	11 (8 - 17)	0.680
Symptoms				
Fever, n (%)	40 (97.56%)	8 (100%)	32 (96.97%)	1.000
Cough, n (%)	26 (63.41%)	5 (62.5%)	21 (63.64%)	1.000
Dyspnea, n (%)	30 (73.17%)	4 (50%)	26 (78.79%)	0.178
Chest pain, n (%)	6 (14.63%)	3 (37.5%)	3 (9.09%)	0.077
Diarrhea , n (%)	13 (31.71%)	2 (25%)	11 (33.33%)	1.000
Comorbidities				
Hypertension, n (%)	29 (70.73%)	4 (50%)	25 (75.76%)	0.202
Diabetes, n (%)	11 (26.83%)	2 (25%)	9 (27.27%)	1.000
Chronic heart diseases, n (%)	9 (21.95%)	1 (12.5%)	8 (24.24%)	0.659
Active Cancer, n (%)	3 (7.32%)	0 (0%)	3 (9.09%)	1.000
Smoking, n (%)	0 (0%)	0 (0%)	0 (0%)	1.000
CCI, median (IQR)	1 (0 - 1)	0 (0 - 1)	1 (0 - 2)	0.173
Treatment				
Heparin at prophylactic dose before performing CTPA, n (%)	4 (9.76%)	0 (0%)	4 (12.12%)	0.569
Heparin at anticoagulant dose before performing CTPA, n (%)	29 (70.73%)	5 (62.5%)	24 (72.73%)	0.672
Hydroxychloroquine, n (%)	39 (95.12%)	8 (100%)	31 (93.94%)	1.000
Any antiviral therapy, n (%)	12 (29.27%)	3 (37.5%)	9 (27.27%)	0.672
Steroids, n (%)	33 (80.49%)	7 (87.5%)	26 (78.79%)	1.000
CPAP, n (%)	25 (60.98%)	5 (62.5%)	20 (60.61%)	1.000
Wells score within 48 hours before CTPA, median (IQR)	2 (2 - 2)	2 (1.8 - 2)	2 (2 - 2)	0.681
Outcome				
Discharged, n (%)	37 (90.24%)	7 (87.5%)	30 (90.91%)	1.000
Still hospitalized, n (%)	2 (4.88%)	1 (12.5%)	1 (3.03%)	1.000
In-hospital mortality, n (%)	2 (4.88%)	0 (0%)	2 (6.06%)	1.000

TABLE 2. Laboratory data in patients with APE confirmed and excluded.

	Normal Range Missing Data (n)	All patients (n=41)	APE confirmed (n=8)	APE excluded (n=33)	p value (APE confirmed vs excluded)
D-dimer (ug/mL), median (IQR)	0 - 243 ug/mL (0)	1488 (446 - 4211)	3236 (1943 - 4735)	1056 (446 - 2634)	0.316
INR, median (IQR)	0.8 - 1.2 (9)	1.2 (1.1 - 1.3)	1.2 (1.1 - 1.2)	1.2 (1.1 - 1.3)	0.749
Albumin (g/dL), median (IQR)	3.7 - 5.3 g/dL (10)	3.0 (2.9 - 3.3)	2.7 (2.4 - 3.1)	3.1 (3 - 3.3)	0.284
CRP (mg/dL), median (IQR)	0.0 - 8.0 mg/dL (0)	51 (18 - 140)	67 (40.2 - 157.8)	50 (16 - 135)	0.439
WBCC ($*10^9$/L) , median (IQR)	4.0 - 11.0 $*10^9$/L (0)	9.1 (7 - 12.2)	12.4 (10.4 - 13.4)	8.4 (6.4 - 10.5)	0.007
LDH (U/L), median (IQR)	135 - 225 U/L (1)	332 (251.8 - 419.2)	330 (249.2 - 340.8)	354.5 (251.8 - 441.8)	0.437
ALT (U/L), median (IQR)	5 - 43 U/L (1)	41 (27.8 - 53.2)	34.5 (23 - 39)	44.5 (28.8 - 55)	0.058
AST (U/L), median (IQR)	3 - 45 U/L (0)	43.5 (30.8 - 70)	44 (28 - 58.2)	43.5 (30.8 - 73.2)	0.488
Cr (µmol/L), median (IQR)	0.6 - 1.2 µmol/ (0)	0.9 (0.8 - 1)	0.9 (0.8 - 1.1)	0.8 (0.8 - 1)	0.383
Interleukin 6 (pg/mL), median (IQR)	< 7 pg/mL (15)	11.9 (7.8 - 38.7)	20.8 (10.6 - 37.8)	11.6 (7 - 35.9)	0.287
Antithrombin III, median (IQR)	80 - 120 (19)	100.5 (90.2 - 114.2)	89 (88 - 103)	102 (95 - 115)	0.456
PaCO2 (mmHg), median (IQR)	32 – 45 mmHg (0)	37 (34 - 42)	42 (38 - 43.2)	36 (34 - 39)	0.171
PaO2 (mmHg, median (IQR))	83 – 108 mmHg (0)	95 (71 - 143)	129 (65.2 - 146.2)	91 (71 - 139)	0.934
PaO2/FiO2 ratio, median (IQR)	> 350 (0)	123 (93 - 186)	161 (127.8 - 195.8)	117 (93 - 174)	0.633

APE: acute pulmonary embolism; IQR: interquartile range; INR: international normalized ratio; CRP:c-reacted protein; WBCC:white blood cell count; LDH: lactate dehydrogenase; ALT: alanine aminotransferase; AST:aspartate transaminase; Cr: Creatinine; PaCO2: arterial partial pressure of carbon dioxide; PaO2:arterial oxygen partial pressure; FiO2: fraction of inspired oxygen.

Table 3. Diagnostic performance of different D-dimer cut-offs and Wells score for the diagnosis of APE.

	N of cases (%) with values higher than the cut-off	RR (CI95%) for the confirmed diagnosis of APE	P value
D-dimer (standard cut-off:243 ng/mL)	36 (87.8%)	0.97 (0.23 - 16.22)	0.977
D-dimer (Age adjusted: patients' age x 5)	34 (82.93%)	1.44 (0.32 - 24.77)	0.711
D-dimer (cut-off: ROC CURVE best discriminating value: 2454 ng/mL)	14 (34.15%)	3.21 (0.92 - 13.97)	0.073
Wells score (> 2: likely)	6 (14.63%)	0.83 (0.05 - 3.67)	0.851

APE: acute pulmonary embolism; RR: relative risk;CI95%: 95% confidence interval.

Figures

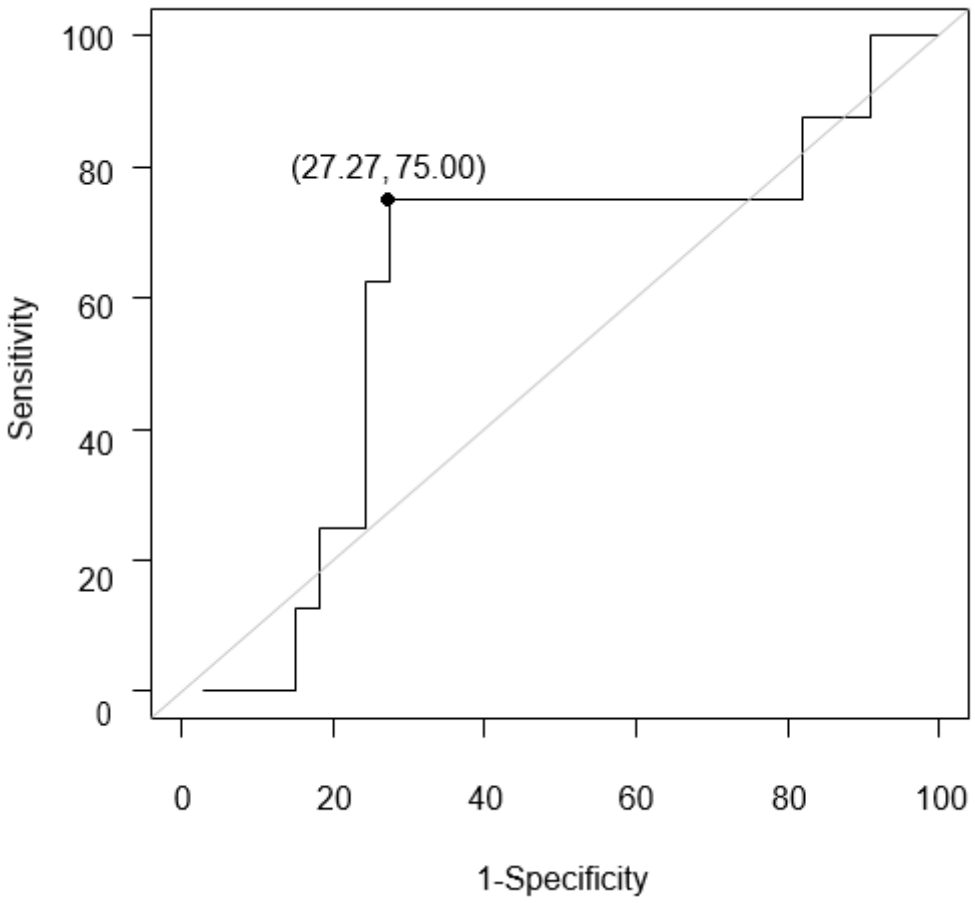

Figure 1

ROC curve to estimate the optimal cut-off value of D-dimer for predicting APE. APE: acute pulmonary embolism.