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Epidemiology and diagnosis of pulmonary embolism in lung cancer patients: is there a role for age adjusted D-dimers cutoff?

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Abstract
Our knowledge about the incidence of pulmonary embolism (PE) and the performance of age adjusted D-dimers (Dd) cutoff amongst patients with lung cancer (LC) and suspected PE, remains limited. We retrospectively analyzed all clinically suspected patients who underwent computed tomography pulmonary angiography (CTPA) in a tertiary hospital during a 19 month period. Cancer diagnosis was established using ICD10 code. Eligible for Dd analysis were those tested up to 24 h prior to the scan. We analyzed 2549 patients (54.6% males, median age 68.8 years, IQR 57–78), 15.8% had active LC and 5.4% other cancers (oC), while 70% were scanned in the Emergency Department (ED) and the rest during hospitalization. Overall incidence of PE was 16%. LC, but not oC, increased significantly the risk for PE (OR 1.58, 95% CI 1.21–2.06). LC patients were less likely to have bilateral (aOR 0.16, 95% CI 0.07–0.4) or central PE (aOR 0.2, 95% CI 0.09–0.48). Amongst those diagnosed with PE in the ED, LC increased all-cause inhospital mortality (aOR 6.7, 95% CI 2.64–16.95). When age adjusted instead of conventional Dd cutoff was used for ruling out PE in the ED, specificity for LC patients increased (10.16% vs 3.91%) without false negative tests (negative likelihood ratio—NLR = 0). A higher cutoff of 1.13 mg/l raised specificity to 28.9%, with only one case missed (sensitivity: 97.4%, NLR: 0.09, 95% CI 0.01–0.64). LC increases the risk for PE and adversely affects prognosis. Age adjusted and probably an even higher, "LC adjusted" Dd cutoff, could increase the specificity of the test without compromising its sensitivity.

Keywords D-dimers · Lung cancer · Pulmonary embolism · Diagnosis

Highlights

- Incidence of pulmonary embolism (PE), short term prognosis and the performance of age-adjusted D-dimers (Dd) cutoff in lung cancer (LC) patients with suspected PE remain poorly investigated.
- We retrospectively evaluated patients with suspected PE who underwent diagnostic imaging with computed tomography pulmonary angiography (CTPA), emphasizing on those with concomitant LC.
- Incidence of PE was significantly higher in LC patients and it seems to adversely affect their short term prognosis, compared to patients without malignancies.
- Age adjusted Dd cutoff doubled the number of LC patients who could have avoided imaging.
- A higher Dd cutoff could probably safely increase test's specificity in patients with LC.
- Dd cutoff adjustment for cancer type could possibly improve test's performance. Further studies are required.

Introduction

Cancer is often complicated with venous thromboembolic events (VTE), including the most severe manifestation of pulmonary embolism (PE) [1, 2]. Lung cancer (LC) is amongst malignancies with increased risk for VTE [3–5], while VTE have been associated with compromised survival amongst cancer patients [5–8]. Despite recent progress in cancer-associated thrombosis, still little is known about

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the cancer type-specific incidence of PE and the short term prognosis of patients with concurrent malignancy and PE [6, 9].

Additionally, recent concerns about over-imaging patients with clinically suspected PE [10], led to the development of a new strategy which combines clinical probability assessment and an age-adjusted D-dimers (Dd) cutoff [11], in order to achieve better triage of patients who should undergo diagnostic computed tomography pulmonary angiography (CTPA). Although this strategy has been validated in general population [11], data for patients with active malignancies are limited [12]. Furthermore, cancer patients are no more considered as an homogenous group. Given that these patients have often a baseline Dd elevation, probably depending on tumour type and stage [13, 14], several studies underline the urgent need to establish a different cutoff for cancer patients with clinical suspicion of PE, presumably type- and stage-adjusted, in order to improve the diagnostic yield and minimize the unnecessary imaging studies [12].

Primary purpose of this retrospective study is to provide evidence about the performance of the age-adjusted and a "LC adjusted" Dd cutoff for ruling out PE in patients with LC and clinically suspected PE. Moreover we include data about incidence, embolus location and short term prognosis of these patients compared to those with and without other malignancies.

Materials and methods

Study population and data collection

We retrospectively analyzed all adult patients with clinical suspicion of PE who underwent diagnostic imaging with CTPA from September 01, 2017 to March 31, 2019 in a large tertiary hospital—which serves as a referral center for patients presenting with acute respiratory symptoms with or without cancer and for patients with chronic respiratory diseases including lung malignancies. For all patients electronic records were reviewed and the following data (if available) were collected: age, sex, hospitalization outcome (death/survival), diagnoses (using the 10th revision of the International Statistical Classification of Diseases and Related Health Problems—ICD10 coding), date and result of both imaging and Dd measurement. Exclusion criteria were: evidence of old PE, inconclusive scans due to poor imaging quality, unavailable age and multiple (≥ 2) primary cancer sites.

Imaging and Dd testing

Imaging diagnosis of PE was established by a CTPA scan, performed in a 64-slice CT scanner (Philips Ingenuity Core 64) according to the dedicated protocol, using 80–100 ml of iodinated intravenous contrast agent (350 mg/ml). CT images were assessed by experienced chest radiologists, specifically addressing the presence of contrast filling defects within the pulmonary arterial tree down to a sub-segmental level. Those with positive scans, were further categorized according to the most proximal site of occlusion as having central PE (main trunk, left/right main pulmonary arteries and lobar branches) or peripheral PE (segmental and subsegmental branches). Unilateral or bilateral embolus location was also recorded.

Plasma Dd were measured by quantitative latex photometric immunoassay (STA Compact Hemostasis System, Stago), using the cutoff of 0.5 mg/l according to the manufacturer. Age-adjusted Dd cutoff was defined as Dd = age*0.01 mg/l, for those ≥ 50 years old [11].

Study design

Patients were initially classified into those who performed diagnostic imaging in the ED (ED group) and those who underwent scanning while being inhospital (INH group). Each group was further divided in three subgroups, according to the corresponding ICD10 diagnosis. The non-cancer (nC) group consisted of patients without a cancer-related code, the lung cancer (LC) group involved exclusively patients with lung cancer (irrespectively of the histological type and stage) and last, the other cancers (oC) group included those with active malignancy, either solid (except LC) or hematologic. We evaluated incidence and location of PE, all cause inhospital mortality, positive and negative predictive values of various Dd cutoffs, for different subgroups. Eligible for Dd analysis, were only those tested up to 24 h prior to CTPA.

Statistical analysis

All quantitative variables were checked for normality according to the Kolmogorov–Smirnov normality test. Data were summarized as median (interquartile range-IQR: Q1–Q3) for non-parametric numeric variables and as frequencies (percentages) for categorical variables. The Chi Squared (χ^2) test was used to assess differences between qualitative data. Comparisons between dichotomous variables and non-normal continuous data were performed using Mann–Whitney U-test. The impact of qualitative and quantitative data on dichotomous variables was assessed using binary multiple logistic regression. Variables with a P value < 0.15 at the univariate analysis were considered for the multivariate model. Results were expressed in terms of odds ratio (OR) and adjusted OR (aOR) with their 95% confidence interval (95% CI). P value < 0.05 was considered to be statistically significant.

Performance of different Dd thresholds for ruling out PE was assessed by calculating sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and negative likelihood ratio (NLR) with the corresponding 95% CI. To identify a better cutoff for the ED-LC subgroup a receiver operating characteristic (ROC) curve was constructed and the threshold was selected according to the equation NLR = 1 − sensitivity/specificity, for a sensitivity around 97%.

Regarding Dd performance in ruling out PE in ED-LC patients, internal validation of our findings was performed by estimating the 95% CI of the NLR using the bias-corrected and accelerated (BCa) bootstrapping method, according to Marill et al. [15].

Analyses were performed using IBM Statistical Package for the Social Science (SPSS; version 21), MedCalc statistical software (MedCalc Software bvba, Ostend, Belgium). and R (version 3.6.1), for Windows.

Results

2610 patients were initially identified. Sixty-one did not meet the inclusion criteria and were excluded, leaving 2549 patients eligible for analysis (Fig. 1). Their median age was 68.8 years old (IQR: 57–78) and 54.6% were males. The ED group consisted of 1778 (69.75%) individuals, 53.8% were males, while active LC was present in 16.3% of them. Compared to the INH group (771 individuals, 14.9% with active LC), these patients were younger (P < 0.001) and had lower levels of plasma Dd (P = 0.03). The overall incidence of PE was 16% (15.9% for ED and 16.2% for INH groups, P = NS). Compared to ED-nC, ED-LC and ED-oC subgroups had significantly higher levels of plasma Dd (P < 0.001) (Table 1).

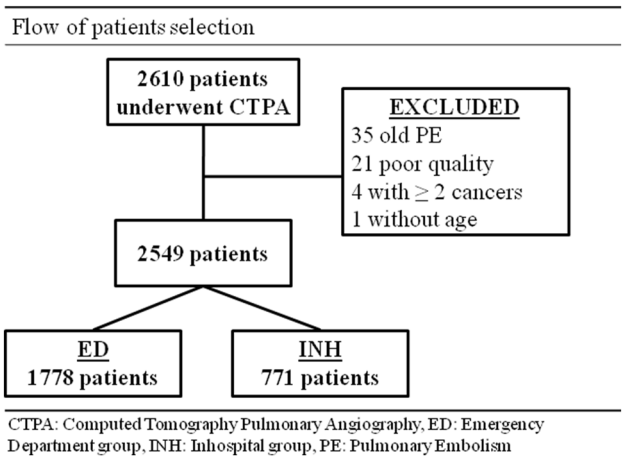

Fig. 1 Flow of patients selection

Association between incidence/location of PE and active cancer

Amongst all patients tested, incidence of PE was 14.8 in nC, 21.5% in LC and 17.5% in oC subgroup. Active cancer (LC and oC) was associated with increased number of positive scans compared to nC (OR 1.49, 95% CI 1.17–1.9 for all). This relationship was stronger for those with active LC (OR 1.58, 95% CI 1.21–2.06; 1.45, 95% CI 1.05 1.99 for all and ED group respectively). On the other hand, for patients with oC this association was not statistically significant (OR 1.22, 95% CI 0.77 1.93; 0.97, 95% CI 0.54–1.75 for all and ED group respectively).

Amongst all patients with PE (N = 408), central and bilateral embolism was present in 47.5% and 43.9%, respectively. In univariate analysis, a strong correlation between plasma Dd and central/bilateral PE was documented (P < 0.001 for both). Younger age and male sex were associated with unilateral (P = 0.01 for both) and peripheral (P = 0.07 and P = 0.12, respectively) embolism. After adjusting for age, sex and Dd; LC was found to decrease the probability for both central (aOR 0.2, 95% CI 0.09–0.48) and bilateral PE (aOR 0.16, 95% CI 0.07–0.4). Data for patients with other malignancies were inconclusive.

All cause in hospital mortality

For patients who were diagnosed with PE in the ED (N = 283), all cause inhospital mortality was 4.3% for nC and 22% for LC subgroup (P < 0.001). Neither central/bilateral embolus location nor plasma Dd levels were significantly associated with mortality (P = NS). After adjusting for age, LC patients had nearly 6.5 times greater probability for death compared to nC (aOR 6.7, 95% CI 2.64–16.95). Amongst INH group patients diagnosed with PE, LC was also associated with increased mortality (aOR: 6.06, 95% CI 2.18–16.8).

Dd for ruling out and in PE

Efficacy of Dd in ruling out PE, using conventional (0.5 mg/l) and age-adjusted cutoff, was assessed for ED group. For ED-nC subgroup, the age-adjusted cutoff almost doubled the number of patients who could have avoided imaging (from 69 to 133) and missed only one patient who had PE despite having plasma Dd below the adjusted cutoff. (NLR: 0.12, 95% CI 0.04–0.37 for age-adjusted and 0.15, 95% CI 0.04–0.62 for conventional cutoff).

For ED-LC and ED-oC subgroups NLR was 0 for both cutoffs, but when age-adjusted cutoff was used true negative tests increased from 5 to 13 and from 1 to 2 respectively. Given that ED-LC patients had significantly higher levels of plasma Dd compared to ED-nC (P < 0.001) a ROC curve

Table 1 Patients characteristics

	ED	Hospitalized	All
N	1778	771	2549
Age (IQR)[a]	67 (54–77)	71 (61–80)*	68.8 (57–78)
Male sex%	53.8%	56.5%	54.6%
Non cancer (%)	1394 (78.4)	614 (79.6)	2008 (78.8)
Lung cancer (%)	289 (16.3)	115 (14.9)	4.4 (15.8)
Other cancer (%)	95 (5.3)	42 (5.5)	137 (5.4)
PE (%)	283 (15.9)	125 (16.2)	408 (16)
D-dimers (IQR)[a]	1.83 (0.88–3.51)	2.14 (1.14–3.61)*	1.85 (0.92–3.51)
ED subgroups patients characteristics			
	Non cancer	Lung cancer	Other cancers
N	1394	289	95
Male sex%	50.7	72.3**	43.2
Age (IQR)[a]	67 (51–78)	68 (61–72.5)	70 (61–79)
D-dimers (IQR)[a]	1.68 (0.82–3.23)	2.7** (1.22–6.94)	2.42** (1.72–6.15)
PE (%)	210 (15.1)	59* (20.4)	14 (14.7)
Central (%)	113 (53.8)	22* (37.3)	9 (64.3)
Bilateral (%)	113 (53.8)	15** (25.4)	6 (42.9)

IQR interquartile range, *PE* pulmonary embolism, *ED* emergency department

*P < 0.05 between groups (for ED subgroups non cancers represent the reference group)

**P < 0.001 between groups (for ED subgroups non cancers represent the reference group)

[a]Results are given as median (IQR)

was constructed to identify which value could ameliorate the specificity of the test while keeping the sensitivity around 97%. In fact, for plasma Dd = 1.13 mg/l, 37 tests were correctly classified as true negative and only 1 as false negative, resulting in NLR:0.09 (95% CI 0.01–0.64) (Table 2). Findings regarding ED-LC subgroup were internally validated by calculating the 95% CI for the NLR, using a BCa bootstraping method (protocol repeating 10.000 samples 50 times). The corresponding 95% CI were 0–0.882 and 0–0.346, for the age-adjusted and the 1.13 mg/l cutoffs respectively.

For INH group patients with active cancer who underwent CTPA and had a Dd test (n = 30), specificity of classic and age adjusted cutoff was 0.

ED-nC subgroup patients who had a plasma Dd value in the upper quartile (i.e. ≥ 3.23 mg/l) had an OR 4.74 (95% CI 3.34–6.72) for a positive scan. Respectively the OR for

Table 2 Performance of different D-dimers cutoffs for ruling out PE amongst ED subgroups

	Non cancer (N = 1040)		Lung cancer (N = 166)			Other cancer (N = 53)	
	Conventional	AA	Conventional	AA	New cutoff (1.13)	Conventional	AA
Sensitivity (%) (95% CI)	98.78 (95.7–99.9)	98.17 (94.8–99.6)	100 (90.8–100)	100 (90.8–100)	97.4 (86.2–99.9)	100 (59–100)	100 (59–100)
Specificity (%) (95% CI)	7.88 (6.2–9.9)	15.18 (12.9–17.7)	3.91 (1.3–8.8)	10.16 (5.5–16.7)	28.9 (21.2–37.6)	2.17 (0.1–11.5)	43.5 (0.5–15)
PPV (%) (95% CI)	16.72 (16.4–17.1)	17.81 (17.3–18.3)	23.60 (23–24.2)	24.84 (23.8–25.9)	28.91 (26.5–31.5)	13.46 (13–14)	13.73 (13–14.5)
NPV (%) (95% CI)	97.18 (89.5–99.3)	97.79 (93.5–99.3)	100	100	97.37 (84–99.6)	100	100
NLR (%) (95% CI)	0.15 (0.04–0.6)	0.12 (0.04–0.37)	0	0	0.09 (0.01–0.6)	0	0

PE pulmonary embolism, *ED* Emergency Department, Conventional: 0.5 mg/l, *AA* age-adjusted cutoff, *PPV* positive predictive value, *NPV* negative predictive value, *NLR* negative likelihood ratio

ED-LC patients with Dd ≥ 6.94 mg/l was 4.82 (95% CI 2.2–10.6).

Discussion

This retrospective study was conducted in a large tertiary hospital, which serves as a referral center for patients suffering acutely from respiratory complaints with or without cancer and for patients with chronic respiratory diseases including lung malignancies. Therefore, it provides data from a large population residing in the metropolitan area of Athens. Findings confirm that lung cancer consists a major risk factor for PE, increasing almost by 50% the probability for a positive scan in clinically suspected patients, either they are tested in the ED or while they are already hospitalized. However, we were not able to demonstrate that other malignancies (except LC) increase this risk to a statistically significant level, something that can be explained by the relatively small sample size of this group. Another plausible explanation could be the underrepresentation of high thrombogenic risk cancers in the oC group, like gastrointestinal solid tumors (23.4%), while almost 30% of these patients had either breast or prostate cancer, which carry the lowest risk for VTE according to various researchers [3–5, 16].

Furthermore, our results confirm the established [17] correlation between plasma Dd and embolus location. Unexpectedly, LC patients, despite having higher levels of Dd were in lower risk for central/bilateral embolism. The clinical significance of this observation, in line with the literature [18], may be uncertain, since no association was demonstrated between central/bilateral PE and inhospital mortality. The latter was determined to be highly dependent on cancer status. Active LC adversely affected the short term prognosis of patients diagnosed with PE in the ED, increasing almost 5 times all cause inhospital mortality compared to nC (from 4.3 to 22%). Although the mortality rates for nC is similar to that previously mentioned in the literature [19, 20], the counterpart for patients with LC seems to largely differ existing reports. In a prospective Italian study exploring inhospital mortality of patients with PE and cancer, Casazza et al. reported that those with active malignancy (treated as an homogenous group) had only 2.2 times higher probability of inhospital death [9]. Even though the lower bound of our 95% CI remains greater than 2.2, our results should be interpreted under the limitation of the small sample size which resulted in a wide 95% CI.

The most interesting finding, in our opinion, was the performance of Dd in ruling out PE amongst patients with active malignancy in the ED. Although application of age-adjustment has significantly improved the utility of the test, especially for elderly [11], little is known about its efficiency in those with cancer. Thus, only limited data support that conventional [20] and age-adjusted cutoff [12] offer reliable NPV and NLR for ruling out PE in cancer patients, but at the cost of an extremely low specificity. Limitation of these studies was that cancer patients were analyzed as a uniform group. According to our data, conventional cutoff safely excluded PE in 5/166 (3%) of ED-LC and in 1/53 (1.9%) of ED-oC patients. After age-adjustment these numbers increased to 13/166 (7.8%) and 2/53 (3.8%). When a higher cut off (1.13 mg/dl) was used, we observed that the number of ED-LC patients who could safely avoid imaging increased to 37/166 (22.3%) at the expense of losing one with negative test and positive scan. On the other hand, only extremely high Dd values can significantly increase the probability for a positive CTPA. Our analysis focused in the ED group since the number of INH patients with Dd test prior to imaging was relatively small. This probably reflects the limited performance of Dd testing in hospitalized patients, as mentioned by Miron et al. [21].

This study has also some limitations. First of all, the retrospective nature of this work renderd the accurate data collection about patients pretest clinical probability difficult. Thus, we should take under consideration the possibility that patients with high clinical probability underwent Dd measurement in contrast to current guidelines, which recommend urgent imaging [22]. Moreover, given that elevated Dd correlate with advanced cancer stages [23, 24] a potential over representation of patients with stage III/IV disease could have influenced our results since data about lung cancer histological type and stage were not collected.

Conclusions

In conclusion, this study provides clear evidence that LC is strongly associated with higher incidence of PE and adversely affects the short-term prognosis of those diagnosed with PE. Furthermore this is the first study, to our knowledge, to examine the performance of age-adjusted Dd cutoff exclusively in patients with LC. Our observations confer promising messages that age-adjusted and possibly an even higher—"LC adjusted"—cutoff could safely ameliorate test's performance, limiting the number of unnecessary scans in this population. Finally, we believe that these findings raise the question of whether Dd cutoffs adjusted to cancer type, and probably stage, could improve the diagnostic approach to patients with active malignancy and low or intermediate clinical probability of PE. Further studies are required to address the abovementioned questions.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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