Original Article

Incidence of Pleural Effusion in Patients with Pulmonary Embolism

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Abstract

Background: No data on the incidence of pleural effusion (PE) in Chinese patients with pulmonary embolism are available to date. The aim of the current study was to investigate the frequency of PE in a Chinese population of patients with pulmonary embolism.
Methods: This was a retrospective observational single-center study. All data of computed tomography pulmonary angiography (CTPA) performed over 6-year period on adult patients with clinically suspected pulmonary embolism were analyzed.
Results: From January 2008 until December 2013, PE was identified in 423 of 3141 patients (13.5%) with clinically suspected pulmonary embolism who underwent CTPA. The incidence of PE in patients with pulmonary embolism (19.9%) was significantly higher than in those without embolism (9.4%) ($P < 0.001$). Majority of PEs in pulmonary embolism patients were small to moderate and were unilateral. The locations of emboli and the numbers of arteries involved, CT pulmonary obstruction index, and parenchymal abnormalities at CT were not associated with the development of PE.
Conclusions: PEs are present in about one fifth of a Chinese population of patients with pulmonary embolism, which are usually small, unilateral, and unsuitable for diagnostic thoracentesis.

Key words: Computed Tomography Pulmonary Angiography; Pleural Effusion; Pulmonary Embolism

Introduction

Pulmonary embolism is a common and potentially lethal disorder that frequently recurs and is associated with long-term impairment and suffering. The overall mortality rate of patients with untreated pulmonary embolism is approximately 30%; however, prompt diagnosis and appropriate therapy can reduce the mortality rate to <10%.[1,2] Pulmonary embolism is the most commonly overlooked disease in patients with pleural effusion (PE).[3]

It has been reported that the numbers of patients with pulmonary embolism from 20% of the acute hospital beds were 229,637 in 2005 in USA.[4] If these numbers are extrapolated to all acute hospital beds, the estimated annual occurrence of pulmonary embolism is 1.15 million. Given that 30–50% of patients with pulmonary embolism have a PE, the annual prevalence of PE due to pulmonary embolism in USA is 300,000–500,000.[3,5] Pulmonary embolism has been established to be the fourth main cause of PE in USA after congestive heart failure, parapneumonic effusion, and malignant effusion.[6]

In China, the annual incidence of pulmonary embolism is 0.1% (95% confidence interval, 0.1–0.2%) in overall hospitalized patients, and an increasing incidence gradient for pulmonary embolism is noticed from Southern to Northern China.[7] However, no data about the incidence of PE in Chinese patients with pulmonary embolism are available to date. We therefore performed the current study to investigate the incidence and computed tomography (CT) characteristics of PE in a Chinese population of patients with pulmonary embolism. Our data showed that PEs, usually small and unilateral effusions, are present in about one fifth of a Chinese population of patients with pulmonary embolism.

Methods

Study population

The study protocol was approved by the Institutional Review Boards for Human Studies of Beijing Chao-Yang Hospital, Beijing, China and no ethical concerns were raised. We

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retrospectively reviewed the consecutive medical records of CT pulmonary angiography (CTPA) scan data on all patients with clinically suspected pulmonary embolism from January 2008 until December 2013 at Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China. In our hospital, CTPA is ordered for all for patients with suspected pulmonary embolism.

Using the electronic database deposited in the Department of Radiology, we reviewed the study population's clinical records to ascertain demographic details of patients.

Evaluation of pulmonary embolism and pleural effusion

All CTPA scans were analyzed independently by two thoracic radiologists, who were blinded to the original CT report and patients' diagnoses. The images were viewed on a picture archiving and communications system workstation with these settings: Width 400 and level 60 Hounsfield Units. The picture archiving and communications system allowed the radiologists to scroll through the images. Next, the radiologists independently determined if pulmonary embolism and PE were present in each patient: Any discrepancies were resolved by reanalyzing the images until consensus was reached.

In patients with pulmonary embolism, the clots were classified as central, peripheral or both as described by de Monyé *et al*.[8] A central clot was defined as the presence of filling defects within the main to lobar pulmonary arteries, whereas a peripheral clot was defined as the presence of filling defects within the segmental and subsegmental arteries.

The pulmonary CT obstruction index was calculated as the method described by Qanadli *et al*.[9] to quantify arterial obstruction with CT in acute pulmonary embolism. Briefly, The CT obstruction index was defined as $\Sigma(n \bullet d)$ (n, value of the proximal clot site, equal to the number of segmental branches arising distally; d, degree of obstruction scored as partial obstruction [value of 1] or total obstruction [value of 2]).

If a PE was present, the size was semi-quantified as small, moderate, or large according to the CT imaging features with anteroposterior quartile and maximum anteroposterior depth measured at the midclavicular line as described by Moy *et al*.:[10] First anteroposterior-quartile effusion was small, second quartile effusion was moderate, and third or fourth quartile effusion was large. In borderline cases, anteroposterior depth was measured with 3-cm and 10-cm thresholds for the upper limits of small and moderate, respectively.

Statistical analysis

Data are presented as proportions or means (±standard division), as appropriate. Descriptive statistics was used, to summarize, patient characteristics, as well as CTPA and pleural fluid findings. Chi-square test was used to compare the incidence of PE in patients with or without embolism, and to determine the statistical significance of the association between the clot score, clot location, and PE. Student's *t*-test was also used, as appropriate. Analysis was completed with SPSS version 16.0 Statistical Software (SPSS Inc., Chicago, IL, USA), and a $P < 0.05$ was considered to indicate statistical significance.

Results

Diagnosis of pulmonary embolism

During the 6-year study period from January 2008 through December 2013, there was a population of 3196 patients with clinically suspected pulmonary embolism underwent CTPA at the Department of Radiology in our hospital. Fifty-five cases were excluded due to poor image quality. The final study population consisted of 3141 patients (1504 male) with a mean age of 60.2 ± 15.1 years (range 15−93 years).

A diagnosis of pulmonary embolism on CTPA was made in 1220 of the total 3141 patients (38.8%). As shown in Table 1, patients with pulmonary embolism had more dyspnea and chest pain syndromes and less chest tightness than those without pulmonary embolism did. The other syndromes, such as hemoptysis, cough, and fever, between two groups were not different.

Concomitant central and peripheral emboli were seen in the majority (n = 735, 60.2%) of patients, peripheral emboli were seen in the remaining patients (n = 485, 39.8%), and no central clots alone were seen. The percentages of concomitant central and peripheral emboli or peripheral emboli alone in patients with PE were similar to those in patients without PE [Table 2].

Table 1: Comparisons of symptoms in patients with and without pulmonary embolism

Characteristics	Patients with pulmonary embolism	Patients without pulmonary embolism	Statistics
Sex, male/female, *n*	628/592	876/1045	$\chi^2 = 10.317$, $P = 0.001$
Age, years, mean ± SD	58.5 ± 15.2	61.2 ± 15.0	$t = 0.118$, $P = 0.731$
Symptoms, *n* (%)			
Chest tightness	758 (62.1)	1628 (84.7)	$\chi^2 = 210.355$, $P < 0.001$
Dyspnea	174 (14.3)	113 (5.9)	$\chi^2 = 64.087$, $P < 0.001$
Chest pain	160 (13.1)	77 (4.0)	$\chi^2 = 122.904$, $P < 0.001$
Hemoptysis	17 (1.4)	16 (0.8)	$\chi^2 = 7.939$, $P = 0.006$
Cough	6 (0.5)	6 (0.3)	$\chi^2 = 1.141$, $P = 0.341$
Fever	42 (0.4)	29 (0.2)	$\chi^2 = 13.353$, $P < 0.001$

SD: Standard deviation.

Table 2: Types of pulmonary emboli in patients with and without PEs

Location of emboli	Patients with PEs, *n* (%)	Patients without PEs, *n* (%)
Central only	0 (0)	0 (0)
Central + peripheral	153 (63.0)	582 (59.6)
Peripheral only	90 (37.0)	395 (40.4)

$\chi^2 = 0.935$, $P = 0.342$. PE: Pleural effusion.

Identification of pleural effusion

A total of 423 patients had PE identified on CT in 3141 patients (13.5%) who underwent CTPA. The incidence of PEs was significantly higher in patient with pulmonary embolism (243/1220, 19.9%) than that in those without embolism (180/1921, 9.4%) ($\chi^2 = 71.236$, $P < 0.001$). As shown in Table 3, the presence of PE drove more patients with pulmonary embolism suffering from chest pain and hemoptysis, but not other related syndromes, including chest tightness, dyspnea, cough, and fever, etc.

Among the 243 pulmonary embolism patients with a PE, 88 patients (36.2%) had unilateral left-sided effusions, 74 (30.5%) had unilateral right-sided effusions and 81 (33.3%) had bilateral effusions. In either left or right side, the size of most PEs was small or moderate, very few patients showed large effusions [Table 4].

Pulmonary embolism and pleural effusion

The incidence of PE in patients with peripheral pulmonary embolism (18.6%) and in those with concomitant central and peripheral embolism (20.8%) was similar ($\chi^2 = 0.935$, $P = 0.342$) [Table 2].

We noted that pulmonary embolism was bilateral in 922 patients (75.6%), on the right side in 254 (20.8%), and on the left side in 44 (3.6%). In 243 pulmonary embolism patients with PE, pulmonary embolism was bilateral in 166 patients (68.3%), on right side in 67 (27.6%), and on left side in 10 (4.1%). We further noted that unilateral pulmonary embolism and PE were on the ipsilateral side in 30 patients, on the contralateral side in 24 patients.

We calculated CT pulmonary obstruction index according to the method described by Qanadli *et al*.,[9] and found that the obstruction index in the total population studied was 15.7 ± 10.8 (range 1 − 40). The obstruction index in pulmonary embolism patients without PE (15.6 ± 10.9) was not different from that in the patients with PE (16.6 ± 10.9) ($t = -0.921$, $P = 0.357$).

CT findings and pleural effusion

As expected, CT abnormalities, including wedge-shaped opacity, linear opacity, and ground-glass attenuation, were more frequently seen in patients with pulmonary embolism than in those without embolism [Table 5].

Of 243 patients with pulmonary embolism and PE, 89 had wedge-shaped opacity, 51 had atelectasis, 98 had consolidation, 15 had pulmonary masses, 20 had nodule, 96 had Mosaic sign, 77 had emphysematous bullae. All the above abnormalities on CT, excluding lung nodule, were much more in pulmonary embolism patients with PE than in those without effusion [Table 6]. In a bivariate analysis of these parameters, none was associated with the presence of PE.

Discussion

There were several mechanisms might be responsible for the development of PE secondary to pulmonary

Table 3: Comparisons of symptoms in pulmonary embolism patients and without PE

Characteristics	Patients with PE	Patients without PE	Statistics
Sex, male/female, *n*	141/102	487/490	$\chi^2 = 5.211$, $P = 0.022$
Age, years, mean ± SD	57.8 ± 16.6	58.8 ± 14.8	$t = 0.966$, $P = 0.344$*
Symptoms, *n* (%)			
Chest tightness	277 (65.5)	481 (60.4)	$\chi^2 = 0.394$, $P = 0.552$
Dyspnea	41 (19.6)	190 (16.9)	$\chi^2 = 0.886$, $P = 0.410$
Chest pain	53 (21.9)	159 (16.3)	$\chi^2 = 4.101$, $P = 0.043$
Hemoptysis	11 (4.5)	16 (1.6)	$\chi^2 = 7.474$, $P = 0.012$
Cough	6 (2.5)	19 (2.0)	$\chi^2 = 0.262$, $P = 0.613$
Fever	12 (0.3)	30 (0.5)	$\chi^2 = 1.883$, $P = 0.173$

*Student's *t*-test. PE: Pleural effusion; SD: Standard deviation.

Table 4: Size of PEs in patients with pulmonary embolism

Effusion size	Left, *n* (%)	Right, *n* (%)
Small	109 (66.5)	162 (92.0)
Moderate	55 (33.5)	12 (6.8)
Large	0	2 (1.1)

$\chi^2 = 44.918$, $P < 0.001$. PE: Pleural effusion.

Table 5: Parenchymal CT findings in patients with and without pulmonary embolism

CT abnormalities *n* (%)	Patients with pulmonary embolism (*n* = 1220)	Patients without pulmonary embolism (*n* = 1921)	*OR* (95% *CI*)
Wedge-shaped opacity	264 (21.6)	54 (2.8)	9.42 (6.96–12.75)
Atelectasis	62 (5.1)	94 (4.9)	1.03 (0.74–1.43)
Linear opacity	647 (53.0)	402 (20.9)	4.20 (3.59–4.91)
Ground-glass attenuation	459 (37.6)	314 (16.3)	3.04 (2.57–3.59)
Consolidation	204 (16.7)	336 (17.5)	0.93 (0.77–1.13)
Nodule	132 (10.8)	185 (9.6)	1.12 (0.89–1.42)
Mass	20 (1.6)	28 (1.5)	1.07 (0.60–1.90)

OR: Odds ratio; *CI*: Confidence interval; CT: Computed tomography.

Table 6: Parenchymal CT findings in pulmonary embolism patients with and without PEs

CT abnormalities *n* (%)	Patients with PEs (*n* = 423)	Patients without PEs (*n* = 797)	*OR* (95% *CI*)
Wedge-shaped opacity	89 (36.6)	175 (17.9)	2.65 (1.95–3.60)
Atelectasis	51 (21.0)	11 (1.1)	23.33 (11.94–45.57)
Linear opacity	149 (61.3)	498 (51)	1.53 (1.14–2.03)
Ground-glass attenuation	96 (39.5)	363 (37.2)	1.11 (0.83–1.47)
Consolidation	98 (40.3)	106 (10.8)	5.55 (4.01–7.70)
Nodule	20 (8.2)	112 (11.5)	0.69 (0.42–1.14)
Mass	15 (6.1)	5 (0.5)	12.76 (4.59–35.48)

OR: Odds ratio; *CI*: Confidence interval; CT: Computed tomography; PE: Pleural effusion.

embolism: (1) Pulmonary hypertension and increases in the right ventricular pressure can result in an increase of the systemic venous pressure at the parietal pleural surface.[3] (2) The embolus occludes the artery and leads to ischemia distal to the embolus, which leads to an increase in the amount of interstitial fluid in the lung. The interstitial fluid resulting from this increased permeability traverses the visceral pleura, enters the pleural space and leads to PE.[11] (3) When the embolus lodges in the pulmonary artery, cytokine are released, which also increase the permeability of the vessels.[3] A PE occurs when the amount of fluid formed overwhelms the capacity of the lymphatic vessels to remove the fluid from the pleural space.

Porcel *et al.* retrospectively analyzed the medical records of a total of 230 consecutive patients with pulmonary embolism over an 8-year period, and found that PE was observed in 32% and 47% of patients by chest X-ray and CT, respectively.[12] By reviewing all CTPA data performed over the past 6 years on patients with clinically suspected pulmonary embolism, we noted in the present study that a Chinese population with pulmonary embolism was more likely to have a PE than those without pulmonary embolism, and the incidence of PE in Chinese patients with pulmonary embolism was 19.9%, which was significantly higher than that in those without embolism (9.4%). The incidence of PE in Chinese pulmonary embolism patients was lower than the finding reported by Porcel *et al*.[12] and was similar to the finding reported by Yap *et al.* that PE was diagnosed in 21% of 285 patients.[13]

The incidence of PE in patients with pulmonary embolism varied dependent on different methods used in different populations. Using thorax ultrasound, Mathis *et al.* reported that a small PE is found in 49% of patients with pulmonary embolism.[14] However, in the most series, pulmonary embolism accounts for <5% of PEs in patients who have undergone a thoracentesis.[15] More recently, Hooper *et al*.[16] performed a prospective study to evaluate the incidence of pulmonary embolism in patients with unilateral PE, and found that pulmonary embolism is detected in 6.4% patients, indicating that pulmonary embolism is not a common primary cause for unilateral PE. There may be three explanations for this contradiction:[17] (1) The majority of PEs secondary to pulmonary embolism are small, which preclude a diagnostic and therapeutic thoracentesis; (2) Most patients with clinically suspected pulmonary embolism are immediately anticoagulated while awaiting a confirmatory test, and PE gradually resolve, a thoracentesis is not necessary; (3) Pulmonary embolism is frequently not considered in patients with undiagnosed PE.

The study by Porcel *et al.* showed that most PEs are small and unilateral, but occasionally they reach more than a half of the hemithorax.[12] A study of Yap *et al.* also showed that PEs are generally very small.[13] Our current data confirmed that most PEs presented in patients with pulmonary embolism were unilateral and small, and the frequency was similar to the findings in patients without pulmonary embolism. These findings indicated that the presence of pulmonary embolism increases the possibility of PE formation; however, it does not affect the size of PE.

In most of our patients, the emboli were located in both central and peripheral pulmonary arterials, and the percentages of concomitant central and peripheral emboli in patients with or without PE were similar. We also found that in pulmonary embolism patients with or without PE, more emboli were bilateral than unilateral, and the frequencies of bilateral PEs in two groups were quite similar. In addition, the CT pulmonary obstruction index in pulmonary embolism patients with or without PE was not different. The above data indicated that the locations of pulmonary emboli in central and peripheral pulmonary arterials, sidedness of pulmonary embolism, as well as the CT pulmonary obstruction indexes are not related to the development of PE.

Parenchymal abnormalities at CT, especially peripheral wedge-shaped opacity, have gained attention to be associated with having pulmonary embolism.[18-20] Our current data showed that CT abnormalities, including wedge-shaped opacity, atelectasis, consolidation, masses, Mosaic sign, and emphysematous bullae, were more frequently seen in patients with pulmonary embolism than in those without embolism. Although wedge-shaped opacity, atelectasis, consolidation, pulmonary masses, Mosaic sign, and emphysematous bullae was much more in pulmonary embolism patients with PE than in those without PE, a bivariate analysis did not show a relationship between any one of these CT abnormalities and the presence of PE.

A significant strength of the present study was that a quite big study population (more than 3000 patients with clinically suspected pulmonary embolism) was included, and 243 pulmonary embolism patients with PE were finally identified. To the best of our knowledge, our series was the biggest one of this kind of studies. As a matter of fact, the numbers of patients with pulmonary embolism diagnosed and treated in our hospital have been being more than those in any one hospital around over the country.

It has been documented that PE due to pulmonary embolism is always exudates, frequently hemorrhagic, and with a marked mesothelial hyperplasia.[3,12,21] One limitation of our current study was that no data concerning on specimens were available for analyzing biochemical and cytological characteristics of PEs, because very few pulmonary embolism patients with PE in our study underwent diagnostic or therapeutic thoracentesis. We also noted that all patients' PEs gradually resolved soon after the treatment with anticoagulants. Another limitation was that patients undergoing CTPA came from multiple departments of our hospital, including emergency, outpatient departments, and inpatient departments, it therefore was not possible for us to analyze the relationship between the appearance of PE and the prognosis of patients with pulmonary embolism.

In summary, we have demonstrated that PEs, usually small and unilateral effusions, are present in about one

fifth of a Chinese population of patients with pulmonary embolism. Therefore, when the etiology of an exudative PE is uncertain, the diagnosis of pulmonary embolism should be considered, and confirmatory tests for pulmonary embolism should be added to the routine evaluations. Our data also suggested that CTPA is a suitable way to identify the presence of PE in patients with pulmonary embolism and to evaluate the possibility of pulmonary embolism in patients with PE.

References

1. Matsumoto AH, Tegtmeyer CJ. Contemporary diagnostic approaches to acute pulmonary emboli. Radiol Clin North Am 1995;33:167-83.
2. Dalen JE, Alpert JS. Natural history of pulmonary embolism. Prog Cardiovasc Dis 1975;17:259-70.
3. Findik S. Pleural effusion in pulmonary embolism. Curr Opin Pulm Med 2012;18:347-54.
4. Park B, Messina L, Dargon P, Huang W, Ciocca R, Anderson FA. Recent trends in clinical outcomes and resource utilization for pulmonary embolism in the United States: Findings from the nationwide inpatient sample. Chest 2009;136:983-90.
5. Worsley DF, Alavi A, Aronchick JM, Chen JT, Greenspan RH, Ravin CE. Chest radiographic findings in patients with acute pulmonary embolism: Observations from the PIOPED Study. Radiology 1993;189:133-6.
6. Light RW. Clinical practice. Pleural effusion. N Engl J Med 2002;346:1971-7.
7. Yang Y, Liang L, Zhai Z, He H, Xie W, Peng X, *et al.* Pulmonary embolism incidence and fatality trends in chinese hospitals from 1997 to 2008: A multicenter registration study. PLoS One 2011;6:e26861.
8. de Monyé W, van Strijen MJ, Huisman MV, Kieft GJ, Pattynama PM. Suspected pulmonary embolism: Prevalence and anatomic distribution in 487 consecutive patients. Advances in New Technologies Evaluating the Localisation of Pulmonary Embolism (ANTELOPE) Group. Radiology 2000;215:184-8.
9. Qanadli SD, El Hajjam M, Vieillard-Baron A, Joseph T, Mesurolle B, Oliva VL, *et al.* New CT index to quantify arterial obstruction in pulmonary embolism: Comparison with angiographic index and echocardiography. AJR Am J Roentgenol 2001;176:1415-20.
10. Moy MP, Levsky JM, Berko NS, Godelman A, Jain VR, Haramati LB. A new, simple method for estimating pleural effusion size on CT scans. Chest 2013;143:1054-9.
11. Light RW. Pleural effusion due to pulmonary emboli. Curr Opin Pulm Med 2001;7:198-201.
12. Porcel JM, Madroñero AB, Pardina M, Vives M, Esquerda A, Light RW. Analysis of pleural effusions in acute pulmonary embolism: Radiological and pleural fluid data from 230 patients. Respirology 2007;12:234-9.
13. Yap E, Anderson G, Donald J, Wong CA, Lee YC, Sivakumaran P. Pleural effusion in patients with pulmonary embolism. Respirology 2008;13:832-6.
14. Mathis G, Blank W, Reissig A, Lechleitner P, Reuss J, Schuler A, *et al.* Thoracic ultrasound for diagnosing pulmonary embolism: A prospective multicenter study of 352 patients. Chest 2005;128:1531-8.
15. Porcel-Pérez JM, Vives Soto M, Esquerda Serrano A, Jover Sáenz A. Cuttoff values of biochemical tests on pleural fluid: Their usefulness in differential diagnosis of 1,040 patients with pleural effusion. An Med Interna 2004;21:113-7.
16. Hooper C, Laurence I, Harvey J, Morley A, Darby M, Edey A, *et al.* The role of CT pulmonary angiography in the investigation of unilateral pleural effusions. Respiration 2014;87:26-31.
17. Porcel JM, Light RW. Pleural effusions due to pulmonary embolism. Curr Opin Pulm Med 2008;14:337-42.
18. Greaves SM, Hart EM, Brown K, Young DA, Batra P, Aberle DR. Pulmonary thromboembolism: Spectrum of findings on CT. AJR Am J Roentgenol 1995;165:1359-63.
19. Coche EE, Müller NL, Kim KI, Wiggs BR, Mayo JR. Acute pulmonary embolism: Ancillary findings at spiral CT. Radiology 1998;207:753-8.
20. Shah AA, Davis SD, Gamsu G, Intriere L. Parenchymal and pleural findings in patients with and patients without acute pulmonary embolism detected at spiral CT. Radiology 1999;211:147-53.
21. Romero Candeira S, Hernández Blasco L, Soler MJ, Muñoz A, Aranda I. Biochemical and cytologic characteristics of pleural effusions secondary to pulmonary embolism. Chest 2002;121:465-9.

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