Original Article

Prevalence and clinical significance of pleural effusion in patients with acute pulmonary embolism: a retrospective study

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Background: Pleural effusion is observed in a subset of patients with acute pulmonary embolism (APE) and may be linked to clinical outcome, but findings from previous studies have been inconsistent. This study aimed to investigate the prevalence and clinical significance of pleural effusion in Chinese patients with APE.

Methods: Clinical data from hospitalized patients with APE were retrospectively collected and the prevalence of pleural effusion was determined. The relationship between the presence of pleural effusion and clinical outcome of APE was analyzed by Cox proportional hazards regression and Kaplan-Meier survival analysis.

Results: The study enrolled 635 patients with APE. The prevalence of pleural effusion was 57.01% (362/635). Patients with pleural effusion had significantly higher in-hospital mortality (9.9% *vs.* 4.8%, P<0.05) and longer length of hospital stay (LOS) (19.99 *vs.* 15.31 days, P<0.05) than whose without pleural effusion. However, pleural effusion was not an independent risk factor for in-hospital mortality in patients with APE by multivariate Cox proportional hazards regression analysis [hazard ratio (HR) =1.70, 95% confidence interval (CI): 0.73–3.92, P=0.216] and Kaplan–Meier survival analysis (P=0.174).

Conclusions: Pleural effusion is a frequent occurrence in patients with APE and therefore merits greater attention from clinicians; however, it is not an independent risk factor for in-hospital mortality.

Keywords: Acute pulmonary embolism (APE); pleural effusion; mortality

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Introduction

Acute pulmonary embolism (APE) is a disease characterized by occlusion of one or more pulmonary arteries by a thrombus, and is a frequent reason for visits to the emergency room and hospital admission (1,2). APE is a common cause of morbidity and mortality worldwide: In the past decade in Denmark, the annual prevalence increased from 45 to 83 per 100,000, and the prevalence in Sweden was reported as 60 per 100,000 per year (3,4). In Australia in 2007, there were 320 deaths due to APE, corresponding to a mortality rate of 1.73 per 100,000 per year (5). In the United States, APE accounts for 100,000–180,000 deaths per year (1). Although the mortality rate of APE has been declining in recent years because of progress in standard anticoagulant and thrombolytic therapies (6), it remains a significant public health concern. Mortality rates can be difficult to estimate because up to 25% of cases present as sudden death, while the rate ranges from 5% to 30% within the first 30 days of hospitalization (7). Timely identification of risk factors for mortality in APE patients can inform treatment decisions and improve prognosis.

Pleural effusion is commonly observed in patients with

APE, with a prevalence of 32% and 47% based on chest X-ray and chest computed tomography (CT), respectively (8). In contrast, the prevalence of pleural effusion was just 19.9% in 1,220 patients with PE (9). Pleural effusion has been linked to the severity and prognosis of APE, but the findings have been inconsistent. A study from Korea found that pleural effusion did not predict short-term outcome or length of hospital stay (LOS) in patients with APE (10), whereas investigations conducted in China and Turkey showed that pleural effusion in patients with APE was significantly correlated with higher mortality and was a potential independent risk factor of poor clinical outcome (11,12). Thus, the clinical significance of pleural effusion in patients with APE remains unclear. To address this issue, the present study investigated the prevalence of pleural effusion and its impact on the outcome of Chinese patients with APE. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/jtd-20-2552).

Methods

Study design and patients

This retrospective, single-center cohort study was conducted at West China Hospital of Sichuan University, China, and enrolled patients aged ≥18 years with APE diagnosed by CT pulmonary angiography (CTPA) between January 2015 and April 2019. The severity of APE was evaluated with the simplified PE severity index (13,14). The presence of pleural effusion was determined based on CTPA findings by 2 experienced radiologists who were blinded to the medical history of the patients. Additionally, 2 pulmonary physicians determined the cause of pleural effusion by checking patients' medical records. There are many types of pleural effusion including parapneumonic, heart failure-associated, malignant, and tuberculous types (15,16); these cases were excluded from the study. Parapneumonic pleural effusion results from pneumonia or lung infection and declines as the infection improves. Malignant pleural effusion is defined by the presence of malignant cells in the effusion or biopsy specimens. Tuberculous pleural effusion refers to any effusion secondary to *Mycobacterium tuberculosis* infection of pleura. Heart failure-associated pleural effusion is diagnosed when there is a medical history of heart failure and symptoms are relieved by diuretic therapy (16). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of West China Hospital of Sichuan University (WCH 2017-351). The requirement for written, informed consent was waived because of its retrospective nature.

Data collection

All patients were followed up until discharge from the hospital, and their information was collected by reviewing medical records. Demographic characteristics, clinical presentation, comorbidities, laboratory and radiographic findings, and clinical outcome were recorded. Demographic data included age, sex, body mass index (BMI), and smoking history. Clinical presentation included initial vital signs, dyspnea, pleuritic chest pain, hemoptysis, syncope, fever, and leg pain or swelling. Predisposing or comorbid conditions included immobilization, trauma, cancer, stroke, chronic pulmonary disease (chronic obstructive pulmonary disease, asthma, bronchiectasis, idiopathic pulmonary fibrosis, pneumoconiosis, and tuberculosis-destroyed lung), pulmonary tuberculosis, and congestive heart failure. Laboratory findings included N-terminal pro-B-type natriuretic peptide (NT-pro BNP), troponin T, creatine kinase-MB (CK-MB), white blood cell (WBC), and blood platelet (PLT) count. Radiologic findings included the location of pulmonary emboli detected by CTPA, deep vein thrombosis detected by ultrasonography, right ventricle dilation, and pulmonary infarction (defined as the appearance of peripheral consolidation secondary to PE detected by CT). Clinical outcomes were all-cause in-hospital mortality, rate of respiratory failure, tracheal intubation, mechanical ventilation, systemic thrombolysis, hospital bleeding, and LOS.

Statistical analysis

As none of the analyses were predefined based on previous reports they were considered as post hoc analyses. Categorical variables are presented as number count with a percentage value, and continuous variables are expressed as mean ± standard deviation or median and interquartile range. The independent Student's *t*-test was used to assess differences between continuous variables and the Mann–Whitney U test was used for data that were not normally distributed. The chi-squared test was used to analyze categorical variables. Clinical characteristics and laboratory and radiologic findings were compared between patients with and those without pleural effusion as well as between

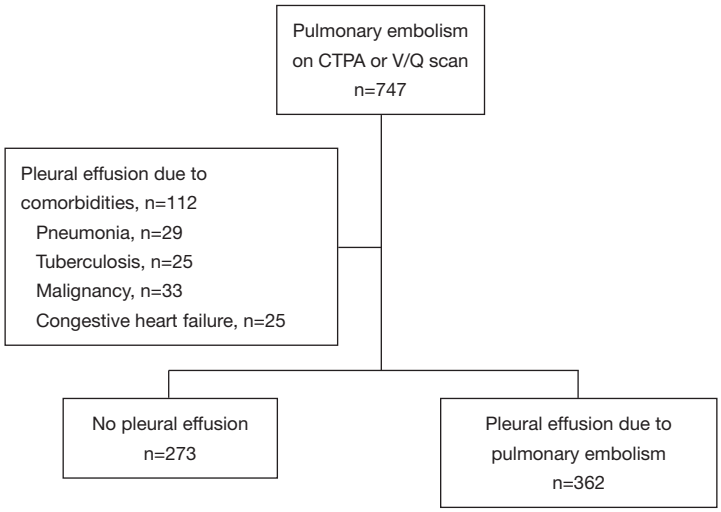

Figure 1 Flow diagram of the study protocol.

survivors and non-survivors. Logistic regression analysis was performed to identify the predictors of pleural effusion due to PE, and odds ratio (OR) with 95% confidence interval (95% CI) was calculated to assess the discriminatory power of these parameters. A Cox proportional hazards regression model was used to assess the impact of pleural effusion on survival and the results are presented as hazard ratio (HR) with 95% CI. Follow-up data of patients were analyzed with a time-to-event model by the Kaplan-Meier method and the log-rank test. All statistical analyses were performed using SPSS v21.0 (IBM, Chicago, IL, USA), and $P<0.05$ was considered statistically significant.

Results

Demographic and clinical characteristics of patients

We screened 747 patients with APE by CTPA, and 112 were excluded because the cause of pleural effusion was not APE (*Figure 1*). Among the 635 patients with APE included in the analysis, the prevalence of pleural effusion was 57.01% (362/635).

Patients with pleural effusion were younger than those without effusion (control group) (57.04±17.81 *vs.* 59.74±15.38 years, P=0.041). Additionally, the pleural effusion group had a lower frequency of unprovoked PE than controls (18.0% *vs.* 27.5%, P=0.004) and more clinical symptoms including dyspnea (74.2% *vs.* 63.4%, P=0.003), pleuritic chest pain (39.3% *vs.* 28.9%, P=0.007), hemoptysis (30.2% *vs.* 21.2%, P=0.011), and fever (9.8% *vs.* 4.9%, P=0.024). The demographic and clinical information is summarized in *Table 1*.

Laboratory and radiographic findings

Patients with pleural effusion had higher WBC counts and serum levels of NT-pro BNP, troponin T, and CK-MB relative to controls, and more frequently exhibited pulmonary infarction in the radiographic examination (26.0% *vs.* 19.0%, P=0.038) (*Table 1*). There were no significant differences between groups in terms of the location of pulmonary emboli, occurrence of deep vein thrombosis, and right ventricle dilation in the CT scan or ultrasonic cardiogram.

Predictive factors for pleural effusion caused by APE

To identify factors that could potentially contribute to the development of pleural effusion in APE, we performed a multivariate logistic regression analysis with age, immobilization, respiration rate, WBC count, and PLT count as candidate predictive factors based on their clinical significance and the results of the univariate analysis (all $P<0.05$). We found that immobilization (OR =1.575; 95% CI: 1.022–2.429, P=0.04) and WBC count (OR =1.056; 95% CI: 1.006–1.109, P=0.028) were independent predictors of pleural effusion (*Table 2*).

Pleural effusion and clinical outcome

The in-hospital mortality rate was significantly higher in the pleural effusion group than in the control group (9.9% *vs.*

Table 1 Demographics and clinical characteristics of patients with pulmonary embolism group by pleural effusion

Variables	Pleural effusion (n=362)	Controls (n=273)	P value
General information			
Age, years	57.04±17.81	59.741±15.38	0.041
Female gender	145 (40.1)	124 (45.4)	0.176
Smoking status			0.372
Smoker/ever smoker	103 (59.9)	69 (40.1)	
Non-smoker	259 (55.9)	204 (44.1)	
Body mass index	23.74±4.28	23.792±3.73	0.896
Presenting manifestation			
Dyspnea	268 (74.2)	173 (63.4)	0.003
Pleuritic chest pain	142 (39.3)	79 (28.9)	0.007
Hemoptysis	109 (30.2)	58 (21.2)	0.011
Leg pain or swelling	127 (35.1)	77 (28.2)	0.066
Syncope	45 (12.5)	43 (15.8)	0.236
Fever	34 (9.8)	13 (4.9)	0.024
Predisposing or comorbid condition			
Immobilization	126 (34.8)	72 (26.4)	0.023
Trauma	7 (1.9)	1 (0.4)	0.147
Cancer	70 (19.3)	51 (18.7)	0.835
Stroke	26 (7.2)	17 (6.2)	0.635
Chronic pulmonary disease*	103 (28.5)	93 (34.1)	0.13
Pulmonary tuberculosis	19 (5.2)	13 (4.8)	0.781
Congestive heart failure	23 (6.4)	18 (6.6)	0.903
Vital signs			
Blood pressure			0.521
Hypotension, systolic blood pressure	24 (61.5)	15 (38.5)	
Normal blood pressure or hypertension	323 (56.3)	251 (43.7)	
Heart rate	88.59±17.41	85.93±15.61	0.048
Respiratory rate	20.99±3.12	20.36±2.40	0.005
SpO_2	95.70 (92.80–98.03)	96 (93–98.60)	0.63
SPESI			0.463
High risk	211 (55.8)	167 (44.2)	
Low risk	151 (58.8)	106 (41.2)	

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Pleural effusion (n=362)	Controls (n=273)	P value
Pulmonary embolism, risk stratification			0.615
High risk	1 (33.3)	2 (66.7)	
Intermediate high	77 (61.1)	49 (38.9)	
Intermediate low	245 (55.8)	194 (44.2)	
Low risk	39 (58.2)	28 (41.8)	
Laboratory findings			
WBC ($\times 10^9$/L)	8.82 (6.17–11.74)	7.32 (5.30–9.63)	0.00
PLT ($\times 10^9$/L)	178.00 (124.50–256.00)	171.00 (129.50–231)	0.083
NT-proBNP (pg/mL)	793.00 (152.00–2,709.00)	387.00 (104.75–1,880.75)	0.029
Troponin T (ng/L)	19.30 (8.00–50.90)	15.80 (7.35–37.65)	0.078
CK-MB (ng/mL)	1.98 (0.98–4.52)	1.43 (0.90–2.49)	0.024
Radiologic findings			
Location of the largest pulmonary emboli (bilateral)	188 (51.9)	140 (51.7)	0.946
Deep vein thrombosis	131 (57.7)	105 (54.4)	0.496
Right ventricle dilation on computed tomography	118 (32.7)	84 (30.8)	0.608
Pulmonary infarction	94 (26.0)	52 (19.0)	0.038
Clinical outcome			
In-hospital mortality	36 (9.9)	13 (4.8)	0.015
Respiratory failure	74 (20.4)	30 (11.0)	0.001
Systemic thrombolysis	1 (0.5)	0 (0)	1.00
Length of hospital stay, days	19.99±24.41	15.314±9.656	0.006
Mechanical ventilation	14 (3.9)	7 (2.6)	0.363
Tracheal intubation	9 (15.0)	3 (7.1)	0.35
Hospital bleeding	23 (22.1)	11 (10.4)	0.021

4.8%, P=0.015) (*Table 1*). The presence of pleural effusion was associated with longer LOS (19.99±24.41 *vs.* 15.31±9.66 days, P=0.006), more frequent hospital bleeding (22.1% *vs.* 10.4%, P=0.021), and a higher rate of respiratory failure (20.4% *vs.* 11.0%, P=0.001). However, there were no differences between groups in terms of tracheal intubation, mechanical ventilation, and systemic thrombolysis (all P<0.05).

Predictors of mortality and survival analysis

All patients were followed up until discharge from the hospital. In total, 49 patients died during hospitalization (in-hospital mortality rate of 7.72%). We compared the data of survivors and non-survivors in order to identify potential predictors of in-hospital mortality in patients with APE. The prevalence of pleural effusion was significantly higher in non-survivors than in survivors (73.5% *vs.* 55.8%, P=0.016) (*Table 3*). To determine whether the presence of pleural effusion or other indicators could predict in-hospital mortality in patients with APE, we carried out Cox proportional hazards regression analyses (*Table 4*). The results of the univariate analysis indicated that pleural

Table 2 Univariate and multivariate analysis for predictors of pleural effusion due to acute pulmonary embolism

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
Age, years	0.99	0.981–1.000	0.046	0.99	0.978–1.002	0.116
Immobilization	1.49	1.055–2.105	0.023	1.575	1.022–2.429	0.04
Heart rate	1.01	1.000–1.020	0.052			
Respiratory rate	1.089	1.022–1.159	0.008	1.078	0.995–1.167	0.067
WBC ($\times10^9$/L)	1.088	1.044–1.134	<0.001	1.056	1.006–1.109	0.028
PLT ($\times10^9$/L)	1.002	1.001–1.004	0.008	1.002	1.000–1.004	0.099
NT-proBNP (pg/mL)	1.000	1.000–1.000	0.066			
Troponin T (ng/L)	1.001	1.000–1.002	0.082	1.001	1.000–1.002	0.084
CK-MB (ng/mL)	1.001	0.999–1.003	0.439			

Table 3 Demographics and clinical characteristics of patients with pulmonary embolism group by mortality

Variables	Non-survivors (n=49)	Survivors (n=586)	P value
General information			
Age, years	68.15±16.47	57.37±16.63	<0.001
Female gender	12 (24.5)	257 (43.9)	0.008
Smoking status			0.67
Smoker/ever smoker	12 (24.5)	160 (27.3)	
Non-smoker	37 (75.5)	426 (72.7)	
Body mass index	22.67±3.54	23.83±4.07	0.183
Presenting manifestation			
Dyspnea	44 (89.8)	397 (67.9)	<0.001
Pleuritic chest pain	5 (10.2)	216 (36.9)	<0.001
Hemoptysis	6 (12.2)	161 (27.5)	0.02
Leg pain or swelling	19 (38.8)	185 (31.6)	0.299
Syncope	15 (30.6)	73 (12.5)	<0.001
Fever	7 (14.9)	40 (7.1)	0.053
Predisposing or comorbid condition			
Immobilization	18 (36.7)	180 (30.7)	0.382
Trauma	1 (2.0)	7 (1.2)	0.476
Cancer	12 (24.5)	109 (18.6)	0.313
Stroke	5 (10.2)	38 (6.5)	0.366
Chronic pulmonary disease*	21 (42.9)	175 (29.9)	0.059
Pulmonary tuberculosis	5 (10.2)	27 (4.6)	0.091
Congestive heart failure	9 (18.4)	2 (5.5)	<0.001

Table 3 (*continued*)

Table 3 (*continued*)

Variables	Non-survivors (n=49)	Survivors (n=586)	P value
Vital signs			
Blood pressure			
Hypotension, systolic blood pressure	6 (12.8)	33 (5.8)	0.061
Normal blood pressure or hypertension	41 (87.2)	533 (94.2)	0.061
Heart rate	97.62±22.98	86.59±15.79	0.002
Respiratory rate	21.45±4.45	20.66±2.66	0.236
SpO_2	92.33±5.71	94.75±5.57	0.047
SPESI			<0.001
High risk	41 (83.7)	337 (57.5)	
Low risk	8 (16.3)	249 (42.5)	
Laboratory findings			
WBC ($\times 10^9$/L)	10.68 (7.42–12.86)	7.84 (5.64–10.75)	<0.001
PLT ($\times 10^9$/L)	115 [78–190]	177 [132–243]	<0.001
NT-proBNP (pg/mL)	2800 (889.25–8,085.5)	425 (106.5–2,163.5)	<0.001
Troponin T (ng/L)	69.45 (33.45–269.95)	16.3 (7.30–38.00)	<0.001
CK-MB (ng/mL)	4.51 (1.97–13.99)	1.55 (0.90–3.32)	<0.001
Radiologic findings			
Pleural effusion	36 (73.5)	327 (55.8)	0.016
Small pleural effusion	35 (97.2)	320 (97.9)	0.805
Mass pleural effusion	1 (2.8)	7 (2.1)	0.570
Location of the largest pulmonary emboli (bilateral)	29 (59.2)	299 (51.2)	0.283
Deep vein thrombosis	4 (57.1)	232 (56.2)	1
Right ventricle dilation on computed tomography	18 (37.5)	184 (31.4)	0.383
Pulmonary infarction	9 (18.8)	137 (23.4)	0.464
Clinical outcome			
Respiratory failure	24 [49]	80 (13.7)	<0.001
Systemic thrombolysis	0 (0)	1 (0.3)	1
Length of hospital stay, days	18.76±21.40	17.90±19.57	0.810
Mechanical ventilation	9 (18.4)	12 (2.0)	<0.001
Tracheal intubation	7 (50.0)	5 (5.7)	<0.001
Hospital bleeding	7 (28.0)	27 (14.6)	0.142

Table 4 Univariate and multivariate Cox-regression analysis for predictors of in–hospital mortality

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age, years	1.045	1.024–1.067	<0.001	1.028	0.995–1.061	0.093
Sex	0.498	0.258–0.960	0.037	0.492	0.179–1.352	0.169
Congestive heart failure	3.575	1.736–7.406	0.001	1.552	0.455–5.295	0.483
Heart rate	1.034	1.018–1.051	<0.001	1.028	1.005–1.052	0.017
SpO_2	0.946	0.899–0.996	0.035	0.983	0.914–1.058	0.647
SPESI	2.190	1.638–2.927	<0.001	1.763	0.987–3.152	0.056
WBC ($\times10^9$/L)	1.013	0.996–1.031	0.126			
PLT ($\times10^9$/L)	0.994	0.990–0.998	0.002	0.998	0.992–1.004	0.591
NT-proBNP (pg/mL)	1.000	1.000–1.000	<0.001	1.000	1.000–1.000	0.215
Troponin T (ng/L)	1.001	1.000–1.001	<0.001	1.000	1.000–1.000	0.087
CK-MB (ng/mL)	1.000	0.997–1.003	0.928			
Pleural effusion	1.775	0.930–3.354	0.077			

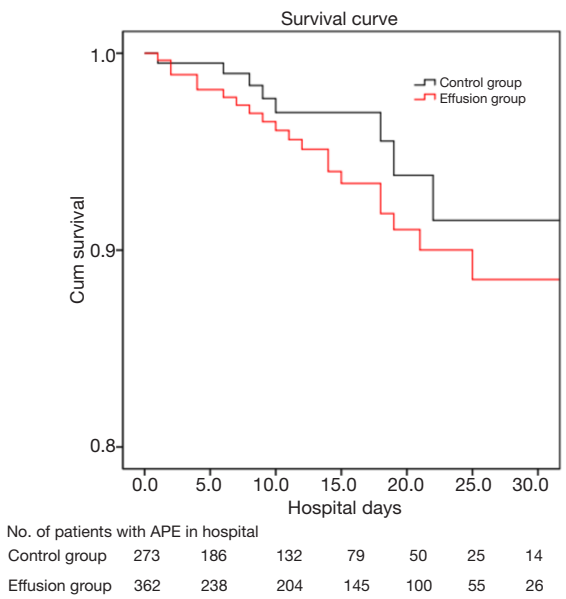

Figure 2 Kaplan-Meier curves of overall survival in patients with APE. The event was defined as in-hospital mortality, and patients were divided into effusion and control groups according to the presence of pleural effusion. The P value of the log-rank test was 0.174.

effusion was a potential predictor (HR =2.21; 95% CI: 1.15–4.25, P=0.018), but this was not confirmed in the multivariate analysis (HR =1.70, 95% CI: 0.73–3.92, P=0.216).

The Kaplan-Meier survival analysis revealed a difference in in-hospital mortality between the pleural effusion and non-pleural effusion groups; however, the log-rank analysis showed that the difference was not statistically significant (P=0.174) (*Figure 2*).

Discussion

The prevalence of pleural effusion and its relationship to clinical outcome in patients with APE is known. This was investigated in the present study and our results showed that pleural effusion was present in 57.01% of patients of APE, and was associated with higher in-hospital mortality, longer LOS, and higher rate of respiratory failure, although the Cox proportional hazards regression analysis did not support pleural effusion as an independent predictor of in-hospital mortality in patients with APE.

The prevalence of pleural effusion has been reported as 16.32–61% (8,10,12,17,18); 2 studies of Chinese patients with APE reported prevalence rates of 19.9% and 23.2% (9,11). The prevalence in our study (57.01%) suggests that pleural effusion is a common issue in patients with APE and merits greater attention from clinicians. Based on a retrospective analysis of more than 3,000 consecutive thoracentesis, PE was the cause of pleural effusion in just 1.6% of cases (19). Pleural effusion in APE is typically

mild and bilateral, and most cases are not suitable for thoracentesis, making it more difficult to diagnose (20). The actual prevalence of pleural effusions due to APE may be different to calculate and the key-point is that physicians may neglect the differential diagnosis of undiagnosed pleural effusion regarding on APE, and missed the diagnosis of APE, which should pay more attention in clinical activities.

We carried out a multivariate logistic regression analysis to investigate potential indicators of pleural effusion caused by APE and found that immobilization and WBC were independent predictors. Patients with PE show an enhanced inflammatory response (21); WBC count, which is considered a marker of inflammation and hypercoagulability, was increased in patients with APE and was an independent predictor of short-term mortality (22). The increased WBC count in APE suggests that during the inflammatory response, inflammatory mediators released by pulmonary thrombi increase capillary permeability, which can lead to (although not required for) the development of pleural effusion in APE patients.

In our study, patients with pleural effusion had a higher in-hospital mortality rate than controls (9.9% *vs.* 4.8%, P=0.015). A higher 30-day all-cause mortality rate was previously reported in APE patients with pleural effusion compared to those without pleural effusion (23% *vs.* 9%, P<0.001) (23). Pleural effusion was found to be an independent risk factor for poor prognosis in patients with APE, as its presence was correlated with higher mortality (11,12). However, our Cox proportional hazards regression analysis showed that pleural effusion was not an independent predictor of in-hospital mortality in patients with APE (HR =1.70; 95% CI: 0.73–3.92, P=0.216); this is consistent with a previous study demonstrating that pleural effusion did not predict short-term outcome in patients with APE (10). Thus, the impact of pleural effusion on the short-term mortality of patients with APE is complex and requires further investigation. On the other hand, given that many factors contribute to mortality in patients with APE, the effect of effusion should not be overstated.

In this study, NT-proBNP—a widely used cardiac biomarker for risk stratification in APE—was elevated in APE patients with pleural effusion relative to controls. Several studies have demonstrated that abnormal NT-proBNP level is an indicator of right ventricular dysfunction, which is associated with poor outcome (24). APE patients who died in the first 30 days of hospitalization had significantly higher levels of NT-proBNP than those with longer survival times (25). For a full prognostic evaluation of patients with APE, pleural effusion must be considered along with other clinical data. In our analysis, mean LOS in patients with APE was longer than previously reported (26). This may be explained by the extreme values of LOS in a subset of our cohort, which may have skewed the results; alternatively, as China is a developing country, hospitalized patients have high expectations for treatment, resulting in a relatively long LOS.

Our study had 2 major limitations. Firstly, because of the retrospective single-center cohort design some data may have been missed, which could undermine the accuracy of the findings. Secondly, because of the limited follow-up time, there were no data on long-term clinical outcome of patients with APE; therefore, additional studies are needed to clarify whether this is affected by the presence of pleural effusion.

In conclusion, the results of this study demonstrate that pleural effusion is highly prevalent in patients with APE and may be associated with mortality, although it does not predict in-hospital mortality. These findings can guide the management of patients with APE by identifying those who might benefit from specific types of intervention, thereby improving their clinical outcome.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd-20-2552). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of the West China Hospital of Sichuan University (WCH 2017-351). Individual consent for this retrospective analysis was waived.

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