

# BMJ Open Retrospective cohort study of new-onset atrial fibrillation in acute pulmonary embolism on prognosis

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## ABSTRACT

**Objectives** To investigate the characteristics of new-onset atrial fibrillation (AF) and its impact on prognosis in acute pulmonary embolism (aPE).

**Design** A retrospective cohort study

**Setting** The study cohort included patients diagnosed with aPE who were admitted to the Renmin Hospital of Wuhan University from January 2017 to January 2019.

**Participants** Patients were  $\geq 18$  years of age and hospitalised for aPE.

**Outcome measures** AF was diagnosed based on an ECG recording or a Holter monitor during hospitalisation. aPE was diagnosed by CT pulmonary angiography. The prescription was determined from the discharge medication list. All-cause mortality was observed after 6-month follow-up. The logistic regression model and Cox proportional hazards model were used to study the risk factor of the new-onset AF and the predictor of all-cause mortality, respectively.

**Results** A total of 590 patients with aPE were enrolled, 23 (3.9%) in the new-onset paroxysmal AF group, 31 (5.3%) in the new-onset persistent AF group and 536 (90.8%) in the sinus rhythm (SR) group. The incidence of the new-onset AF was 9.2% (54/590). A significant difference in age, heart rate, cardiac troponin I ultra, amino-terminal pro-brain natriuretic peptide, D-dimer, left atrial diameter, left ventricular ejection fraction, pulmonary infection, venous thromboembolism, congestive heart failure, chronic cor pulmonale and ischaemic heart disease was found among the three groups ( $p < 0.05$ ). Risk factors for the new-onset AF were massive PE, ischaemic heart disease and congestive heart failure. The survival rate of the paroxysmal and persistent AF group was significantly lower than that of the SR group within 6 months (60.9% and 51.6% vs 88.8%,  $p < 0.001$ ). New-onset persistent AF (OR 2.73; 95% CI 1.28 to 5.81;  $p = 0.009$ ) was an independent predictor affecting the 6-month survival in aPE patients.

**Conclusions** Massive PE, ischaemic heart disease and congestive heart failure are high-risk factors which were related to new-onset AF in aPE. New-onset persistent AF was an independent predictor for 6-month all-cause mortality in PE patients.

## BACKGROUND

The incidence of acute pulmonary embolism (aPE) has gradually increased in the

## Strengths and limitations of this study

- Our study is the largest cohort study on acute pulmonary embolism (aPE) combined with atrial fibrillation (AF) in China, and we first confirmed new-onset persistent AF is an independent predictor for aPE.
- Previous studies did not distinguish AF types, while AF was more carefully divided into paroxysmal and persistent in our study.
- The study was a retrospective analysis of patient medical records and the follow-up time was relatively short.

past decades due to increased old people.<sup>1</sup> PE causes more than 0.3 million deaths each year in the USA and European countries, ranking third among mortality rates from cardiovascular diseases.<sup>2 3</sup> PE contributes to the 5%–10% of deaths in hospitalised patients, and venous thromboembolism (VTE) is a leading preventable cause of in-hospital death.<sup>4 5</sup> Even though the global data show that the mortality rate from aPE decreases every year,<sup>6</sup> it may be related to more effective treatments, interventions and strict adherence to guidelines, but thromboembolism is estimated to have caused one in four deaths worldwide in 2010.<sup>7</sup> aPE has many complications due to haemodynamic disturbances. Cardiovascular disease is the main comorbidity or complication in aPE, which affects the prognosis of patients. Spencer *et al* demonstrated that congestive heart failure is an independent predictor of mortality in patients with aPE and the short-term mortality rate was 11.1%–22.2%.<sup>8 9</sup> Besides, a previous study reported that patients with aPE are at higher risk of developing a subsequent cardiovascular disease that affects the prognosis.<sup>10</sup> However, the pathophysiological mechanism and the effects on prognosis of an episode of atrial fibrillation (AF) as a complication of aPE is still not yet studied enough. Therefore,

this study aimed to investigate whether the new-onset AF might be considered a marker of the severity of aPE and its impact on the prognosis.

## METHOD

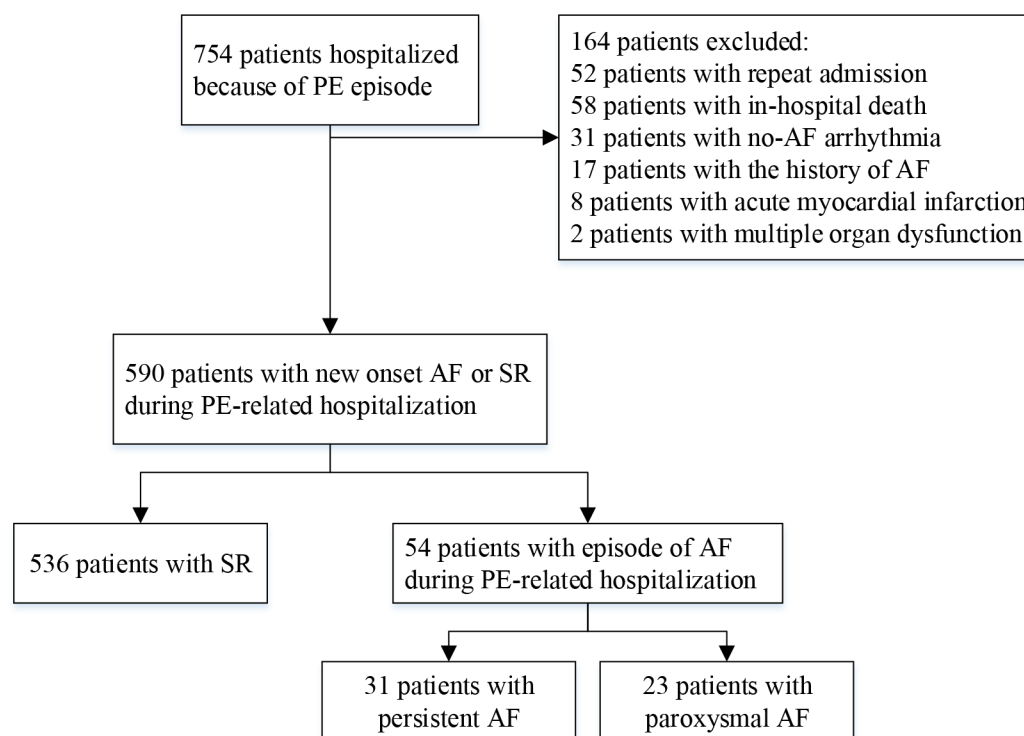
### General information

The study cohort included patients diagnosed with aPE admitted to the Renmin Hospital of Wuhan University from January 2017 to January 2019. The inclusion criteria were the following: (1) patients were all over the age of 18 and their medical records were retrospectively analysed; (2) the diagnosis of aPE was made according to the guidelines for the diagnosis and treatment of aPE developed by the ESC in 2014.<sup>11</sup> All patients were diagnosed using CT pulmonary angiography. The diagnosis of congestive heart failure is based on echocardiography, biochemistry and clinical symptoms. All stages of congestive heart failure were included. It is necessary that medical history records have coronary angiography, exercise treadmill test or apparent signs of myocardial ischaemia on the ECG during hospitalisation for the diagnosis of ischaemic heart disease. Pulmonary infection is diagnosed by CT or X-ray of chest radiographs.

The exclusion criteria were the following: (1) patients with other arrhythmias, such as supraventricular or ventricular tachycardia; (2) patients with valvular heart disease, previous AF as shown by the medical records, chronic PE or multiple organ failure; (3) patients with acute myocardial infarction and (4) patients who died in hospital (figure 1).

The final number of patients enrolled in this study was 590, and they were divided into three groups, (a) sinus rhythm (SR) group, which included patients with SR at admission; (b) paroxysmal AF group, which included patients with one or more episodes of paroxysmal AF documented by ECG at any time during index hospitalisation; (c) persistent AF group, which included patients suffering from AF episodes that lasted for more than 48 hours, failed to recover spontaneously and required medical or non-pharmacological intervention during the index hospitalisation. All AF cases in this cohort were new-onset (figure 1).

Demographic and clinical characteristics on admission, including symptoms, haemodynamic profile and comorbidities, were evaluated and compared among groups. Besides, the Simplified Pulmonary Embolism Severity Index (sPESI) was retrospectively calculated.<sup>12</sup> Blood routine (Sysmex HST302, Japan), biochemistry (Siemens ADVIA 2400, Germany), cardiac troponin I ultra (cTnI-ultra, Siemens ADVIA CENTAUR XP, Germany), amino-terminal pro-brain natriuretic peptide (NT-proBNP, Roche, Switzerland) and blood gas analysis (GEM 4000, America) were also measured at admission. Transthoracic echocardiography was performed within 24 hours of admission. Haemodynamic parameters were measured using Philips iE33 (Philips Medical Systems, Netherlands) equipped with S5-1 sensors or GE Vivid 7 (GE Healthcare, America) equipped with M4S sensors. After the patient was diagnosed with aPE, low molecular weight heparin was administered subcutaneously



**Figure 1** Study population, inclusion and exclusion criteria based on patient's heart rhythm. Study population, and inclusion and exclusion criteria based on patient's heart rhythm. AF, atrial fibrillation; SR, sinus rhythm; PE, pulmonary embolism.

**Table 1** Baseline demographic and laboratory parameters with and without new-onset AF on admission

	All patients (n=590)	SR (n=536)	Paroxysmal AF (n=23)	Persistent AF (n=31)	P value
<b>Baseline</b>					
Age (years)	67±14	67±15	74±10*	71±11	0.026
Gender (male)	287 (48.6%)	259 (48.3%)	14 (60.9%)	14 (45.2%)	0.46
Body mass index (kg/m <sup>2</sup> )	23 (19–26)	23 (19–26)	22 (19–26)	23 (20–25)	0.78
Systolic blood pressure (mm Hg)	130±22	130±22	122±20	127±25	0.13
Diastolic blood pressure (mm Hg)	75±14	75±14	74±14	74±12	0.96
Heart rate (bpm)	85±16	85±14	88±24	96±30***	0.001
pH	7.42 (7.35–7.49)	7.42 (7.35–7.49)	7.42 (7.41–7.44)	7.43 (7.34–7.45)	0.83
PO <sub>2</sub> (mm Hg)	75 (64–85)	75 (64–84)	80 (64–93)	64 (61–88)	0.06
O <sub>2</sub> sat (%)	92 (88–95)	92 (88–95)	94 (90–97)	92 (90–95)	0.38
PCO <sub>2</sub> (mm Hg)	38±10	37±10	39±11	38±10	0.75
Lactate (mmol/L)	2.12±1.10	2.12±1.10	1.96±0.67	2.26±1.36	0.65
White blood cells (10 <sup>12</sup> )	8.12 (5.46–11.87)	8.18 (5.35–11.93)	7.12 (6.10–10.25)	7.75 (5.88–10.62)	0.65
Haemoglobin (g/L)	121 (103–138)	121 (103–137)	121 (88–141)	124 (104–144)	0.82
Creatinine (umol/L)	273±133	271±130	328±167*	266±153	0.12
NT-proBNP (pg/mL)	1564 (794–3309)	1447 (780–3222)	2356 (1084–4097)	3121 (1213–5260)**	0.002
cTNI-ultra (ng/mL)	0.057 (0.029–0.075)	0.063 (0.031–0.075)	0.035 (0.015–0.103)	0.016 (0.008–0.107)*	0.04
D-dimers (mg/L)	4.00 (2.79–6.46)	4.04 (2.86–6.50)	4.31 (2.14–9.21)	3.09 (1.63–5.16)**	0.009
<b>Echocardiography</b>					
MPAD (mm)	31±8	31±8	32±7	28±7	0.17
LAD (mm)	38±9	38±9	42±9	42±7*	0.011
LVDD (mm)	47±9	47±9	49±7	51±6*	0.054
RAD (mm)	40 (32–48)	39 (32–48)	47 (34–50)*	42 (36–46)	0.07
RVDD (mm)	30±7	30±7	33±8	30±7	0.24
RV/LV	0.63 (0.50–0.80)	0.63 (0.49–0.80)	0.70 (0.48–0.83)	0.57 (0.50–0.66)	0.24
LVEF (%)	51±7	52±7	46±8*	46±8***	<0.001
<b>Symptoms</b>					
Dyspnoea	241 (40.8%)	215 (40.1%)	12 (52.2%)	14 (45.2%)	0.45
Chest pain	57 (9.7%)	48 (9.0%)	3 (13.0%)	6 (19.4%)	0.14
Chest tightness	102 (17.3%)	87 (16.2%)	7 (30.4%)	8 (25.8%)	0.09
Syncope	49 (8.3%)	44 (8.2%)	2 (8.7%)	3 (9.7%)	0.96
Cough	273 (46.3%)	253 (47.2%)	10 (43.5%)	10 (32.3%)	0.26
Haemoptysis	78 (13.2%)	69 (12.9%)	4 (17.4%)	5 (16.1%)	0.73
<b>Comorbidity</b>					
Malignancy	66 (11.2%)	60 (11.2%)	1 (4.3%)	5 (16.1%)	0.40
Septicaemia	55 (9.3%)	47 (8.8%)	4 (17.4%)	4 (12.9%)	0.30
COPD	47 (8.0%)	40 (7.5%)	3 (13.0%)	4 (12.9%)	0.36
Pulmonary artery hypertension	56 (9.5%)	51 (9.5%)	0	5 (16.1%)	0.14
History of VTE	180 (30.5%)	175 (32.6%)	3 (13.0%)	2 (6.5%)**	0.005
Cerebral infarction	79 (13.4%)	67 (12.5%)	5 (21.7%)	7 (22.6%)	0.14
Diabetes	28 (4.7%)	23 (4.3%)	3 (13.0%)	12 (6.5%)	0.14
Ischaemic heart disease	76 (12.9%)	59 (11.0%)	9 (39.1%)**	8 (25.8%)*	<0.001

Continued

Table 1 Continued

	All patients (n=590)	SR (n=536)	Paroxysmal AF (n=23)	Persistent AF (n=31)	P value
Pulmonary infection	179 (30.3%)	156 (29.1%)	8 (34.8%)	15 (48.4%)*	0.07
Chronic cor pulmonale	25 (4.2%)	20 (3.7%)	1 (4.3%)	4 (12.9%)*	0.048
Congestive heart failure	124 (21.0%)	98 (18.3%)	10 (43.5%)**	16 (51.6%***)	<0.001
Risk stratification					
sPESI $\geq 1$	375 (63.6%)	336 (62.7%)	15 (65.2%)	24 (77.4%)	0.25
Massive PE	125 (21.2%)	89 (16.6%)	10 (43.5%)	13 (41.9%)	
Submassive PE	332 (56.3%)	312 (58.2%)	9 (39.1%)	11 (35.5%)	
Non-massive PE	133 (22.5%)	135 (25.2%)	4 (17.4%)	7 (22.6%)	<0.001

\*, \*\*, \*\*\*: AF group vs SR group,  $p < 0.05$ ,  $p < 0.01$  and  $p < 0.001$ , respectively.

AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; cTnI-ultra, cardiac troponin I; LAD, left atrium diameter; LVDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; MPAD, main pulmonary artery diameter; NT-proBNP, amino-terminal pro-brain natriuretic peptide;  $O_2$ sat, peripheral oxygen saturation;  $PCO_2$ , partial pressure of carbon dioxide; PE, pulmonary embolism;  $PO_2$ , blood oxygen pressure; RAD, right atrium diameter; RVDD, right ventricular end-diastolic dimension; RV/LV, right ventricle/left ventricle; sPESI, Simplified Pulmonary Embolism Severity Index; SR, sinus rhythm; VTE, venous thromboembolism.

at a dose of 100 IU/kg every 12 hours without contraindications. As regard patients using warfarin, the international normalised ratio (INR) target is usually set at 2.0–3.0. Regarding patients using novel oral anticoagulants (NOAC), dabigatran 110 mg twice daily or rivaroxaban 20 mg once daily recommended.

#### Follow-up

All-cause mortality was measured by telephone, message and email at 6 month after discharge.

#### Statistical analysis

Statistical analysis was performed using SPSS Statistics V.25.0 software (IBM Corp, New York, USA). Patients' characteristics were presented as frequencies for the categorical variables and as mean $\pm$ SD or median with the IQR depending on the normal distribution of the numerical variables. Differences among three groups (SR, paroxysmal AF and persistent AF) were evaluated using Fisher's exact test,  $\chi^2$  test, one-way analysis of variance test with LSD corrections for multiple comparisons, or independent samples Kruskal-Wallis test depending on the normal distribution of the variables. Covariates used in the regression model included demographics, laboratory parameter, comorbidities and PE severity indexes. Statistically different variables were screened out and included in multivariate regressions. AF risk factors were analysed by binary logistic regression and carried out with the enter method. Kaplan-Meier analysis was used to compare the probability of 6-month survival and the log-rank test was used for comparison. Cox regression analysis was used to identify predictors of 6-month survival in patients discharged and carried out with the enter method. A value of  $p < 0.05$  was considered statistically significant.

#### Patient and public involvement

No patient was involved in this study.

## RESULTS

### Clinical characteristics

In the present real-world single-centre cohort, 590 aPE patients were included consecutively over a 2-year period, and 10.1% (71/702) of them suffered from AF on admission. The prevalence of new-onset AF in the present study was 7.7% (54/702). The incidence of paroxysmal AF and persistent AF are 3.3% (23/702) and 4.4% (31/702), respectively. Patients with AF at admission were older and with more comorbidities. In the study cohort, a statistically significant difference in age was observed between the paroxysmal AF group and the SR group. The average age of the paroxysmal AF group was 7 years older than that in the SR group (74 $\pm$ 10 vs 67 $\pm$ 15,  $p < 0.05$ ). The heart rate of the persistent AF group was faster (96 $\pm$ 30 vs 85 $\pm$ 14,  $p < 0.01$ ) than the SR group. No statistical difference in gender and arterial blood gas analysis was observed among the three groups. The SR group had a significantly lower NT-proBNP and cTNI-ultra than the persistent AF ( $p < 0.05$ ). However, the level of D-dimers was lower in the persistent AF group than in the SR group ( $p < 0.01$ ). The proportion of pulmonary infection, ischaemic heart disease, congestive heart failure and chronic cor pulmonale in the AF group were significantly higher than that in the SR group ( $p < 0.05$ ), but the proportion of VTE was lower than that in the SR group ( $p < 0.05$ ). In echocardiography parameters, the left ventricular ejection fraction (LVEF) in the SR group was higher than that in the AF group (52% $\pm$ 7% vs 46 $\pm$ 8%,  $p < 0.01$ ), but the left atrium diameter (LAD) and the left ventricular end-diastolic dimension were lower than those in

**Table 2** Treatment and outcome

	All patients (n=590)	SR (n=536)	Paroxysmal AF (n=23)	Persistent AF (n=31)	P value
<b>Treatment on admission</b>					
Anticoagulation	525 (89.0%)	481 (89.7%)	19 (82.6%)	25 (80.6%)	0.18
Warfarin	490 (83.1%)	451 (84.1%)	17 (73.9%)	22 (71.0%)	0.08
NOAC	35 (5.9%)	30 (5.6%)	2 (8.7%)	3 (9.7%)	0.55
INR at the time of hospital discharge	2.52 (1.88–3.20)	2.34 (2.07–2.89)	2.38 (1.90–3.24)	2.54 (2.13–3.29)	0.69
INR at the time of readmission (n=52)	2.49±0.69	2.51±0.68	2.40±0.47	2.36±0.97	0.85
Thrombolytic	54 (9.2%)	49 (9.1%)	2 (8.3%)	3 (9.7%)	0.99
Inferior vena cava filter	62 (10.5%)	59 (11.0%)	2 (8.7%)	1 (3.2%)	0.37
Antiplatelet	67 (11.4%)	40 (7.5%)	12 (52.2%)*	15 (48.4%)*	<0.001
Statins	116 (19.7%)	90 (16.8%)	12 (52.2%)*	14 (45.2%)*	<0.001
β-blocker	91 (15.4%)	67 (12.5%)	9 (39.1%)*	15 (48.4%)*	<0.001
Endotracheal intubation	34 (5.8%)	32 (6.0%)	0 (0.0%)	2 (6.5%)	0.49
<b>Outcome</b>					
In-hospital mortality	54 (7.7%)	44 (7.5%)	3 (11.5%)	7 (18.4%)*	0.021
30-day mortality	23 (3.9%)	14 (2.6%)	3 (12.5%)*	6 (19.4%)*	<0.001
6-month mortality	84 (14.2%)	60 (11.2%)	9 (39.1%)*	15 (48.4%)*	<0.001

\*, \*\*, \*\*\*: AF group vs SR group,  $p < 0.05$ ,  $p < 0.01$  and  $p < 0.001$ , respectively.

AF, atrial fibrillation; INR, international normalised ratio; NOAC, novel oral anticoagulant; SR, sinus rhythm.

the persistent AF group ( $p < 0.05$ ). In addition, the right atrium diameter in the paroxysmal group was higher than that in the SR group ( $p < 0.01$ ). When it comes to risk stratification, although no significant difference in sPESI was found among the three groups, the incidence of massive PE in the persistent AF group was the highest ( $p < 0.01$ ) (table 1). As regards the treatment, the AF group was subjected to β-blockers, statins and antiplatelet therapy in significantly higher proportions than the SR group ( $p < 0.01$ ) (table 2).

#### Subgroup analysis of the massive PE and risk factors for new-onset AF

Considering that the AF group has a high incidence of massive PE, we conducted a subgroup analysis. In the massive PE group, the LVEF in the paroxysmal AF group was significantly lower than that in the SR group ( $p < 0.05$ ). The proportion of congestive heart failure in the persistent AF group was higher than that in the SR group, and heart rate and LAD also showed the same trend ( $p < 0.05$ ). In the paroxysmal and the persistent AF group, the heart rate of the persistent AF group was significantly higher than that of the paroxysmal AF group ( $p < 0.05$ ) (table 3). In the entire cohort, the multivariable analysis showed that massive PE (OR 2.67; 95% CI 1.19 to 5.99;  $p = 0.017$ ), ischaemic heart disease (OR 3.25; 95% CI 1.65 to 6.39;  $p < 0.001$ ) and congestive

heart failure (OR 3.33; 95% CI 1.81 to 6.12;  $p < 0.001$ ) were independent predictors of new-onset AF (table 4).

#### Prognostic relevance of new-onset AF on admission

During the follow-up, one patient died from other causes, and 12 patients were censored. The follow-up rate was 98% (578/590). The survival analysis was performed on 578 patients with complete data. The overall 30-day survival rate was 96.1% (567/590), and the 6-month survival rate was 85.8% (506/590). The 30-day survival rates in the SR group, paroxysmal AF group and persistent AF group were 97.4% (522/536), 87.5% (20/23) and 80.6% (25/31), respectively. The 6-month survival rates in the SR group, paroxysmal AF group and persistent AF group were 88.8% (476/536), 60.9% (14/23) and 51.6% (16/31), respectively (table 2). Kaplan-Meier analysis showed that the survival rate of the paroxysmal and persistent AF groups was significantly lower than the SR group within 6 months (60.9% and 51.6% vs 88.8%,  $p < 0.001$ ) (figure 2). Cox survival analysis revealed that new-onset persistent AF (OR 2.36; 95% CI 1.22 to 4.55;  $p = 0.011$ ), malignancy (OR 3.84; 95% CI 2.13 to 6.95;  $p < 0.001$ ), congestive heart failure (OR 2.77; 95% CI 1.64 to 4.68;  $p < 0.001$ ), ischaemic heart disease (OR 2.40; 95% CI 1.43 to 3.99;  $p = 0.001$ ), cerebral infarction (OR 1.93; 95% CI 1.09 to 3.40;  $p = 0.023$ ) and massive PE (OR 2.76; 95% CI 1.51 to

**Table 3** Baseline demographic and laboratory parameters with and without new-onset AF in massive PE (only showed statistically different indicators)

	All patients (n=125)	SR (n=101)	Paroxysmal AF (n=11)	Persistent AF (n=13)	P value
Congestive heart failure	41 (36.6%)	26 (29.2%)	5 (50.0%)	10 (76.9%)**	0.003
Diabetes	7 (6.5%)	3 (3.4%)	2 (20.0%)	2 (15.4%)	0.042
Heart rate (bpm)	87±20	85±16	88±10	105±37**#	0.004
LVEF (%)	49 (45–54)	49 (46–54)	45 (39–50)*	46 (42–49)	0.009
Chronic cor pulmonale	5 (4.5%)	2 (2.2%)	1 (10.0%)	2 (15.4%)	0.068
LAD	38 (30–45)	36 (30–44)	39 (36–48)	47 (39–54)*	0.019
History of VTE	33 (29.5%)	31 (34.8%)	1 (10.0%)	1 (7.7%)	0.049

\*, \*\*, \*\*\*: AF group vs SR group,  $p < 0.05$ ,  $p < 0.01$  and  $p < 0.001$ , respectively.; #: paroxysmal AF group vs persistent AF group,  $p < 0.05$ .

AF, atrial fibrillation; LAD, left atrium diameter; LVEF, left ventricular ejection fraction; PE, pulmonary embolism; SR, sinus rhythm; VTE, venous thromboembolism.

5.03;  $p = 0.001$ ) were independent predictors of mortality within 6 month (table 5).

## DISCUSSION

This present real-world single-centre cohort study identified several risk factors for new-onset AF in patients with aPE. In particular, massive PE, ischaemic heart disease and congestive heart failure were associated with higher odds of new-onset AF. In addition, new-onset persistent AF was an independent predictor for 6-month all-cause mortality in PE patients.

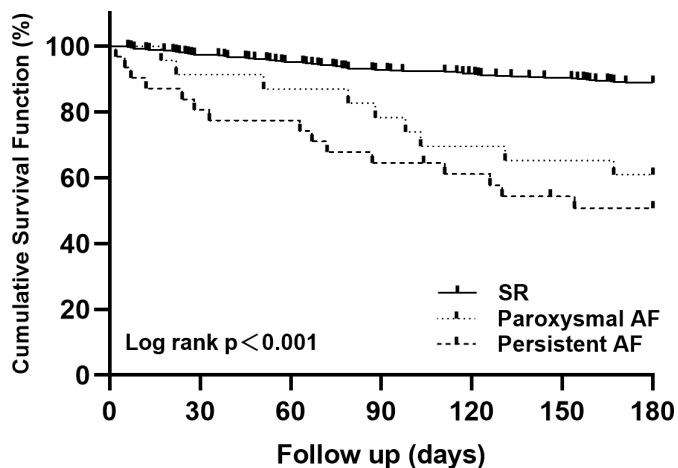
PE is a different clinical manifestation of VTE. Previous studies found that only 50%–70% of PE patients have VTE, but the proportion of AF in PE

patients without a history of VTE reaches 54%.<sup>13</sup> According to the largest population-based autopsy cohort, the thrombosis of the right atrium is difficult to assess. However, it is as common as the thrombosis of the left atrium. Of note, 38% of patients with intracardiac thrombosis had a manifest PE, and more than half had right-side intracardiac thrombosis.<sup>14</sup> In addition, several studies suggested that isolated PE may arise from right atrial thrombi due to AF.<sup>15 16</sup> Intriguingly, our study demonstrated that the prevalence of VTE was different in SR and AF groups. In those patients whose embolus origin cannot be determined, we speculated that it may be associated with those ‘silence AF’ that were not previously diagnosed.

**Table 4** Predictors of new-onset AF after acute PE in univariate and multivariate model

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.03 (1.01 to 1.05)	0.011	1.02 (1.00 to 1.04)	0.053
Cerebral infarction	2.00 (1.00 to 3.99)	0.049	1.95 (0.92 to 4.11)	0.08
Chronic cor pulmonale	2.63 (0.95 to 7.32)	0.06		
Congestive heart failure	4.15 (2.33 to 7.39)	<0.001	3.33 (1.81 to 6.12)	<0.001
COPD	1.85 (0.78 to 4.35)	0.16		
Diabetes	2.28 (0.83 to 6.25)	0.11		
Ischaemic heart disease	3.72 (1.97 to 7.01)	<0.001	3.25 (1.65 to 6.39)	<0.001
Malignancy	0.99 (0.41 to 2.42)	0.99		
Massive PE	3.12 (1.47 to 6.83)	0.003	2.67 (1.19 to 5.99)	0.017
Submassive PE	0.79 (0.37 to 1.69)	0.54	0.81 (0.37 to 1.79)	0.61
Pulmonary artery hypertension	0.97 (0.37 to 2.55)	0.95		
Pulmonary infection	1.81 (1.02 to 3.20)	0.042		
Septicaemia	1.81 (0.81 to 4.06)	0.15		
History of VTE	0.26 (0.11 to 0.61)	0.002		
sPESI	1.55 (0.83 to 2.88)	0.17		

AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; PE, pulmonary embolism; sPESI, Simplified Pulmonary Embolism Severity Index; VTE, venous thromboembolism.



**Figure 2** Kaplan–Meier curve depicting all-cause mortality for paroxysmal AF and persistent AF. AF, atrial fibrillation; SR, sinus rhythm. No statistical difference was found between paroxysmal AF and persistent AF. Paroxysmal AF (HR 3.75, 95% CI 1.01 to 13.90) and persistent AF (HR 5.74, 95% CI 1.76 to 18.72) have significantly higher mortality than sinus rhythm.

New-onset AF may be triggered by acute, potentially reversible precipitants. It has been confirmed that right ventricular failure and stretch injuries may trigger AF.<sup>17 18</sup> Nevertheless, limited data are available on the risk factor of new-onset AF in PE patients. It has been reported age,

congestive heart failure as independent predictors for subsequent AF in PE cohort.<sup>19–21</sup> Massive PE, which causes a sharp increase in afterload and stretch injuries, could also be associated with AF. Our study confirmed that massive PE was a risk factor for new-onset AF. In addition, we also found that patients with congestive heart failure or ischaemic heart disease had a higher prevalence of AF compared with patients without that, which is consistent with previous studies.

To find out who is susceptible to paroxysmal or persistent AF in massive PE group, we reclassified patients using risk stratification proposed by AHA/ACC and conducted an analysis of subgroups. In massive PE group, we found that when patients have congestive heart failure, fast heart rate and LAD, they were susceptible to persistent AF. We surmised that the occurrence of persistent AF may be related to the severity of congestive heart failure. When cardiac function or afterload cannot be improved, the occurrence of myocardial remodelling provides a substrate for the development of persistent AF. Considering that we included small samples, more in-depth research may be needed.

Our cohort demonstrated that in-hospital and 6-month mortality were higher than the previous studies.<sup>19–22</sup> Ng *et al* found that PE with baseline AF had higher mortality than subsequent AF in the first year (23.7% vs 9.5%) and the fifth year (45.4% vs 34.9%), but the latter had

**Table 5** Univariate and enter multivariate Cox hazard analysis for the predictors of 6-month mortality

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.01 (0.99 to 1.03)	0.18	1.01 (0.99 to 1.03)	0.37
NT-proBNP	2.44 (1.37 to 4.35)	0.002	0.88 (0.45 to 1.72)	0.71
cTNI-ultra	0.88 (0.53 to 1.49)	0.64		
LVEF	0.99 (0.95 to 1.02)	0.35		
Paroxysmal AF	4.04 (2.00 to 8.14)	<0.001	1.43 (0.65 to 3.18)	0.37
Persistent AF	5.93 (3.36 to 10.46)	<0.001	2.36 (1.22 to 4.55)	0.011
Ischaemic heart disease	3.02 (1.88 to 4.86)	<0.001	2.40 (1.43 to 3.99)	0.001
Malignancy	2.82 (1.71 to 4.67)	<0.001	2.77 (1.57 to 4.87)	<0.001
Septicaemia	1.45 (0.75 to 2.81)	0.27		
COPD	1.48 (0.74 to 2.95)	0.27		
Pulmonary artery hypertension	1.50 (0.80 to 2.84)	0.21		
History of VTE	0.70 (0.42 to 1.15)	0.16		
Cerebral infarction	2.22 (1.34 to 3.67)	0.002	1.93 (1.09 to 3.40)	0.023
Diabetes	1.38 (0.56 to 3.41)	0.49		
Pulmonary infection	1.36 (0.87 to 2.12)	0.18		
Chronic cor pulmonale	1.90 (0.83 to 4.35)	0.13		
Congestive heart failure	4.06 (2.64 to 6.24)	<0.001	2.50 (1.51 to 4.12)	<0.001
Massive PE	3.50 (1.98 to 6.19)	<0.001	2.76 (1.51 to 5.03)	0.001
Submassive PE	0.69 (0.38 to 1.27)	0.24	0.68 (0.36 to 1.29)	0.24

cTnl-ultra; cardiac troponin I ultra; AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; NT-proBNP, amino-terminal pro-brain natriuretic peptide; PE, pulmonary embolism; VTE, venous thromboembolism.



higher all-cause mortality during long-term follow-up.<sup>19</sup> These results suggested that the subsequent AF may have an adverse effect on the long-term prognosis. Ebner *et al* reported that AF on admission with PE 1-year mortality was 17.5%, and it do not affect the prognostic performance.<sup>20</sup> However, they neither distinguished whether AF was subsequent or existed before, nor it was persistent or paroxysmal. In addition, Ng *et al* showed that subsequent AF with PE 6-month mortality was 10%,<sup>19</sup> while they did not investigate the effects of different AF types on the mortality. In our cohort, we found that the 6-month mortality of persistent AF group reached a staggering 48.4%. These results implicit that there may be regional differences in the management of AF in PE, and AF affects the prognosis of PE patients in multiple dimensions.

There is no consensus on the impact of AF on PE risk stratification. A recent study showed that the inclusion of AF in sPESI could improve the prediction of in-hospital adverse events.<sup>23</sup> In another PE cohort, they found AF group had a high proportion of massive PE and in-hospital mortality.<sup>24</sup> Indeed, the in-hospital mortality of PE combined with AF is 20%–32%, and nearly half of the patients suffer from right-sided intracardiac thrombus.<sup>21 25</sup> The incidence of complications is also significantly higher in these patients than in the ones without AF.<sup>20</sup> A meta-analysis performed on 10 studies, including 3007 patients with aPE, demonstrated that AF is associated with an increased risk of circulatory shock and death.<sup>26</sup> Our research found that massive PE is a risk factor for AF. Therefore, the occurrence of AF may reflect the severity of PE to a certain extent. On the pathophysiology, providing the corresponding preload to the left heart by the right heart is essential to maintain haemodynamic stability and long-term survival in PE patients. However, the episode of AF aggravates haemodynamic disturbances. Furthermore, persistent fast ventricular rhythm causes progressive heart failure, which in turn causes death. In addition, persistent AF, which provokes a hypercoagulable state and induces platelet aggregation, may aggravate the embolic area of PE. Eventually, the complex interaction between AF and PE leads to increased mortality.

Our result implied that the complementary treatment for comorbidities, especially the control of cardiovascular disease, could also be essential for the prognosis. In our cohort, the proportion of congestive heart failure (48.1% vs 20.6%) and ischaemic heart disease (31.5% vs 26.5%) in the new-onset AF group was higher than that in the study of the Ebner *et al*. However, the use of  $\beta$ -blocker and antiplatelet ratios were lower than the previous studies when combined with cardiovascular disease.<sup>20</sup> When patients had anaemia or chronic obstructive pulmonary disease, whether those relative contraindications affecting the use of  $\beta$ -blocker and antiplatelet is worthy of our thinking. In addition, some patients might be first diagnosed with cardiovascular disease in our cohort. These fatal complications or comorbidities affected the prognosis because patients were not appropriately examined or treated by the cardiologist. As regard patients with malignancy, they underwent more palliative treatment.

Due to economic factors, nearly 80% of patients used warfarin in our cohort. The ratios of INR values between 2.0 and 3.0 in the SR group, paroxysmal AF group and persistent AF group were 59.0%, 39.1% and 54.8%, respectively. Therefore, the overall compliance rate of warfarin was unsatisfactory. Interestingly, among the 8.8% (52/590) of patients who were readmitted to our hospital, 26.9% (14/52) had malignancy. The compliance rates of the SR group, paroxysmal AF group and persistent AF group were 42.9% (18/42), 50.0% (2/4) and 33.3% (2/6), respectively. This result suggested that their compliance rate was further reduced. Their all-cause mortality was 17.3% (9/52) within 6 months and 77.8% (7/9) of death did not meet the target INR. Since warfarin has a high risk of bleeding, patients with comorbidities have a high incidence of interrupting or adjusting the warfarin dose by themselves. A treatment range time >70% could hardly be achieved.<sup>27</sup> In brief, interdisciplinary cooperation, outpatient management and follow-up are vital.

As regards the treatments, the following points should be underlined. Compared with warfarin, patients with AF treated with apixaban and dabigatran showed the low risk of subsequent VTE.<sup>28 29</sup> NOAC could be an alternative drug for PE.<sup>30 31</sup> The primary and secondary prevention of cardiovascular diseases should be enhanced after the diagnosis of aPE due to the high incidence of cardiovascular diseases. Besides, drugs used to treat cardiovascular diseases are also effective for PE, and the transition from acute treatment to long-term treatment after discharge may reduce mortality.

Our research has some strength. Previous studies did not distinguish AF types,<sup>20</sup> while AF was more carefully divided into paroxysmal and persistent AF in this study. In addition, our study is currently the largest PE cohort study in China and provides sufficient detailed follow-up data. Besides, we first confirmed that new-onset persistent AF is an independent predictor affecting the prognosis of patients with PE. Our research also has some limitations. First, the study was based on the retrospective analysis of patient medical records. So, some data were missing, and the follow-up time was relatively short. Second, we could only get patients' all-cause mortality. The incidence of sudden death or cardiovascular mortality in the PE patients is unclear. Third, our data maybe not applicable for different cohorts in other developed countries. However, our results suggested that the PE patients with persistent AF should be paid more attention to improve the prognosis.

## CONCLUSION

Massive PE, ischaemic heart disease and congestive heart failure are high-risk factors which were related to new-onset AF in aPE. New-onset persistent AF was an independent predictor for 6-month all-cause mortality in PE patients.



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