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Identification of Prognostic Factors for Recurrence and Mortality in Patients With Acute Pulmonary Embolism

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ABSTRACT

Background: This study aimed to explore prognostic factors for 1-year recurrence and mortality in patients with acute pulmonary embolism (APE).

Methods: APE patients who attended the Emergency Department of Fujian Provincial Hospital from January 2016 to June 2020 were recruited. Univariate and multivariate logistic regression analyses were carried out to determine the prognostic factors for 1-year recurrence and mortality.

Results: A total of 458 APE patients were included, of whom 81 (17.69%) had recurrence, and 97 (21.18%) died. Multivariate logistic regression analyses revealed that smoke (OR: 1.949; 95% CI: 1.094–3.470; P = 0.023), abnormal platelet distribution width (OR: 3.013; 95% CI: 1.574–5.767; P = 0.001), and interrupted maintenance therapy (OR: 18.280; 95% CI: 9.777–34.179; P < 0.001) were significantly associated with an increased risk of 1-year recurrence in APE patients. Age ≥65 years (OR: 3.492; 95% CI: 1.876–6.500; P < 0.001), history of malignancy (OR: 7.190; 95% CI: 3.804–13.587; P < 0.001), history of long-term immobilization (OR: 6.244; 95% CI: 3.472–11.228; P < 0.001), mechanical ventilation (OR: 5.971; 95% CI: 3.154–11.304; P < 0.001), and interrupted maintenance therapy (OR: 2.414; 95% CI: 1.315–4.432; P = 0.004) were independent prognostic factors for 1-year mortality. The AUC of 1-year mortality and recurrence prediction models were 0.852 (95% CI: 0.805–0.898) and 0.868 (95%CI: 0.832–0.905).

Conclusion: In patients with APE, history of smoking, abnormal PDW, and interrupted maintenance therapy were significantly associated with the risk of 1-year recurrence, while age ≥65 years, history of malignancy, history of long-term immobilization, mechanical ventilation, and interrupted maintenance therapy were independent prognostic factors for 1-year mortality.

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INTRODUCTION

Acute pulmonary embolism (APE) is the third most common acute vascular disease worldwide and is a fatal cardiopulmonary vascular disease with a high mortality rate that is only lower than that of acute myocardial infarction and stroke [Ruiz-Fernández 2016]. In patients with APE, arrhythmia and/or severe right ventricle (RV) failure can cause acute hemodynamic abnormalities, leading to inadequate arterial blood flow to the organs and ultimately death. Even non-fatal APE can have serious adverse effects on patients' short- and long-term quality of life [Haddad 2008; van der Bijl 2011]. Despite the dramatic advances in the diagnosis and management of APE in recent years, its short- and long-term mortality rates remain high [Søgaard 2014]. Previous studies have investigated the short-term mortality of patients with APE, while studies on the long-term mortality of patients with APE are rare. The results from the Multicenter Emergency Medicine Pulmonary Embolism in the Real World Registry (EMPEROR) and Registro Informatizado de la Enfermedad TromboEmbólica (RIETE) showed that the mortality rate of patients with PE within 30 days is 3.3–5.4% [Pollack 2011; Laporte 2008]. A few studies have reported long-term mortality rates of APE of up to 25% [Gupta 2018; Konstantinides 2020; Faller 2017]. A study including 1023 patients with PE showed that the cumulative mortality rates at 3 months, 6 months, 1 year, 3 years, and 5 years after discharge were 8.3%, 11.1%, 16.3%, 26.7%, and 31.6%, respectively [Ng 2011]. How best to reduce the mortality rate of APE patient remains a hot topic and challenge in the context of current clinical research. Carrying out an accurate prognostic assessment is an effective approach to reduce the APE mortality rate.

In the acute phase, the thrombotic burden of patients with APE is directly related to the short-term recurrence rate and mortality, while the long-term prognosis may be more heavily influenced by potential comorbidities or predisposing factors, such as cancer, heart failure, and pulmonary diseases [Furlan 2012; Delcroix 2016; Goldhaber 2003; Goldhaber 1999; Meneveau 2003]. There is a dearth of systematic and comprehensive research on the prognostic factors for recurrence and mortality in patients with APE. This study aimed to explore the risk factors linked to 1-year recurrence and mortality in patients with APE.

METHODS

Participants: Patients who visited the emergency department of Fujian Provincial Hospital from January 1, 2016, to June 30, 2020, and were diagnosed with APE were recruited. The diagnostic criteria for APE followed the Guidelines for the Diagnosis and Treatment of Acute Pulmonary Embolism published by The European Society of Cardiology (ESC) in 2019 [Konstantinides 2020]. The study was approved by the Ethics Committee of Fujian Provincial Hospital (K2020-04-053), and the informed consent was signed from the patients.

The inclusion criteria were as follows: (1) patients who visited the emergency department of our hospital from January 1, 2016, to June 30, 2020, and (2) patients diagnosed with APE/acute pulmonary artery embolism/pulmonary embolism/pulmonary thromboembolism. The exclusion criteria were as follows: (1) age <18 years; (2) patients with APE not first diagnosed in our hospital; (3) patients whose conditions were complicated by other serious diseases or acute fatal diseases, including acute myocardial infarction, acute aortic dissection or aneurysm, heart valve disease, severe hepatic or renal impairment, hematologic disorders, bone marrow suppression, severe infection, shock due to non-pulmonary embolism, or hemodynamic instability; (4) being pregnant; (5) having incomplete clinical data and (6) being lost to follow up.

Data sources: We queried the emergency electronic medical record system and inpatient electronic medical record system to collect clinical indicators on patients, including the following: (1) demographic information such as age and sex; (2) smoke; (3) vital signs including pulse rate, respiratory rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), and peripheral oxygen saturation (SpO2); (4) blood investigations including white blood cell count (WBC), neutrophil count, platelet count (PLT), lymphocyte count, red blood cell distribution width (RDW), mean platelet volume (MPV), platelet distribution width (PDW), neutrophil count/lymphocyte count ratio (NLR; the ratio of absolute neutrophil count to absolute lymphocyte count in the same blood specimen), and platelet count/lymphocyte count ratio (PLR; the ratio of absolute platelet count to absolute lymphocyte count in the same blood specimen); (5) D-dimer levels; (6) levels of myocardial injury markers including troponin I (cTnI) and N-terminal pro-brain natriuretic peptide (NT-ProBNP); (7) presence of any comorbidity, including hypertension, hyperlipidemia, diabetes mellitus (DM), coronary artery disease (CHD), deep vein thrombosis/varicose veins of lower extremities, malignancy, arrhythmia (atrial fibrillation, atrial flutter, high-grade atrioventricular block, paroxysmal supraventricular tachycardia, frequent premature ventricular beats), chronic lung disease, chronic heart failure (ischemic cardiomyopathy, dilated cardiomyopathy, hypertensive heart disease, hypertrophic cardiomyopathy), nephrotic syndrome, or long-term immobilization (bed rest for more than 7 consecutive days); (8) APE severity stratification, as evaluated by a patient's hemodynamic status, myocardial injury markers and right ventricular function according to the ESC Guidelines in 2019 [Konstantinides 2020]; and (9) treatment including in the form of mechanical ventilation, acute phase (anticoagulant therapy, anticoagulant plus thrombolytic therapy, and others), maintenance phase (anticoagulant therapy, antiplatelet therapy, and others), and interrupted maintenance therapy.

Study endpoints: The outcomes were 1-year recurrence and mortality rates in patients with APE. Recurrent APE was diagnosed based on new-onset acute chest symptoms with a new or enlarged segmental perfusion defect under normal ventilation by a high-probability V/Q lung scan, according to Prospective Investigation of Pulmonary Embolism Diagnosis criteria, or segmental or more proximal pulmonary artery with an intraluminal filling defect, or recurrent proximal deep vein thrombosis. Mortality was defined as patient death from any cause within 1 year of admission.

Statistical methods: Statistical analyses were conducted using SPSS 24.0 software (IBM, Chicago, IL, USA). Graphs were plotted with the use of GraphPad Prism 7.01 (GraphPad Software Inc., San Diego, CA, USA). Normally distributed continuous variables are described as mean±standard deviation (SD). Non-normally distributed continuous variables are expressed as the median and interquartile range (IQR). Categorical variables are displayed as count and percentage. Factors correlated with 1-year recurrence/mortality risk were analyzed using a univariate logistic regression model.

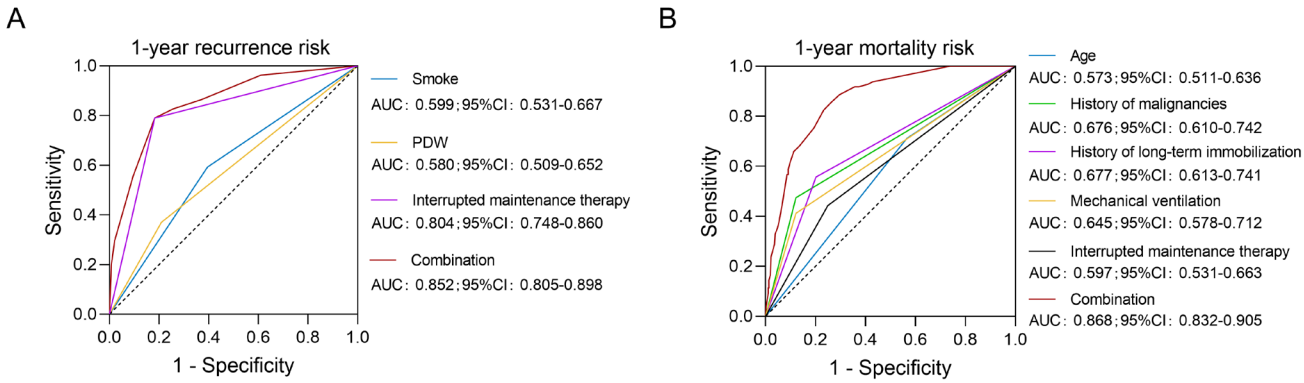

Figure 1. Prognostic factors linked to 1-year recurrence and 1-year mortality risk

Table 1. Clinical characteristics of patients with APE

Items	PE patients (*N* = 458)
Demographics	
Age (years), mean±SD	66.7±13.1
Gender, n (%)	
Male	235 (51.3)
Female	223 (48.7)
Smoke, n (%)	
No	261 (57.0)
Yes	197 (43.0)
Medical history, n (%)	
Hypertension	253 (55.2)
Hyperlipidemia	94 (20.5)
Diabetes mellitus	138 (30.1)
CHD	56 (12.2)
Varicose veins/vein thrombosis of lower extremity	198 (43.2)
Malignancies	90 (19.7)
Arrhythmia	62 (13.5)
Chronic lung disease	69 (15.1)
Chronic cardiac failure	33 (7.2)
Nephrotic syndrome	17 (3.7)
Long-term immobilization	127 (27.7)
Risk classification, n (%)	
Low	103 (22.5)
Moderate	164 (35.8)
High	191 (41.7)
Laboratory indexes, median (IQR)	103 (22.5)
Pulse rate (bpm)	90.0 (78.0-117.0)
Respiratory rate (bpm)	21.0 (20.0-25.0)
SBP (mmHg)	122.0 (105.0-136.0)
DBP (mmHg)	75.0 (64.0-81.3)
SpO_2 (%)	94.0 (89.0-97.0)
WBC (×109/L)	9.5 (7.3-12.3)
Neutrophil (×109/L)	6.8 (4.8-9.6)
PLT (×109/L)	236.0 (193.0-294.5)
Lymphocyte count (×109/L)	1.57 (1.21-1.90)
RDW (%)	13.3 (12.5-14.1)
MPV (fl)	9.9 (9.2-10.7)
PDW (%)	12.7 (10.8-15.9)
D-dimer (mg/L)	17.3 (8.7-26.2)
NT-proBNP (pg/L)	1570.0 (345.0-4108.0)
cTn I (ng/mL)	0.13 (0.02-0.80)
NLR	4.4 (2.7-7.5)
PLR	157.3 (108.4-218.4)
Mechanical ventilation, n (%)	
No	374 (81.7)
Yes	84 (18.3)
Treatment in acute phase, n (%)	
Anticoagulant therapy	380 (83.0)
Anticoagulant+thrombolytic therapy	74 (16.2)
Others	4 (0.9)
Maintenance, n (%)	
Anticoagulant therapy	266 (58.1)
Antiplatelet therapy	189 (41.3)
Others	3 (0.7)
Interrupted maintenance therapy, n (%)	
No	325 (71.0)
Yes	133 (29.0)

PE, pulmonary embolism; SD, standard deviation; CHD, coronary heart disease; IQR, interquartile range; SBP, systolic blood pressure; DBP, diastolic blood pressure; SpO2, oxygen saturation; WBC, white blood cell; PLT, platelet; RDW, red blood cell distribution width; MPV, mean platelet volume; PWD, platelet distribution width; NT-proBNP, N-terminal fragment of the brain natriuretic peptide precursor; cTn I, cardiac troponin I; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio

The factors with $P < 0.1$ in the univariate logistic regression model were further analyzed in a multivariate logistic regression model to select independent predictors of 1-year recurrence/mortality risk using a forward stepwise method. The prognostic model for 1-year recurrence/mortality risk was then built, according to the results of the multivariate logistic regression analyses. The abilities of independent predictors and the model to predict 1-year recurrence/mortality risk were evaluated using a receiver operating characteristic (ROC) curve and the area under the ROC curve (AUC). All tests were two-tailed. A *P*-value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics of patients with APE: A total of 458 patients with APE were included, with a mean age of 66.7 ± 13.1 years; 235 were male (51.3%). Regarding medical history, 253 (55.2%) patients had hypertension, 94 (20.5%) had hyperlipidemia, 138 (30.1%) had DM, 56 (12.2%) had CHD, 198 (43.2%) had varicose veins/venous thrombosis of the lower extremities, 90 (19.7%) had malignant tumors, 62 (13.5%) had arrhythmia, 69 (15.1%) had chronic lung disease, 33 (7.2%) had chronic heart failure, and 127 (27.7%) had prolonged immobilization. There were 103 (22.5%), 164 (35.8%), and 191 (41.7%) patients with low-, medium-, and high-risk PE, respectively. Other variables are detailed in Table 1. (Table 1)

1-year recurrence: Of the 458 patients with APE, 81 (17.69%) experienced recurrence within 1 year. Univariate

Table 2. Univariate logistic regression model analysis of factors predicting 1-year recurrence risk

Items	*P*-value	Univariate logistic regression model		
		OR	95% CI Lower	95% CI Higher
Age (≥65 years vs. <65 years)	0.286	0.769	0.474	1.247
Gender	0.070	1.572	0.964	2.564
Smoke (yes vs. no)	0.001	2.226	1.365	3.629
History of hypertension (yes vs. no)	0.579	1.147	0.706	1.865
History of hyperlipidemia (yes vs. no)	0.307	1.342	0.763	2.363
History of diabetes mellitus (yes vs. no)	0.914	0.971	0.575	1.642
History of CHD (yes vs. no)	0.971	1.013	0.488	2.104
History of varicose veins/vein thrombosis of lower extremity (yes vs. no)	0.997	0.999	0.615	1.622
History of malignancies (yes vs. no)	<0.001	3.108	1.832	5.273
History of arrhythmia (yes vs. no)	0.711	1.137	0.575	2.248
History of chronic lung disease (yes vs. no)	0.945	0.976	0.497	1.917
History of chronic cardiac failure (yes vs. no)	0.309	1.543	0.669	3.557
History of nephrotic syndrome	0.061	2.662	0.955	7.421
History of long-term immobilization (yes vs. no)	0.216	1.385	0.827	2.319
High risk classification	0.056	1.364	0.992	1.876
Pulse rate (abnormal vs. normal)	0.257	1.324	0.815	2.151
Respiratory rate (abnormal vs. normal)	0.341	1.381	0.711	2.683
SBP (abnormal vs. normal)	0.069	0.606	0.353	1.039
DBP (abnormal vs. normal)	0.874	1.043	0.620	1.755
SpO2 (abnormal vs. normal)	0.024	1.752	1.076	2.853
WBC (abnormal vs. normal)	0.400	0.813	0.502	1.317
Neutrophil (abnormal vs. normal)	0.528	0.856	0.529	1.385
PLT (abnormal vs. normal)	0.279	1.432	0.747	2.745
Lymphocyte count (abnormal vs. normal)	0.436	1.275	0.692	2.351
RDW (abnormal vs. normal)	0.082	1.635	0.940	2.846
MPV (abnormal vs. normal)	0.531	0.838	0.482	1.457
PDW (abnormal vs. normal)	0.002	2.219	1.326	3.712
D-dimer (high vs. low)*	0.068	1.575	0.968	2.564
NT-proBNP (high vs. low)*	0.061	1.592	0.978	2.591
cTn I (abnormal vs. normal)	0.188	1.387	0.852	2.257
NLR (high vs. low)*	0.937	0.981	0.607	1.585
PLR (high vs. low)*	0.290	1.297	0.801	2.102
Mechanical ventilation (yes vs. no)	0.787	0.916	0.487	1.724
Treatment in acute phase				
Anticoagulant therapy	Reference	-	-	-
Anticoagulant+thrombolytic therapy	0.466	0.773	0.387	1.543
Others	0.999	-	-	-
Maintenance treatment				
Anticoagulant therapy	Reference	-	-	-

Antiplatelet therapy	0.033	0.572	0.342	0.956
Others	0.999	-	-	-
Interrupted maintenance therapy (yes vs. no)	<0.001	16.805	9.268	30.470

Boldface represents P value < 0.1. *Divided as high group and low group, according to median value. OR, odds ratio; CI, confidence interval; CHD, coronary heart disease; IQR, interquartile range; SBP, systolic blood pressure; DBP, diastolic blood pressure; SpO2, oxygen saturation; WBC, white blood cell; PLT, platelet; RDW, red blood cell distribution width; MPV, mean platelet volume; PDW, platelet distribution width; NT-proBNP, N-terminal fragment of the brain natriuretic peptide precursor; cTn I, cardiac troponin I

Table 3. Multivariate logistic regression model analysis of independent factors predicting 1-year recurrence risk

Items	Forward stepwise multivariate logistic regression model			
	P-value	OR	95% CI Lower	95% CI Higher
Smoke (yes vs. no)	0.023	1.949	1.094	3.470
PDW (abnormal vs. normal)	0.001	3.013	1.574	5.767
Interrupted maintenance therapy (yes vs. no)	<0.001	18.280	9.777	34.179

The model was as follows: P = exp [-3.583 + 0.667*(smoke) + 1.103*(PDW) + 2.906*(Interrupted maintenance therapy)]/1+ exp [-3.583 + 0.667*(smoke) + 1.103*(PDW) + 2.906*(Interrupted maintenance therapy)]. OR, odds ratio; CI, confidence interval; PDW, platelet distribution width

logistic regression analyses revealed that smoke, history of malignancy, SpO2, PDW, antiplatelet therapy at maintenance phase, and interrupted maintenance therapy were significantly associated with 1-year recurrence. (Table 2) After adjusting for confounders, multivariate logistic regression analyses revealed that smoke (odds ratio [OR]: 1.949; 95% confidence interval [CI]: 1.094–3.470; P = 0.023), PDW (OR: 3.013; 95% CI: 1.574–5.767; P = 0.001), and interrupted maintenance therapy (OR: 18.280; 95% CI: 9.777–34.179; P < 0.001) were significantly associated with the risk of 1-year recurrence in patients with APE. (Table 3)

1-year mortality: Of the 458 patients with APE, 97 (21.18%) died within 1 year. As represented in Table 4, univariate logistic regression analyses revealed that age ≥65 years, history of DM history, malignancy history, long-term immobilization, higher risk stratification, faster pulse rate, SBP, DBP, SpO2, WBC, neutrophil, platelet, lymphocyte count, RDW, PDW, NT-ProBNP, cTnI, NLR, PLR, mechanical ventilation, antiplatelet therapy at maintenance phase, and interrupted maintenance therapy were associated with the risk of 1-year mortality in patients with APE. (Table 4) Multivariate logistic regression analyses revealed that age ≥65 years (OR: 3.492; 95% CI: 1.876–6.500; P < 0.001), malignancy history (OR: 7.190; 95% CI: 3.804–13.587; P < 0.001), long-term immobilization history (OR: 6.244; 95% CI: 3.472–11.228; P < 0.001), mechanical ventilation (OR: 5.971; 95%CI: 3.154–11.304; P < 0.001), and interrupted maintenance therapy (OR: 2.414; 95% CI: 1.315–4.432; P = 0.004) were independent prognostic factors for 1-year mortality in patients with APE. (Table 5)

Prognostic models for 1-year recurrence and mortality: We constructed a prediction model for 1-year recurrence and mortality in patients with APE using variables with P < 0.05 in the multivariate logistic regression results. Results revealed that the AUCs of smoking history, PDW, interrupted maintenance therapy, and the combination of these three prognostic factors for predicting the 1-year recurrence in patients with APE were 0.599 (95% CI: 0.531–0.667), 0.580 (95% CI: 0.509–0.652), 0.804 (95% CI: 0.748–0.860), and 0.852 (95% CI: 0.805–0.898), respectively. The AUCs for age ≥65 years, malignancy history, long-term immobilization history, mechanical ventilation, interrupted maintenance therapy, and the combination of these five prognostic factors for predicting the 1-year mortality in patients with APE were 0.573 (95% CI: 0.511–0.636), 0.676 (95% CI: 0.610–0.742), 0.677 (95% CI: 0.613–0.741), 0.645 (95% CI: 0.578–0.712), 0.597 (95% CI: 0.531–0.663), and 0.868 (95% CI: 0.832–0.905), respectively.

DISCUSSION

This study retrospectively assessed the prognostic factors linked to 1-year recurrence and mortality in patients with APE. In this study, the 1-year recurrence rate and mortality rate of patients with APE were 17.69% and 21.18%, respectively, which were similar to the results of other studies [Gupta 2018; Konstantinides 2020; Faller 2017]. We noted that the prognostic factors for 1-year recurrence included smoke, PDW, and interrupted maintenance therapy, while the prognostic factors for 1-year mortality included age ≥65 years, history of malignancy, history of long-term immobilization, mechanical ventilation, and interrupted maintenance therapy. The prognostic model for recurrence and mortality

Table 4. Univariate logistic regression model analysis of factors predicting 1-year mortality risk

Items	*P*-value	Univariate logistic regression model		
		OR	95% CI Lower	95% CI Higher
Age (≥65 years vs. <65 years)	0.010	1.897	1.167	3.083
Gender (male vs. female)	0.460	1.185	0.756	1.858
Smoke (yes vs. no)	0.530	0.864	0.548	1.363
History of hypertension (yes vs. no)	0.924	1.022	0.651	1.605
History of hyperlipidemia (yes vs. no)	0.097	0.592	0.319	1.100
History of diabetes mellitus (yes vs. no)	0.042	0.576	0.339	0.980
History of CHD (yes vs. no)	0.691	1.145	0.588	2.226
History of varicose veins/thrombosis of lower extremity (yes vs. no)	0.111	0.686	0.431	1.090
History of malignancies (yes vs. no)	<0.001	6.498	3.909	10.802
History of arrhythmia (yes vs. no)	0.298	0.683	0.333	1.400
History of chronic lung disease (yes vs. no)	0.658	1.148	0.624	2.113
History of chronic cardiac failure (yes vs. no)	0.382	0.646	0.243	1.721
History of nephrotic syndrome	0.150	0.225	0.029	1.715
History of long-term immobilization (yes vs. no)	<0.001	4.954	3.078	7.974
Higher risk classification	<0.001	2.761	1.991	3.829
Pulse rate (abnormal vs. normal)	<0.001	2.987	1.883	4.737
Respiratory rate (abnormal vs. normal)	0.999	1.000	0.562	1.780
SBP (abnormal vs. normal)	0.014	1.776	1.125	2.805
DBP (abnormal vs. normal)	<0.001	2.789	1.754	4.434
SpO_2 (abnormal vs. normal)	<0.001	2.730	1.703	4.377
WBC (abnormal vs. normal)	<0.001	2.610	1.629	4.182
Neutrophil (abnormal vs. normal)	<0.001	3.308	1.984	5.516
PLT (abnormal vs. normal)	<0.001	2.795	1.579	4.945
Lymphocyte count (abnormal vs. normal)	<0.001	2.781	1.636	4.726
RDW (abnormal vs. normal)	0.016	1.883	1.125	3.154
MPV (abnormal vs. normal)	0.666	0.894	0.537	1.488
PDW (abnormal vs. normal)	<0.001	2.631	1.623	4.265
D-dimer (high vs. low)*	0.138	1.407	0.896	2.211
NT-proBNP (high vs. low)*	<0.001	3.131	1.926	5.089
cTn I (abnormal vs. normal)	<0.001	2.881	1.765	4.701
NLR (high vs. low)*	<0.001	4.325	2.591	7.218
PLR (high vs. low)*	<0.001	2.880	1.779	4.663
Mechanical ventilation (yes vs. no)	<0.001	5.056	3.028	8.442
Treatment in acute phase				
Anticoagulant therapy	Reference	-	-	-
Anticoagulant+thrombolytic therapy	0.193	0.635	0.320	1.259
Others	0.999	-	-	-
Maintenance treatment				
Anticoagulant therapy	Reference	-	-	-

Antiplatelet therapy	0.005	0.495	0.302	0.810
Others	0.999	-	-	-
Interrupted maintenance therapy (yes vs. no)	<0.001	2.398	1.504	3.822

Boldface represent *P* value < 0.1. *Divided as high group and low group, according to median value. OR, odds ratio; CI, confidence interval; CHD, coronary heart disease; IQR, interquartile range; SBP, systolic blood pressure; DBP, diastolic blood pressure; SpO_2, oxygen saturation; WBC, white blood cell; PLT, platelet; RDW, red blood cell distribution width; MPV, mean platelet volume; PDW, platelet distribution width; NT-proBNP, N-terminal fragment of the brain natriuretic peptide precursor; cTn I, cardiac troponin I

Table 5. Multivariate logistic regression model analysis of independent factors predicting 1-year mortality risk

Items	Forward stepwise multivariate logistic regression model			
	P-value	OR	95% CI Lower	95% CI Higher
Age (≥65 years vs. <65 years)	<0.001	3.492	1.876	6.500
History of malignancies (yes vs. no)	<0.001	7.190	3.804	13.587
History of long-term immobilization (yes vs. no)	<0.001	6.244	3.472	11.228
Mechanical ventilation (yes vs. no)	<0.001	5.971	3.154	11.304
Interrupted maintenance therapy (yes vs. no)	0.004	2.414	1.315	4.432

The model was as follows: *P* = exp [-4.147 + 1.250*(age) + 1.973*(history of malignancies) + 1.832*(history of long-term immobilization) + 1.787*(Mechanical ventilation) + 0.881*(Interrupted maintenance therapy)]/1+ exp [-4.147 + 1.250*(age) + 1.973*(history of malignancies) + 1.832*(history of long-term immobilization) + 1.787*(Mechanical ventilation) + 0.881*(Interrupted maintenance therapy)]. OR, odds ratio; CI, confidence interval

at 1-year based on the above factors was found to have a relatively good performance.

The International Cooperative Pulmonary Embolism Registry (ICOPER) study reported that age >70 years and malignancy were significant risk factors for poor prognosis in patients with APE [Goldhaber 1999]. Yildirimturk et al. also noted that older age and malignancy history were independent predictors of death in patients with APE [Yildirimturk 2012]. In the present study, age ≥65 years and history of malignancy were independent prognostic factors for 1-year mortality in patients with APE, similar to the results of previous studies. APE is overwhelmingly due to thromboembolism in the pulmonary artery and is more likely to occur in older patients. It has been shown that malignancy can lead to thrombosis or place patients in a hypercoagulable state by altering the balance between the coagulation and fibrinolytic systems, rendering thrombosis a common complication of malignancy [Caine 2002]. There is an association between malignancy and a 4–7-fold increased risk of venous thromboembolism [Falanga 2017]. These previously reported associations were consistent with the results of the present study.

Platelets are involved in the process of thrombosis and development, and changes in platelet parameters reflect a state of platelet activation. MPV represents the mean volume of platelets in the blood and reflects platelet regeneration. PDW reflects the dispersion of platelet size in the blood and an increase in PDW implies an increase in the differences in platelet size. Park et al. found that larger platelets have higher activity and stronger blood clotting function [Park 2002]. Studies have found that platelet activation occurs in patients with APE [Chung 2007; Varol 2011]. It also has been demonstrated that PDW and MPV are significantly higher in patients with APE than in healthy populations, and that patients with APE with significantly elevated PDW and MPV have a higher risk of stratification [Huang 2015; Günay 2014]. In our study, abnormal PDW was found to be significantly associated with recurrence within 1 year in patients with APE, which was similar to the results of previous studies. However, we found no significant association between abnormal MPV and death in patients with APE. This may be due to the fact that both PDW and MPV levels are increased in the presence of diseases related to platelet activation, but PDW is not affected in the presence of platelet swelling alone. Thus, PDW is a more definitive marker of platelet activation than MPV [Vagdatli 2010].

In this study, long-term immobilization was found to be an independent risk factor for 1 year-mortality in patients with APE. An Italian study revealed that immobilization history was an independent predictor of in-hospital death in APE [Casazza 2012]. Another study indicated that a total of 43% of patients who died from PE had a recent history of ≥4 days of immobilization [Nauffal 2012]. These previously published studies confirm that long-term immobilization is strongly linked to a poor prognosis in APE. In patients with long-term immobilization following trauma and surgery, blood concentration, blood fibrinogen levels, and prothrombin content increase, thereby leading to increased blood viscosity. In addition, the application of hemostatic drugs for a long time after surgery and long-term rest puts the blood in

a hypercoagulable state and prone to thrombosis. Therefore, clinicians should remain alert to the risk of pulmonary embolism in such patients.

Smoking history was considered an independent risk factor for the incidence of PE [Zhou 2021; Gregson 2019; Cheng 2013], while the prognostic role of smoking in APE remained unclear. A study performed by Gambhir et al. found that smoking history was associated with an increased risk of early PE in patients with trauma [Gambhir 2019]. Our study found that the risk of 1-year recurrence was increased for smokers, which could be explained by the fact that a prethrombotic state could be induced by smoking by increasing fibrinogen and tissue factor levels, thereby increasing blood viscosity [Salahuddin 2012]. Moreover, Nielsen et al. found that roughly 20% of smokers had hypercoagulable blood with carboxyhemefibrinogen, which could induce the progression of PE [Nielsen 2013; Li 2018].

The simplified Pulmonary Embolism Severity Index (sPESI) is a predictor of 30-day death in APE, and hypoxemia is a main item of the sPESI [Jiménez 2016]. It was found that 92% of patients with APE develop shortness of breath [The urokinase 1973], 63% develop severe hypoxemia (PaO2 < 70 mmHg), and 20% develop severe hemodynamic impairment [Goldhaber 1999]. This suggests that APE not only results in hemodynamic impairment, but, more commonly, in pulmonary physiological impairment, as well as consequent gas exchange impairment, which plays a major role in the risk of death in patients with APE [Fernandes 2019]. The main short-term complications in patients with APE include respiratory failure, circulatory shock, and cardiac arrest, and high-risk patients with APE tend to develop these acute symptoms [Kline 2011]. Patients with APE in the intensive care unit (ICU) generally require sedation and mechanical ventilation [Mabrouk 2014], as mechanical ventilation is one of the main treatment for hypoxemic respiratory failure [Kapil 2019]. In this study, the use of mechanical ventilation was found to be a predictor of death in patients with APE. Comfere et al. found that the need for mechanical ventilation was an important univariate predictor of 30-day mortality following PE in patients who had undergone non-cardiac surgery [Comfere 2007]. Another study found that the need for mechanical ventilation represented an independent predictor of death in high-risk patients with PE in the ICU [Ergan 2016]. These were consistent with the results of this study.

Our study found that interrupted maintenance therapy was associated with an increased risk of 1-year recurrence and mortality for patients with APE. One study demonstrated that the use of anticoagulation at the maintenance stage played an important protective role in thromboembolism by mitigating the thrombosis promoting activity of recombinant erythropoietin [Wiesholzer 1999]. Moreover, the use of maintenance therapy remained higher trough concentrations, while the peak-to-trough fluctuations in plasma was smaller, as well as anti-factor Xa activity [Frost 2014]. Furthermore, the existing thrombin and thrombin production remained stable, and were suppressed by factor Xa inhibitors at the maintenance stage [Wong 2009]. Therefore, interrupted maintenance therapy was associated with a poor prognosis for patients with APE.

In the present study, 1-year recurrence and mortality prediction models for patients with APE were constructed based on key variables, with $P < 0.05$ in multivariate logistic regression analyses. The predictive value of multiple variables combined outperformed that of any single variable. The AUCs of the combined prediction models for recurrence and 1-year mortality were 0.852 and 0.868, respectively. The study demonstrated that the models effectively could predict the 1-year risk of recurrence and mortality in patients with APE.

The results of this study will help in the management of patients with APE. Clinicians can provide personalized interventions for patients with APE with different risk factors, which may reduce the risk of recurrence and mortality. For example, for APE patients with smoking history, PDW abnormalities, and interrupted maintenance therapy, clinicians should take measures to reduce the risk of recurrence.

This study has some limitations. First, it is a single-center retrospective study. Second, the sample size enrolled in the study was small. Therefore, the results of this study need to be verified in a large-sample prospective study. Therefore, prospective, multi-center studies enrolling a larger number of study subjects are needed to confirm our findings and draw more definitive conclusions.

CONCLUSION

Our findings demonstrated that smoke, PDW, and interrupted maintenance therapy were significantly associated with the risk of 1-year recurrence in patients with APE, and that age ≥65 years, history of malignancy, history of long-term immobilization, mechanical ventilation, and interrupted maintenance therapy were independent risk factors for 1-year mortality in patients with APE. These results will facilitate clinicians' assessment of the risk of recurrence and mortality in patients with APE and help them develop and implement personalized treatment plans for patients.

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