Trends in risk stratification, in-hospital management and mortality of patients with acute pulmonary embolism: an analysis from the China pUlmonary thromboembolism REgistry Study (CURES)

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The considerable reduction over the years in the mortality of acute PE during hospitalisation can plausibly be associated with risk stratification-guided management. This finding highlights the importance of implementing evidence-based guidelines throughout the nation. https://bit.ly/2P6gV7I

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Abstract

Similar trends of management and in-hospital mortality of acute pulmonary embolism (PE) have been reported in European and American populations. However, these tendencies are not clear in Asian countries. We retrospectively analysed the trends of risk stratification, management and in-hospital mortality for patients with acute PE through a multicentre registry in China (CURES).

Adult patients with acute symptomatic PE were included between 2009 and 2015. Trends in disease diagnosis, treatment and death in hospital were fully analysed. Risk stratification was retrospectively classified by haemodynamic status and the simplified Pulmonary Embolism Severity Index (sPESI) score according to the 2014 European Society of Cardiology/European Respiratory Society guidelines.

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Among 7438 patients, the proportions with high (haemodynamic instability), intermediate (sPESI⩾1) and low (sPESI=0) risk were 4.2%, 67.1% and 28.7%, respectively. Computed tomographic pulmonary angiography was the most widely used diagnostic approach (87.6%) and anticoagulation was the most frequently adopted initial therapy (83.7%). Between 2009 and 2015, a significant decline was observed for all-cause mortality (from 3.1% to 1.3%, adjusted $p_{for\ trend}$=0.0003), with a concomitant reduction in the use of initial systemic thrombolysis (from 14.8% to 5.0%, $p_{for\ trend}$<0.0001). The common predictors for all-cause mortality shared by haemodynamically stable and unstable patients were co-existing cancer, older age and impaired renal function.
The considerable reduction of mortality over the years was accompanied by changes in initial treatment. These findings highlight the importance of risk stratification-guided management throughout the nation.

Introduction

Pulmonary embolism (PE) leads to high mortality among hospitalised patients and is one of the biggest threats to healthcare worldwide [1, 2]. Death due to PE is the third most common cause of vascular death after myocardial infarction and stroke [3]. The mortality of PE can be reduced if it is diagnosed and managed properly based on optimal assessment and risk stratification.

Rigorous clinical studies have provided robust evidence on the effect of risk stratification-based treatments in patients with acute symptomatic PE; these studies have changed clinical practice and have been included in the European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines [4–6]. The Pulmonary Embolism Severity Index (PESI) [4] and the simplified PESI (sPESI) [5] have been widely used and validated for risk stratification in hospitalised patients with acute PE, and have been included in the ESC/ERS guidelines [3, 6]. Implementation of these clinical guidelines along with widespread use of advanced diagnostic techniques may have a positive impact on patient prognosis, as demonstrated by a decrease in the mortality of acute PE in European and North American populations in recent years [7–10]. The downward trend in PE mortality has also been observed in Asian populations, including in China [2, 11]. One possible explanation for the trends is the successful implementation of risk-adjusted diagnostic and therapeutic algorithms recommended by current guidelines in clinical practice.

There is a growing body of evidence that suggests a rise in PE incidence in Asian countries [12–14], which is partly due to increased awareness of the disease and improvement of the diagnostic scheme. Previous small-scale studies have reported the implementation in China of ESC/ERS guidelines, which include severity assessment and risk stratification using haemodynamic status and sPESI score, and determining clinical treatment and disease management strategies according to the stratified risk [15, 16].

In this study, we studied the trends of in-hospital management strategies and mortality of acute PE by retrospectively calculated risk classes, using data from a nationwide registry in China (China pUlmonary thromboembolism REgistry Study (CURES)).

Methods

Study design and patient inclusion

The CURES is an ongoing nationwide registry (NCT02943343) that is recruiting patients with acute symptomatic PE from 100 medical centres across China. The rational and design of the study have been comprehensively described previously [17]. Eligible patients were recruited based on the following inclusion criteria: age ⩾18 years and objectively confirmed acute symptomatic PE or PE with deep vein thrombosis (DVT). PE was confirmed by helical computed tomographic pulmonary angiography (CTPA), ventilation-perfusion lung scintigraphy (V/Q scan) or pulmonary angiography. Transthoracic echocardiography was used in patients to assess right ventricular (RV) function. DVT was diagnosed by compression ultrasonography (CUS) or computed tomographic venography. Patients were excluded if any of the following exclusion criteria was met: age <18 years, participating in any other clinical trial with an unknown drug, and suspected venous thromboembolism (VTE) or PE without confirmed evidence. This study was conducted in accordance with the Declaration of Helsinki and was approved by the ethical committees of all participating centres. Written informed consent was obtained from all recruited participants. Diagnostic methods were at the discretion of the attending physicians of the participating centres, and management decisions such as to initiate, maintain or change treatment were at the discretion of the physicians and patients.

Data collection

Demographics, risk factors, medical history, symptoms and signs, physical and laboratory examinations, image examinations, diagnostic methods and results, therapeutic management and clinical outcomes of the

disease during hospitalisation were collected *via* designated case report forms and entered into the electronic data capture system.

At each participating centre, the local investigator was responsible for the quality of data entry for data collected from each patient and uploaded to a computer-based case report form. Data quality was also monitored by members of a contract research organisation who compared the data on medical records with those transferred online during periodic visits to selected participating centres. The study protocol did not dictate any interference with patient management.

Risk stratification, management and study outcomes

Risk stratification for all patients was retrospectively calculated by haemodynamic status and sPESI score using the 2014 ESC/ERS guidelines [6]. Patients with cardiac arrest, obstructive shock or persistent hypotension were defined as having haemodynamically unstable PE. For patients with haemodynamic stability, the sPESI score was calculated for each individual.

Initial anticoagulation therapy was defined as when, on admission, a patient was first given anticoagulant therapy rather than systemic thrombolysis agents or interventional procedures (*e.g.* inferior vena cava filter, interventional thrombectomy or surgical embolectomy). Initial thrombolysis therapy was defined as when systemic thrombolysis was given prior to any pharmacological treatment, with the exclusion of thrombolysis after a failure of initial anticoagulation treatment.

The primary outcome in our study was death from any cause during hospitalisation. In the event of death, it was attributed to PE if the diagnosis was documented at autopsy or if the patient died shortly after objectively confirmed symptomatic PE and in the absence of any alternative diagnosis. Major bleeding was defined according to the International Society on Thrombosis and Haemostasis criteria [18]. The outcome events were reviewed by a central adjudication committee.

Statistical analyses

Demographics and clinical characteristics of patients are expressed in terms of descriptive statistics. Categorical variables are summarised as frequency (%) and continuous variables are presented as median (interquartile range (IQR)) because of skewed distribution. A univariable logistic regression model was used to assess the association between individual potential prognosis factors and all-cause mortality. Variables that achieved a significance level of $p<0.05$ and those of interest according to expert opinion or the literature review were included in the multivariable stepwise logistic regression model. A stepwise framework was adopted in the multivariable regression model with an entry level of 0.10 and a stay level of 0.05. A collinearity diagnosis was performed before the multivariable analysis was conducted. Odds ratios and 95% confidence intervals were used to quantify the magnitude and precision of associations. The Cochran–Armitage trend test, Mantel–Haenszel Chi-squared test or a general linear regression model was used to determine the trends of changes of disease characteristics, diagnostic approaches, treatments and hospitalised outcomes over time as appropriate. A generalised linear mixed-effect model was used to obtain age- and gender-adjusted all-cause and PE-related mortalities accounting for patient individual information as well as clustering of observation at the hospital level. A p-value <0.05 was considered statistically significant. All analyses were performed using SAS 9.4 software (Cary, NC, USA).

Results

Demographics, clinical characteristics and risk stratifications

A total of 7438 hospitalised patients with acute symptomatic PE recruited between January 1, 2009, and December 31, 2015, were evaluable for this analysis. Of these patients, 310 (4.2%) were haemodynamically unstable, 4991 (67.1%) were intermediate risk (sPESI$\geqslant$1) and 2137 (28.7%) were low risk (sPESI=0) (table 1). Among the 4991 haemodynamically stable patients with sPESI$\geqslant$1, 3346 (67.0%) had signs of RV dysfunction on echocardiography or CTPA. 589 patients (11.8%) were aged >80 years, including 63 patients (1.3%) without any other indicators of sPESI score.

The median age of all included patients was 63.0 years (IQR 51.7–72.9 years) and 53.0% of patients were male. The basic clinical characteristics, risk factors, disease management and in-hospital all-cause and PE-related mortality of patients stratified by haemodynamic status and sPESI score are listed in table 1. The changes in demographics, clinical characteristics, disease management and in-hospital mortality in patients with PE between 2009 and 2015 are shown in supplementary table S1. The median age gradually increased from 61.3 to 64.7 years, and the male proportion decreased from 57.0% to 49.0% (both unadjusted $p_{for\ trend}<0.0001$, supplementary table S1).

TABLE 1 Clinical characteristics, disease management and in-hospital mortality in patients with PE stratified by haemodynamic status and sPESI score

Characteristics	Total	Haemodynamically unstable	Haemodynamically stable	
			sPESI⩾1	sPESI=0
Subjects	7438 (100.0)	310 (4.2)	4991 (67.1)	2137 (28.7)
Demographic characteristics				
Age years	63.0 (51.7, 72.9)	61.7 (51.8, 70.2)	66.6 (56.6, 74.9)	54.6 (43.8, 64.5)
Male sex	3939 (53.0)	156 (50.3)	2543 (51.0)	1240 (58.0)
BMI kg·m^{-2}	23.8 (21.7, 26.0)	23.5 (21.2, 26.1)	23.9 (21.6, 26.1)	23.8 (22.0, 25.9)
Complications and risk factors				
Cardiovascular disease	3187 (42.9)	128 (41.3)	3059 (61.4)	0
Chronic pulmonary disease	1643 (22.1)	58 (18.7)	1585 (31.8)	0
Cancer	899 (12.1)	38 (12.3)	861 (17.3)	0
Metabolic and endocrine diseases	1112 (15.0)	48 (15.6)	897 (18.1)	167 (7.9)
Stroke	753 (10.2)	27 (8.7)	641 (12.9)	85 (4.0)
History of thrombotic disease	2104 (28.4)	81 (26.1)	1422 (28.6)	601 (28.2)
Surgery history				
<1 month	749 (31.7)	45 (42.9)	465 (29.1)	239 (36.1)
1–3 months	259 (11.0)	13 (12.4)	149 (9.3)	97 (14.6)
>3 months	1358 (57.4)	47 (44.8)	984 (61.6)	327 (49.3)
Recent surgery with immobilisation over 72 h	330 (14.6)	25 (23.8)	193 (12.7)	112 (17.4)
Smoking				
Non-smoker	3870 (63.1)	193 (66.3)	2578 (63.1)	1099 (62.8)
Ever smoker	818 (13.4)	32 (11.0)	633 (15.5)	153 (8.8)
Current smoker	1441 (23.5)	66 (22.7)	878 (21.5)	497 (28.4)
Deep vein catheterisation	42 (0.6)	2 (0.7)	26 (0.6)	14 (0.7)
Female-specific characteristics				
Oral contraceptives	26 (0.8)	2 (1.3)	11 (0.5)	13 (1.5)
Pregnancy	83 (2.4)	4 (2.6)	75 (3.1)	4 (0.5)
Postpartum	596 (17.3)	33 (21.4)	419 (17.4)	144 (16.2)
Initial medications				
Anticoagulation	6227 (83.7)	142 (45.8)	4250 (85.2)	1835 (85.9)
Thrombolysis	695 (9.3)	128 (41.3)	390 (7.8)	177 (8.3)
Other initial treatments				
Intervention	420 (5.6)	29 (9.6)	230 (4.8)	161 (7.7)
Inferior vena cava filter	386 (5.2)	26 (8.6)	208 (4.2)	152 (7.1)
Interventional thrombectomy	26 (6.2)	3 (10.3)	18 (7.8)	5 (3.1)
Surgical embolectomy	51 (0.7)	5 (1.7)	34 (0.7)	12 (0.6)
Length of hospital stay days	15 (10, 20)	14 (10, 21)	15 (11, 20)	14 (10, 19)
All-cause mortality	254 (3.4)	49 (15.8)	188 (3.8)	17 (0.8)
PE-related mortality	118 (1.6)	35 (11.3)	78 (1.6)	5 (0.2)

Data are presented as n (%) or median (interquartile range). PE: pulmonary embolism; sPESI: simplified Pulmonary Embolism Severity Index; BMI: body mass index.

Over the study period the proportion of haemodynamically unstable patients with PE decreased from 3.9% to 3.6%, and the proportion of haemodynamically stable patients slightly increased from 96.1% to 96.4% (both unadjusted $p_{for\ trend}$=0.0085, figure 1a). Among the haemodynamically stable patients, the proportion of patients with intermediate risk (sPESI⩾1) slightly decreased while the proportion of patients with low risk (sPESI=0) increased over time (both unadjusted $p_{for\ trend}$=0.0151, figure 1b).

Changes in diagnostic approaches and management over time

In our study, CTPA was the most widely used approach for PE diagnosis (87.6%), and quantitative D-dimer tests were performed in 7032 patients (94.5%), of which 6111 (86.9%) had positive results (as per local laboratory normal range). 762 patients (10.2%) underwent a V/Q scan and 5775 (77.6%) underwent transthoracic echocardiography. Between 2009 and 2015, CTPA use declined from 87.6% to 84.1% (unadjusted $p_{for\ trend}$=0.0074), whereas the proportion of patients undergoing V/Q scan increased from 10.6% to 11.5% (unadjusted $p_{for\ trend}$=0.0018) and transthoracic echocardiography usage remained stable (unadjusted $p_{for\ trend}$=0.8840, supplementary figure S1). All patients received bilateral lower limb CUS for DVT screening and diagnosis.

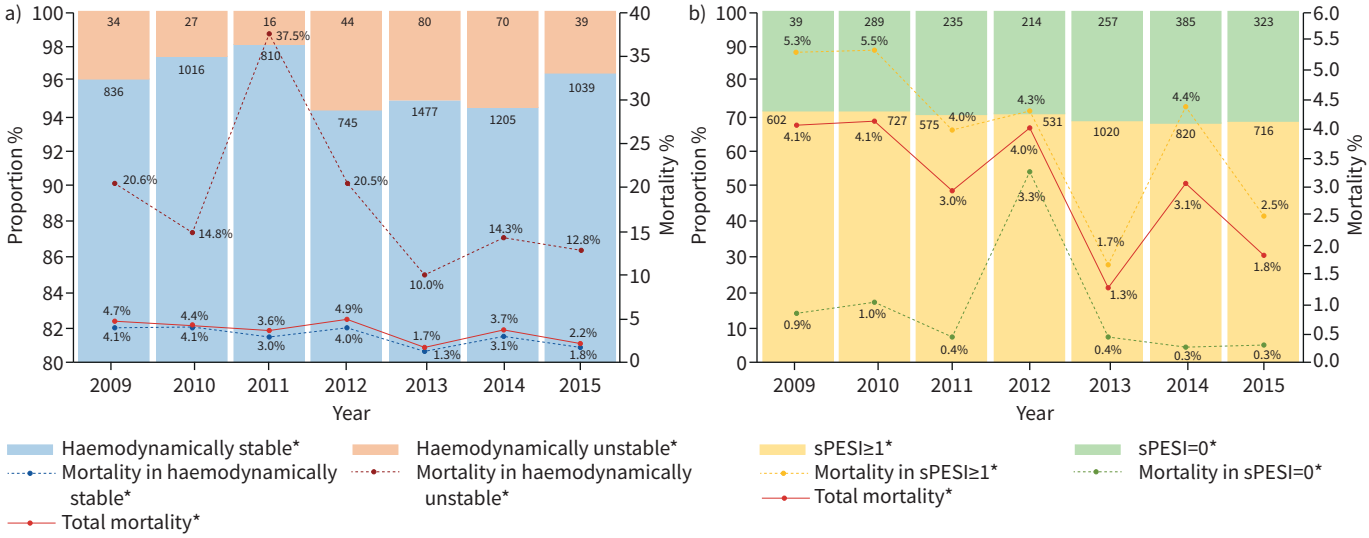

FIGURE 1 a) Changes in proportion and all-cause mortality in haemodynamically stable and unstable patients with pulmonary embolism (PE) between 2009 and 2015. Unadjusted all-cause mortality among haemodynamically unstable and stable patients was 15.8% and 2.9%, respectively. In haemodynamically stable patients, the unadjusted all-cause mortality dropped from 4.1% in 2009 to 1.8% in 2015 (unadjusted $p_{for\ trend}$=0.0001). The unadjusted all-cause mortality in patients with haemodynamic instability did not change significantly during the study period (unadjusted $p_{for\ trend}$=0.1267). b) Changes in proportion and all-cause mortality in PE patients with simplified Pulmonary Embolism Severity Index (sPESI)≥1 and sPESI=0 between 2009 and 2015. Among the haemodynamically stable patients, the proportion of patients with intermediate risk (sPESI≥1) slightly decreased from 69.2% in 2009 to 66.4% in 2015 (unadjusted $p_{for\ trend}$=0.0151) and their unadjusted all-cause mortality decreased from 5.3% in 2009 to 2.5% in 2015 (unadjusted $p_{for\ trend}$=0.0006). The unadjusted all-cause mortality for patients with low risk (sPESI=0) was stable over time (unadjusted $p_{for\ trend}$=0.1554). *: unadjusted $p_{for\ trend}$<0.05.

Over the study period, a greater proportion of the patients received anticoagulant treatment (83.7%) as the initial medication compared with thrombolytic treatment (9.3%) (table 1). Between 2009 and 2015, the use of initial thrombolysis therapy dropped from 14.8% to 5.0% (unadjusted $p_{for\ trend}$<0.0001, supplementary table S1). In both haemodynamically stable and unstable patients with PE, there was also a downward trend in thrombolysis use as the initial therapy over the study period. The use of initial thrombolysis therapy in haemodynamically stable patients with PE decreased from 13.3% in 2009 to 4.0% in 2015 (unadjusted $p_{for\ trend}$<0.0001, supplementary table S2).

Initial anticoagulation therapy included unfractionated heparin, low-molecular-weight heparin (LMWH), warfarin and direct oral anticoagulants (DOACs). LMWH and warfarin remained the main anticoagulants used as initial therapy, although their use decreased slightly from 2009 to 2015 (LMWH: 91.7% to 87.5%, unadjusted $p_{for\ trend}$<0.0001; warfarin: 92.5% to 86.2%, unadjusted $p_{for\ trend}$<0.0001). There was an upward trend in the use of DOACs, from 2.3% in 2009 to 7.2% in 2015 (unadjusted $p_{for\ trend}$<0.0001). The use of inferior vena cava filter implantation and interventional thrombectomy remained stable over the years (unadjusted $p_{for\ trend}$=0.1785 and 0.4208, respectively, supplementary figure S2).

Trends of in-hospital mortality in different risk stratifications and related risk factors

A total of 254 patients (3.4%) died during hospitalisation, and the all-cause mortality for patients with haemodynamic instability, sPESI≥1 and sPESI=0 was 15.8%, 3.8% and 0.8%, respectively. The PE-related mortality for all patients and patients with haemodynamic instability, sPESI≥1 and sPESI=0 was 1.6%, 11.3%, 1.6% and 0.2%, respectively (table 1). The in-hospital major bleeding rates for all patients and patients with haemodynamic instability, sPESI≥1 and sPESI=0 was 2.2%, 4.7%, 2.3% and 1.5%, respectively (supplementary table S3).

From 2009 to 2015, both the adjusted and unadjusted in-hospital all-cause mortalities significantly declined (adjusted mortality: 3.1% to 1.3%, $p_{for\ trend}$=0.0003; unadjusted mortality: 4.7% to 2.2%, $p_{for\ trend}$=0.0002; table 2, supplementary table S4). Adjusted all-cause mortality among haemodynamically unstable patients decreased from 16.6% to 7.7%, although the change was not significant (adjusted $p_{for\ trend}$=0.7476). Adjusted all-cause mortality of haemodynamically stable patients significantly dropped from 2.9% to 1.1% (adjusted $p_{for\ trend}$=0.0001). The adjusted all-cause mortality of the haemodynamically stable patients with intermediate

TABLE 2 Adjusted changes in in-hospital all-cause and PE-related mortality with different risk stratifications

Adjusted mortality	2009	2010	2011	2012	2013	2014	2015	p-value for trend
All patients								
All-cause mortality	3.1 (2.1–4.7)	2.7 (1.8–4.1)	2.0 (1.2–3.1)	2.9 (1.8–4.5)	1.1 (0.7–1.7)	2.2 (1.5–3.3)	1.3 (0.8–2.2)	0.0003
PE-related mortality	1.4 (0.8–2.5)	1.9 (1.2–3.1)	0.9 (0.5–1.8)	1.1 (0.6–2.2)	0.6 (0.3–1.2)	1.3 (0.8–2.2)	0.6 (0.3–1.3)	0.0176
Haemodynamically unstable patients								
All-cause mortality	16.6 (5.9–38.6)	7.3 (2.0–23.4)	17.4 (5.1–45.1)	12.3 (5.0–27.1)	7.7 (3.2–17.5)	9.9 (4.4–21.0)	7.7 (2.5–21.1)	0.7476
PE-related mortality	6.8 (1.8–22.6)	4.6 (1.0–19.4)	17.9 (5.7–44.2)	9.4 (3.6–22.7)	6.3 (2.5–15.2)	9.2 (4.0–19.7)	10.0 (3.5–25.1)	0.7341
Haemodynamically stable patients								
All-cause mortality	2.9 (1.9–4.4)	2.7 (1.8–4.1)	1.8 (1.1–3.0)	2.6 (1.6–4.2)	0.8 (0.5–1.4)	1.9 (1.2–2.9)	1.1 (0.6–1.9)	0.0001
PE-related mortality	1.3 (0.7–2.5)	1.9 (1.2–3.2)	0.6 (0.3–1.4)	0.8 (0.3–1.7)	0.4 (0.2–0.9)	1.0 (0.6–1.8)	0.4 (0.1–0.9)	0.0006
Haemodynamically stable sPESI⩾1 patients								
All-cause mortality	4.1 (2.7–6.3)	3.9 (2.6–5.9)	2.6 (1.6–4.3)	3.3 (1.9–5.4)	1.2 (0.7–2.0)	2.9 (1.9–4.5)	1.7 (1.0–2.9)	0.0008
PE-related mortality	1.9 (1.0–3.4)	2.5 (1.5–4.2)	0.9 (0.4–2.1)	1.2 (0.5–2.8)	0.6 (0.3–1.2)	1.6 (0.91–2.9)	0.6 (0.2–1.4)	0.0043
Haemodynamically stable sPESI=0 patients								
All-cause mortality	0.4 (0.1–2.2)	0.4 (0.1–1.8)	0.2 (0.0–1.9)	0.9 (0.2–3.3)	0.15 (0.0–0.9)	0.1 (0.0–0.9)	0.1 (0.0–1.0)	0.3013

Data are presented as % (95% CI). A generalised linear mixed-effect model was used to obtain age- and gender-adjusted all-cause and PE-related mortalities accounting for individual patient information as well as clustering of observation at the hospital level. PE: pulmonary embolism; sPESI: simplified Pulmonary Embolism Severity Index.

risk (sPESI⩾1) decreased from 4.1% to 1.7% (adjusted $p_{for\ trend}$=0.0008). The adjusted all-cause mortality for patients with low risk (sPESI=0) was stable over time (0.4% to 0.1%, adjusted $p_{for\ trend}$=0.3013) (table 2). The proportion of PE patients with intermediate risk (sPESI⩾1) receiving initial anticoagulation significantly increased from 78.7% to 87.4% (unadjusted $p_{for\ trend}$=0.0415) and the unadjusted all-cause mortality in patients under initial anticoagulation declined from 4.6% to 2.4% (unadjusted $p_{for\ trend}$=0.0095), while the unadjusted all-cause mortality in patients receiving initial thrombolysis was stable (unadjusted $p_{for\ trend}$=0.3628, figure 2). The proportion of PE patients with low risk (sPESI=0) receiving initial anticoagulation significantly increased from 82.1% to 90.7% (unadjusted $p_{for\ trend}$=0.0415), whereas the unadjusted all-cause mortality in patients initially receiving either anticoagulation or thrombolysis did not change significantly (unadjusted $p_{for\ trend}$=0.4683 and 0.4553, respectively, figure 2).

For haemodynamically stable sPESI⩾1 patients with signs of RV dysfunction on echocardiography or CTPA, the unadjusted all-cause and PE-related mortalities did not significantly change over the study period (unadjusted $p_{for\ trend}$=0.1038 and 0.3886, respectively, supplementary table S4). For haemodynamically stable sPESI⩾1 patients aged >80 years, the unadjusted all-cause and PE-related mortalities in hospital were also stable (unadjusted $p_{for\ trend}$=0.7874 and 0.1153, respectively, supplementary table S4).

In haemodynamically unstable patients, the proportion of initial thrombolysis use decreased from 52.9% in 2009 to 33.3% in 2015 (unadjusted $p_{for\ trend}$=0.1020, supplementary table S2), but the mortality of this group did not significantly change (unadjusted $p_{for\ trend}$=0.9320, supplementary table S5).

Multivariable regression analysis revealed that patients with cancer exhibited a 4.9-fold (95% CI 3.2–7.3) higher risk of all-cause death than patients without cancer. Lower platelet count ($<100\times10^9\cdot L^{-1}$), hypoxia (arterial oxygen tension <60 mmHg), higher level of white blood cells ($>10\times10^9\cdot L^{-1}$), high Borg scale score (⩾4), lower body mass index ($<18.5\ kg\cdot m^{-2}$), age >80 years, impaired renal function (estimated glomerular filtration rate $<60\ mL\cdot min^{-1}\cdot1.73\ m^{-2}$), anaemia, high pulse rate ($\geqslant110\ beats\cdot min^{-1}$), comorbid with cardiovascular diseases and high respiratory rate ($>20\ breaths\cdot min^{-1}$) were also significantly associated with death from all causes during hospitalisation (table 3). Further analysis identified co-existing factors of cancer, older age and impaired renal function as significant predictors of mortality in both haemodynamically stable and unstable patients (supplementary table S6).

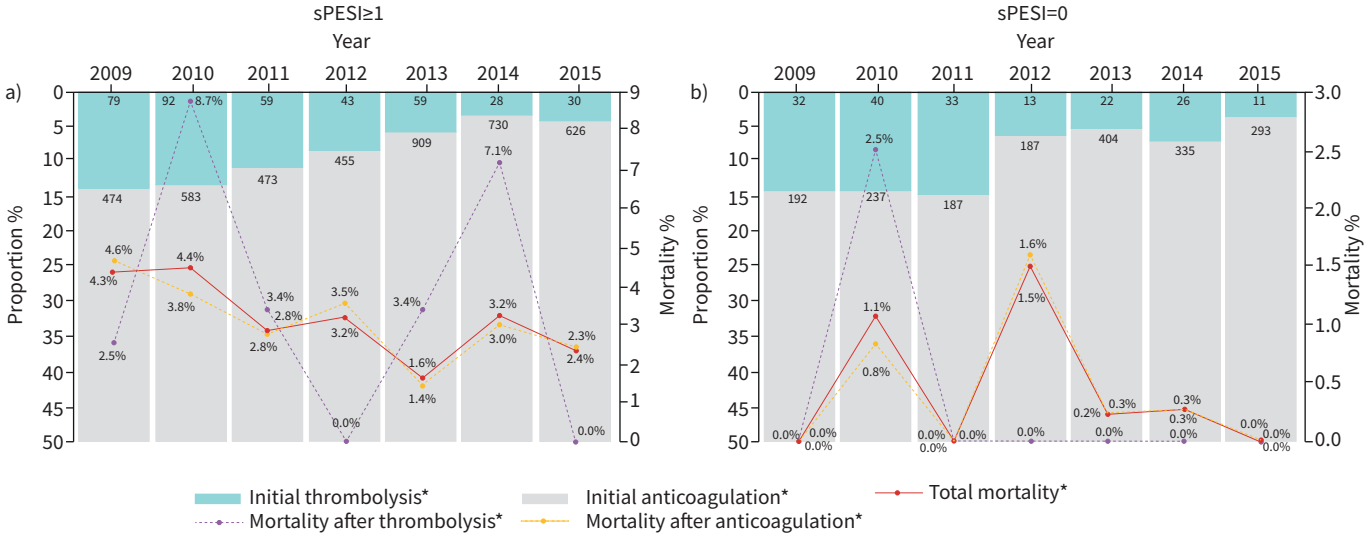

FIGURE 2 a) Changes in proportion and all-cause mortality in pulmonary embolism (PE) patients with intermediate risk (simplified Pulmonary Embolism Severity Index (sPESI)≥1) treated with different initial pharmacological strategies between 2009 and 2015. The proportion of initial anticoagulation significantly increased from 78.7% in 2009 to 87.4% in 2015 (unadjusted $p_{for\ trend}$=0.0415) and the unadjusted all-cause mortality in patients under initial anticoagulation declined from 4.6% to 2.4% between 2009 and 2015 (unadjusted $p_{for\ trend}$=0.0095), while the unadjusted all-cause mortality in patients receiving initial thrombolysis was stable (unadjusted $p_{for\ trend}$=0.3628). b) Changes in proportion and all-cause mortality in PE patients with low risk (sPESI=0) treated with different initial pharmacological strategies between 2009 and 2015. The proportion of initial anticoagulation significantly increased from 82.1% in 2009 to 90.7% in 2015 (unadjusted $p_{for\ trend}$=0.0415), whereas the unadjusted all-cause mortality in patients initially receiving either anticoagulation or thrombolysis did not changed significantly (unadjusted $p_{for\ trend}$=0.4683 and 0.4553, respectively). *: unadjusted $p_{for\ trend}$<0.05.

Discussion

Our study provided insights into the real-world trends of PE diagnosis, management and in-hospital outcomes based on the ESC/ERS risk model stratified by haemodynamic status and sPESI score in a large

TABLE 3 Prognostic predictors for overall in-hospital all-cause mortality in patients with PE

Risk factors	OR (95% CI)[¶]	p-value
Cancer	4.9 (3.2–7.3)	<0.0001
Platelet count <100×10^9·L^{-1}	3.0 (1.7–5.0)	<0.0001
P_{aO_2} <60 mmHg	2.8 (1.9–4.0)	<0.0001
WBC count >10×10^9·L^{-1}	2.4 (1.6–3.5)	<0.0001
Borg scale ⩾4	2.3 (1.2–4.3)	0.0130
BMI <18.5 kg·m^{-2}	2.2 (1.2–4.2)	0.0116
Age >80 years	2.0 (1.1–3.5)	0.0185
eGFR <60 mL·min^{-1}·1.73 m^{-2}	1.9 (1.2–3.0)	0.0046
Anaemia[#]	1.8 (1.2–2.7)	0.0039
Pulse ⩾110 beats·min^{-1}	1.7 (1.0–2.7)	0.0351
Cardiovascular diseases	1.5 (1.0–2.3)	0.0314
Respiratory rate >20 breaths·min^{-1}	1.5 (1.0–2.3)	0.0383

Variables were selected by clinical practice and statistical significance using a stepwise method with significance thresholds of 0.10 for entry and 0.05 for staying in the model. Potential risk factors input into the model included age >80 years, sex, BMI <18.5 kg·m^{-2}, cardiovascular disease, respiratory disease, cancer, temperature >37.3°C, pulse ⩾110 beats·min^{-1}, respiratory rate >20 breaths·min^{-1}, systolic pressure <100 mmHg, diastolic pressure <60 mmHg, anaemia, platelet count <100×10^9·L^{-1}, WBC count >10×10^9·L^{-1}, P_{aO_2}<60 mmHg, eGFR<60 mL·min^{-1}·1.73 m^{-2}, Borg scale group defined as <4 and >4, right ventricular dysfunction and elevated cardiac laboratory biomarker. PE: pulmonary embolism; P_{aO_2}: arterial oxygen tension; WBC: white blood cell; BMI: body mass index; eGFR: estimated glomerular filtration rate assessed by CKD-EPI formula. [#]: haemoglobin level <120 g·L^{-1} for male and <110 g·L^{-1} for female; [¶]: odds ratios and 95% confidence intervals were estimated using multivariable logistic regression models with non-missing data.

cohort of PE patients in China. We noticed a significant decrease for both all-cause and PE-related mortalities after accounting for patient-level variance and clustering of observations. Our findings are consistent with previously and recently published reports in Europe and North America [7, 9, 10, 19, 20]. The reduction of mortality seen with our data could be attributable to adherence to evidence-based clinical guidelines, such as optimal employment of diagnostic methods, accurate risk stratification and proper management [21]. Nevertheless, PE could still result in a considerable healthcare cost in our country. Continuous efforts are warranted to improve the awareness of PE and implement appropriate preventive and therapeutic measures.

Accurate risk stratification for patients with PE is a crucial step in clinical management and could help improve the prognosis and reduce PE-related mortality [22]. Haemodynamic status, sPESI score, RV dysfunction and elevated cardiac biomarker levels are the most common predictors for prognosis of acute PE and could assist the therapeutic decisions of physicians, and have been evaluated as parameters of risk stratification in previous studies [23–26]. Although information on the application of risk stratification, in particular the PESI/sPESI scores, in China is still limited in the literature, the concept has been adopted by the Chinese guidelines [27, 28] and used in real clinical practice [15, 16]. In this study, we observed a significant reduction of in-hospital mortality in patients with acute PE over the years, which might be associated with the application of risk stratification-guided management in our nation.

Advances in and proper utilisation of diagnostic approaches might be an alternative reason for the reduction of mortality. From 2009 to 2015, CTPA has been widely used, in an average of >80% of cases, for PE diagnosis in China. It can detect the disease at an earlier phase and increase the proportion of patients with less severe forms. The Registro Informatizado de la Enfermedad TromboEmbólica (RIETE) study reported a significantly increased use of CTPA between 2002 (46.5%) and 2018 (91.7%) among confirmed PE in Europe [29], of which the application in later years was similar to our data. Venkatesh *et al.* [30] reported that use of chest computed tomography for suspected PE in the emergency department steadily rose from 2000 to 2009 in the USA. After CTPA, transthoracic echocardiography was the second most dominant diagnostic method, and use of V/Q scan has increased on balance, especially in a few populations, *e.g.* pregnant women and patients allergic to the contrast agent or with renal dysfunction.

Changes to and appropriate use of pharmacological treatment modalities could also have affected the clinical outcomes. We found a continuous increase in initial anticoagulation therapy over the years, and a steady decline in initial thrombolysis therapy. Systemic thrombolysis was not recommended as the initial treatment for non-high-risk patients in the 2008 ESC guidelines [31]. Similar suggestions have been adopted by the Chinese guidelines [27, 28] and employed in clinical practice [15, 16]. Meyer *et al.* [32] demonstrated that thrombolysis therapy prevents haemodynamic decompensation but increases the risk of major bleeding and stroke in patients with intermediate-risk PE [32]. Keller *et al.* [33] reported that haemodynamically unstable patients treated with systemic thrombolysis have lower in-hospital mortality; however, the risk of mortality was increased in haemodynamically stable patients who were treated with thrombolysis. This evidence supports the optimal use of thrombolysis therapy in PE with different risk stratifications.

Additionally, with the development of therapeutic agents, the pattern of anticoagulation in our records has changed. In our study, LMWH and warfarin remained the most commonly used anticoagulants for initial therapy, and the intake of the two drugs together with unfractionated heparin decreased, whereas the use of DOACs steadily increased during the research period, though with slight but significant trends. The increased use of DOACs probably reflected the clinical application of the medications in patients with a relatively lower risk who were likely to experience less VTE recurrence and fewer bleeding events [34]. However, the RIETE study reported different modalities and changes in initial pharmacological treatment of PE between 2001 and 2013 in Europe [9]. Further comparison of physicians' therapeutic decisions among countries is needed.

Many predisposing factors can affect the outcomes and prognoses of acute PE, such as age, immobilisation, comorbidities and disease severity [3, 6, 35]. In our study, multivariable analysis revealed that predictors of in-hospital all-cause mortality in patients with acute PE included older age, co-existing cancer, cardiovascular and respiratory diseases, and impaired renal function, most of which were consistent with previous research. However, variation in prognostic predictors existed across studies and populations. Hence, the parameters included in clinical risk stratification should be cautiously selected and validated in large-scale and long-term follow-up prospective studies.

Strengths and limitations

Reliable multicentre data from patients with acute PE in China are still scarce. To the best of our knowledge, this is the first report from an ongoing nationwide registry in China to evaluate the trends of in-hospital mortality in patients with PE based on their haemodynamic status and sPESI score and stratified with different initial pharmacological strategies. Unlike traditional randomised controlled trials in which patients are selected through strict eligibility criteria, our study population could well represent real-world clinical practice.

However, as a *post hoc* analysis, our study was unable to identify any causal correlation between the initial treatment strategies and in-hospital outcomes owing to the natural features of real-world study. Given that the aim of this study was to evaluate outcomes during hospitalisation, we did not analyse post 30-day hospitalisation or longer-term outcomes. Because the CURES is an ongoing registry, further studies with a focus on long-term outcomes stratified by risk are feasible. It is important to compare patient characteristics and prognosis on a global level, with a view to assess the global burden of disease related to PE and to standardise clinical practice and convergence towards common guidelines in Asian countries in the future.

Conclusions

We present a large-scale analysis of the trends in characteristics, management and prognosis of patients with acute PE from a multicentre registry in China. The considerable reduction in mortality during hospitalisation over the years was accompanied by changes of patterns in initial treatment strategies. These findings may also reveal a plausible association of risk stratification-guided management and prognosis of acute PE.

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