Predictors of mid-term prognosis and adverse factors in acute pulmonary embolism

Xin Liu, Suchi Chang, Cuiping Fu, Zhirong Huo, Jing Zhou, Chengying Liu, Shanqun Li and Aijun Sun

Abstract

Background: To explore the differences in short and middle term adverse factors of pulmonary embolism (PE) outcome.

Methods: This was a single-center retrospective study of inpatients admitted from Zhongshan Hospital, Fudan University, with first-time PE. Clinical data were collected from patients with objectively confirmed PE, and a 2-year follow up was conducted.

Results: The sample contained 310 patients with PE, ranging in age from 18 to 86 years old (mean 63.28 ± 15.30) and including 165 men (53.2%) and 145 women (46.8%). Successful treatment was achieved in 285 cases (91.9%) and unsuccessful treatment turned out in 25 cases (8.1%). Logistical regression analysis showed that massive PE [odds ratio (OR) = 23.625, 95% confidence interval (CI) 6.248–89.333], hypoxemia (OR = 11.915, 95% CI 1.900–74.727), leukocytosis (OR = 9.120, 95% CI 2.227–37.349) and active cancer (OR = 6.142, 95% CI 1.233–30.587) were associated with a poor prognosis for acute PE in the short term (in hospital). Seventy-seven PE cases with complete electronic records were finally included in the follow up. Cox regression analysis showed that elevated pulmonary artery systolic pressure (PASP, ⩾50 mmHg) (HR = 9.240, 95% CI, 2.307–37.013) and active cancer with PE (HR = 3.700, 95% CI, 1.010–13.562) were associated with an increased risk of mid-term mortality after a follow-up period of 2 years.

Conclusions: Massive PE, hypoxemia, leukocytosis and active cancer may contribute to a poor prognosis for patients with acute PE in hospital. Elevated PASP and active cancer may negatively impact survival time and increase the risk of death for patients with acute PE after 2-year follow up. Short-term adverse factors of acute PE are not exactly the same as the mid-term risk factors of acute PE.

Keywords: pulmonary embolism, adverse factors, therapeutic effect, prognosis, survival time

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Introduction

Pulmonary embolism (PE) is the most serious manifestation of venous embolism and is a potentially life-threatening condition. Prompt diagnosis, risk stratification and treatment can improve the outcome. Numerous data revealed that short- and long-term predictors of PE outcome were not identical. Jo and colleagues reported that leukocytosis was significantly correlated with the mortality of PE and thus was an important predictive factor in determining the short-term outcome of PE.[1] Gong and colleagues reported that idiopathic PE, Right Ventricular Dysfunction (RVD), D-dimer positivity, anticoagulation treatment less than 3 months, cardiac Troponin I (cTnI) positivity and post-treatment pulmonary artery systolic pressure (PASP) greater than 40 mmHg were adverse factors that would affect the long-term prognosis of PE.[2] We hypothesized that mid-term predictors of PE would differ from

short-term predictors. To explore the short-term predictors and the survival of patients, we investigated the data of inpatients with acute PE.

Methods

Study design

This was a retrospective study of a large series of patients with PE and was conducted in accordance with the Declaration of Helsinki. The Ethics Committee of Zhongshan Hospital, Fudan University, approved the study protocol (permit number: 27-2956), which waived any need for patient informed consent.

Study population

The study population was composed of inpatients with first-time PE from Zhongshan Hospital, Fudan University (Shanghai, China) from January 2008 to July 2014.

Inclusion criteria

There were four primary qualifications used for inclusion criteria in this study. First, patients had to meet the 2001 criteria for PE as adopted by the Chinese Thoracic Society.[3] Definite PE was confirmed by computed tomography pulmonary angiography (CTPA) or lung ventilation perfusion scanning. Second, based on the Management of Massive and Submassive Pulmonary Embolism, Iliofemoral Deep Vein Thrombosis, and Chronic Thromboembolic Pulmonary Hypertension (version 2011), patients with massive PE received thrombolytic therapy while those with submassive PE received either thrombolytic or anticoagulant therapy as indicated by the clinical circumstances and wishes of the patients.[4] Patients with low-risk PE received anticoagulant therapy. Third, catheter-based interventions and surgical embolectomies were performed for patients with massive PE who could not receive thrombolytic therapy or who remained unstable after receiving thrombolytic therapy, submassive PE that was judged to have an adverse prognosis. Inferior vena cava filters were used in patients with acute PE, complicating deep vein thrombosis (DVT) with contraindications to anticoagulation. Fourth, patients discharged from the hospital to continue secondary prophylaxis with the vitamin K antagonist warfarin for at least 3 months were included in the follow up.

Exclusion criteria

Patients who had a clinical diagnosis with an indeterminate result or who were without objective confirmatory testing were excluded from the study, as were patients with cases of re-embolism.

Definition of clinical outcomes

Definitions for PE subgroups were coded with reference to the management of PE from the American Heart Association (version 2011).[4] Elevated PASP was defined as exceeding 50 mmHg according to tricuspid regurgitation jet velocity by echocardiography.[5]

Active cancer referred to cancer diagnosed no more than 6 months prior to the onset of PE, metastatic cancer or any malignancies requiring curative or palliative treatment within the previous 6 months.[6]

PE cases were divided into a valid and an invalid group in light of a curative effect. For patients in the valid group, the symptoms of dyspnea either abated or disappeared, the number of filling defected segments was reduced or the embolus disappeared. For patients in the invalid group, dyspnea worsened, there was no change in embolus by CTPA, an adverse event occurred (such as cardiopulmonary resuscitation or major bleeding) or death occurred.

Data collection

All clinical data and laboratory results were abstracted retrospectively from medical electronic records. Two trained investigators (Xin LIU, Cuiping FU) identified inpatients on the basis of the discharge diagnostic codes for PE found in the International Classification of Disease (ICD-9 and ICD-10). Adjudication differences were resolved by a consensus procedure. The data from the first 24 h after admission were extracted, which included relevant clinical symptoms and signs, predisposing risk factors, arterial blood gas values, D-dimer, electrocardiograms, and the Pulmonary Embolism Severity Index (PESI). In addition, the following information was recorded in the medical records: previous DVT, trauma, surgery, spinal cord injury, central venous lines, immobility (specified as paralytic stroke, bed rest >3 days, or >8 h travel) within the last 3 months, active cancer, pregnancy or puerperium at the time of the event, oral contraceptives used at the

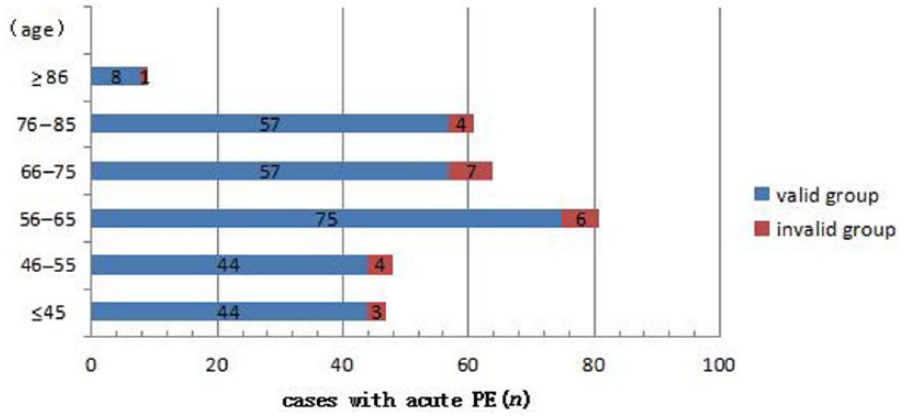

Figure 1. The occurrence frequency and the curative effect of inpatients with acute pulmonary embolism (PE) in different age groups.

time of the event or up to 1 month prior to the event, hormone replacement therapy, complications from malignancies, and chronic heart or respiratory failure.

PE cases with complete electronic records were finally included in the follow up. There existed retinue clinical care but no additional clinical intervention or any trial protocol. We observed the outcome of these patients through physician reporting in the hospital or telephone consultation. Objective data were obtained during hospital readmission or clinic visits. Death certificates of patients who died during the follow-up period were also reviewed. The end event was the all-cause mortality. Mortality data were obtained through hospital record reviews or review of death certificates. Survival time was calculated from the date of confirmed PE to the day of death or the end of follow up. Participants were followed for a maximum of 24 months. The estimated number of endpoint events was at least 22 based on a statistical model presented by Schoenfeld.[7] The follow-up period ended in July 2014.

Statistical analysis

We used SPSS version 20.0 (IBM Corporation, USA) for all data analyses. The mean and standard deviation (SD) were used as measures of statistical dispersion and were applied to normality plots with tests. Measurement data were presented as the mean ± SD and range. An independent samples t test was used to compare measurement data between the two groups. We expressed enumeration data in percentages and used the χ^2 test to examine differences in the enumeration data between groups. Multivariable logistic regression models, with odds ratios (ORs) and 95% confidence intervals (CIs), were used to examine the relationship between risk factors and curative effects (in hospital). Cox proportional hazards regression models were used to analyze the prognostic factors affecting patient survival. Those results were expressed as hazard ratios along with the corresponding 95% CIs. The impact of loss to follow up was estimated by performing sensitivity analysis. All p values were two tailed, and statistical significance was set as a p value less than 0.05.

Results

After excluding unavailable data, a total of 310 PE cases were identified from the electronic medical record database. As indicated on the P-P plots, the sample distribution approximated the normal distribution.

The sample contained 310 patients (165 men, 145 women), ranging in age from 18 to 86 years old (mean ± SD, 63.28 ± 15.30 years). The mean hospital stay was 6.7 ± 4.2 days. Based on the curative effect, patients with PE were divided into a valid group (n = 285) and an invalid group (n = 25). The occurrence frequency and the curative effect of inpatients with PE in different age groups is illustrated in Figure 1.

Patient-related and setting-related predisposing factors

Immobility due to sitting, major trauma or major general surgery reached up to 17.4% (54 of 310).

In addition, 37 cases of previous DVT and 35 cases of active cancer were observed. Out of the 35 cases, 11 were lung cancers. All the pathological results showed that tumor cells were non-small cells. Of these, eight cases involved adenocarcinoma and three cases were not further specified.

Clinical symptoms and signs

Breathing difficulty was the most common clinical symptom, accounting for 89 out of 310 cases (28.7%), followed by 74 cases of chest pain (23.9%), 51 cases of asymmetry edema of lower limbs (16.5%), 45 cases of syncope (14.5%), and 39 cases of hemoptysis (12.6%). The classic triad of chest pain, dyspnea, and hemoptysis occurred infrequently in our sample, accounting for only seven out of 310 cases (2.3%).

Auxiliary examinations

Arterial blood gas analysis was conducted in each of the 310 cases. Of these, there were 123 cases of Partial pressure of oxygen in artery (PaO_2) less than 60 mmHg (39.7%) and 130 cases of Partial pressure of carbon dioxide in artery ($PaCO_2$) less than 35 mmHg (41.9%). Of the 289 PE cases, 274 (94.8%) exhibited elevated levels of D-dimer (above the standard threshold of 500 ng/ml). PASP of at least 50 mmHg was observed *via* echocardiography in 102 of 228 cases (44.7%). Of the 247 cases that completed the color Doppler ultrasound of the blood vessels, 127 (51.4%) were confirmed to have DVT of the lower extremities, and 27 of these (21.3%) involved deep veins in the bilateral lower extremities.

In light of the management of PE from American Heart Association (AHA) (version 2011), among the 310 cases with acute PE, the massive, submassive and low-risk PE groups accounted for 25 cases (8.1%), 92 cases (29.7%) and 193 cases (62.3%), respectively.[4]

The PESI classification showed 165 patients in the low-risk group and 66 patients in the high-risk group. The mean ± SD of the PESI score was 82.11 ± 26.86 in the valid group and 178 ± 40.45 in the invalid group.

The causes of PE for patients in the invalid group were as follows: seven cases of active cancer with PE, two cases complicated by renal failure, two cases of acute massive hemoptysis, one case of interstitial lung disease complicated by spontaneous abdominal hematoma due to anticoagulant therapy, 13 cases of sudden death (including one case that occurred after extubation treated by catheter-directed thrombolysis and one case that occurred after surgical embolectomy).

Multivariable logistical regression analysis showed that massive PE, hypoxemia, leukocytosis and active cancer may be associated with a poor prognosis for PE. The estimated OR showed that patients with massive PE were 23.625 (95% CI 6.248–89.333) times more likely to have had a confirmed adverse outcome than those with non-massive PE. Furthermore, patients with leukocytosis were 9.120 (95% CI 2.227–37.349) times more likely to have had a confirmed adverse outcome than those with non-leukocytosis. Active cancer was shown to be an independently poor prognostic factor for PE, with an OR of 6.142 (95% CI 1.233–30.587). Hypoxemia was significantly associated with the occurrence of an adverse outcome, with an OR of 11.915 (95% CI 1.9–74.727) in a multivariable model (see Table 1). Due to short hospital stay, we take the above-mentioned adverse factors as short-term poor prognosis.

With regard to longitudinal follow up, 77 patients were followed for a period ranging from 0.5 to 24 months (22.59 ± 19.27 months). During this follow-up period, 22 patients died, 55 patients survived. The 1-month, 2-month and 24-month survival rates were 78.2%, 74.4% and 71.8%, respectively. Cox regression analysis showed that elevated PASP (⩾50 mmHg) and active cancer significantly predicted adverse consequences in the mid-term follow up. Specifically, the elevated PASP group (⩾50 mmHg) was associated with an increased risk of mid-term mortality, with a hazard ratio of 9.240 (95% CI 2.307–37.013), relative to the nonelevated PASP group. Likewise, active cancer with PE was associated with an increased risk of mid-term mortality, yielding a hazard ratio of 3.700 (95% CI 1.010–13.562; see Table 2). Figure 2 demonstrates the 24-month cumulative survival function of acute PE. Figure 3 demonstrates that the survival rate for patients in the elevated PASP group was lower than that for patients in the nonelevated PASP group.

Discussion

Our study demonstrated a significant adverse association between massive PE and a curative

Table 1. Risk factors associated with a curative effect (in hospital) as indicated by the multivariable logistic regression model and parameter estimation.

	β	SE	Wald	Sig.	OR	95% CI for Exp (B)	
						Lower	Upper
Leukocytosis	2.210	0.719	9.444	0.002	9.120	2.227	37.349
Hypoxemia	2.478	0.937	6.996	0.008	11.915	1.900	74.727
Active cancer	1.815	0.819	4.910	0.027	6.142	1.233	30.587
Massive PE	3.162	0.679	21.714	0.000	23.625	6.248	89.333
Constant	−6.498	1.079	36.270	0.000	0.002		

CI, confidence interval; OR, odds ratio; PE, pulmonary embolism; SE, standard error; Sig., significance.

Table 2. Prognostic factors affecting survival time as indicated by the Cox proportional hazards regression model and parameter estimation.

	β	SE	Wald	Sig.	HR	95% CI for Exp (B)	
						Lower	Upper
The elevated PASP group	2.224	0.708	9.861	0.002	9.240	2.307	37.013
Active cancer	1.308	0.663	3.898	0.048	3.700	1.010	13.562

CI, confidence interval; HR, hazard ratio; PE, pulmonary embolism; SE, standard error; Sig., significance.

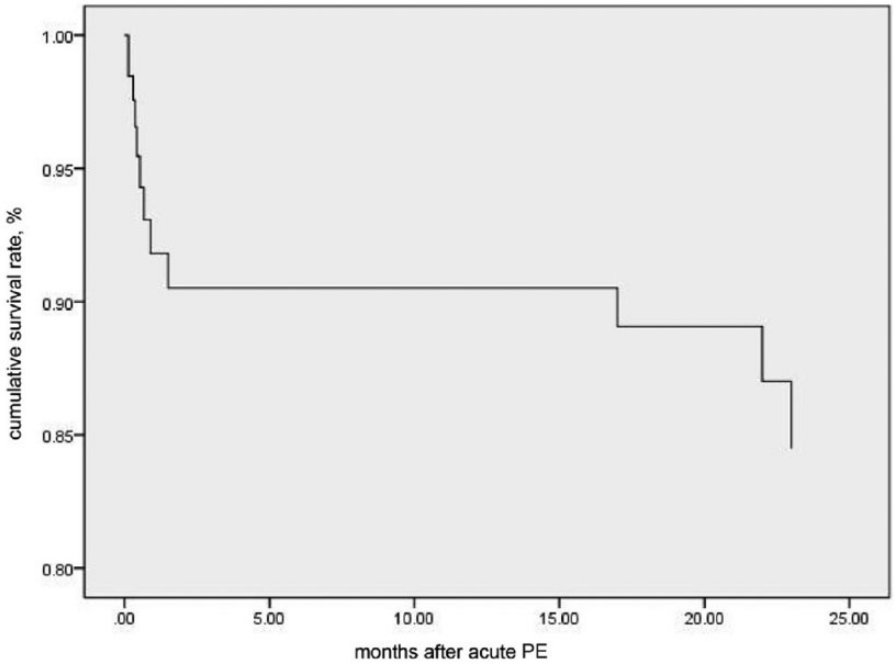

Figure 2. The cumulative survival function at the 24-month follow up for patients with acute pulmonary embolism (PE).

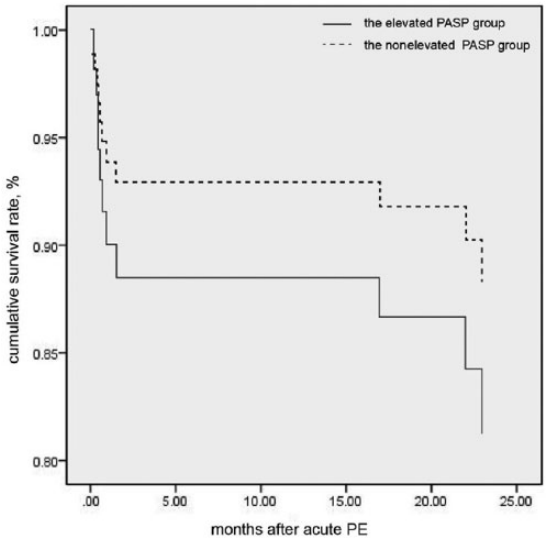

Figure 3. Cumulative survival functions at different pulmonary artery systolic pressures (PASPs). PE, pulmonary embolism.

effect (in hospital). The estimated OR showed that the massive PE was the maximum weight of assessment indicator in our study. It is believed that hemodynamic change rather than the Miller Index represents clinically reliable evidence, and provides a more accurate judgment of adverse prognoses. The 2008 management of PE from the European Society of Cardiology and the 2011 management of PE from the AHA both focused on the study of short-term mortality rates for people with an acute PE reported from the International Cooperative Pulmonary Embolism Registry (ICOPER), the results of which showed that a systolic blood pressure below 90 mmHg correlated with the 90-day mortality of patients with acute PE.[8–10] Hemodynamic compromise was the most critical clinical feature of massive PE, and the estimated mortality for inpatients with hemodynamic instability increased to 15%.[9] In addition, hypotension as an important index was included in the PESI scale. As is well known, PESI has discriminative power to predict short-term death in patients with acute PE. A meta-analysis showed that the overall weighted area under the curve for PESI predicting all-cause mortality and PE-related mortality was 0.78 and 0.82 respectively.[11] Our study showed that the PESI value of the invalid group rose to 178 ± 40.45, apparently higher than that of the valid group (82.11 ± 26.86). Nevertheless, because PESI includes 11 subitems that we believed might increase the model instability, PESI did not ultimately enter into the multivariable logistic regression model.

Research on the relationship between malignancies and venous thromboembolism (VTE) has existed since the nineteenth century. Meta-analyses in recent years have provided reliable data. A 2006 study involving 41 million patients with 19 types of malignancies showed that 2% of these patients developed VTE, and the incidence was twice as much as that in patients without malignancies. The malignancy with the highest VTE incidence was mucinous carcinoma of the pancreas, followed by brain malignancy and myeloproliferative malignancy.[12] Another meta-analysis involving 114,922 patients with lung cancer showed the incidence of PE to be 3.6%, while adenocarcinoma of the lung was the pathological type with the highest incidence of VTE.[13] In addition, Sun and colleagues demonstrated that adenocarcinomas were the most prevalent histologic type associated with PE in a study involving 8014 patients with lung cancer.[14] A major reason for this relationship is that active cancer secretes more procoagulant substances, which are related to the biological characteristics of tumor cells. Another reason is the medical interventions among patients with tumor, such as surgical trauma, deep vein catheterization, antitumor drugs and glucocorticoids, which can directly or indirectly influence the dynamic equilibrium of the coagulation–fibrinolysis system and lead to thrombosis. In this study, 35 cases of malignancy with PE were observed. The 11 cases of lung cancer were all non-small cell lung cancer, and adenocarcinoma (8/11) was the most common pathological type. There were four patients with diffuse large B-cell lymphoma and three patients with breast invasive ductal carcinoma, which was consistent with the pathological types with high VTE incidence in the literature.

With the increasing research on the prognosis of PE, large-sample long-term follow ups brought us new ideas, but the results from different studies were inconsistent and even conflicting. Naess and colleagues studied the general population of North-Trøndelag County in Norway for 6.5 years and suggested that the risk of mortality was highest in the first months after the VTE, after which it gradually approached the mortality rate in the general population.[15] Schulman evaluated 545 patients at a 10-year follow up and found that the morbidity and mortality during the 10 years after the first episode of VTE were high and were not reduced by the

extension of secondary prophylaxis from 6 weeks to 6 months.[16] These different results may be attributed to factors such as different study designs, different races and environmental impacts. As shown in Figure 3, the survival curve during the first 90 days after PE was significantly decreased, followed by a slower decrease after that, which was consistent with the results from Naess and colleagues.[15] However, discovering whether the survival rate will approach that of the general population requires further demonstration by strict follow up of larger samples over a longer period of time.

Spencer and colleagues reported that the 30-day, 1-year and 3-year mortality of 1691 patients with validated acute PE were 13.0%, 26.0% and 35.3%, respectively.[17] In our study, the 1-month mortality was higher than that of the study above, which may have been affected by sample size and an admission bias. Clearly, stratification analysis enables more accurate results. The data from ICOPER displayed that the 90-day mortality rates were 52.4% (95% CI 43.3%–62.1%) in patients with massive PE and 14.7% (95% CI 13.3%–16.2%) in patients with nonmassive PE, respectively.[9]

Pulmonary hypertension (PH) has been thought to be the final result of hemodynamic compromise and persistent pulmonary artery perfusion defect. A recent pathological study demonstrated that if acute PEs have not resolved in 1–4 weeks, the embolic material becomes incorporated into the pulmonary arterial wall at the pulmonary artery and its branches.[18] Remodeling of the pulmonary circulation leads to elevated pulmonary artery pressure and progressive right ventricular failure. Riedel and colleagues followed 76 patients with PE for 1–15 years, finding that the mortality of patients with an initial average pulmonary artery pressure greater than 40 mmHg was approximately 70%, while the mortality increased to 90% when the average pulmonary artery pressure increased to 50 mmHg, suggesting that PH and its severity were important prognostic indicators.[19] Our study showed that the elevated PASP group ($\geqslant$50 mmHg) had an adverse effect on survival time. As shown in Figure 3, the survival rate of the elevated PASP group ($\geqslant$50 mmHg) was significantly lower than that for controls ($<$50 mmHg).

Limitations

Several limitations of the present study should be mentioned. First, an echocardiogram is useful for screening but insufficient for diagnosis. Diagnostic evaluation including pulmonary angiography and invasive cardiac valuation were largely limited in clinical applications because of the higher costs and risks. Taleb and colleagues conducted a meta-analysis including nine articles, which demonstrated that the correlation between PASP estimated by Doppler echocardiography (DE) and right heart catheterization ranged from $r = 0.65$ ($p < 0.001$) to $r = 0.97$ ($p < 0.001$).[20] The pooled sensitivity, specificity and accuracy of DE for the diagnosis of PH were 88% (95% CI 84%–92%), 56% (95% CI 46%–66%) and 63% (95% CI 53%–73%) respectively. Therefore, there was some impact on the accuracy of the estimated PASP. Second, due to the low autopsy rates, we are unable to estimate accurately the rates of fatal PE and can only observe all-cause mortality. Third, because this study was a retrospective study, there were many reasons for missing data, like referral to other hospitals, data incomplete and so on. Two years later, complete electronic records of 77 patients were finally obtained during hospital readmission or clinic visits. High-quality cohort studies with bigger samples were suggested to be further developed.

Conclusion

Massive PE, hypoxemia, leukocytosis and active cancer may contribute to a poor prognosis for patients with acute PE in the short term. Elevated PASP and active cancer may negatively impact survival time in the mid-term follow up. In addition, adverse factors of acute PE in the short term are not exactly the same as risk factors in the mid-term follow up.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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