Simplified pulmonary embolism severity index is associated with recurrent venous thromboembolism in patients with pulmonary embolism

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Pulmonary embolism (PE) patients have a high recurrence rate of venous thromboembolism (VTE) and recurrences are more often fatal. Recurrence can be effectively prevented by prolonged anticoagulation treatment, but the risk of bleeding also increases. Consequently, risk assessment of VTE recurrence is important in PE patients, as high-risk patients will benefit from long-term anticoagulation treatment, whereas low-risk patients will unnecessarily be exposed to an increased bleeding risk. Several risk factors for VTE recurrence have been identified in non-Asian populations, including male gender, advanced age, thrombophilia, obesity, persistent elevation of D-dimer one month after discontinuation of anticoagulation and residual thrombosis. However, risk factors for VTE recurrence have not been clearly evaluated in Chinese and Asian populations. A recent study found that the European Society of Cardiology (ESC) risk stratification for PE patients (2008 version), which is used to assess the disease severity of acute PE patients, was associated with VTE recurrence.[1] The simplified pulmonary embolism severity index (sPESI) is also widely validated for the assessment of disease severity of PE, has good prognostic value for early and even long-term mortality. It is less clear whether the model predicts VTE recurrence. The aim of this prospective study was to investigate the short-term and long-term incidence of recurrent VTE after a first episode of acute PE and associated risk factors of recurrent VTE. The association between VTE recurrence and disease severity assessed by sPESI was also evaluated.

Consecutive patients with symptomatic, objectively confirmed acute PE from the West China Hospital of Sichuan University, were included between January 2014 and December 2017 in this prospective cohort. The study protocol was approved by the Institutional Review Board of the West China Hospital of Sichuan University (No. 351). Inclusion criteria were acute symptomatic PE with or without DVT. Patients with previous history of symptomatic PE or DVT were excluded. The sPESI score was calculated for all patients at the time of diagnosis. One point was assigned for each of the following variables: age >80 years, history of cancer, chronic heart failure or chronic pulmonary disease, pulse rate > 110 beats/min, systolic blood pressure < 100 mmHg, arterial oxyhemoglobin saturation < 90%. Patients with none of these variables (0 points) were categorized as low-risk, and those with a score of ≥1 were high-risk. Detailed information on demographics, medical history, laboratory and imaging tests, and treatment were collected for all patients. The patients were followed at 3, 6, 9, 12, 18, and 24 months after the initial PE event by outpatient visits and hospitalization (if necessary). VTE recurrence was evaluated during the follow-up.

Continuous variables with a normal distribution are described as mean values with standard deviations, and group comparisons were done using the Student's *t*-test. Discrete variables are presented as frequencies and percentages, and group comparisons were carried out using the chi-square test. Cox regression was used to identify risk factors for VTE recurrence. The time-courses for the recurrence of VTE in PE patients were depicted as Kaplan–Meier curves. All reported *P* values are two-tailed. $P < 0.05$ was considered significant. Data were analyzed using SPSS v25.0 (IBM, Armonk, NY, USA).

A total of 836 patients with acute PE were considered for inclusion in this study and 710 were ultimately included.

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Reasons for non-inclusion are reported in Supplementary Figure 1, http://links.lww.com/CM9/A357. Demographic features and baseline clinical characteristics of patients are reported in Supplementary Table 1, http://links.lww.com/CM9/A358. There were no significant differences between recurrent and non-recurrent patients with respect to sex, age, body mass index (BMI), parameters of complete blood count (including hemoglobin level, hematocrit, white blood cell and platelet count), and D-dimer level at diagnosis (all $P > 0.05$). The median sPESI scores of the patients with VTE recurrence was higher than that of the patients without VTE recurrence (1 (1–2) *vs.* 1 (0–1), $P = 0.001$).

After 2 years follow-up, 53 (7.5%) patients had VTE recurrence. The 3-, 6-, 12-, 24-month cumulative incidences of recurrent VTE were 3.5% (95% confidence interval [CI] 2.2%–4.9%), 4.5% (3.0%–6.1%), 6.4% (4.6%–8.2%), and 7.5% (5.6%–9.5%), respectively. By univariable analysis, cancer, chronic heart failure, chronic pulmonary disease, nephrotic syndrome, sPESI high risk and inappropriate anticoagulation therapy were more frequently seen in the recurrent group than the non-recurrent VTE group (all $P < 0.05$) (Supplementary Table 2, http://links.lww.com/CM9/A359). In a multivariable Cox regression model (Supplementary Table 3, http://links.lww.com/CM9/A360), nephrotic syndrome (HR 4.32, 95% CI 1.71–10.91, $P = 0.002$) and sPESI high risk (HR 2.41, 95% CI 1.31–4.46, $P = 0.005$) were independently associated with VTE recurrence. The time course of VTE recurrence at 24 months according to sPESI risk levels and whether patients had nephrotic syndrome or not are reported in Figure 1A and 1B (both P values are <0.05 by log-rank test). The 2-year cumulative VTE recurrence rate of patients with sPESI high risk was significantly higher than that of patients with sPESI low risk (9.9% *vs.* 4.4%, $P = 0.006$). The 2-year cumulative VTE recurrence rate of patients with nephrotic syndrome was significantly higher than that of patients without nephrotic syndrome (23.8% *vs.* 7.0%, $P = 0.002$). Interestingly, most VTE recurrences in nephrotic syndrome patients occurred within the first 3 months after initial diagnosis of PE.

The cumulative incidences of recurrent VTE were 7.5% at 24 months follow-up, which was close to that reported in Asian populations.[2] sPESI has been recognized as a widely validated model for assessment of severity and prediction of short-time mortality, and been recommended by the ESC guidelines to guide physicians' decisions with regard to early management strategies of acute PE patients.[3] However, there are few studies investigating the prediction value of sPESI for VTE recurrence in PE patients. This is the first study to show that sPESI high risk was associated with increased risk of VTE recurrence. The mechanism of the association between sPESI risk stratification and VTE recurrence remains to be established, but there are several possible explanations. 1) The risk factors of mortality incorporated in the sPESI are also risk factors for VTE recurrence, including advanced age, history of cancer, chronic heart failure and chronic pulmonary disease. These factors have been reported to be associated with VTE recurrence, which was also shown by our univariable analysis. 2) A recent study found that the 2008 ESC risk stratification for disease severity of acute PE patients gave a good prediction for long-term VTE recurrence after initial PE. A possible explanation by the authors for its high predictive value was that the factors involved in the 2008 ESC risk stratification reflect clot burden and right heart dysfunction, which are related to recurrence in PE patients. When considering that disease severity of acute PE evaluated by the 2008 ESC risk stratification is highly consistent with that evaluated by sPESI,[4] it is possible that high sPESI score is also

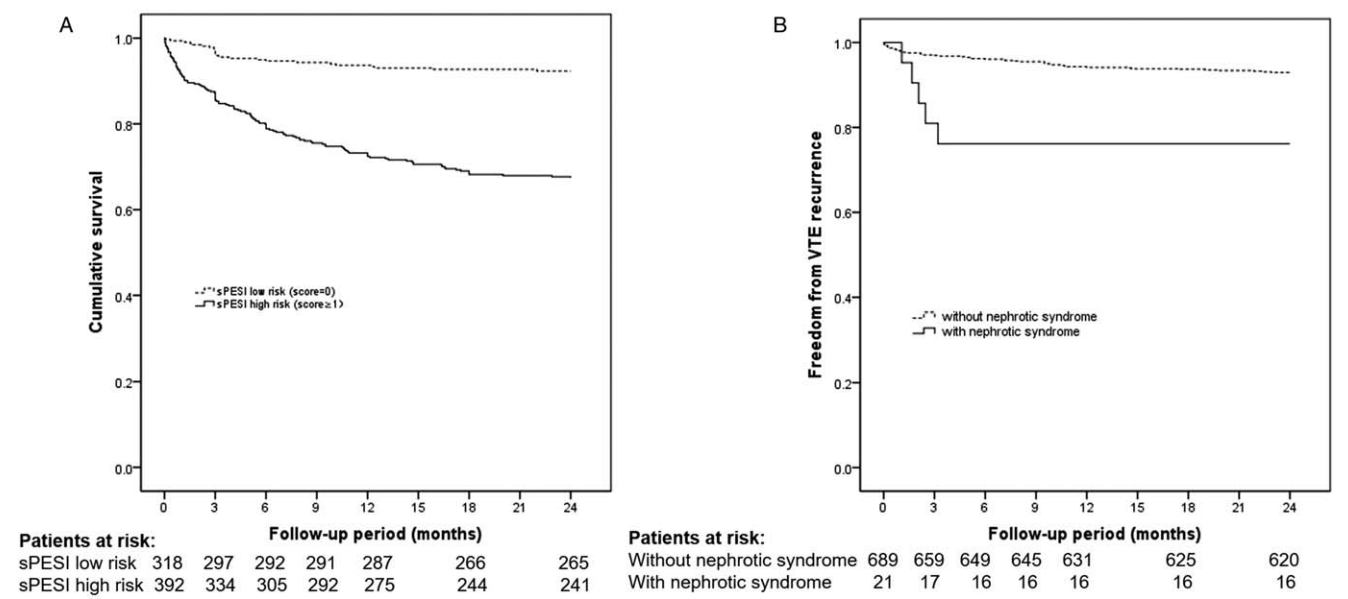

Figure 1: Kaplan–Meier estimates of the absence of VTE recurrence according to the sPESI risk categories (A) and whether pulmonary embolism patients had nephrotic syndrome or not (B) ($P = 0.006$ and 0.002, respectively, by the log-rank test for comparison of the outcome between groups at 24 months). VTE: Venous thromboembolism; sPESI: Simplified pulmonary embolism severity index.

associated with higher clot burden and prevalence of residual thrombus. Even though the association of sPESI risk stratification with VTE recurrence and possible mechanisms still need to be investigated in larger populations and other centers, our study has suggested the possible value of sPESI in predicting the risk for long-term recurrence.

Nephrotic syndrome is a risk factor of initial VTE,[5] but the association between nephrotic syndrome and VTE recurrence has not been well studied. We observed that PE patients with nephrotic syndrome had a higher incidence of VTE recurrence, especially of short-time recurrence (within 3 months). In patients with nephrotic syndrome, damage to the glomerular membrane results in increased filtration of small proteins such as antithrombin III, plasminogen, protein C, and protein S, which in turn leads to increased coagulability. The loss of albumin in patients with nephrotic syndrome and resultant hypoalbuminemia results in increased hepatic synthesis of fibrinogen which also favors formation of thrombus. These are some known causes of this hypercoagulable state and these contribute to the initial VTE event in patients with nephrotic syndrome. The high risk of short-time VTE recurrence in nephrotic syndrome patients may in part be due to the same mechanisms, which last usually for 2 to 3 months after the onset of nephrotic syndrome. The administration of glucocorticoids is also a risk factor for VTE and use of glucocorticoids for the treatment of nephrotic syndrome during the first 8 to 12 weeks after diagnosis could also increase the risk of VTE recurrence. To note, most nephrotic syndrome patients received standard anticoagulant therapy after a first episode of PE in our study, thus the high risk of VTE recurrence may be explained by other mechanisms besides those mentioned above. Increased intensity of anticoagulation therapy and closely monitoring of VTE recurrence should be considered in the management of PE in patients with nephrotic syndrome. However, this was an observation from one center, confirmation in other center and potential mechanisms should be studied in the future.

In conclusion, PE patients with sPESI high risk had an increased risk of VTE recurrence. The severity of disease may need to be not only considered in determining the initial treatment, but also for the duration and intensity of follow-up anticoagulation therapy. Nephrotic syndrome also increases recurrent risk, especially recurrence within the first three months after an initial PE. In PE patients with nephrotic syndrome, close monitoring of VTE recurrence is needed, and increased intensity of anticoagulant treatment may need to be considered in the early stage of disease. Validation of our findings with a larger population in a well-designed multicenter study is needed.

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Conflicts of interest

None.

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