Derivation and Validation of a Clinical Prediction Scale for Isolated Distal Deep Venous Thrombosis in Patients after Acute Ischemic Stroke

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Background: Isolated distal deep venous thrombosis (IDDVT) is a common complication after ischemic stroke. However, there is a paucity of evidence regarding the clinical features and risk factors of IDDVT in patients with acute ischemic stroke. This study aimed to establish and validate a clinical prediction scale of IDDVT at an early stage of ischemic stroke development. *Methods:* We retrospectively studied consecutive patients with stroke admitted to our neurology department between January and December 2016. Selected clinical variables were assessed by multivariable logistic regression to determine the independent risk factors for IDDVT. A prediction scale was developed and verified by the receiver operating characteristic curve. *Results:* A total of 671 patients with ischemic stroke were included in the study, with 450 patients allocated into the derivation group and 221 patients into the validation group. A substantial proportion (22.1%) of patients developed IDDVT. A 16-point prediction scale (female gender = 2, older age [≥60 years] = 3, atrial fibrillation = 2, acute infection = 2, active cancer = 5, and higher [≥2.6 mmol/L] level of low-density lipoprotein = 2) derived from a multivariable logistic regression model was highly predictive of 10-day risk of IDDVT in both the validation group (c statistic = .70, 95% confidence interval [CI], .63-0.78, $P < .0001$) and the derivation group (c statistic = .68, 95% CI, .63-0.74, $P < .0001$). *Conclusions:* This prediction scale may help to identify patients with ischemic stroke who are at a higher risk of developing IDDVT. **Key Words:** Acute ischemic stroke—isolated distal deep venous thrombosis—clinical prediction scale—derivation and validation—cohort study—risk factors.

Introduction

Deep venous thrombosis (DVT) is a common post-stroke complication, with its prevalence ranging from approximately 10% to 50%,[1-4] depending on the timing and the criteria of diagnosis. Most DVTs are developed between day 2 and day 7 after stroke onset, and 80% of all DVTs occur within the first 10 days.[2,5] The incidence of DVT decreases in patients with stroke transferred to the rehabilitation center.[6] Therefore, it is necessary to identify the risk of having post-stroke DVT in an early stage of ischemic stroke development. Among various tools for detecting DVT, Doppler ultrasound (DUS) is probably the most used because it is inexpensive, convenient, and non-invasive. However, certain levels of skill and experience are required of the operator.

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DVT in the lower limbs can be further identified as proximal DVT and distal calf DVT by its affected locations. Thromboses restricted in the infrapopliteal deep veins are named as isolated distal DVT (IDDVT), which may account for approximately half of all properly diagnosed DVTs.[7-9] Compared with proximal DVT, IDDVT appears to be associated with a lower rate of recurrence[10] and pulmonary embolism (PE).[11,12] Unlike proximal DVT, which permits anticoagulation treatment without doubt, controversies exist in regard to the treatment of IDDVT because of its unclear natural history. Guidelines for treating IDDVT provide different suggestions, ranging from 2 weeks of serial imaging of the deep veins to 3 months of oral anticoagulants.[13,14] Therefore, IDDVT is treated as a different entity in a clinical scenario. Likewise, in many clinical centers, only the proximal veins of patients suspected with DVT are examined, forgoing any possibilities of detecting acute IDDVT.[7] It should be noted that IDDVT can extend to proximal veins with a rate ranging from 0% to 44% in various studies,[7] and a systematic review suggests that silent PE may occur in 13% of patients with IDDVT.[12] Therefore, IDDVT might be a clinically important complication that is not fully investigated.[15]

The purpose of the present study is to evaluate the risk factors of IDDVT in patients admitted with acute ischemic stroke and to establish and validate a clinical prediction scale to enable the health-care professional to predict the risk of IDDVT at an early stage of stroke development.

Methods

Subjects

We retrospectively studied consecutive patients with acute stroke who were admitted to our neurology department between January and December 2016. We included in the study patients satisfying the following criteria: ischemic stroke, age ≥ 18 years, stroke onset within 7 days, and neurological deficit present at admission (National Institutes of Health Stroke Scale [NIHSS] ≥ 3). Patients were excluded if they had acute hemorrhagic stroke, cerebral venous thrombosis, brain tumors, or PE. The diagnosis of ischemic stroke was confirmed by stroke specialists with brain computed tomography scan or magnetic resonance imaging. All patients received antiplatelet or antithrombotic therapy if necessary. None received DVT prophylaxis management such as thigh-length or below-knee elastic stockings, or intermittent pneumatic compression. Ethical approval was obtained from the ethics committee of The First Affiliated Hospital of Wenzhou Medical University.

Screening Protocol for IDDVT

After the admission, patients were screened for DVT in both lower limbs 10 (±2) days after the stroke onset. Real-time B-mode and color-mode ultrasonography was performed by an experienced sonographer using an HDI 5000 system (Philips ATL, Bothell, WA, USA) equipped with a 3.0- to 7.0-MHz linear array transducer. DVT was diagnosed based on the detection of a non-compressible segment or inadequately compressible lesion. A vein was also classified as abnormal if a lesion or defect was observed on color-mode ultrasound. IDDVT was defined as incompressible thrombus on ultrasound isolated to veins below the level of the popliteal vein (posterior and anterior tibial veins, peroneal veins, and the muscular veins), without coexistence of proximal DVT.

Data of Interest

The following clinical characteristics were obtained for each patient: age, gender, selected medical comorbidities (hypertension, diabetes mellitus, atrial fibrillation, acute infection, active malignancy, and acute gouty arthritis), selected laboratory results (triglyceride, low-density lipoprotein [LDL], fast glucose, etc.), stroke severity, and treatment after the admission. The acute infection includes acute pulmonary infection, urinary infection, skin infection, or septicemia.

Statistical Analysis

Derivation of Post-Stroke IDDVT Prediction System

The patients were randomly assigned to a derivation group or a validation group with a 2:1 ratio. Statistical analysis was performed using SAS (version 9.13, SAS Institute, Cary, NC). $P < .05$ was considered as statistically significant.

The data from the derivation group were used to develop the post-stroke IDDVT prediction system. First, the correlation between each of the clinical variables and the outcome of IDDVT was determined by the bivariate analyses (χ^2 test on discrete variables and *t*-test on continuous variables). Second, the variables associated with IDDVT in the bivariate analyses ($P < .05$) were assessed by a multivariable logistic regression model. Third, we assigned prediction points for each of the clinical variables. The points were determined by the odds ratios from the multivariable model, which were rounded to the nearest whole number. Fourth, a risk prediction scale was developed by summing the points for each risk factor present. Finally, we examined the outcome rate according to the prediction scale to identify 3 classifications of risk: low, medium, and high risk of post-stroke IDDVT.

Validation of Post-Stroke IDDVT Prediction System

The prediction scale and 3-category risk classification system were tested in the validation population. To test