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Establishment and validation of a prediction model for ischemic stroke risks in patients with type 2 diabetes

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ABSTRACT

Aims: A risk scoring system for predicting ischemic stroke incidence may identify type 2 diabetes patients at high risk for ischemic stroke who can benefit from preventive intervention programs. Such a risk scoring system can serve as a benchmark to test novel putative risk factors.

Methods: The study adopted a retrospective cohort, including 28,124 Chinese patients with type 2 diabetes aged 30–84 years during 2001–2004. Participants were randomly assigned to the derivation and validation sets at a 2:1 ratio. Cox's proportional hazard regression model was used to identify risk factors of ischemic stroke incidence in the derivation set. And then the steps proposed by the Framingham Heart Study for establishing an ischemic stroke prediction model with a scoring system was used.

Results: Among 9374 patients in the validation set, 1076 subjects (11.48%) developed ischemic stroke with a mean follow up period of 8.0 years. We identified the following risk factors: age, gender, smoking habit, duration of type 2 diabetes, blood pressure, HbA1c level, total cholesterol to high-density lipoprotein ratio, creatinine, fasting plasma glucose variation (FPG-CV), arterial embolism and thrombosis, diabetes retinopathy, hypoglycemia, anti-diabetes medication use, and cardiovascular medication. The area under receiver operating characteristic curve of the 3-year, 5-year, and 8-year ischemic stroke incidence risks were 0.72, 0.71, and 0.68 for the validation set, respectively.

Conclusions: This proposed ischemic stroke incidence risk prediction model is the first model established for Chinese patients with type 2 diabetes recruited from nationwide clinical settings.

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1. Introduction

Diabetes is a formidable global health threat because of its high prevalence and numerous complications. Furthermore, diabetes is a leading cause of mortality and microvascular and macrovascular diseases, including coronary diseases, cerebrovascular diseases, and peripheral vascular diseases. A recent study reports that risk of stroke in patients with type 2 diabetes is two to five times higher than the general population [1]. The World Health Organization MONICA project reported that stroke incidence is higher among ethnic Chinese population than among Western population [2]. Risk prediction models and scoring systems are extensively used for many cardiovascular diseases [3–10]. Simplified prediction models employing point scoring and charts can be easily used by clinicians and patients to facilitate the initiation of lifestyle modification or preventive medical treatment. Although prediction models and scoring systems are widely utilized [11–14], they are mainly exclusive to the Western population [1,11,15,16]. For people with diabetes, the United Kingdom Prospective Diabetes Study (UKPDS) developed a prediction model for stroke specific to type 2 diabetes patients [1]. To our knowledge, only Hong Kong has developed a stroke prediction model for patients with type 2 diabetes in the Asian pacific population [16].

A scheme to identify patients clinically treated for type 2 diabetes who are at higher risks of stroke could assist clinicians in directing preventive interventions to these individuals. Information from this identification scheme could further help identify the baseline risk factors for stroke to allow for the comparison of stroke risks across different clinical settings and consequently improve the quality of care for patients at risk. The factors associated with patients with type 2 diabetes developing stroke are well defined; they include old age [16], gender [1,15], duration of diabetes [1], poor glycemic control [15], age at onset [1], total cholesterol (TC) to high-density lipoprotein (HDL) ratio [1], systolic blood pressure (SBP) [1,15], coefficient variation of fasting plasma glucose variation (FPG-CV) [17], atrial fibrillation [1], white cell count [15], and albumin to creatinine ratio (ACR) [16].

Prior studies suggested stroke mortality varied across nations [18]. It was observed there were striking differences in distribution of cardiovascular risk factors and conditions across South Asian, Chinese, black, and white ethnic groups living in Ontario [19]. Migration studies pointed out significant variations in major cardiovascular events across ethnic groups. East Asian immigrants (predominantly Chinese) had the lowest incidence of major cardiovascular events, but this incidence increased as the duration of stay in Canada became greater [20]. On the contrary, South Asian immigrants had the highest incidence. The differences in cardiovascular conditions across ethnic groups may be due to lifestyle behaviors, environmental factors, and inherited genetics. Prior genetic studies had identified some genetic variations were associated with ischemic stroke specifically in East Asian populations [21,22] whereas some were linked with ischemic stroke in white but not in Chinese population [23]. Similar genetic association was observed for pathological factors of stroke such as hypertension [24]. Due to variation in distributions of lifestyle behaviors and genetic factors across ethnic groups and nations, the effects of lifestyle behaviors and cardiovascular risk factors on stroke may differ. Thus, there is a need to develop a risk prediction model for Chinese population living East Asia. This study aimed to develop a prediction model for new ischemic stroke event by adopting the Framingham Heart Study approach to Chinese patients with type 2 diabetes enrolled in the National Diabetes Care Management Program (NDCMP). NDCMP is a nurse case management program launched by the Bureau of National Health Insurance of Taiwan in 2001.

2. Methods

2.1. Study design and population

A retrospective cohort study, Taiwan Diabetes Study (TDS), was conducted in patients who were diagnosed with type 2 diabetes during 2001–2004 and enrolled in NDCMP. The date of entry to NDCMP was defined as the index date. If the patients were identified to have experienced an event of stroke before the index date, then these patients were excluded. The study sample consisted of approximately 63,000 ethnic Chinese patients with type 2 diabetes enrolled in the NDCMP of Taiwan. After the exclusion of 1864 subjects with type 1 diabetes (ICD-9-CM; code 250.X1/X3), 878 subjects aged less than 30 years or more than 85 years, and 8875 subjects with a history of stroke, 51,467 individuals were considered eligible and enrolled in this study. After excluding patients with less than one year of enrollment in the NDCMP before 2004 or with missing data on gender, fasting blood glucose, HbA1c, duration of diabetes, and age at diabetes onset (n = 23,343), a total of 28,124 patients were included in the data analysis (Fig. 1). The Ethical Review Board of China Medical University Hospital approved the study protocol.

2.2. Ascertainment of covariates and outcomes

Medication use consisted of anti-diabetes medications, antihypertension medications, cardiovascular medications, and lipid-lowering medications. The use of medication for treatment was defined as the 12-month period before cohort entry in their outpatient prescriptions. If a patient used medication for more than three months, then we defined him/her as a user. For anti-diabetes medication use, patients were grouped into four categories, namely, no medication, oral medication (e.g., metformin, sulfonylurea, thiazolidinedione, α-glucosidase inhibitors, and glinides), insulin only, and insulin and oral medication combination. The antihypertension medications included ACE inhibitors, ARBs, β-blockers, calcium channel blockers, and diuretics. Cardiovascular medications consisted of antiarrhythmic, digoxin, anticoagulants, antiplatelet, and digoxin. Lipid-lowering medications are divided into two types, namely, statins and fibrates.

Comorbidity included heart failure, acute myocardial infarction, ischemic heart disease, hypertension, peripheral arterial occlusive disease, atrial fibrillation, peripheral neuropathy, diabetes retinopathy, disease of peripheral circulatory disturbance, hypoglycemia, chronic kidney disease,