Research Article

Gender Differences and Risk Factors of Recurrent Stroke in Type 2 Diabetic Malaysian Population with History of Stroke: The Observation from Malaysian National Neurology Registry

Sohail Aziz, Siti Maisharah Sheikh Ghadzi, Nur Ezzati Abidin, Balamurugan Tangiisuran, Hadzliana Zainal, Irene Looi, Khairul Azmi Ibrahim, Norsima Nazifah Sidek, Loo Keat Wei, Lee Keng Yee, Zariah Abdul Aziz, and Sabariah Noor Harun

1School of Pharmaceutical Sciences, Universiti Sains Malaysia, 11800 USM, Penang, Malaysia
2Pusat Racun Negara, Universiti Sains Malaysia, 11800 USM, Penang, Malaysia
3Clinical Research Centre, Seberang Jaya Hospital, Ministry of Health, Penang, Malaysia
4Clinical Research Centre, Hospital Sultanah Nur Zahirah, Ministry of Health, Terengganu, Malaysia
5Department of Biological Science, Faculty of Science, Universiti Tunku Abdul Rahman, Bandar Barat, 31900 Kampar, Perak, Malaysia
6National Institutes of Health (NIH), Ministry of Health, Malaysia, Kuala Lumpur, Malaysia

Correspondence should be addressed to Sabariah Noor Harun; sabariahnoor@usm.my

Received 16 July 2019; Revised 25 September 2019; Accepted 8 November 2019; Published 11 December 2019

Academic Editor: Akira Sugawara

Copyright © 2019 Sohail Aziz et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Background and Purpose. Diabetes mellitus has been reported as a strong independent risk factor for stroke recurrence. Data on the modifiable factors contributing to the recurrence of stroke in type 2 diabetic Malaysian population with a history of stroke stratified by genders are lacking, and this supports the importance of this study. Method. The data of 4622 patients with T2DM who had a history of stroke was obtained from the Malaysian National Stroke Registry. Univariate analysis was performed to differentiate between genders with and without stroke recurrence in terms of demographics, first stroke attack presentations, and other clinical characteristics. The significant factors determined from the univariate analysis were further investigated using logistic regression. Results. Ischemic heart diseases were found significantly associated with the stroke recurrence in males (OR = 1.738; 95% CI: 1.071-2.818) as well as female (OR = 5.859; 95% CI: 2.469-13.752) diabetic patients. The duration of hypertension, as well as the duration of diabetes, has been associated with the recurrence in both male and female subjects (p value < 0.05). Smoking status has an impact on the stroke recurrence in male subjects, while no significant association was observed among their peers. Conclusions. Most of the predictive factors contributing to the recurrence of stroke in type 2 diabetic Malaysian population with a history of stroke are modifiable, in which IHD was the most prominent risk factor in both genders. The impact of optimizing the management of IHD as well as blood glucose control on stroke recurrence may need to be elucidated. No major differences in recurrent stroke predictors were seen between genders among the Malaysian population with type 2 diabetes mellitus who had a previous history of stroke.

1. Introduction

According to the 2016 survey, 5.53 million people worldwide suffered from stroke. On the basis of premature mortality and secondary disabilities, stroke was the second highest in ranking [1]. Based on epidemiological data, patients with diabetes mellitus (DM) are at a higher risk of developing atherosclerotic vascular disorders than individuals without DM [2]. Prospective studies have shown that hyperglycemia plays a vital role in the development of vascular complications [3].
Although the impact of diabetes and hyperglycemia on stroke can be observed in various studies [3, 4, 7], there is a lack of defining factors responsible for strokes in diabetes. Diabetes is considered one of the most consistent predictors of recurrent stroke. Diabetic patients carry an astounding three-fold risk for recurrent stroke in comparison to normoglycemic individuals [4]. Patients with diabetes have a cluster of established risks, such as hypertension, dyslipidemia, and obesity that contribute to stroke [5]. An estimated one-third of acute stroke patients have been found to be hyperglycemic at the time of presentation, with increased mortality and morbidity in the immediate poststroke period [6]. As observed in earlier studies, the effects of DM were worst in females than in males [7]. These deteriorating effects are associated with endothelial dysfunction and more severe hypertension in diabetic females as well as the inflammatory effects of diabetes, which play an important role in stroke prevalence and in aggravating the damage to the brain from stroke [8, 9]. Understanding these gender-based factors is indeed important in minimizing the risk factors associated with diabetes as well as poststroke complications.

An intriguing relationship can be seen between diabetes, stroke, and gender of the individuals. Based on data from a meta-analysis, it has been estimated that diabetic female carries a 27% higher risk of stroke in comparison to diabetic male [9]. Some other studies suggest that the survival and functional outcomes in females are worse than those in males [10–12]. Similarly, hypercholesterolemia, smoking, physical inactivity, obesity, hypertension, and a family history of stroke in a patient with diabetes can be considered major risk factors for the development of recurrent stroke [13]. Although all of these factors can individually contribute to the recurrence of stroke, a systematic analysis reported that 90% of stroke burden from 1990 to 2013 was caused by the combined effects of all these modifiable factors [12]. Despite the available research based on the impact of diabetes on stroke recurrence, the defining factors which contribute to the stroke recurrence in diabetes patients are still lacking. Based on gender, our study focused on multiple factors that contribute to stroke recurrence in the Malaysian population with type 2 diabetes mellitus (T2DM).

2. Aim of the Study

The aims of the current study were (a) to determine the prevalence of recurrent stroke in type 2 diabetic Malaysian population with a history of stroke and (b) to differentiate all those intriguing factors which contribute to the recurrence of stroke in T2DM patients based on gender.

3. Ethics Approval

The ethical approval for this study was obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health, Malaysia.

4. Method

4.1. Patients’ Data Collection. All patients’ data from August 2009 to December 2016 were extracted from the National Stroke Registry of Malaysia. Data of patients who were diagnosed with type 2 diabetes mellitus (T2DM) and had a history of stroke were extracted from the registry and included in the analysis. The clinical diagnosis of stroke was made according to the World Health Organization’s criteria [7]. All diagnoses were confirmed using brain computed tomography or magnetic resonance imaging. The patient’s neurological function deficit was evaluated using the National Institute of Health Stroke Scale (NIHSS), Barthel index (BI), and the modified rank scale (mRS) on admission. Stroke severity was categorized using the NIHSS into three groups: mild (NIHSS: ≤7), moderate (NIHSS: 8–16), and severe (NIHSS: ≥17) [14]. Diabetes was either defined as self-reported physician diagnosis or based on the use of hypoglycemic medications prior to the first stroke attack during hospitalization secondary to stroke attack or at discharge. Similarly, hyperlipidemia and ischemic heart disease were also defined either by self-report or by the medications prescribed. Patients were followed up for a minimum of 1 year for clinical outcomes of recurrent stroke, death, and functional outcome. The recurrent stroke risk factors included the medical history of hypertension, diabetes mellitus (DM), dyslipidemia, atrial fibrillation (AF), and ischemic heart disease (IHD). We also evaluated modifiable lifestyle factors, including current smoking (≥1 cigarette per day for ≥1 year), alcohol consumption (≥1 drink per week for 1 year), and obesity [body mass index (BMI) ≥ 30 kg/m²].

4.2. Stroke Registry in Malaysia. The multiethnic National Neurology Registry (NNEUR) in Malaysia was first established in 2009. The NNEUR has collected information on stroke cases from 13 states in the country. NNEUR represents an ongoing multicenter, hospital-based registry that is aimed at providing comprehensive epidemiological data on the country’s stroke statistics, trend, and management. The registry is funded by the Ministry of Health, Malaysia (MOH), with support from the National Network Clinical Research Centre, MOH. The complete details on the stroke registry (http://acrm.org.my/nneur/) have been previously described elsewhere [27].

4.3. Analysis. The cross-sectional analysis employed univariate and multivariate logistic regression to evaluate the association between explanatory factors and recurrent stroke using SPSS version 22.0 (SPSS Inc., Chicago, III, USA). The values for continuous variables were expressed as the mean ± standard deviation, while categorical variables were presented in percentage. A chi-square test was used for the univariate analysis of categorical variables while an independent sample t-test/Mann–Whitney U test was used for continuous data. The significant variables from the univariate analysis were further analyzed using multiple logistic regression. The association between exposure and outcomes was reported as an odds ratio (OR) with a 95% confidence interval (CI). In order to minimize bias from missing data,
the pattern of missing values of independent variables was analyzed. Multiple imputations were used to handle variables with missing values above 5%. Missing values in BMI, prior medications, uric acid level on the first stroke event, and total cholesterol level on the first stroke event were imputed from multivariate imputation. Five imputations were used, and Rubin’s rules were implemented to combine the results. A two-tailed probability value of \( p < 0.05 \) was considered significant.

### 5. Results

5.1. Descriptive Results. Overall, 4622 diabetes patients who had a history of stroke were included in the analysis. As shown in Table 1, from the total diabetic patients with a history of stroke, 2280 (49.32%) were female, age < 65 years (54.3%). The ischemic stroke was the most prominent type of stroke in both genders. The majority of patients in both genders were diagnosed with diabetes for 1-5 years. 1513 male patients (64.6%) were smokers, and those with ischemic heart diseases (16.9%) were the most with prevalent concomitant disease in this population as compared to their counterparts. 2063 female patients (90.5%) had hypertension while 753 (33.0%) had hyperlipidemia. The mortality was found to be less prevalent in females (9.1%) as compared to male patients (12.2%), as recorded in Table 1.

5.2. Factors Associated with Stroke Recurrence in Female Diabetic Patients with History of Stroke. Associations between the variables and stroke recurrence in diabetic female patients with a history of stroke are represented in univariate and multivariate logistic regression as shown in Table 2. An independent association was found between IHD and stroke recurrence among diabetic female patients, being diagnosed with IHD prior to the first time stroke attack was also a significant prediction of recurrent stroke among males with diabetes (OR, 1.738; 95% CI [1.017-2.818]; \( p < 0.001 \)). In the ethnicity group in the patients, being diagnosed with IHD prior to the first-time stroke attack was also a significant prediction of recurrent stroke among males with diabetes (OR, 1.738; 95% CI [1.017-2.818]; \( p < 0.001 \)).

5.3. Factors Associated with Stroke Recurrence in Diabetic Male Patients with History of Stroke. Associations between variables and stroke recurrence in diabetic male patients with a history of stroke are presented in Table 3. As in female

---

**Table 1: Characteristic of female and male diabetic patients presented as the number of subjects in each category (\( N = 4622 \)).**

| Variables               | Female \((n = 2280)\) | Male \((n = 2342)\) |
|-------------------------|------------------------|----------------------|
| WHO classification      |                        |                      |
| Intracerebral hemorrhage| 265                    | 11.6                 |
| Ischemic stroke         | 1924                   | 84.4                 |
| Subarachnoid hemorrhage | 7                      | 0.3                  |
| Transient ischemic attack| 63                    | 2.8                  |
| Unclassified            | 20                     | 0.9                  |
| Age (years)             |                        |                      |
| <65                     | 1237                   | 54.3                 |
| ≥65                     | 1043                   | 45.7                 |
| Ethnicity               |                        |                      |
| Malay                   | 558                    | 24.5                 |
| Chinese                 | 69                     | 3.0                  |
| Indian                  | 48                     | 2.1                  |
| Others                  | 1605                   | 70.4                 |
| Education               |                        |                      |
| Informal                | 988                    | 43.3                 |
| Formal                  | 1292                   | 56.7                 |
| Marital status          |                        |                      |
| Single                  | 36                     | 1.6                  |
| Married                 | 1982                   | 86.9                 |
| Divorced                | 14                     | 0.6                  |
| Widowed                 | 96                     | 4.2                  |
| Unknown                 | 152                    | 6.7                  |
| Smoker                  | 856                    | 37.5                 |
| Duration of diabetes (years) |                        |                      |
| >1                      | 155                    | 6.8                  |
| 1-5                     | 861                    | 37.8                 |
| 6-10                    | 365                    | 16.0                 |
| >10                     | 377                    | 16.5                 |
| Unknown                 | 522                    | 22.9                 |
| BMI                     |                        |                      |
| Normal                  | 423                    | 18.6                 |
| Overweight              | 601                    | 26.4                 |
| Obese                   | 1192                   | 52.3                 |
| Underweight             | 52                     | 2.3                  |
| Hypertension            | 2063                   | 90.5                 |
| IHD                     | 235                    | 10.3                 |
| Hyperlipidemia          | 753                    | 33.0                 |
| Atrial fibrillation     | 68                     | 3.0                  |
| Death                   | 208                    | 9.1                  |

Abbreviations: BMI = body mass index; IHD = ischemic heart disease; WHO = World Health Organization.
Table 2: Univariate and multivariate logistic regression analyses of variables associated with stroke recurrence in female patients with diabetes.

|                        | Univariate analysis | Logistic regression* |
|------------------------|---------------------|----------------------|
|                        | Without recurrence  | With recurrence      | p value | OR [95% CI] | p value |
|                        | N = 2171 N (%)      | N = 109 N (%)        |         |             |         |
| Constant               | —                   | —                    | 0.217   | 0.763       | —       |
| Age (years)            |                     |                      |         |             |         |
| <65                    | 1165 (53.6)         | 72 (66.1)            | 0.013   | 1.537 [0.229-10.318] | 0.658 |
| ≥65                    | 1006 (46.4)         | 37 (33.9)            | —       | —           | —       |
| Duration of diabetes   |                     |                      |         |             |         |
| <1 year                | 147 (6.8)           | 8 (7.3)              | —       | —           | —       |
| 1-5 years              | 810 (37.3)          | 51 (46.8)            | 1.537   | [0.229-10.318] | 0.658 |
| 6-10 years             | 347 (16.0)          | 18 (16.5)            | 0.005   | 1.161 [0.153-8.823] | 0.885 |
| >10 years              | 354 (16.3)          | 23 (21.1)            | 1.334   | [0.165-10.780] | 0.787 |
| Unknown                | 513 (23.6)          | 9 (8.3)              | 0.291   | [0.018-4.793] | 0.388 |
| Education              |                     |                      |         |             |         |
| Formal                 | 1204 (55.4)         | 88 (80.7)            | 0.000   | —           | —       |
| Informal               | 967 (44.6)          | 21 (19.3)            | —       | —           | —       |
| Mode of arrival at emergency at the first-time stroke attack* | — | — |         |         |
| Ambulance              | 1036 (47.7)         | 71 (65.1)            | —       | —           | —       |
| Own transport          | 1026 (47.2)         | 37 (34.0)            | 0.001   | —           | —       |
| Unknown                | 109 (5.1)           | 1 (0.9)              | —       | —           | —       |
| Duration of hypertension|                     |                      |         | Reference   | (0 years) |
| <1 year                | 105 (4.8)           | 5 (4.5)              | 1.488   | [0.147-15.040] | 0.736 |
| 1-5 years              | 720 (33.1)          | 45 (41.5)            | 2.078   | [0.184-23.417] | 0.554 |
| 6-10 years             | 326 (15.0)          | 18 (16.5)            | 1.875   | [0.171-20.539] | 0.607 |
| >10 years              | 372 (17.1)          | 27 (24.7)            | 2.137   | [0.105-43.543] | 0.622 |
| Unknown                | 437 (19.3)          | 8 (7.3)              | 1.374   | [0.117-16.184] | 0.801 |
| Smoking status         |                     |                      |         |             |         |
| Current smoker         | 28 (1.3)            | 0 (0.0)              | —       | —           | —       |
| Former smoker          | 27 (1.2)            | 1 (0.9)              | —       | —           | —       |
| Never                  | 2089 (96.3)         | 108 (99.1)           | 0.401   | —           | —       |
| Unknown                | 27 (1.2)            | 0 (0.0)              | —       | —           | —       |
| Hyperlipidemia         | 707 (93.9)          | 46 (6.1)             | 0.025   | —           | —       |
| Ischemic heart disease | 212 (90.2)          | 23 (9.8)             | 5.859   | [2.496-13.752] | 0.000 |
| ACEIs received at baseline** | 2088 (95.4) | 101 (4.6) | 0.066 | — | — |
| ARBs received at baseline** | 2105 (95.4) | 101 (4.6) | 0.023 | — | — |
| ADM received at baseline** | 909 (93.1) | 67 (6.9)  | 0.000 | 1.409 [0.467-4.251] | 0.542 |
| Received OHA upon discharge*** | 726 (93.3) | 52 (6.7)  | 0.002 | 0.909 [0.327-2.525] | 0.855 |
| Received diuretics upon discharge*** | 143 (89.9) | 16 (10.1) | 0.003 | 3.476 [1.146-10.538] | 0.028 |
| Glasgow Coma Scale: motor response | 58 (2.7) | 1 (0.9) | — | — | — |
| No response            |                     |                      |         |             |         |
| Extension response in response to pain | 15 (0.7) | 4 (3.7) | — | — | — |
| Flexion in response to pain | 31 (1.4) | 0 (0.0) | 0.006 | — | — |
| Withdraws in response to pain | 46 (2.1) | 1 (0.9) | — | — | — |
| Purposeful movement to painful stimulus | 244 (11.4) | 8 (7.4) | — | — | — |
| Obey commands for movement | 1747 (81.6) | 94 (87.0) | — | — | — |
subcategory “others” originating from East Malaysia, the odds of stroke recurrence was significantly less among males with diabetes (OR, 0.330; 95% CI [0.207-0.528]; p < 0.001). Male patients who have been diagnosed with diabetes for a duration of less than a year and more than a decade were found to have a significant increase in the odds of stroke recurrence in the final regression model (OR, 2.917; 95% CI [1.163-11.466]; p < 0.05) and (OR, 2.917; 95% CI [1.163-11.466]; p < 0.05), respectively (Table 3). In addition, having had a clinical manifestation of monoparesis at the first-time stroke event increased the probability of stroke recurrence (OR, 4.076; 95% CI [1.230-13.506]; p < 0.05). Nevertheless, experiencing an altered sensorium during the first-time stroke event reduced the probability of stroke recurrence (OR, 0.172; 95% CI [0.41-0.724]; p < 0.05) among diabetic male patients with a history of stroke.

6. Discussion

This current study is based on a multiethnic Malaysian population, which to our knowledge, is the first study focusing on the associated predictors of recurrent stroke in the type 2 diabetic Malaysian population with a history of stroke stratified by gender. According to a study conducted in Japan on the recurrence of stroke, it has been observed that some predictors of stroke are time-specific and may differ in late and early recurrences, such as T2DM which is considered a specific predictor of late recurrence [15]. Most studies based on the predictors of recurrent stroke were conducted in the general population, and diabetes was commonly found as the significant risk factor [4]. Moreover, those studies were mostly done in the white population, with the data being extrapolated to other population groups [6-8]. As in other Asian populations, ischemic stroke was identified as the most common type among the Malaysian diabetic populations [16]. However, there was no difference found in the incidence of recurrent stroke between males (4.6%) and females (4.8%) in our population, which contradicted the findings from previous studies [17, 18]. This suggests that the overall difference between genders for the risk of recurrent stroke stratified by diabetes is still inconclusive. A possible explanation of this might be that the distribution of age range in both genders is similar, which was <65 years old. As shown previously, a diabetic male aged <75 years has a higher risk of recurrent stroke than a female [7].

As shown in the current study, IHD was the independent predictor of recurrent stroke in both genders. Thisobservation was in concordance with previous studies, suggesting that factors such as malfunctioning nitric oxide (NO) system, hypercoagulability, and endothelial dysfunction in patients with diabetes having IHD are responsible for the recurrence of stroke [19-22]. The NO system protects vessels from platelet aggregation. An increased metabolism of NO or a decrease in production leads to hypercoagulability and endothelial dysfunction in patients with diabetes having IHD are responsible for the recurrence of stroke [19-22]. The NO system protects vessels from platelet aggregation. An increased metabolism of NO or a decrease in production leads to hypercoagulability and narrowing of vessels, which thus contributes to ischemia and any increase in the metabolism of NO, or its decrease production leads to hypercoagulability and narrowing of vessels [19]. Furthermore, impairment in fibrinolysis markers, coagulation factors, and inflammatory markers in diabetes patients also contributes directly to the recurrence of stroke [22]. This is also suggesting that irrespective of gender, IHD is the modifiable indicator for the high risk of the occurrence
Table 3: Univariate and multivariable logistic regression analysis of variables associated with stroke recurrence in male patients with diabetes.

| Variable                                      | Univariate analysis   | Logistic regression* |
|------------------------------------------------|-----------------------|----------------------|
|                                                | Without recurrence N = 2234 | With recurrence N = 108 | p value | OR [95% CI] | p value |
| Constant                                       | —                     | —                     | 0.108   | 0.001       |         |
| AGE (years)                                    |                       |                       |         |             |         |
| <65                                            | 1345 (60.3)           | 75 (69.4)            | 0.069   | —           | —       |
| ≥65                                            | 886 (29.7)            | 33 (30.6)            | —       | —           | —       |
| Duration of diabetes                           |                       |                       |         |             |         |
| <1 year                                        | 167 (7.5)             | 5 (4.6)              | —       | Reference   |         |
| 1-5 years                                      | 831 (37.2)            | 54 (50.0)            | 2.917   | [1.007-8.454] | 0.049   |
| 6-10 years                                     | 309 (13.8)            | 14 (13.0)            | 2.540   | [0.782-8.244] | 0.121   |
| >10 years                                      | 294 (13.2)            | 25 (23.1)            | 3.652   | [1.163-11.466] | 0.027   |
| Unknown                                        | 633 (28.3)            | 10 (9.3)             | 1.277   | [0.343-4.752] | 0.715   |
| Education                                      |                       |                       |         |             |         |
| Formal                                         | 1461 (65.4)           | 86 (79.6)            | 0.001   | —           | —       |
| Informal                                       | 773 (34.6)            | 22 (20.4)            | —       | —           | —       |
| Ethnicity                                      |                       |                       |         |             |         |
| Malay                                          | 479 (21.4)            | 54 (50.0)            | —       | Reference   |         |
| Chinese                                        | 70 (3.1)              | 4 (3.7)              | 0.714   | [0.231-2.208] | 0.559   |
| Indian                                         | 33 (1.5)              | 3 (2.8)              | 0.827   | [0.212-3.228] | 0.784   |
| Others*                                        | 1652 (73.9)           | 47 (43.5)            | 0.330   | [0.207-0.528] | 0.001   |
| Mode of arrival at emergency upon the first-time stroke attack* |                       |                       |         |             |         |
| Ambulance                                      | 992 (44.4)            | 43 (39.8)            | —       | —           | —       |
| Own transport                                  | 1104 (49.4)           | 64 (59.3)            | 0.026   | —           | —       |
| Unknown                                        | 138 (6.2)             | 1 (0.9)              | —       | —           | —       |
| Duration of hypertension                       |                       |                       |         | Reference   | 0.736   |
| <1 year                                        | 116 (5.2)             | 7 (6.5)              | 1.488   | [0.147-15.040] | 0.736   |
| 1-5 years                                      | 721 (32.3)            | 40 (37.0)            | 2.078   | [0.184-23.417] | 0.554   |
| 6-10 years                                     | 279 (12.5)            | 11 (10.2)            | 1.875   | [0.171-20.539] | 0.607   |
| >10 years                                      | 268 (12.0)            | 20 (18.5)            | 2.137   | [0.105-43.543] | 0.622   |
| Unknown                                        | 522 (23.4)            | 9 (8.3)              | 1.374   | [0.117-16.184] | 0.801   |
| Smoking status                                 |                       |                       |         |             |         |
| Current smoker                                 | 518 (23.2)            | 40 (37.0)            | —       | 0.85        |         |
| Former smoker                                  | 432 (19.3)            | 19 (17.6)            | 1.452   | [0.907-2.325] | 0.120   |
| Never                                          | 1171 (52.4)           | 49 (45.4)            | 0.678   | [0.379-1.213] | 0.190   |
| Unknown                                        | 113 (5.1)             | 0 (0.0)              | —       | 0.99        |         |
| Hyperlipidemia                                 | 602 (94.5)            | 35 (5.5)             | 0.224   | —           | —       |
| Ischemic heart disease                         | 368 (93.2)            | 27 (6.8)             | 0.025   | 1.738 [1.071-2.818] | 0.025   |
| ACEIs received at baseline**                   | 2143 (95.9)           | 91 (4.1)             | 0.000   | 0.374 [0.131-1.067] | 0.066   |
| ARBs received at baseline**                    | 2152 (95.9)           | 93 (4.1)             | 0.000   | 1.226 [0.409-3.673] | 0.715   |
| ADM received at baseline**                     | 913 (93.9)            | 59 (6.1)             | 0.005   | 1.409 [0.467-4.251] | 0.542   |
| Received OHA upon discharged***                | 748 (94.2)            | 46 (5.8)             | 0.034   | 0.909 [0.327-2.525] | 0.855   |
| Glasgow Coma Scale: motor response             |                       |                       |         |             |         |
| No response                                    | 61 (2.8)              | 1 (0.9)              | —       | —           | —       |
| Extension response in response to pain         | 20 (0.9)              | 0 (0.0)              | 0.037   | —           | —       |
| Flexion in response to pain                    | 42 (1.9)              | 0 (0.0)              | —       | —           | —       |
| Withdraws in response to pain                  | 37 (1.7)              | 1 (0.9)              | —       | —           | —       |
of recurrent stroke. Further studies to determine the extent of optimal therapy for IHD that may reduce the risk of recurrent stroke may be warranted.

Surprisingly, in contrast to earlier findings in other Asian populations [23, 24], no significant association between hyperlipidemia and recurrent stroke was found in our diabetic population irrespective of gender groups. Nevertheless, our findings are consistent with those of Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS) and Atherosclerosis Risk in Communities (ARIC) study which did not support hyperlipidemia as a predictor of recurrent stroke in diabetic population irrespective of gender groups. Nevertheless, our study did not observe any association between CHD and gender with the occurrence of recurrent stroke.

Hypertension is one of the classical risk factors for the development of stroke in diabetic patients. Without considering other variables into account, the extended duration of hypertension was found to be significantly associated with recurrent stroke in both male and female diabetic patients in the current study. Nevertheless, every 1 mmHg increase in blood pressure increases the risk of recurrent stroke in female diabetic patients. This result is consistent with a previous study that reported that female patients are comparatively more prone to hypertension and are more prone to recurrent stroke [23]. Intensive blood pressure control has been shown to be associated with a significant reduction in total stroke in the general population [31, 32]. Diabetic patients benefited from the antihypertensive treatment as observed in the Systolic Hypertension in Europe Trial with a 73% decrease in stroke incidence in diabetes patients as compared to a 38% decrease in nondiabetic patients by targeting the systolic blood pressure [33]. However, whether the female diabetic population requires more aggressive blood pressure control as compared to males to reduce recurrent stroke may need to be further investigated.

In accordance with the current study, it has been observed that the duration of diabetes significantly increases the chance of stroke [34]. The effects of diabetes duration on the risk of recurrent stroke have been observed in univariate analysis; however, no significant effects were observed by using multivariable analysis. A prospective cohort study was performed to determine the role of duration of diabetes and its impact on stroke, and the authors have reported that the risk of stroke increased by 3% every year and tripled after ten years of diabetes duration [35]. The maximum observed risk was after ten years of diabetes which supports the results of the current study. Many potential mechanisms like atherosclerotic lesions, the prevalence of hypertension, increased microalbuminuria, and endothelial dysfunction, which is directly related to the duration of diabetes, can be associated with the increased risk of stroke [36–38]. Furthermore, our study has observed an increase in odds of stroke recurrence for patients with less than one year of diabetes duration. In accordance to the current study results, a study performed on Canadian population has observed that newly treated

### Table 3: Continued.

| Variable                                | Univariate analysis | Logistic regression* |
|-----------------------------------------|---------------------|----------------------|
| Purposeful movement to painful stimulus | 218 (9.9)           | 10 (9.3)             |
| Obeys commands for movement             | 1820 (82.8)         | 95 (88.9)            |
| Apparent clinical manifestations at baseline** |                     |                      |
| Altered sensorium                       | 242 (99.2)          | 2 (0.8)              | 0.001 | 0.172 [0.41-0.724] | 0.016 |
| Monoparesis                             | 25 (86.2)           | 2 (13.8)             | 0.046 | 4.076 [1.230-13.506] | 0.022 |
| NIH stroke scale at baseline**: consciousness |                     |                      |       |
| Alert                                   | 1335 (82.8)         | 69 (93.2)            |       |
| Sleepiness                              | 161 (10.0)          | 5 (6.8)              |       | 0.007 |
| Stupor                                  | 79 (4.9)            | 0 (0.0)              |       |
| Coma                                    | 38 (2.4)            | 0 (0.0)              |       |
| NIH stroke scale at baseline**: visual field |                     |                      |       |
| No visual loss                          | 1265 (80.8)         | 62 (83.8)            |       |
| Partial hemianopia                      | 195 (12.5)          | 5 (6.8)              |       |
| Complete hemianopia                     | 77 (4.9)            | 0 (0.0)              |       |
| Bilateral hemianopia                    | 29 (1.9)            | 4 (5.4)              |       |

*Significant variables remained in the final logistic regression model (highlighted in grey). ** received prior to the first-time stroke attacks *** discharged from admission during the first-time stroke event; #ethnicity group originated from East Malaysia (Iban, Bidayuh, Kadazan, etc.). Abbreviations: ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin receptor blockers; ADM = antidiabetic medications; NIH=National Institute of health; OHA = oral hypoglycemic agent.
diabetes patients in their first five years have a 10% absolute risk of recurrent stroke in comparison to general population [47]. However, the current study lacks the details about the age or concomitant disease conditions of those newly diagnosed diabetes patients which may be associated with the increase odds of recurrence.

Similarly, on the basis of smoking status, a significant association has been found in the current study which relates smoking status to the increased chances of recurrent stroke. The result was significant in the univariate analysis but was not in the multivariable logistic regression. It has been observed that current smokers are at a higher risk of recurrence stroke, in which males are predominant to recurrence if they are active smokers, as compared to females. As observed in a previous study, smoking increases the risk associated with diabetes and has an impact on the lipid profile of the smoker, hence increasing the risk of stroke recurrence [39]. In accordance with the current study, a study based on the effects of multiple factors on recurrence stroke has observed an association between smoking in males with the recurrence of stroke or death associated with stroke [40]. Still, there is a lack of established literature based on the effect of smoking on stroke recurrence in diabetic patients, and this might be associated with the low number of diabetic patients who smoke.

In the current study, it has been observed that treatment strategies targeting hypertension and hyperglycemia are significantly associated with the prevention of the incidence of recurrent stroke. In the present study, receiving diuretics upon discharge from hospitalization secondary to the first stroke attack was found to increase the odds of recurrent stroke among diabetic females. In common practice, diuretics were commonly indicated for fluid overload management either secondary to heart failure or renal dysfunction which indirectly influences the blood pressure control. Based on a study finding, the variability in the blood pressure may contribute to the recurrence of stroke and low SBP increased the risk of poor outcomes [45]. All these factors can be associated with the use of diuretics which has shown a higher degree of decrease in the blood pressure [46] and may be the reason behind the poor outcomes in the present study which need further elucidated approaches for better understanding of the scenario.

Oral hypoglycemic agents in both male and female patients show a significant beneficial effect on the lower risk of recurrence stroke. Based on the literature supporting the results of the current study, it has been summarized that stroke recurrence can be prevented by the management of risk factors, e.g., hypertension through optimizing the treatment strategies [41]. As diabetes carries the risk of microvascular as well as macrovascular complications, causing an increase in cardiovascular disorders and hence antihypertensive therapy either alone or in combination plays a vital role in reducing the absolute risk of stroke [42]. In contrast to the results of the current study where beta-blockers and diuretics have been found effective, the Intervention as a Goal in Hypertension Treatment (INSIGHT) study suggests that older antihypertensive agents are more likely to impair glucose metabolism in comparison to newer antihypertensive like ACEI which can directly influence the outcomes in diabetic patients [43]. Tight control on hyperglycemia could effectively improve microvascular complications, but its impact on macrovascular complications as well as stroke is still lacking. A former study supports the results of the current study, which suggests that effective glycemic control with oral hypoglycemic agents like metformin can effectively help in the prevention of stroke in diabetes patients [44]. UKPDS trials suggest that glycemic control with hypoglycemic agents in the intensive group has no significant benefits in the reduction of stroke incidence ($p = 0.52$) [45].

7. Conclusions
Most of the predictive factors contributing to the recurrence of stroke in diabetic Malaysian populations with a history of stroke are modifiable in which IHD was the most prominent risk factor in both genders. The impact of optimizing the management of IHD as well as blood glucose control on stroke recurrence may need to be elucidated. No major differences in recurrent stroke predictors were seen between genders among type 2 diabetic Malaysian populations with a history of stroke.

8. Limitations
The current study was retrospective based on the data available from the National Neurology Registry of Malaysia. On the basis of ethnicity, a large number of contributing data were patients from the “others” category which includes the people from Eastern Malaysia. Moreover, diabetic patients with a history of ischemic stroke were more prevalent in the study than other types of stroke and hence there can be bias in generalizing the data to overall stroke incidences in diabetes patients. In our study, the data related to medications at discharge which were taken continuously or were newly prescribed was unknown. Furthermore, the data related to the blood glucose control (e.g. glycated hemoglobin (HbA1c)) was not available which limits our ability to determine the association between blood glucose control and stroke recurrence. Therefore, based on the limitations, we were not able to establish whether the risks were associated with differences in care, worse glycemic control, or poor management after the occurrence of the first stroke event as suggested by others.

Data Availability
The data related to the study have been provided in the article and are also available on request from the corresponding author.

Conflicts of Interest
All authors declare no conflict of interest.

Authors’ Contributions
All authors met the criteria of authorship. SA was responsible for drafting the manuscript. NE was responsible for analyzing the data. SMSG and BT supported the analysis.
and reviewed and edited the manuscript. HZ reviewed and edited the manuscript. IL, KAI, NNS, LKW, LKY, and ZAA supported the data collection and reviewed and edited the manuscript. SNH participated in the concept development, reviewed and supported the analysis, and reviewed and edited the manuscript.

Acknowledgments

We would like to thank the Director-General of Health Malaysia for his permission to publish this article. This study was supported by the short-term grants from Universiti Sains Malaysia.

Supplementary Materials

The table include those variables which were found insignificant in univariate or multivariate analysis. (Supplementary Materials)

References

[1] GBD 2016 Causes of Death Collaborators, “Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016,” The Lancet, vol. 390, no. 10100, pp. 1151–1210, 2017.

[2] J. Shou, L. Zhou, S. Zhu, and X. Zhang, “Diabetes is an independent risk factor for stroke recurrence in stroke patients: a meta-analysis,” Journal of Stroke and Cerebrovascular Diseases, vol. 24, no. 9, pp. 1961–1968, 2015.

[3] M. Lee, J. L. Saver, K. S. Hong, S. Song, K. H. Chang, and B. Ovbiagele, “Effect of pre-diabetes on future risk of stroke: meta-analysis,” BMJ, vol. 344, no. 3, article e3564, 2012.

[4] The Emerging Risk Factors Collaboration, “Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies,” The Lancet, vol. 375, no. 9733, pp. 2215–2222, 2010.

[5] R. G. Hart, L. A. Pearce, M. F. Bakheet et al., “Predictors of stroke recurrence in patients with recent lacunar stroke and response to interventions according to risk status: secondary prevention of small subcortical strokes trial,” Journal of Stroke and Cerebrovascular Diseases, vol. 23, no. 4, pp. 618–624, 2014.

[6] T. Hillen, C. Coshall, K. Tilling et al., “Cause of stroke recurrence is multifactorial: patterns, risk factors, and outcomes of stroke recurrence in the South London Stroke Register,” Stroke, vol. 34, no. 6, pp. 1457–1463, 2003.

[7] T. Truelsen, P. U. Heuchmann, R. Bonita et al., “Standard method for developing stroke registers in low-income and middle-income countries: experiences from a feasibility study of a stepwise approach to stroke surveillance (STEPS Stroke),” The lancet neurology, vol. 6, no. 2, pp. 134–139, 2007.

[8] S. A. E. Peters, R. R. Huxley, and M. Woodward, “Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775 385 individuals and 12 539 strokes,” The Lancet, vol. 383, no. 9933, pp. 1973–1980, 2014.

[9] P. Appelros, B. Stegmayr, and A. Terent, “Sex differences in stroke epidemiology: a systematic review,” Stroke, vol. 40, no. 4, pp. 1082–1090, 2009.

[10] R. A. Grysiwicz, K. Thomas, and D. K. Pandey, “Epidemiology of ischemic and hemorrhagic stroke: incidence, prevalence, mortality, and risk factors,” Neurologic Clinics, vol. 26, no. 4, pp. 871–895, 2008.

[11] C. B. Giorda, A. Avogaro, M. Maggini et al., “Incidence and risk factors for stroke in type 2 diabetic Patients,” Stroke, vol. 38, no. 4, pp. 1154–1160, 2007.

[12] A. Arboix, M. Milian, M. Oliveres, L. Garcia-Eroles, and J. Massons, “Impact of female gender on prognosis in type 2 diabetic patients with ischemic stroke,” European Neurology, vol. 56, no. 1, pp. 6–12, 2006.

[13] W. Zhao, Z. An, Y. Hong et al., “Sex differences in long-term outcomes among acute ischemic stroke patients with diabetes in China,” Biology of sex differences, vol. 6, no. 1, p. 29, 2015.

[14] M. J. O’Donnell, D. Xavier, L. Liu et al., “Risk factors for ischemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study,” The Lancet, vol. 376, no. 9735, pp. 112–123, 2010.

[15] V. L. Feigin, G. A. Roth, M. Naghavi et al., “Global burden of stroke and risk factors in 188 countries, during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013,” The Lancet Neurology, vol. 15, no. 9, pp. 913–924, 2016.

[16] P. Mehndiratta, M. Wasay, and M. M. Mehndiratta, “Implications of female sex on stroke risk factors, care, outcome and rehabilitation: an Asian perspective,” Cerebrovascular Diseases, vol. 39, no. 5-6, pp. 302–308, 2015.

[17] T. Almdal, H. Scharling, J. S. Jensen, and H. Vestergaard, “The independent effect of type 2 diabetes mellitus on ischemic heart disease, stroke, and death: a population-based study of 13 000 men and women with 20 years of follow-up,” Archives of Internal Medicine, vol. 164, no. 13, pp. 1422–1426, 2004.

[18] N. Yesilot, B. A. Koyuncu, O. Çoban, R. Tuncay, and S. Z. Bahar, “Gender differences in acute stroke: Istanbul medical school stroke registry,” Neurology India, vol. 59, no. 2, pp. 174–179, 2011.

[19] A. Tuttolomo, A. Pinto, G. Salemi et al., “Diabetic and non-diabetic subjects with ischemic stroke: differences, subtype distribution and outcome,” Nutrition, Metabolism and Cardiovascular Diseases, vol. 18, no. 2, pp. 152–157, 2008.

[20] Heart Protection Study Collaborative Group, “MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial,” The Lancet, vol. 361, no. 9374, pp. 2005–2016, 2003.

[21] F. S. Nazir, M. Alem, M. Small et al., “Blunted response to systemic nitric oxide synthase inhibition in the cerebral circulation of patients with type 2 diabetes,” Diabetic medicine, vol. 23, no. 4, pp. 398–402, 2006.

[22] Heart Protection Study Collaborative Group, “Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20 536 people with cerebrovascular disease or other high-risk conditions,” The Lancet, vol. 363, no. 9411, pp. 757–767, 2004.

[23] M. Nakamura, T. Fukukawa, K. Kitagawa et al., “Ten-year standardization of lipids and high-sensitivity C-reactive protein in a randomized controlled trial to assess the effects of statins on secondary stroke prevention: Japan Statin Treatment Against Recurrent Stroke,” Annals of Clinical Biochemistry, vol. 55, no. 1, pp. 128–135, 2018.
meta-analysis of cohort studies,” *Journal of Stroke and Cerebrovascular Diseases*, vol. 26, no. 12, pp. 2700–2705, 2017.

[25] E. Shahar, L. E. Chambless, W. D. Rosamond et al., “Plasma lipid profile and incident ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) study,” *Stroke*, vol. 34, no. 3, pp. 623–631, 2003.

[26] D. O. Kleindorfer, J. Khouy, C. J. Moomaw et al., “Stroke incidence is decreasing in whites but not in blacks: a population-based estimate of temporal trends in stroke incidence from the Greater Cincinnati/Northern Kentucky Stroke Study,” *Stroke*, vol. 41, no. 7, pp. 1326–1331, 2010.

[27] Z. A. Aziz, Y. Y. Lee, N. N. Sidek et al., “Gender disparities and thrombolysis use among patient with first-ever ischemic stroke in Malaysia,” *Neurological Research*, vol. 38, no. 5, pp. 406–413, 2016.

[28] K. Vagnerova, I. P. Koerner, and P. D. Hurn, “Renin-angiotensin system blockade safely reduces blood pressure in patients with minor ischemic stroke during the acute phase,” *Journal of Stroke and Cerebrovascular Diseases*, vol. 19, no. 6, pp. 435–440, 2010.

[29] K. Kamishima, H. Ogawa, K. Jujo, Y. Yamaguchi, and N. Hagiwara, “Relationships between blood pressure lowering therapy and cardiovascular events in hypertensive patients with coronary artery disease and type 2 diabetes mellitus: the HIJ-CREATE sub-study,” *Diabetes research and clinical practice*, vol. 149, pp. 69–77, 2019.

[30] H. Matsuoka, “STONE study and INSIGHT study: efficacy of nifedipine in the prevention of cardiovascular disease in hypertensive patients,” *Drugs*, vol. 66, no. Spec. Issue 11, pp. 13–15, 2006.

[31] G. Reboldi, G. Gentile, V. M. Manfreda, F. Angeli, and P. Verdecchia, “Tight blood pressure control in diabetes: evidence-based review of treatment targets in patients with diabetes,” *Current cardiology reports*, vol. 14, no. 1, pp. 89–96, 2012.

[32] K. M. Mohan, S. L. Crichton, A. P. Grieve, A. G. Rudd, C. D. A. Wolfe, and P. U. Heuschmann, “Frequency and predictors for the risk of stroke recurrence up to 10 years after stroke: the South London Stroke Register,” *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 80, no. 9, pp. 1012–1018, 2009.

[33] T. Nakamura, Y. Tsutsui, Y. Shimizu, and S. Uchiyama, “Risk in Communities (ARIC) study, meta-analysis of cohort studies,” *Diabetes Care*, vol. 70, no. 14, pp. 1200–1207, 2007.

[34] K. Berthet, B. Neal, J. Chalmers et al., “Gender and the injured brain,” *Anesthesia and analgesia*, vol. 107, no. 1, pp. 201–214, 2008.

[35] C. Siegel, C. Turtzo, and L. D. McCullough, “Sex differences in cerebral ischemia: possible molecular mechanisms,” *Journal of Neuroscience Research*, vol. 88, no. 13, pp. 2765–2774, 2010.

[36] S. J. Park, S. Do Shin, Y. S. Ro, K. J. Song, and J. Oh, “Gender differences in emergency stroke care and hospital outcome in acute ischemic stroke: a multicenter observational study,” *The American journal of emergency medicine*, vol. 31, no. 1, pp. 178–184, 2013.

[37] I. Idris, G. A. Thomson, and J. C. Sharma, “Diabetes mellitus and stroke,” *International journal of clinical practice*, vol. 60, no. 1, pp. 48–56, 2006.

[38] G. Hu, C. Sarti, P. Joussilval et al., “The impact of history of hypertension and type 2 diabetes at baseline on the incidence of stroke and stroke mortality,” *Stroke*, vol. 36, no. 12, pp. 2538–2543, 2005.

[39] K. Berthet, B. Neal, J. Chalmers et al., “Reductions in the risks of recurrent stroke in patients with and without diabetes: the PROGRESS Trial,” *Blood pressure*, vol. 13, no. 1, pp. 7–13, 2004.

[40] E. L. Air and B. M. Kissela, “Diabetes, the metabolic syndrome, and ischemic stroke: epidemiology and possible mechanisms,” *Diabetes Care*, vol. 30, no. 12, pp. 3131–3140, 2007.

[41] C. Banerjee, Y. P. Moon, M. C. Paik et al., “Duration of diabetes and risk of ischemic stroke: the Northern Manhattan Study,” *Stroke*, vol. 43, no. 5, pp. 1212–1217, 2012.

[42] J. B. Lindsey, J. A. House, K. F. Kennedy, and S. P. Marso, “Diabetes duration is associated with increased thin-cap fibroatheroma detected by intravascular ultrasound with virtual histology,” *Circulation: Cardiovascular Interventions*, vol. 2, no. 6, pp. 543–548, 2009.

[43] T. Rundek, H. Arif, B. Boden-Albala, M. S. Elkind, M. C. Paik, and R. L. Sacco, “Carotid plaque, a subclinical precursor of vascular events The Northern Manhattan Study,” *Neurology*, vol. 70, no. 14, pp. 1200–1207, 2008.

[44] G. Reboldi, G. Gentile, V. M. Manfreda, F. Angeli, and P. Verdecchia, “Tight blood pressure control in diabetes: evidence-based review of treatment targets in patients with diabetes,” *Current cardiology reports*, vol. 14, no. 1, pp. 89–96, 2012.

[45] A. P. Kengne, K. Nakamura, F. Barzi et al., “Smoking, diabetes and cardiovascular diseases in men in the Asia Pacific region,” *Journal of Diabetes*, vol. 1, no. 3, pp. 173–181, 2009.