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Long-term outcomes of ischaemic stroke patients with diabetes in a multi-ethnic cohort in Singapore

Ei Zune The, [1]MRCP, Mei Yen Ng, [2]BSc, Geelyn JL Ng, [2]BSc, Bernadette GC Er, [2]RN, Amy ML Quek, [1]MRCP, Prakash Paliwal, [1]MRCP, Leonard L Yeo, [1]MRCP, Bernard PL Chan, [1]MRCP, Vijay K Sharma, [1,2]MRCP, Hock Luen Teoh, [1]MRCP, Eric YH Khoo, [3] MRCP, Raymond CS Seet, [1, 2]MBBS, FAMS, FRCP

ABSTRACT

Introduction: Diabetes increases the risk of ischaemic stroke especially among Asians. This study aims to investigate contemporaneous long-term cardiovascular outcomes of ischaemic stroke patients with diabetes in a multi-ethnic Asian cohort.

Methods: Consecutive patients with ischaemic stroke were recruited from the National University Hospital, Singapore. Data on age, gender, ethnicity, risk factors (including diabetes status and body mass index [BMI]), stroke severity and mechanisms were collected. These patients were followed up until the day of the first cardiovascular event or July 2016, whichever was earlier. The primary endpoint was the time from enrolment to the first occurrence of a composite of cerebrovascular and coronary artery events.

Results: Between July 2011 and December 2013, 720 patients (mean age 60.6 years, 71% men, 43% with diabetes, median National Institute Health Stroke Severity scale 2) were enrolled and followed up. A total of 175 cardiovascular events occurred during a median follow-up of 3.25 years (6.90 events per 1,000 person-month), comprising 133 cerebrovascular and 42 coronary artery events. The adjusted hazard ratio of diabetes was 1.50 (95% CI 1.08–2.10). In a multivariable Cox proportional hazards model, Malay and Indian ethnicities, BMI <23kg/m^2 and a prior diagnosis of diabetes were identified as independent predictors of recurrent cardiovascular events.

Conclusion: Our study provides quantitative data on the event rates of ischaemic stroke patients with diabetes. These findings provide insights on stroke predictors in a multi-ethnic Asian population, which may have implications in the design of future interventional studies.

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Keywords: Asian, body mass index, cardiovascular, stroke phenotype

INTRODUCTION

Asia faces an epidemic of diabetes.[1-4] The prevalence of diabetes in Asia is projected to grow from 114 million in 2007 to 180 million by 2025, driven in part by marked economic and epidemiologic transition in recent decades.[1] In China, the prevalence of diabetes rose from 1% in 1980 to 9.7% in 2010,[2] whereas in urban South India, these rates have grown from 13.9% in 2000 to 18.6% in 2006.[3] This pattern has also been mirrored in other Asian countries and territories such as Taiwan, Hong Kong, South Korea and Singapore.[1] In the Asia Pacific Cohort Studies Collaboration, ischaemic stroke was a leading cause of death among Asian patients with diabetes (exceeding coronary artery and renal diseases).[4] Conversely, coronary artery disease was the leading cause of death among Caucasians in Australia and New Zealand.[4] The predilection of Asian patients with diabetes for ischaemic stroke was also observed in post hoc analyses of major trials (e.g. Action in Diabetes and Vascular Disease [ADVANCE][5] and Reduction of Endpoints in non-insulin-dependent diabetes mellitus [NIDDM] with the Angiotensin II Antagonist Losartan [RENAAL][6]). Among patients with ischaemic stroke, the prevalence of diabetes is higher among Asians (27–59%)[7-11] compared with Caucasians (21–25%).[12-14]

[1] Division of Neurology, University Medicine Cluster, National University Hospital, Singapore
[2] Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[3] Division of Endocrinology, University Medicine Cluster, National University Hospital, Singapore
Correspondence: Dr Raymond Chee Seong Seet, Division of Neurology, NUHS Tower Block, 1E Kent Ridge Road, Singapore 119228.
Email: raymond_seet@nuhs.edu.sg

Asians harbour a unique phenotype of diabetes, where compared with Caucasians, the risk of diabetes starts at a lower body mass index (BMI), explained in part by reduced beta cell reserves and the inability to produce adequate insulin to counter even mild increases in insulin resistance.[15,16] Few studies have examined the prognostic implications of diabetes among Asian patients with ischaemic stroke. Data from the China National Stroke Registry indicate that diabetes is an independent risk factor for death or dependency at 6 months from stroke onset[11] and in India, diabetes predicted death or dependency at 3 months.[10] Previous studies involving Asians, however, did not elaborate on the risk of cardiovascular recurrence (an endpoint that is widely used in clinical trials) and followed study subjects for less than 1 year.[10,11] Reliable data on cardiovascular recurrence rates among ischaemic stroke patients with diabetes are lacking in Asia where access to modern healthcare resources vary considerably according to country and geography. Few cohort studies have meticulously followed outcomes of these patients to provide important event estimates to guide design of clinical trials in such a population.

Our primary objective is to investigate the prevalence and impact of diabetes on cardiovascular recurrence among ischaemic stroke patients in Singapore, where medications and healthcare resources are widely accessible. Our secondary objective is to identify risk predictors of cardiovascular recurrence among ischaemic stroke patients with diabetes. We hypothesise that, compared with non-diabetics, ischaemic stroke patients with diabetes are predisposed to the development of recurrent cardiovascular events.

METHODS

Patients

Between July 2011 and December 2013, consecutive patients with ischaemic stroke were recruited from the Stroke Unit at the National University Hospital, Singapore. Diagnosis of ischaemic stroke was made based on a corroborative history-taking, neurological assessment and neuroimaging investigation (brain computed tomography [CT] or magnetic resonance imaging [MRI]). Stroke severity was measured using the National Institutes of Health Stroke Scale (NIHSS). Information on risk factors—including diabetes mellitus, hypertension, hyperlipidaemia, prior stroke, coronary artery disease, atrial fibrillation, peripheral vascular disease and chronic renal disease—was systematically collected using a standardised questionnaire. This required physician diagnosis and verification against medical records, whereas information on cigarette smoking (current or before) was obtained through self-reporting. Age, gender and ethnicity were verified against their National Registration Identity Card. Diabetes was diagnosed using the American Diabetes Association recommendations (either fasting glucose ≥7.0mmol/L, 2-hour oral glucose tolerance test ≥11.1mmol/L or HbA1c ≥6.5%).[17] Diabetes was considered "newly-diagnosed" if diagnosed within 3 months and "pre-existing" if diagnosed more than 3 months prior to stroke onset. BMI was calculated as weight in kilogrammes (kg) divided by height in metres (m) squared; these values were classified using the modified Asian BMI cut-offs, where normal BMI was considered as <23.0 kg/m^2, overweight 23.0–27.0kg/m^2 and obese >27.0kg/m^2. Central obesity was considered when abdominal circumference exceeded 90cm in men and 80cm in women. Medication adherence was assessed by asking patients whether they had ever missed taking their medications on at least 2 days within the past 2 weeks. Laboratory investigations (full blood count, renal, liver and lipid parameters) were measured in each subject. Angiography (CT or MRI), echocardiogram and 24-hour electrocardiogram investigations were performed to investigate stroke mechanisms and, on the basis of these results, patients were classified into large artery disease (LAD), cardioembolism, small artery disease, undetermined and other causes, using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.[18] Patients who are below 21 years old; unable to provide written informed consent; unwilling to be contacted following hospitalisation; with severe and life-threatening stroke with an expected survival <1 month; with pregnancy, intracranial haemorrhage, active cancer or autoimmune diseases were excluded. Following their hospital discharge, we followed up the study subjects through active surveillance by 3-monthly telephone calls until the day of the first cardiovascular event or July 2016, if study subjects did not develop a cardiovascular event.

Primary and secondary endpoints

The primary endpoint was the time to first occurrence to a composite of cerebrovascular (fatal stroke, nonfatal stroke and transient ischaemic attack) and coronary artery events (fatal myocardial infarction, nonfatal acute myocardial infarction and unstable angina). Secondary endpoints comprised separate cerebrovascular and coronary artery events. All potential endpoints were adjudicated by a blinded committee of investigators against medical records, and causes of death were verified with the Registry of Birth and Death, Ministry of Home

Affairs, Singapore. The study protocol was reviewed and approved by the Domain-Specific Review Board, National Healthcare Group, and all patients provided written informed consent prior to their study participation.

Data analysis

Categorical variables are expressed as numbers and percentages. Continuous variables are expressed as mean (standard deviation) or median (interquartile range). On the basis of their distribution, continuous variables were compared using parametric test of Student's t-test or non-parametric test of Wilcoxon rank-sum test as appropriate. Categorical variables were compared using the chi-square test. Bonferroni method was used to correct for multiple comparisons. The time to the first episode of adjudicated vascular events were analysed; patients without outcome events were censored at the date of the last completed follow-up contact. Cumulative event-free rates were calculated by the method of Kaplan-Meier, and differences in diabetes status were tested by the log-rank statistic using a type I error of 0.05 (2-sided). The effect of each baseline variable for diabetics relative to non-diabetics was estimated as an odds ratio (OR) from a logistics regression model with 95% confidence intervals (CI). The effect of each baseline variable for a cardiovascular event relative to no event was estimated as a hazard ratio (HR) from a Cox proportional hazard model with 95% CI. Variables with $P<0.10$ were included in a stepwise multivariable Cox proportional hazard model and compared with the incidence of the composite primary endpoint to derive adjusted hazard ratios (95% CI). We conducted interaction analyses in each subgroup to evaluate heterogeneity. Two-tailed values of $P<0.05$ were considered statistically significant. SPSS Statistics software version 24 (IBM Corp, Armonk, US) was used for all analyses.

RESULTS

Comparison between diabetic and non-diabetic patients with ischaemic stroke

Of the 826 patients who were assessed, 720 (mean age 60.6 years, 71% men) were recruited and formed the study cohort. Risk factors are summarised in Table 1. Diabetes mellitus was present in 308 (43%) patients (30% were newly diagnosed and 70% were pre-existing); all fulfilled the criteria of adult-onset type 2 diabetes. For those with pre-existing diabetes, median duration of disease was 5 years (interquartile range [IQR] 3–7 years). Overall, diabetic patients developed an ischaemic stroke at about the same age as non-diabetic patients (61 years and 60 years, respectively), despite a higher burden of obesity, hypertension, hyperlipidaemia, coronary artery disease and peripheral artery disease. There were also more Malay ethnic patients with diabetes. Compared with non-diabetics, diabetic patients had higher levels of white blood cell count, mean platelet volume and triglycerides, but lower levels of haemoglobin and high-density l ipoprotein at stroke presentation. Mean glycated haemoglobin of diabetes patients was 8.54% compared with 5.70% in non-diabetes patients.

Median NIHSS of the cohort was 2 (IQR 1–4) and acute reperfusion treatment was administered in 87 (12%) patients (intravenous thrombolysis, n=82; endovascular, n=5). Small vessel disease (n=302, 42%) was the most common stroke mechanism, followed by intracranial large artery disease (LAD) (n=176, 24%) and cardioembolism (n=87, 12%); the cause of stroke was undetermined in 113 (n=16%) patients. There were no differences in stroke severity and mechanisms between diabetic and non-diabetic patients.

Of the 227 patients who had prior antiplatelet use before their stroke presentation; 150 patients were strictly adherent to their medications and the remaining 77 were not adherent. After excluding those who were not adherent to medications, the prevalence of patients who developed ischaemic stroke despite being strictly adherent to antiplatelet treatment was 21%, higher among those with diabetes compared with non-diabetic patients (26% versus 17%; OR 1.71, 1.19–2.46). Mean platelet volume (MPV), a biomarker of platelet reactivity,[19] was similarly higher in diabetic patients compared with non-diabetic patients (9.69 vs 9.40fL, $P=0.023$).

Recurrent cardiovascular events in ischaemic stroke patients with diabetes

Follow-up was complete in the study cohort. A total of 175 cardiovascular events (6.90 events per 1,000 person-month) occurred during a median follow-up of 3.25 years (IQR, 1.08–4.67 years). These cardiovascular events comprised 133 cerebrovascular (29 fatal stroke, 85 non-fatal stroke and 19 transient ischaemic attacks) and 42 coronary artery events (5 fatal myocardial infarction and 37 non-fatal myocardial infarction/ unstable angina) (Table 2). Two (2.4%) patients from the non-diabetic group were diagnosed with new-onset diabetes at the time of cardiovascular recurrence. The overall incidence of the primary cardiovascular endpoint was higher among diabetic patients (log-rank $P=0.001$; Table 2 and Fig. 1A), and the unadjusted HR of diabetes was 1.75 (95% CI 1.30–2.36). Adjustments for potential confounders reduced, but did not nullify, the significance of this association (HR 1.50, 95% CI 1.08–2.10)

Table 1. Comparison in baseline characteristics between diabetic and non-diabetic patients

	All n=720	**Diabetes** n=308	**No diabetes** n=412	**Odds ratio**	**95% CI**	***P* value**[a]
Demographics						
Age (%), years	60.6 (12.3)	61.3 (10.6)	60.1 (13.4)	1.01	0.99–1.02	0.197
Man, no. (%)	513 (71)	221 (72)	292 (71)	0.96	0.69–1.33	0.796
Race, no. (%)						0.011
Chinese	502 (70)	195 (63)	307 (75)	Reference		
Malay	152 (21)	81 (26)	71 (17)	1.80	1.25–2.59	
Indian	56 (8)	28 (9)	28 (7)	1.57	0.91–2.74	
Body mass index (%), kg/m^2						<0.001
<23 (normal)	215 (30)	72 (23)	143 (35)	Reference		
23–27 (overweight)	281 (39)	116 (38)	165 (40)	1.40	0.97–2.02	
>27 (obese)	224 (31)	120 (39)	104 (25u)	2.29	1.56–3.37	
Central obesity (%)	441 (61)	211 (69)	230 (56)	1.72	1.26–2.35	0.001
Stroke characteristics						
NIHSS, median (interquartile range)	2 (1–4)	3 (1–6)	2 (0–5)	1.01	0.99–1.04	0.284
Reperfusion treatment, no. (%)	87 (12)	34 (11)	53 (13)	0.84	0.53–1.33	0.458
Stroke mechanisms, no. (%)						0.749
Intracranial large artery disease	176 (24)	82 (27)	94 (23)	Reference		
Extracranial large artery disease	39 (5)	17 (6)	22 (5)	0.89	0.44–1.78	
Cardioembolism	87 (12)	41 (13)	46 (11)	1.02	0.61–1.71	
Small vessel disease	302 (42)	121 (39)	181 (44)	0.77	0.53–1.12	
Undetermined	113 (16)	0	3 (0.7)	0.82	0.51–1.32	
Risk factors, no. (%)						
Hypertension	485 (67)	230 (7%)	255 (62)	1.82	1.31–2.51	<0.001
Hyperlipidaemia	349 (49)	177 (58)	172 (42)	1.89	1.40–2.54	<0.001
Cigarette smoking (ever or current)	374 (48)	153 (50)	194 (47)	1.11	0.83–1.49	0.492
Coronary artery disease	132 (18)	74 (24)	58 (14)	1.93	1.32–2.83	<0.001
Prior stroke	115 (16)	58 (19)	57 (14)	1.45	0.97–2.16	0.071
Atrial fibrillation	36 (5)	14 (5)	22 (5)	0.84	0.43–1.68	0.629
Peripheral artery disease	9 (1)	8 (3)	1 (0.2)	11.0	1.36–8.1	0.024
Chronic renal disease	8 (1)	6 (2)	2 (0.5)	4.07	0.82–20.3	0.087
Antiplatelet failure	150 (21)	80 (26)	70 (17)	1.71	1.19–2.46	0.005
Laboratory investigations						
Haematology parameters						
White blood cell count, mean (SD), x 10^9/L	8.57 (2.55)	8.93 (2.62)	8.29 (2.47)	1.10	1.04–1.17	0.001
Haemoglobin, mean (SD), g/dL	14.16 (1.86)	13.98 (1.95)	14.29 (1.78)	0.91	0.84–0.99	0.027

Table 1. Comparison in baseline characteristics between diabetic and non-diabetic patients (Cont'd)

	All n=720	Diabetes n=308	No diabetes n=412	Odds ratio	95% CI	*P* value[a]
Platelets count, mean (SD), x 10^9/L	249 (78)	252 (72)	247 (82)	1.00	0.99–1.00	0.446
Mean platelet volume, mean (SD), fL	9.42 (1.47)	9.56 (1.53)	9.32 (1.42)	1.12	1.01–1.24	0.031
Lipid profile						
Total cholesterol, mean (SD), mmol/L	4.98 (1.30)	4.93 (1.42)	5.01 (1.21)	0.96	0.85–1.08	0.457
Triglycerides, mean (SD), mmol/L	1.64 (1.05)	1.83 (1.07)	1.50 (1.02)	1.38	1.17–1.61	<0.001
High-density lipoprotein, mean (SD), mmol/L	1.13 (0.34)	1.06 (0.34)	1.18 (0.32)	0.31	0.18–0.52	<0.001
Low-density lipoprotein, mean (SD), mmol/L	3.11 (1.12)	3.04 (1.23)	3.16 (1.03)	0.90	0.79–1.04	0.156

CI: confidence interval; IQR: interquartile range; NIHSS: National Institutes of Health Stroke Scale
[a] *P* value comparing diabetic and non-diabetic patient

(Table 3). The increase in the cardiovascular endpoints was contributed by a higher burden of non-fatal stroke and myocardial infarction/unstable angina in diabetic patients.

Predictors of recurrent cardiovascular events in ischaemic stroke patients with diabetes

Diabetes control was comparable between initial stroke hospitalisation and cardiovascular recurrence (mean glycated haemoglobin, 8.54% vs 8.23%, *P*=0.452). Compared to Chinese, Malay and Indian patients were more prone to develop recurrent cardiovascular events. Those with BMI <23kg/m^2, prior diagnosis of diabetes, coronary artery disease and atrial fibrillation had a higher risk of recurrent cardiovascular events (log-rank, *P*<0.05). By contrast, variables such as age, sex, central obesity, stroke severity, stroke mechanisms, the presence of risk factors such as hypertension, hyperlipidaemia, cigarette smoking, history of prior stroke, peripheral artery disease, chronic renal disease, and other laboratory parameters, did not predict recurrent cardiovascular events. By considering significant predictors in a stepwise multivariable Cox proportional model, Malay and Indian ethnicity, BMI <23kg/m^2 and a prior diagnosis of diabetes were identified as independent predictors of recurrent cardiovascular events (Table 4). Kaplan-Meier survival plots according to ethnicity, BMI categories and prior diagnosis of diabetes are summarised in Figs. 1B–1D. The event rates of diabetes patients were estimated according to the presence or absence of these predictors in Fig. 2. A stepwise increment in event rates was observed across risk categories, and was highest among Malay/Indian ethnic group with previously diagnosed diabetes and BMI <23kg/m^2.

DISCUSSION

The population of Singapore comprises 3 major ethnic groups (Chinese, Malay and Indians) whose medical needs are provided affordably by a network of modern healthcare facilities.[12-14] A high prevalence of diabetes was observed in this cohort, many of whom were newly diagnosed; those with pre-existing diabetes were especially prone to recurrent cardiovascular events.

Approximately 43% patients with ischaemic stroke harboured diabetes mellitus in our cohort, exceeding rates reported in Caucasian populations of between 21% and 25%,[15-17] but within the range of rates reported in Asian cohorts from China (27–42%),[11,23] Japan (34%),[7] India (36%),[10] Taiwan (38%)[8] and Malaysia (59%),[9] supporting previous suggestions that Asian patients with diabetes are more prone to developing ischaemic stroke.[4-6] Although diabetic patients are widely considered to have a predilection for accelerated and young-onset atherosclerosis, we and other investigators[15-17] did not observe age differences between ischaemic stroke patients with and without diabetes, despite a greater burden of cardiovascular risk factors. Previous reports have implied a tendency for patients with diabetes to develop atherosclerosis of the large and small cerebral arteries.[9,11,15,17] One meta-analysis has suggested an increased risk of atrial fibrillation among individuals with diabetes[24] and that diabetes increases the risk of embolic complications in patients with atrial fibrillation.[25] In the current study, however, we did not observe differences in stroke mechanisms between diabetic and non-diabetic patients. The lack of differences in age and stroke mechanisms could be explained by good glycemic and vascular risk factor control among those with pre-existing diabetes, thereby delaying the progression of atherosclerosis and onset of ischaemic stroke. An

Table 2. Details of the recurrent cardiovascular event

	All (N=720)			Diabetic group (n=308)			Non-diabetic group (n=412)		
	n	%	n/1,000 person-month	n	%	n/1,000 person-month	n	%	n/1,000 person-month
Primary endpoint[a]	175	24.3	6.90	95	30.8	9.48	80	19.4	5.22
Secondary endpoints									
Cerebrovascular events	133	18.9	5.37	70	22.7	6.99	63	15.3	4.11
Fatal stroke	29	4.0	1.14	14	4.6	1.40	15	3.6	0.98
Non-fatal stroke	85	11.8	3.35	46	14.9	4.59	39	9.5	2.55
Transient ischaemic attack	19	2.6	0.75	10	3.3	1.00	9	2.2	0.59
Coronary artery events	42	5.8	1.66	25	8.1	2.50	17	4.1	1.11
Fatal myocardial infarction	5	0.7	0.20	3	1.0	0.30	2	0.5	0.13
Non-fatal myocardial infarction and unstable angina	37	5.1	1.46	22	7.1	2.20	15	3.6	0.98

[a] The primary and secondary endpoints were considered as the time of stroke onset to the first occurrence of any cardiovascular event.

alternative explanation is the preferential involvement of the coronary arteries (vs cerebral arteries) in diabetes (24% of diabetic patients had pre-existing coronary artery diseases vs 14% in non-diabetics). In the current study, 30% of diabetics was newly diagnosed during their acute stroke hospitalisation, highlighting the need for healthcare providers to continually promote periodic community-based screening for diabetes.

Despite wide access to healthcare resources in Singapore, stroke outcomes vary considerably between different ethnic groups. Compared with Chinese, there were more Malays and Indians with diabetes, and the risk for recurrent cardiovascular events were significantly higher in the latter. These findings are consistent with population registry data that showed more Malays and Indians with diabetes compared to Chinese,[13,14] and poorer outcomes of Malays and Indians in other cardiovascular diseases such as end-stage renal failure[26] and coronary artery disease.[27] In the Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Asia (DECODA) study, Indians consistently had a higher prevalence of diabetes across all BMI categories compared with Chinese.[28] Preliminary studies that examined pancreatic beta cell function (using the euglycemic-hyperinsulinemic clamp method) suggest than Indians are biologically predisposed to insulin resistance despite a comparable age, sex and BMI.[29] Consistent with these findings, we observed a higher hazard ratio of adverse cardiovascular outcomes in Indians (vs Chinese and Malays). Collectively, these observations could in part explain the wide heterogeneity in stroke outcomes in Asian populations, which could have a wider implication on stroke prevention and management in Asia.

Contrary to common knowledge of the deleterious effects of obesity, several studies have reported a protective effect of obesity on stroke, particularly after a prior cardiovascular event, a phenomenon described as the "obesity paradox".[30,31] Limited data, however, are available in diabetic patients. In the current study, all diabetic patients fulfilled the criteria for adult-onset type 2 diabetes mellitus where close to a quarter of patients developed ischaemic stroke despite BMI <23kg/m^2, which, typically, is considered a desirable body weight for patients with type 2 diabetes. However, data from multivariable analysis paradoxically observe detrimental consequences in diabetic patients with BMI <23kg/m^2, who have a 2-fold increased risk of recurrent c ardiovascular events. By contrast, the presence of central obesity does not confer an increased risk of cardiovascular recurrence. These findings shed further insights to prognostic significance of apparently "normal"

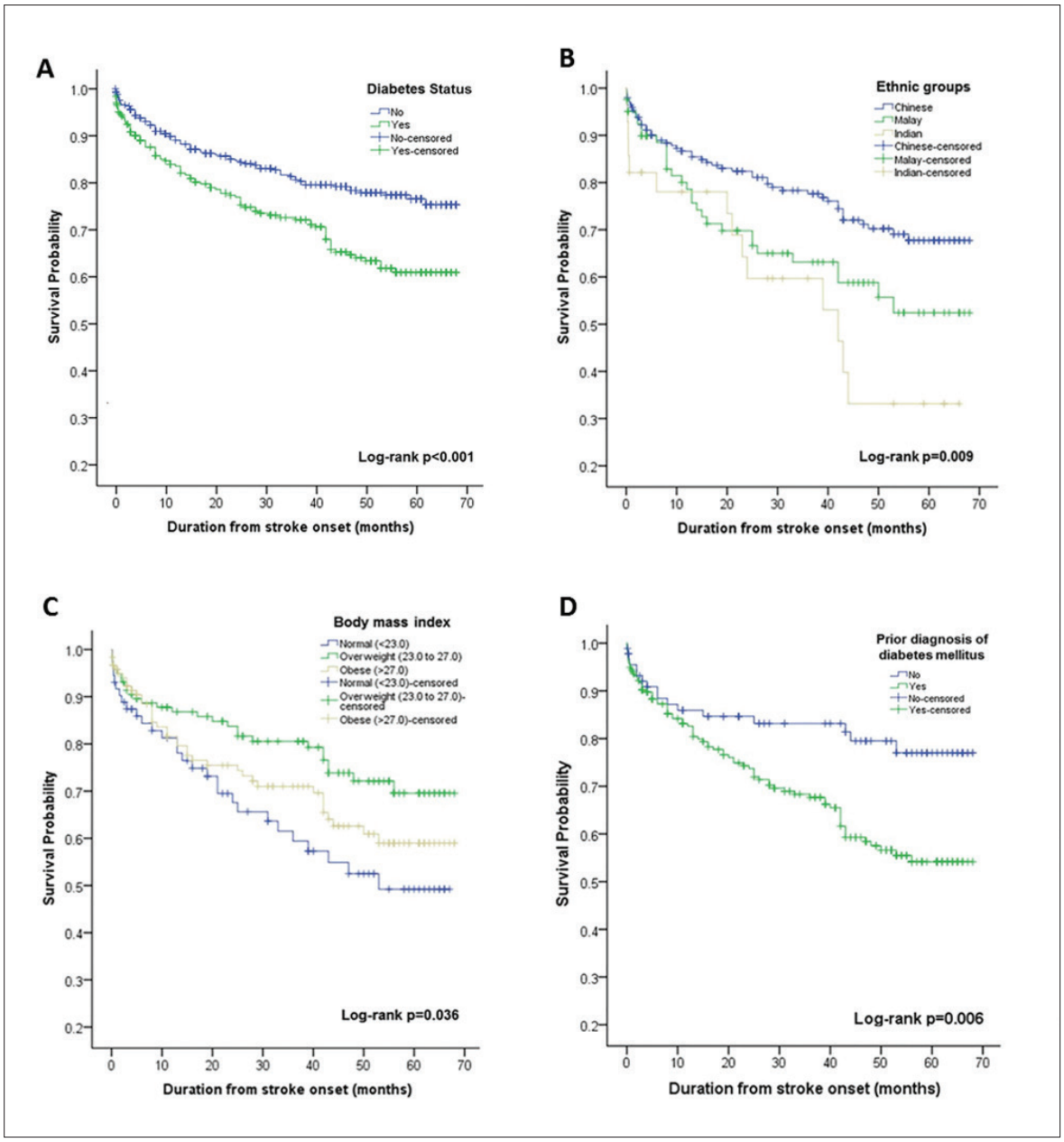


Fig.1A. Kaplan-Meier survival curves show survival probability from cardiovascular recurrence between diabetic and non-diabetic patients. Fig. 1B. Kaplan-Meier survival curves show survival probability from cardiovascular recurrence according to the different ethnic groups. Fig.1C. Body mass index. Fig. 1D. Prior diagnosis of diabetes mellitus.

BMI in ischaemic stroke patients with diabetes and expand on previous findings that diabetes develop at lower BMI thresholds in Asians. Although insulin resistance is a hallmark feature of type 2 diabetes, it remains possible that patients with lower BMI levels also harbour a certain extent of pancreatic beta cell insufficiency and treatment strategy that centres around improving insulin sensitivity alone may be inadequate. It is uncertain whether, in addition to measures to improve insulin sensitivity, an early treatment strategy of replacing and/or stimulating the production of insulin could reduce the risk of cardiovascular recurrence in patients with high-risk disease phenotype (Fig. 2). Furthermore, it is also possible that lower BMI could indicate malnutrition and self-neglect, which would not only contribute to their stroke hospitalisation but also an increased likelihood of cardiovascular recurrence.

This study also highlights a higher prevalence of ischaemic stroke among diabetic patients despite their strict adherence to antiplatelet treatment. These findings,

Table 3. Hazard ratios of recurrent cardiovascular events according to diabetes status using a multivariable Cox proportional hazard model

	Model 1[a]			Model 2[b]		
	Hazard ratio	**95% CI**	***P* value**	**Hazard ratio**	**95% CI**	***P* value**
Primary endpoint	1.75	1.30–2.36	<0.001	1.50	1.08–2.10	0.017
Secondary endpoints						
Cerebrovascular events	1.63	1.16–2.29	0.005	1.54	1.05–2.24	0.026
Fatal stroke	1.34	0.65–2.78	0.429	1.37	0.56–3.32	0.493
Non-fatal stroke	1.73	1.13–2.66	0.011	1.74	1.09–2.78	0.020
Transient ischaemic attack	1.65	0.67–4.07	0.275	1.26	0.46–3.46	0.654
Coronary artery events	2.22	1.20–4.12	0.011	1.31	0.62–2.75	0.480
Fatal myocardial infarction	4.52	0.37–13.42	0.377	1.64	0.13–19.8	0.700
Non-fatal myocardial infarction and unstable angina	2.22	1.15-4.29	0.017	1.39	0.62–3.12	0.424

CI: confidence interval
[a] Model 1 summarises the unadjusted hazard ratios and confidence intervals comparing the time of stroke onset to the first occurrence of any cardiovascular event according to diabetes status.
[b] Model 2 summarises the adjusted hazard ratios and confidence intervals after adjusting for potential confounders (race, body mass index category, central obesity, hypertension, hyperlipidaemia, coronary artery disease, prior stroke, peripheral vascular disease, chronic renal disease, antiplatelet failure, white blood cell count, haemoglobin, mean platelet volume, triglycerides and high-density lipoprotein).

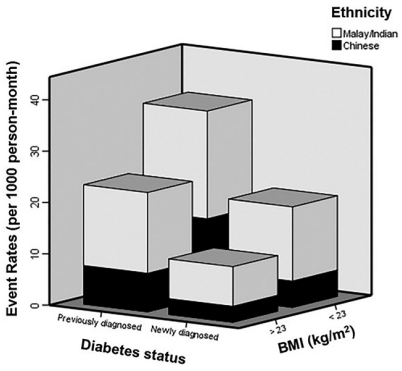
Table 4. Multivariate predictors of recurrent cardiovascular events in diabetic patients

Predictors	**Hazard ratio**	**95% CI**	***P* value**[a]
Race			0.004
Chinese	Reference[b]	Reference	
Malay	1.90	1.18–3.06	0.008
Indian	2.75	1.47–5.13	0.001
Body mass index			0.020
Normal (<23kg/m^2)	Reference	Reference	
Overweight (23–27kg/m^2)	0.49	0.29–0.84	0.009
Obese (>27kg/m^2)	0.57	0.34–0.94	0.029
Prior diagnosis of diabetes			
No	Reference	Reference	
Yes	2.09	1.21–3.60	0.008

CI: confidence interval
[a] Variables with $P<0.10$ (race, body mass index, prior diagnosis of diabetes, glycated haemoglobin, coronary artery disease, atrial fibrillation, antiplatelet failure and platelet count) were included in a multivariable stepwise Cox proportional model to identify significant predictors of recurrent cardiovascular event. The adjusted r^2 value for the combination of variables (race, body mass index and prior diagnosis of diabetes) to predict primary cardiovascular event is 31.8.
[b] Taken as reference in analysis

interpreted together with a concomitant rise in mean platelet volume,[22] could indicate an increased propensity for diabetic patients to harbour antiplatelet resistance. Using platelet function assay and whole blood electrical aggregometry, previous investigators have suggested that diabetic patients have reduced platelet response to aspirin.[32] Another study has implicated diabetes in the pathogenesis of clopidogrel resistance.[33] The attenuated

A



B

Race	Diabetes Status	Body Mass Index (kg/m^2)	Event Rates (per 1000 person-month)
Chinese	Newly diagnosed	> 23	3.09
Chinese	Newly diagnosed	≤ 23	5.13
Chinese	Previously diagnosed	> 23	7.52
Chinese	Previously diagnosed	≤ 23	15.24
Malay/Indian	Newly diagnosed	> 23	7.72
Malay/Indian	Newly diagnosed	≤ 23	14.45
Malay/Indian	Previously diagnosed	> 23	15.72
Malay/Indian	Previously diagnosed	≤ 23	20.99

Fig. 2A illustrates the event-rates (per 1,000 person-month) of ischaemic stroke patients with diabetes according to diabetes status, body mass index (BMI) and ethnicity (Chinese vs Malays/Indians). Fig. 2B estimates the event-rates (per 1,000 person-month) for different combinations of the triad of risk factors (diabetes status, BMI and ethnicity).

antiplatelet effect could be explained by increased glycosylation of platelet membrane protein, reduced drug bioavailability and accelerated platelet turnover in diabetic patients. Data from this study, however, indicate that the presence of antiplatelet failure prior to stroke did not necessarily contribute to a higher risk of cardiovascular recurrence, suggesting that the risk of antiplatelet failure is modifiable perhaps through a change in antiplatelet agent and tighter risk factor control following their stroke presentation.

Several limitations merit mention. First, we did not serially trend glycemic parameters at fixed intervals that might provide insights into the relationship between glycemic dynamics and cardiovascular recurrence. Second, we did not seek health perceptions, dietary preferences and lifestyle activities of our study participants. Therefore, it remains possible that certain behavioural factors that are specific to individual ethnic groups could account for the differences in cardiovascular outcomes. Third, we measured BMI as a surrogate of obesity but did not perform other anthropometric indices of obesity such as waist-to-hip ratio, skin-fold test and bioelectric impedance. In the absence of confirmatory data using other anthropometric indices, these findings should be interpreted with caution and not be considered as a basis to increase the optimal target body weight in ischaemic stroke patients with diabetes. Fourth, the small number and proportion of Indian subjects could affect the stability of the model derived from this study.

Our study provides quantitative data on the event rates of ischaemic stroke patients with diabetes in a multi-ethnic Asian cohort. To date, no major clinical trials have examined cardiovascular prevention strategies targeting high-risk ischaemic stroke patients with diabetes, who are undergoing intensive glucose-lowering treatment and tighter control of vascular risk factor. These findings provide insights on the predictors of outcomes in an Asian cohort of ischaemic stroke patients with diabetes, which may have implications in the design of future interventional studies.

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