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Control of Diabetes Mellitus and Long-Term Prognosis in Stroke Patients: The Shiga Stroke and Heart Attack Registry

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Keywords
Stroke · Mortality risk · Diabetes mellitus · Glycated hemoglobin

Abstract
Background: The relationship between diabetes control status and long-term prognosis after stroke incidence remains unclear. This study aimed to investigate the effect of diabetes status at admission on long-term survival in patients with first-ever stroke. ***Methods:*** A retrospective cohort study was conducted based on the Shiga Stroke and Heart Attack Registry in Japan. Patients were classified according to their diabetes status and glycated hemoglobin (HbA1c) value at hospital admission into the following: (1) free of diabetes (no history of diabetes and HbA1c <6.5%); (2) good control (history of diabetes and HbA1c <7%; free of history and 6.5% ≤HbA1c <7%); and (3) poor control (with or without a history of diabetes and HbA1c ≥7%). Multivariable Cox regression models were used to evaluate the association between diabetes status and long-term survival from stroke onset. Additionally, we also evaluated the association between diabetes status and conditional survival, beginning 29 days after stroke onset. ***Results:*** A total of 6,331 first-ever stroke patients were eligible for this study. Among study patients, the mean (±SD) age was 72.85 ± 13.19 years, and the mean (±SD) follow-up year was 2.76 ± 1.66 years; additionally, 42.09% of patients were women. Among patients with all strokes, considering the free-of-diabetes group as the reference group, the adjusted hazard ratio (95% confidence interval) for mortality was 1.26 (1.10, 1.44) in the good control group and 1.22 (1.05, 1.41) in the poor control group. Among patients with ischemic stroke, the adjusted hazard ratio was 1.24 (1.06, 1.46) in good control group and 1.27 (1.08, 1.50) in poor con-

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trol group. After excluding patients who died within 28 days, the adjusted hazard ratio for conditional mortality in the poor control group was 1.31 (1.12, 1.54) among all stroke patients and 1.29 (1.08, 1.54) among ischemic stroke patients. No significant associations were observed between diabetic status and long-term mortality in intracerebral hemorrhage patients. ***Conclusions:*** The findings suggest that first-ever stroke patients with diabetes exhibited a higher risk of all-cause mortality than those without diabetes, particularly in the overall stroke and ischemic stroke populations. Additionally, in stroke populations after 28 days of onset, high risk of long-term mortality was stated in stroke patients with poor HbA1c control.

Introduction

Diabetes mellitus is an established risk factor for stroke incidence [1]. Further, patients with diabetes have a higher mortality rate after stroke than those without diabetes. One previous study reported that the mortality proportion within 6 months of stroke in diabetes patients was three times higher than the corresponding proportion of nondiabetes patients [2]. Another study suggested that poorly controlled blood glucose levels in stroke patients with diabetes were related to poor prognoses such as increased mortality within 30 days [3].

Glycated hemoglobin (HbA1c) is a useful biomarker for diagnosis or management of diabetes, representing average glycemic control spanning 3 months [4]. HbA1c levels at admission or prestroke have been associated with mortality outcomes in patients with ischemic stroke [2, 5, 6]. In Asian countries, cerebral hemorrhagic stroke also has high incidence, and the evaluation of long-term prognosis is vital for examining social loss after stroke onset. Therefore, investigating the association between diabetic status and long-term mortality in patients with all stroke types is required. Considering this context, the present study aimed to investigate the effect of diabetes status and HbA1c level at hospital admission on long-term survival after first-ever stroke incidence.

Methods

Study Design and Patients

We conducted the retrospective cohort study using the Shiga Stroke and Heart Attack Registry (SSHR) database [7], a population-based registry. SSHR has conducted surveys in almost all hospitals that accept acute stroke patients in Shiga Prefecture, as detailed in a previous paper [7]. Of the 16,629 patients recorded in SSHR from 2011 to 2015, 12,440 patients were diagnosed with first-ever stroke. We excluded patients outside of Shiga Prefecture, those under 18 years of age, those with missing medical history of diabetes or HbA1c values (Fig. 1).

Variables and Outcomes

We evaluated the following demographic and clinical characteristics extracted from medical records: age, smoking status, comorbidities, myocardial infarction, the Japan Coma Scale (JCS) [8], and modified Rankin Scale (mRS) score before stroke onset and at discharge from the hospital. Current and past smoking status was defined on the basis of the information in medical records. Hypertension was defined as high systolic blood pressure and diastolic blood pressures on admission (≥140/90 mm Hg), use of antihypertension medication before the onset of the index stroke, and/or a history of hypertension. Dyslipidemia was defined as low-density lipoprotein cholesterol ≥4.14 mmol/L, total cholesterol ≥5.69 mmol/L, taking medication for dyslipidemia before the onset of the index stroke, and/or a history of dyslipidemia. Atrial fibrillation was defined as a history of atrial fibrillation and/or a clinical diagnosis based on electrocardiogram and/or electrocardiogram monitoring during hospitalization. The estimated glomerular filtration rate was calculated using the Japanese estimated glomerular filtration rate formula purposed by the Japanese Society of Nephrology.

We stratified patients according to diabetes status and HbA1c values into the following: (1) free of diabetes (no history of diabetes and HbA1c <6.5%); (2) good control (history of diabetes and HbA1c <7%; free of history and 6.5% ≤ HbA1c <7%); and (3) poor control (with or without a history of diabetes and HbA1c ≥7%). We set the survival time from onset to the all-cause mortality as an endpoint. Since all stroke patients were followed up using death certificate data until 2016, the censored date was set to December 2016.

Statistical Analysis

We assessed the summary statistics for the demographic and clinical characteristics as mean ± standard deviation for continuous variables and as frequencies or percentages for categorical variables in overall patients and according to diabetes status groups. We conducted a Cox regression analysis to evaluate the association between diabetes status groups and the survival time from stroke onset. Additionally, we evaluated the association between diabetes status and conditional survival, which began from 29 days after stroke onset. Using the free-of-diabetes group as the reference group, we estimated the hazard ratios (HRs) and 95% confidence intervals for the good and poor control groups using four models with different adjustments for variables. We used the survival time of total stroke, ischemic stroke, intracerebral hemorrhage, and ischemic stroke subtypes as outcomes. The subgroup analysis was also conducted according to age, sex, history of hypertension, dyslipidemia, smoking status, and mRS score for all strokes and each stroke type. Survival proportion was estimated using parameter estimates in Cox regression. We also estimated survival proportions at 1, 2, and 3 years after stroke onset based on results of Cox regression. As the sensitivity analysis to consider the distribution of HbA1c values in our study, we conducted the analysis replacing two diabetes groups (poor and good control groups) with three diabetes groups,

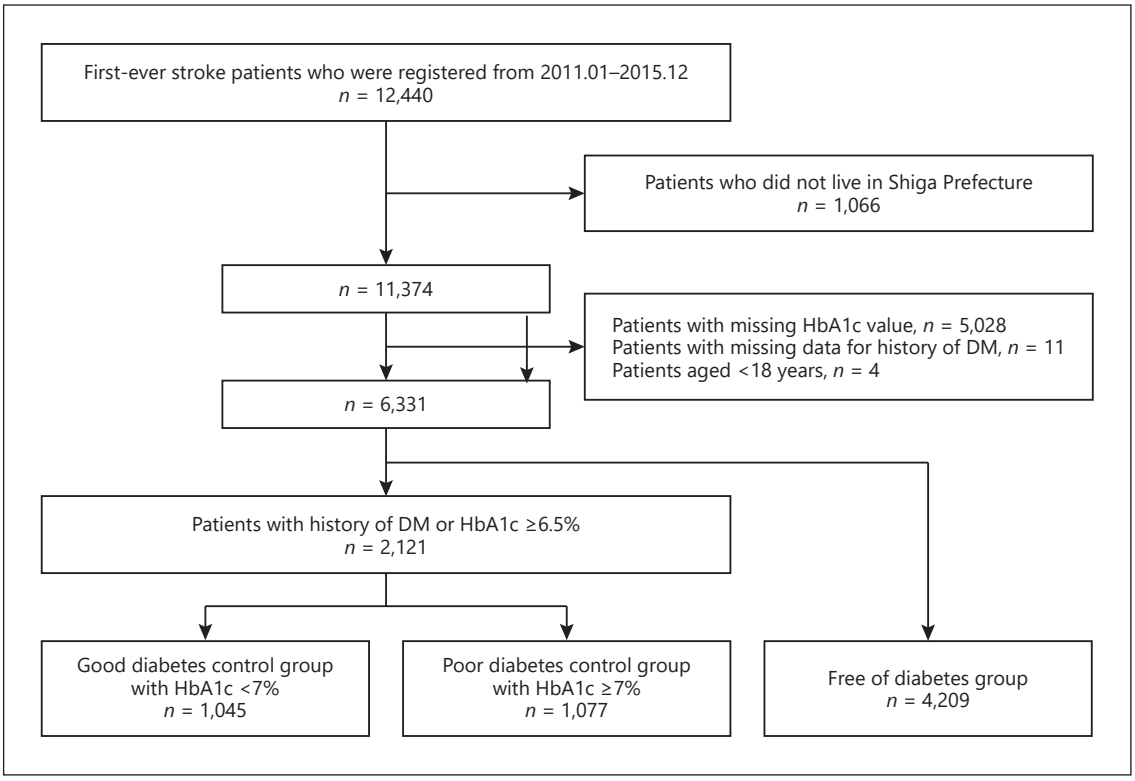

Fig. 1. Flowchart of patient selection.

which was classified by tertiles of HbA1c values. All statistical analyses were performed using SAS version 9.42 (SAS Institute, Cary, NC, USA). Two-sided *p* values <0.05 were considered statistically significant.

Results

Demographics and Clinical Characteristics of Stroke Patients

A total of 6,331 stroke patients were eligible (Fig. 1). The characteristics of the patients according to their diabetes status are shown in Table 1. The average follow-up was 2.76 years. The mean age was 72.85 years, and 42.09% of patients were women. The proportion of smokers was highest in the poor control group (31.11%) and lowest in the good control group (20.66%). Significant differences were found among diabetes status groups for all laboratory test values and comorbidities. The proportions of ischemic stroke were highest (overall 73.23%). Assessments of patients' consciousness level at hospital admission indicated that more than 57.26% of patients in each group were awake with full consciousness, with the JCS score being 0.

Diabetes Status and Long-Term Mortality

Table 2 presents the HRs for all-cause mortality of the good and the poor control groups with the free-of-diabetes group as reference. Among all patients, HR (95% confidence interval) for mortality showed significant differences in both the good and poor control group. As for ischemic stroke patients, the poor control group demonstrated significantly high HRs in all models, while the good control group exhibited significantly high HR in models 2 and 4. As for intracerebral hemorrhage patients, there was no significant association in all models. From further analysis for each type of ischemic stroke (online suppl. Table S1; for all online suppl. material, see www.karger.com/doi/10.1159/000525648), similar tendencies were shown as all ischemic strokes in Table 2. Online supplementary Table S2 shows the sensitivity analysis which evaluated the diabetes groups classified by tertiles of HbA1c. The tendency shown in online supplementary Table S2 has not differed from Table 2.

Diabetes Status and Hospitalization Outcomes

Online supplementary Figure S3 shows the association between diabetes status and functional outcomes during

Table 1. Characteristics of first-ever stroke patients categorized by diabetes status in the SSHR

Variables	All patients (*n* = 6,331)	Free of DM (*n* = 4,209)	Good diabetes control HbA1c <7% (*n* = 1,045)	Poor diabetes control HbA1c ≥7% (*n* = 1,077)	*p* value
Time of follow-up, years	2.76 (1.66)	2.77 (1.64)	2.66 (1.75)	2.85 (1.64)	
Baseline characteristics					
Age, years	72.85 (13.19)	72.92 (13.80)	74.88 (11.26)	70.60 (12.15)	<0.001
Sex (female), *n* (%)	2,665 (42.09)	1,899 (45.12)	426 (40.77)	340 (31.57)	<0.001
Current smoking, *n* (%)					
Nonsmoker	3,375 (56.88)	2,310 (58.29)	575 (59.40)	490 (48.85)	<0.001
Ex-smoker	1,066 (17.96)	672 (16.96)	193 (19.94)	201 (20.04)	
Current smoker	1,493 (25.16)	981 (24.75)	200 (20.66)	312 (31.11)	
Prestroke functional status, *n* (%)					
mRS score 0–1	5,104 (80.86)	3,408 (81.12)	804 (77.61)	892 (82.98)	0.006
mRS score 2–5	1,208 (19.14)	793 (18.88)	232 (22.39)	183 (17.02)	
Comorbidity, *n* (%)					
Hypertension	4,245 (67.13)	2,712 (64.53)	799 (76.53)	734 (68.15)	<0.001
Dyslipidemia	2,465 (39.43)	1,456 (35.09)	483 (46.62)	526 (49.34)	<0.001
Atrial fibrillation	1,100 (17.45)	736 (17.56)	215 (20.63)	149 (13.93)	<0.001
Myocardial infarction	343 (5.44)	171 (4.08)	75 (7.20)	97 (9.05)	<0.001
Admission status					
BMI, kg/m^2	22.80 (4.45)	22.32 (3.86)	23.52 (6.26)	23.89 (4.15)	<0.001
SBP, mm Hg	161.96 (31.99)	161.78 (32.13)	160.39 (31.98)	164.19 (31.35)	0.004
DBP, mm Hg	88.97 (20.34)	89.67 (20.38)	86.13 (20.42)	89.01 (19.86)	<0.001
Blood glucose, mmol/L	8.07 (3.63)	6.71 (1.70)	8.86 (3.08)	12.58 (5.37)	<0.001
HbA1c, %	6.20 (1.32)	5.58 (0.39)	6.24 (0.52)	8.56 (1.55)	<0.001
Total cholesterol, mmol/L	4.99 (1.16)	4.99 (1.12)	4.83 (1.16)	5.12 (1.30)	<0.001
LDLC, mmol/L	2.49 (1.48)	2.51 (1.44)	2.32 (1.50)	2.58 (1.62)	<0.001
Triglyceride, mmol/L	1.38 (0.95)	1.31 (0.89)	1.35 (0.76)	1.69 (1.24)	<0.001
HDLC, mmol/L	1.18 (0.67)	1.23 (0.67)	1.08 (0.65)	1.06 (0.69)	<0.001
eGFR, mL/min/1.73 m^2	68.99 (38.47)	69.81 (42.83)	62.70 (25.95)	71.90 (28.79)	<0.001
Consciousness level, *n* (%)					
JCS 0	3,617 (57.26)	2,359 (56.14)	563 (54.13)	695 (64.65)	<0.001
JCS 1–3	1,639 (25.95)	1,124 (26.75)	267 (25.67)	248 (23.07)	
JCS 10–30	633 (10.02)	442 (10.52)	108 (10.38)	83 (7.72)	
JCS 100–300	428 (6.78)	277 (6.59)	102 (9.81)	49 (4.56)	
Type of stroke, *n* (%)					
Cerebral infarction	4,636 (73.23)	2,984 (70.90)	762 (72.92)	890 (82.64)	<0.001
Intracerebral hemorrhage	1,037 (16.38)	751 (17.84)	164 (15.69)	122 (11.33)	
Subarachnoid hemorrhage	305 (4.82)	228 (5.42)	57 (5.45)	20 (1.86)	
Undetermined	353 (5.58)	246 (5.84)	62 (5.93)	45 (4.18)	
Subtype of ischemic stroke, *n* (%)					
Large-artery infarction	1,471 (31.88)	869 (29.29)	238 (31.32)	364 (41.04)	<0.001
Cardioembolic infarction	1,168 (25.31)	813 (27.40)	206 (27.11)	149 (16.80)	
Lacunar infarction	1,078 (23.36)	670 (22.58)	187 (24.61)	221 (24.92)	
Other/undetermined	897 (19.44)	615 (20.73)	129 (16.97)	153 (17.25)	

Continuous variables are presented as mean (SD), whereas other values are presented as frequency (percentage). The *p* values were calculated using ANOVA for continuous variables and χ^2 test for categorical variables. The JCS score evaluated the consciousness level of patient based on the eye response test which had 4 categories: "0" (fully conscious), 1-digit (awakened with no stimulation), 2-digit (awakened with stimulated), and 3-digit codes (not awake with stimulated). BMI, body mass index; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HDLC, high-density lipoprotein cholesterol; JCS, Japan Coma Scale; LDLC, low-density lipoprotein cholesterol; mRS, modified Rankin Scale; SBP, systolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate.

hospitalization with mRS ≥2–5. Both the good and poor diabetes control groups had poorer functional outcomes than the nondiabetes group. However, the relationship between diabetes status and hospital mortality (mRS = 6) alone was exposed in all stroke and ischemic stroke patients with good diabetes control. Cardio embolic infarction patients with both good and poor diabetes control had high HRs (online suppl. Fig. S3b). Survival proportion at 1, 2, and 3 years after stroke onset based on model 2 by age and sex, and relative survival proportion divided by survival rate of Japanese population are shown in online supplementary Table S4. Relative survival of the free-

Table 2. Association between diabetes status and mortality in first-ever stroke patients

	Free of diabetes	From onset (n = 6,331)					From 29 days after onset (n = 5,989)				
		good diabetes control (n = 1,045)		poor diabetes control (n = 1,077)		p for trend	good diabetes control (n = 950)		poor diabetes control (n = 1,037)		p for trend
		HR (95% CI)	p value	HR (95% CI)	p value		HR (95% CI)	p value	HR (95% CI)	p value	
All strokes											
Model 1	Reference	1.15 (0.96–1.37)	0.123	1.07 (0.88–1.30)	0.488	<0.001	1.11 (0.96–1.28)	0.165	1.32 (1.14–1.53)	<0.001	<0.001
Model 2	Reference	1.19 (1.04–1.36)	0.009	1.16 (1.00–1.33)	0.049	0.010	1.05 (0.90–1.23)	0.508	1.26 (1.08–1.47)	0.004	0.006
Model 3	Reference	1.16 (1.01–1.32)	0.033	1.15 (0.99–1.33)	0.062	0.019	1.04 (0.89–1.21)	0.658	1.26 (1.07–1.47)	0.004	0.008
Model 4	Reference	1.26 (1.10–1.44)	<0.001	1.22 (1.05–1.41)	0.009	<0.001	1.12 (0.96–1.31)	0.163	1.31 (1.12–1.54)	<0.001	<0.001
Intracerebral hemorrhage											
Model 1	Reference	1.47 (1.00–2.16)	0.047	1.27 (0.78–2.06)	0.337	0.096	0.89 (0.59–1.35)	0.594	1.40 (0.92–2.12)	0.113	0.249
Model 2	Reference	1.12 (0.80–1.57)	0.524	1.13 (0.76–1.69)	0.545	0.492	0.81 (0.51–1.27)	0.350	1.37 (0.87–2.15)	0.171	0.487
Model 3	Reference	1.08 (0.77–1.53)	0.658	1.12 (0.75–1.68)	0.573	0.586	0.76 (0.48–1.20)	0.244	1.34 (0.85–2.11)	0.203	0.608
Model 4	Reference	1.18 (0.83–1.67)	0.346	1.18 (0.78–1.79)	0.444	0.349	0.91 (0.58–1.44)	0.688	1.38 (0.86–2.21)	0.179	0.386
Cerebral infarction											
Model 1	Reference	1.05 (0.84–1.31)	0.660	1.20 (0.96–1.49)	0.108	<0.001	1.17 (0.99–1.38)	0.059	1.30 (1.10–1.53)	0.002	<0.001
Model 2	Reference	1.18 (1.01–1.38)	0.033	1.22 (1.03–1.43)	0.018	0.006	1.11 (0.94–1.32)	0.224	1.24 (1.04–1.47)	0.016	0.013
Model 3	Reference	1.16 (0.99–1.35)	0.060	1.21 (1.03–1.43)	0.021	0.009	1.10 (0.93–1.30)	0.277	1.25 (1.05–1.49)	0.013	0.012
Model 4	Reference	1.24 (1.06–1.46)	0.007	1.27 (1.08–1.50)	0.004	<0.001	1.17 (0.99–1.39)	0.073	1.29 (1.08–1.54)	0.004	0.003

Adjusted HRs and 95% CIs for mortality risk are shown according to diabetes status. Adjusted variables were age, sex for model 1; variables in model 1 plus smoking status and mRS before onset for model 2; variables in model 2 plus SBP, LDLC, and HDLC for model 3; and variables in model 2 plus history of hypertension, history of dyslipidemia, and history of atrial fibrillation for model 4. HR, hazard ratio; CI, confidence interval.

Table 3. Subgroup analysis of the association between diabetes status and all-cause mortality in patients with all strokes

	Free of diabetes	Good diabetes control HbA1c <7%			Poor diabetes control HbA1c ≥7%			*p* for interaction
		HR	95% CI	*p* value	HR	95% CI	*p* value	
Age ≥65 years	Reference	1.27	1.10–1.46	0.001	1.32	1.13–1.54	<0.001	<0.001
Age <65 years	Reference	1.69	1.05–2.73	0.030	1.39	0.86–2.23	0.175	
Male	Reference	1.33	1.11–1.59	0.002	1.42	1.17–1.72	<0.001	<0.001
Female	Reference	1.24	1.01–1.52	0.036	1.19	0.95–1.50	0.134	
Hypertension (+)	Reference	1.17	1.00–1.36	0.057	1.29	1.09–1.54	0.003	0.004
Hypertension (–)	Reference	1.60	1.24–2.07	<0.001	1.24	0.94–1.63	0.131	
Dyslipidemia (+)	Reference	1.14	0.90–1.43	0.287	1.33	1.05–1.69	0.018	0.019
Dyslipidemia (–)	Reference	1.35	1.14–1.59	<0.001	1.24	1.03–1.50	0.024	
Current smoking	Reference	1.31	0.94–1.82	0.113	1.27	0.92–1.76	0.140	0.174
Nonsmoking	Reference	1.27	1.10–1.47	0.001	1.30	1.10–1.53	0.002	
mRS 2–5	Reference	1.36	1.09–1.70	0.006	1.26	0.99–1.60	0.062	<0.001
mRS 0–1	Reference	1.16	0.98–1.38	0.092	1.25	1.04–1.50	0.020	

Adjusted HRs and 95% CIs for mortality risk are shown according to diabetes status in each subgroup. The model was adjusted for age, sex, smoking status, JCS score, history of hypertension, and history of dyslipidemia. HbA1c, glycated hemoglobin; HR, hazard ratio; CI, confidence interval; mRS, modified Rankin Scale.

of-diabetes group was less than one even in patients free of diabetes and lowest in patients with poorly controlled diabetes.

Subgroup Analysis

Table 3 shows the results of subgroup analysis. Among all stroke patients, interactions between diabetes status groups and age, sex, hypertension, dyslipidemia, and mRS score were found. Among patients with poor control, higher HRs were shown in strata of older age, men, hypertension, dyslipidemia and smaller mRS score before onset.

Discussion

While several studies evaluated the effects of diabetes on a short-term prognosis in stroke patients [5, 6, 9], there has been little evidence regarding evaluation of the effects of diabetes status and HbA1c levels on long-term mortality in large-scale stroke patients. The present study showed that both good and poor diabetes control were significantly associated with long-term mortality rate in all stroke patients using a population-based registry database. In patients with ischemic stroke, a similar association was found in good diabetes control as well as poor diabetes control. However, this association alone was found in poor diabetes control and cerebral infarction patients with survival after 28 days of onset. Exploring the differences in mortality risk among diabetes control status based on HbA1c is expected to provide useful information for clinical practice in stroke patients with diabetes.

The present results showed that the HRs for all-cause mortality of the poor control group compared to the free-diabetes group in all stroke patients and ischemic stroke patients were 1.22 and 1.27, while these results of good control group were 1.26 in all strokes and 1.24 in ischemic stroke patients (Table 2). A previous study reported that the HR for all-cause mortality at 3 years postdischarge in ischemic stroke patients with diabetes was 1.24; however, this was limited to elderly patients [10]. Another study in Japan showed that ischemic stroke patients with poor prestroke glycemic control (HbA1c ≥8.4%) had poor functional outcomes related to mortality or dependency by grading mRS with the odds ratio of 2.52; however, that study evaluated short-term prognosis [11]. Similarly, our results showed that patients with poor diabetes control had poorer dependency outcomes by mRS from 2 to 5, whereas patients with good diabetes control had higher hospital mortality by mRS = 6 (online suppl. Fig. S3). Another study reported that 1-year mortality rate in patients with the highest tertile of HbA1c compared with the lowest tertile (OR: 1.48) in patients with ischemic stroke and diabetes [9]. The present study showed relevant results with 3rd tertile of HbA1c >7% (online suppl. Table S2).

The results agreed with those of previous studies; nevertheless, we provided additional information on the longer term mortality after stroke incidence as well as a broader type of strokes.

Setting the HbA1c value at 7% for indicating poor diabetes control is relevant as several studies have identified this value as the threshold for macrovascular events and death [5, 6, 12, 13]. There are some explanations for the association between poor glycemic control and long-term mortality. First, high HbA1c levels in diabetes are associated with an unhealthy lifestyle, poor adherence to treatment, and medical conditions. Second, glucose transport through the blood-brain barrier is reduced during the acute phase, leading to hyperglycemia. It reacts to acute stress and tissue injury with associated autonomic, hormonal, and metabolic alterations [14, 15]. These combinations may cause more severe stroke during the acute phase. Third, because of the atherosclerotic status of cerebral vessels related to diabetes, poor HbA1c control may indicate a delay in recovery progression and worsened survival capacity for a long time among stroke patients. In the long term, diabetes also affects the operation and health of multiple organ systems [16]. Therefore, stroke patients with diabetes, particularly those with poor HbA1c control, likely have a lower probability of survival.

As for hemorrhagic stroke, there were no significant differences among diabetes status groups (Table 2). One study from Denmark showed no difference in mortality between diabetic and nondiabetic patients with stroke [17]. Two studies suggested that diabetes was associated with elevated short-term mortality in intracerebral hemorrhagic stroke patients [18, 19]. The inconsistency across studies may be attributable to differences in follow-up duration, statistical analysis, and sociodemographic characteristics.

Our study also showed differences in sex-stratified analysis: both good and poor diabetes control were associated with higher mortalities in men, whereas in women, this association was only shown in good diabetes control. This finding is inconsistent with previous Japanese studies on short-term outcomes and acute ischemic stroke [20, 21]. Although this inconsistency may be because of differences in the study setting, there is not enough evidence to make conclusions about the risk of sex difference. Considering the higher HR in the group without hypertension, the optimal blood pressure management in medication, treatment, and prevention of hypertensive emergencies involving brain damage could be a logical explanation.

This study had some limitations. First, the missing HbA1c data for 5,028 cases may limit the significance of findings. Second, the mortality outcomes were based on death certificate data at Shiga Prefecture, and therefore, the patients who moved out of Prefecture could not be identified. Third, we took further information of stroke prognosis including hemorrhagic stroke; however, the analysis limited to patients with SAH remains to be investigated due to lack of power. Further research of SAH patients is required. Fourth, our study evaluated only the functional prognosis in the acute phase but could not investigate it in the long term. No studies have evaluated long-term functional prognosis, which can be said to be a problem. Finally, there was a lack of information on the duration of diabetes as well as on the diabetes treatment after stroke onset, which plays an important role in outcomes. Despite these limitations, this study also had some notable strengths. The survival outcome after stroke onset was evaluated not only by the presence of diabetes but also by diabetes status according to HbA1c levels. Our study is also one of the few studies that evaluated a lengthy follow-up period for all stroke patients.

Conclusions

This study showed a higher risk of long-term mortality in stroke patients with diabetes compared to those without diabetes. Among all stroke and ischemic stroke patients, the poor HbA1c control group had a higher risk of all-cause mortality than the nondiabetes group. Thus, controlling for HbA1c in stroke patients before first-ever stroke may improve all-cause mortality, particularly in patients with ischemic stroke.

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Statement of Ethics

The present study was approved by the Institutional Review Board of the Shiga University of Medical Science (R2011-186). This study was granted an exemption from requiring written informed consent by the Institutional Review Board of the Shiga University of Medical Science.

Conflict of Interest Statement

Dr. Hisatomi Arima is an Associate Editor of the journal. The other authors have no conflicts of interest to declare.

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Author Contributions

Huynh Thi Hong Tram designed the study protocol, analyzed data, and prepared the manuscript with support from Sachiko Tanaka-Mizuno. Sachiko Tanaka-Mizuno, Naoyuki Takashima, Kawser Khan, Hisatomi Arima, Aya Kadota, Takako Fujii, Satoshi Shitara, Akihiro Kitamura, Naomi Miyamatsu, Yoshikuni Kita, Makoto Urushitani, Yoshihisa Nakagawa, Katsuyuki Miura, and Kazuhiko Nozaki advised the study planning, developed the theoretical content, interpreted the results, and approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are not available on the ethical grounds. Further inquiries can be directed to the corresponding author.

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