Cerebrovascular Diseases Extra

Original Paper

Cerebrovasc Dis Extra 2022;12:7-13
DOI: 10.1159/000521442

Received: September 27, 2021
Accepted: November 18, 2021
Published online: December 13, 2021

# Long-Term Post-Stroke Functional Outcomes: A Comparison of Diabetics and Nondiabetics

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**Keywords**
Functional outcome · Long-term prognosis · Diabetes mellitus · Stroke

**Abstract**
***Introduction:*** Diabetes mellitus (DM) is known to influence outcomes in the short term following stroke. However, the impact of DM on long-term functional outcomes after stroke is unclear. We compared functional outcomes periodically over 7 years between diabetic and nondiabetic ischemic stroke patients, and investigated the impact of DM on the long-term trajectory of post-stroke functional outcomes. We also studied the influence of age on the diabetes-functional outcome association. ***Methods:*** This is a longitudinal observational cohort study of 802 acute ischemic stroke patients admitted to the Singapore General Hospital from 2005 to 2007. Functional outcomes were assessed using the modified Rankin Scale (mRS) with poor functional outcome defined as mRS ≥3. Follow-up data were determined at 6 months and at median follow-up durations of 29 and 86 months. ***Results:*** Among the 802 ischemic stroke patients studied (mean age 64 ± 12 years, male 63%), 42% had DM. In regression analyses adjusting for covariates, diabetic patients were more likely to have poor functional outcomes at 6 months (OR = 2.12, 95% CI: 1.23–3.67) and at median follow-up durations of 29 months (OR = 1.96, 95% CI: 1.37–2.81) and 86 months (OR = 2.27, 95% CI: 1.58–3.25). In addition, age modulated the effect of DM, with younger stroke patients (≤65 years) more likely to have long-term poor functional outcome at the 29-month ($p$ = 0.0179) and 86-month ($p$ = 0.0144) time points. ***Conclusions:*** DM was associated with poor functional outcomes following ischemic stroke in the long term, with the effect remaining consistent throughout the 7-year follow-up period. Age modified the effect of DM in the long term, with an observed increase in risk in the ≤65 age-group but not in the >65 age-group.



## Introduction

Diabetes mellitus (DM) is an important risk factor for stroke. Compared to nondiabetics, diabetics are 2–5 times more likely to have a stroke in age-adjusted analyses [1, 2] and have a higher recurrent stroke rate [3, 4]. DM has

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been shown to be associated with poorer post-stroke outcomes in the short term with higher rates of death [5] and dependency among diabetic stroke patients up to a year [5–8]. However, studies on long-term functional outcomes are scarce [9], and there are no published studies on the impact of DM on outcomes beyond 5 years.

We compared the post-stroke functional outcome between ischemic stroke patients with and without DM at 3 time points over approximately 7 years (6, 29, and 86 months). We also investigated the influence of DM on post-stroke outcome trajectory and whether the effect of DM on functional outcome was modified by age (≤65 vs. > 65 years) over the 7-year follow-up period [10].

## Materials and Methods

*Study Population*

This was a longitudinal observational cohort study on acute stroke patients in the Multi-Centre Retinal Stroke (MCRS) study who were admitted to the Singapore General Hospital from 2005 to 2007 [11]. Inclusion criteria were ischemic stroke within 1 week of onset and tolerance for retinal photography. Ethics approval was obtained from the Institutional Review Board, and written informed consent was obtained from each patient or his/her surrogate.

*Baseline Data*

Demographic data consisting of age, sex, ethnicity, and stroke related risk factors were documented. Patients were dichotomized in the analysis according to age as ≤65 or >65 years. DM was defined as prior diagnosis by a physician and/or present treatment with hypoglycemic agents/insulin. Hypertension and hypercholesterolemia were defined as a physician-confirmed diagnosis or from documentation in medical records. Current smokers were defined as persons who smoked or had stopped smoking less than 1 year prior to admission. Atrial fibrillation was defined from electrocardiographs during admission and from medical records. Stroke was subtyped using modified Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification [12], as defined in the Greater Metropolitan Clinical Taskforce for Stroke in New South Wales [11]. Baseline neurological deficits were documented using the National Institutes of Health Stroke Scale (NIHSS) [13]. The severity of neurological deficits was classified as mild (NIHSS score of 0–4), moderate (NIHSS 5–15), and severe (NIHSS >15).

*Outcomes and Follow-Up Assessment*

Functional outcomes were assessed with modified Rankin Scale (mRS) [14] with poor functional outcome defined as mRS ≥3. Follow-up duration was defined as the time in months from initial stroke presentation to the date of telephone interview. Outcome status was first determined at a follow-up duration of 6 months for all patients. The subsequent 2 follow-up assessments were conducted from August 2008 to July 2009 at a median (interquartile range [IQR]) duration of 29 (24–34) months and from November 2013 to April 2014 at a median (IQR) duration of 86 (71–92) months. Patients were contacted within the aforementioned time periods irrespective of follow-up duration. As such, there is variability in the follow-up times for the second and third follow-ups. Trained study coordinators, masked to clinical findings, assessed mRS status at all follow-ups using a standardized telephone interview with the patient or next of kin. Loss to follow-up was defined as the patient's choice against continued participation or inability to contact the patient via telephone at least 5 times at different times of the day over a period of 3 months, using the contact details provided during the initial admission.

*Statistical Analysis*

Statistical analyses were performed using the SAS software University Edition (SAS Institute Inc., Cary, NC, USA). Patient demographic and clinical characteristics were compared using a 2-sample *t*-test and a $\chi^2$ test as appropriate. Univariate binary and generalized logistic regression analyses were performed on all baseline demographic and clinical variables to identify risk factors associated with poor functional outcome. Selection of variables for multivariate analysis was based on known clinical confounders as well as variables significant at $p < 0.25$ in univariate analysis. Multinomial generalized logistic regression was performed to investigate the association between diabetes and mRS while adjusting for the potential confounders of age, sex, previous stroke, smoking, and follow-up time. Binary logistic regression was performed to investigate the association between DM and poor functional outcomes while adjusting for potential confounders. Follow-up duration was included as a covariate owing to variability in follow-up times for the last two follow-ups. Binary logistic regression was performed to investigate the effect of age category (≤65, >65 years) on poor mRS functional status.

## Results

Among the 1980 ischemic stroke patients (mean age 66 ± 12 years, 58% male, 80% Chinese, and median baseline NIHSS of 3, IQR 1–7) admitted during the study period, 802 patients were eligible and recruited into the study. Patients recruited into this study had a similar profile (mean age 64 ± 11 years, 63% male, 81% Chinese, and median baseline NIHSS score of 3, IQR 1–5). Baseline characteristics are shown in Table 1. The proportion of patients lost to follow-up or death was 64 (8.0%) at 6 months, 90 (11.0%) at a median follow-up of 29 months, and 92 (11.5%) at a median follow-up of 86 months. The incidence of poor functional outcome was 9% at 6 months, 30% at a median follow-up of 29 months, and 50% at a median follow-up of 86 months.

*Analyses Stratified by DM Status*

Patients with DM were more likely to be female, Indian, Malay, hypertensive, have hypercholesterolemia, have large artery strokes, and nonsmokers. Despite adjustment for all factors which were significant in univariate analyses, including sex, previous stroke, smoking, and

**Table 1.** Baseline demographics, risk factors, and stroke phenotypes by diabetic status and age category

| | Total | Diabetes mellitus | | | Age | | |
|---|---|---|---|---|---|---|---|
| | | yes | no | *p* value | >65 | ≤65 | *p* value |
| Frequency, *n* (%) | 806 (100) | 336 (42) | 470 (58) | <0.0001 | 391 (45) | 480 (55) | 0.0026 |
| Sex, *n* (%) | | | | | | | |
| Male | 504 (63) | 194 (58) | 310 (66) | 0.0175 | 221 (57) | 324 (68) | 0.0005 |
| Female | 302 (37) | 142 (42) | 160 (34) | | 170 (43) | 153 (32) | |
| Age, years, *n* (%) | | | | | | | |
| Mean±SD | 64±11 | 64±10 | 64±12 | | | | |
| >65 | 368 (46) | 154 (46) | 214 (46) | 0.9325 | | | |
| ≤65 | 438 (54) | 182 (54) | 256 (54) | | | | |
| Ethnicity, *n* (%) | | | | | | | |
| Chinese | 651 (81) | 254 (76 | 397 (85) | | 310 (84) | 341 (78) | |
| Indian | 57 (7) | 34 (10) | 23 (5) | 0.0074 | 23 (6) | 34 (8) | 0.1267 |
| Malay | 88 (11) | 44 (13) | 44 (9) | | 32 (9) | 56 (13) | |
| Others | 10 (1) | 4 (1) | 6 (1) | | 3 (1) | 7 (1) | |
| Hypertension, *n* (%) | | | | | | | |
| Yes | 551 (69) | 274 (82) | 277 (59) | <0.0001 | 264 (72) | 287 (66) | 0.0446 |
| No | 253 (31) | 61 (18) | 192 (41) | | 102 (28) | 151 (34) | |
| Hypercholesterolemia, *n* (%) | | | | | | | |
| Yes | 366 (45) | 200 (60) | 166 (35) | <0.0001 | 176 (48) | 190 (43) | 0.2066 |
| No | 440 (55) | 136 (40) | 304 (65) | | 190 (52) | 248 (57) | |
| Atrial fibrillation, *n* (%) | | | | | | | |
| Yes | 41 (5) | 13 (4) | 28 (6) | 0.1865 | 31 (8%) | 10 (2%) | <0.0001 |
| No | 764 (95) | 322 (96) | 442 (94) | | 336 (92%) | 428 (98%) | |
| Smoking history, *n* (%) | | | | | | | |
| Yes | 217 (28) | 70 (22) | 147 (32) | | 74 (21) | 143 (34) | |
| Ex-smoker | 135 (18) | 60 (19) | 75 (17) | 0.0097 | 71 (21) | 64 (15) | 0.0003 |
| Never | 415 (54) | 186 (59) | 229 (51) | | 203 (58) | 212 (51) | |
| Previous stroke, *n* (%) | | | | | | | |
| Yes | 152 (19) | 73 (22) | 79 (17) | 0.0750 | 85 (23) | 67 (15) | 0.0045 |
| No | 653 (81) | 262 (78) | 391 (83) | | 282 (77) | 371(85) | |
| TOAST classification, *n* (%) | | | | | | | |
| Cardioembolic | 91 (11.3) | 31 (9.2) | 60 (12.8) | | 54 (14.7) | 37 (8.5) | |
| Lacunar | 354 (44.0) | 133 (39.7) | 221 (47.0) | | 146 (39.7) | 208 (47.6) | |
| Large artery | 278 (34.5) | 141 (42.1) | 137 (29.1) | 0.0040 | 127 (34.5) | 151 (34.6) | 0.0286 |
| Other | 8 (1) | 2 (0.6) | 6 (1.3) | | 3 (0.8) | 5 (1.1) | |
| Undetermined | 74 (9.2) | 28 (8.4) | 46 (9.8) | | 38 (10.3) | 36 (8.2) | |
| NIHSS classification, *n* (%) | | | | | | | |
| Median (IQR) | 3 (1–5) | 3 (1–4) | 3 (1–5) | | 3 (1–5) | 2 (1–4) | |
| 0–4 (mild stroke) | 469 (75.3) | 202 (76.5) | 267 (74.4) | 0.8289 | 192 (70.3) | 277 (79.1) | 0.0185 |
| 5–15 (moderate stroke) | 149 (23.9) | 60 (22.7) | 89 (24.8) | | 77 (28.2) | 72 (20.6) | |
| >15 (severe stroke) | 5 (0.8) | 2 (0.8) | 3 (0.8) | | 4 (1.5) | 1 (0.3) | |

IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

follow-up duration, diabetics had worse mRS distributions (Fig. 1) at all time points; diabetics were also more likely to have poor functional outcome (Fig. 2). There was no interaction between DM and follow-up time interaction after adjustment for confounders with respect to mean mRS values ($p = 0.9725$) or poor functional outcomes ($p = 0.9221$).

*Analyses Stratified by Age-Group*

Older patients were more likely to be female, smokers, have a previous history of stroke, have atrial fibrillation, have lacunar strokes, and have more severe strokes. Ethnic distribution and prevalence of DM, hypertension, and hypercholesterolemia did not differ between the age-groups.

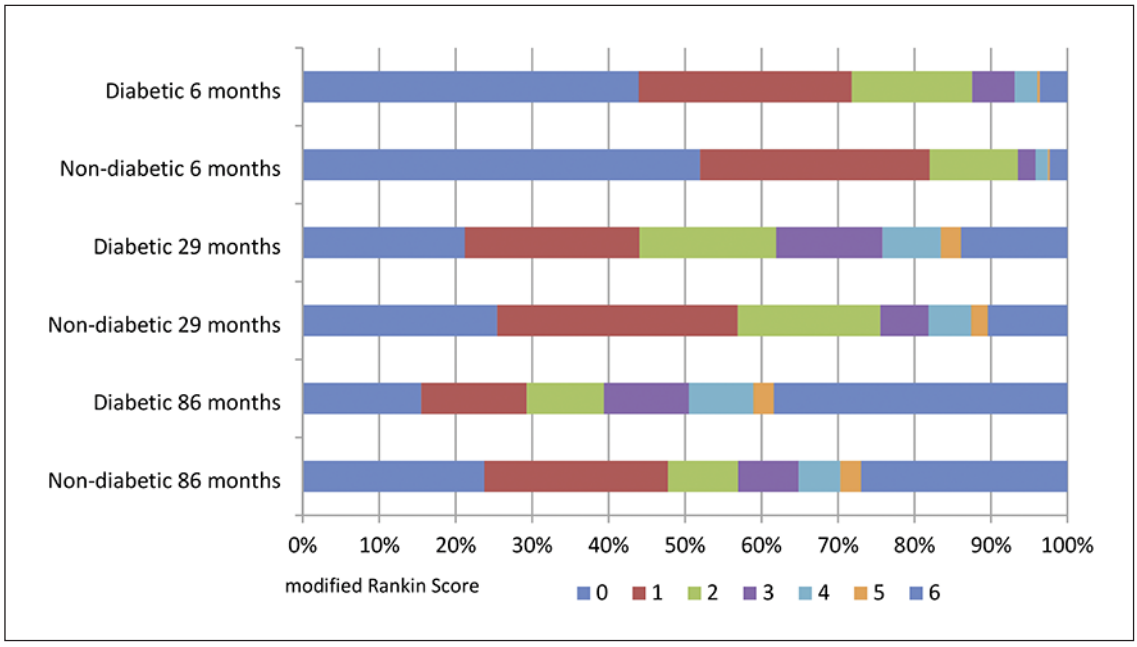


**Fig. 1.** Distribution of mRS at follow-up times by diabetic status.

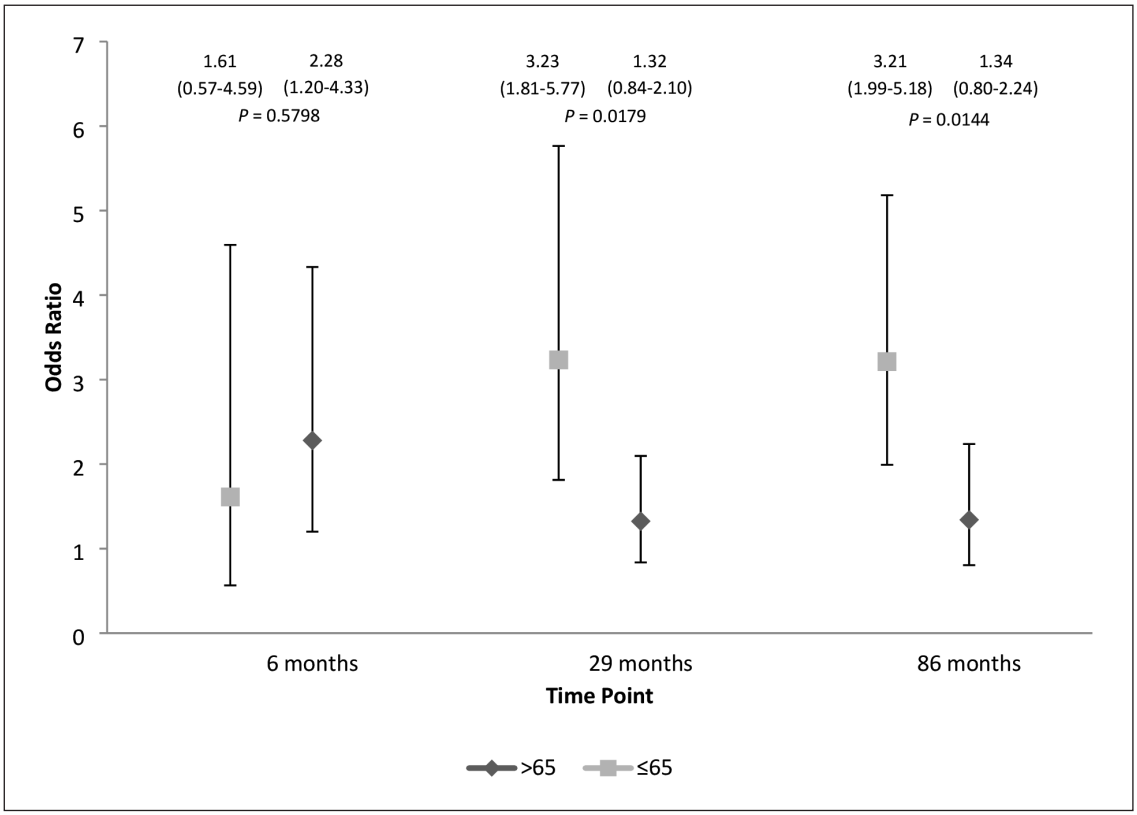


**Fig. 2.** Odd ratios of poor functional outcome (mRS ≥3) between diabetics and nondiabetics by age categories (≤65 and >65 years old) at 6-, 29-, and 86-month follow-up time points.

Among patients ≤65 years, the odds of poor functional outcome were greater in diabetics versus nondiabetics at the 29-month and 86-month follow-ups, but not at 6 months (shown in Fig. 2). There was a significant difference in the risk of poor functional outcomes between diabetics and nondiabetics in the >65 age-group at 6 months as well as no differences at the 29-month or the 86-month follow-ups. Older patients were more likely to have poorer functional outcomes in both diabetics (OR = 4.41, 95% CI: 1.90–10.25 at 6 months; OR = 2.31, 95% CI: 1.40–3.80 at 29 months; OR = 2.75, 95% CI: 1.64–4.64 at 86 months) and nondiabetics (OR = 3.12, 95% CI: 1.26–7.71 at 6 months; OR = 5.63, 95% CI: 3.26–9.72 at 29 months; OR = 6.59, 95% CI: 4.13–10.54 at 86 months). The effect of time was shown to modify the risk of poor functional outcome relative to the age-group.

There were significant interactions between ≤65 and >65 age-groups and DM for the outcome of poor functional status at 29-month ($p = 0.0179$) and 86-month follow-ups ($p = 0.0144$) but not at 6 months ($p = 0.5798$).

## Discussion

Our findings confirm that DM is a predictor of poor functional outcomes in the long term and provide data from a cohort with the longest follow-up duration to date of 7 years. This adds to prior data with 5-year follow-up which showed that DM was associated with independence but not poor functional outcome [9]. Our study found that difference in functional outcomes following ischemic stroke between diabetics and nondiabetics did not change over time in terms of both mRS distribution and proportion with poor functional outcome. A steady decline of functional outcome over a short term of 6 months following stroke in diabetics has been described in other studies [15–17], but this is the first time that the progressive impact of DM over the long term has been described. We conclude that the difference between diabetics and nondiabetics remains consistent from the short term to the longer term (up to 7 years) from stroke onset.

The impact of DM on functional outcomes in this study is independent of age, sex, smoking history, previous stroke, NIHSS, or follow-up. There are several possible explanations for poorer functional outcomes in diabetics over the short and longer term. First, DM is a known prognostic factor for recurrent stroke [3] and clinically silent strokes [18]. Higher rates of recurrent symptomatic and asymptomatic stroke among diabetics may have led to a poorer functional outcome. Second, DM is associated with a multitude of nonstroke complications including heart disease, vision loss, kidney failure, amputations, neuropathy, autonomic dysfunction, and cognitive dysfunction – all of which may contribute to poorer functional outcomes [19]. Third, hyperglycemia is a poor prognostic factor affecting functional outcome in the short term, and has also been shown to have poorer 3-month outcomes after hyperacute intervention [20–22]. Lastly, there is newer evidence that the composition of the thrombus differs between diabetics and nondiabetics, with diabetics having more fibrin and fewer red blood cells, which has been hypothesized to account for poorer recanalization rates during endovascular therapy [23]. This study was not designed to confirm these postulations, and further study is needed to understand the underlying reasons for the poorer post-stroke functional outcomes among diabetics.

In the long term, DM was associated with increased risk of poor functional outcomes in the ≤65-year-old patients, but showed no effect in patients >65, which may be accounted for by a potential ceiling effect of DM and other age-related comorbidities. This novel finding of a significant interaction between age and DM on functional outcome in a cohort of ischemic stroke patients is consistent with findings from a stroke free cohort [24].

The strengths of this study include the large sample size, good retention rate (88.5%), and serial outcomes over a long (7.2 years) follow-up duration. This allowed for assessment of the natural trajectory of functional outcomes after stroke in relation to DM that is described elsewhere. Another strength of our study lies in the use of mRS which confers several advantages over the Barthel Index and self-reported disability scores. The mRS is the most commonly used measure for functional outcome after stroke. It has acceptable inter-rater reliability and captures higher functioning including speech, language, and cognitive function [14]. The Barthel Index has limitations of insensitivity to speech, language, and cognitive dysfunction, and a well-documented ceiling effect [25]. Self-reported scores may be influenced by gender, education, race, or socioeconomic factors, affecting their validity [24].

There are several limitations in our study. There is possible selection bias that is inherent to including only patients who can adequately tolerate retinal photography from the MCRS study. However, the baseline characteristics of the cohort studied were similar to those of all patients admitted during the study period. There was no standardized duration from initial stroke to follow-up for

each patient, except for the 6-month follow-up due to a practical constraint of manpower resources. As such, the follow-up telephone calls were made during specific months of August 2008 to July 2009 and subsequently from November 2013 to April 2014. Another limitation is the lack of glycemic control records such as blood glucose levels and HbA1c; hence, we were unable to determine whether hyperglycemia in the acute stroke period and poor glycemic control at baseline or during follow-up period explain why diabetic ischemic stroke patients have poorer functional outcomes. As mentioned previously, recurrent symptomatic and silent strokes were also unaccounted for in our study.

## Conclusions

This study shows that DM is associated with poor functional outcomes following ischemic stroke in the long term with the effect remaining consistent throughout the 7-year follow-up period. Differences in functional outcomes between diabetics and nondiabetics over this period remained consistent with no interaction between duration from stroke and diabetes status. However, age modified the association of DM on long-term functional outcome, with younger DM patients having an additive association of poor functional outcome.


## Acknowledgments

We would like to acknowledge the collaborators of the MCRS study. The patients described in this paper were from the Singapore site of the MCRS study.


## Statement of Ethics

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. This study protocol was reviewed and approved by the SingHealth Centralised Institutional Review Board, approval numbers 2004/010/A and 2008/614/A. Written informed consent was obtained from participants or their next of kin to participate in the study.

## Conflict of Interest Statement

The authors have no conflicts of interest to disclose.


## Funding Sources

The Singapore site of the MCRS study is supported by grants from the Singapore National Medical Research Council (NMRC grant number 2004/073; NMRC NIG grant numbers NMRC/0914/2004 and NMRC/0914/S2) and SingHealth Foundation (SHF/FG370P/2007).


## Author Contributions

Dr. De Silva drafted the manuscript. Dr. De Silva, Dr. Wong, and Ms. Woon were responsible for the conception and design of this study. Prof Allen and Dr. Huang were responsible for statistical analyses, and Dr. Narasimhalu was responsible for the interpretation of the data. All authors critically reviewed and edited the manuscript.

## Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author upon reasonable request.

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