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Time to recurrence after first-ever ischaemic stroke within 3 years and its risk factors in Chinese population: a prospective cohort study

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ABSTRACT

Objective This study aimed to estimate the time of recurrent ischaemic stroke events among the first 3 years of follow-up after hospitalisation discharge.

Study design A prospective cohort study.

Setting The research was conducted in the Department of Neurology at a tertiary hospital, Chengdu of China, from January 2010 to June 2016.

Outcome measures We estimated the restricted mean survival time (RMST) of ischaemic stroke recurrence for the first 3 years after discharge. Basic sociodemographic characteristics and major potential risk factors for recurrence were collected using a semistructured questionnaire. Regression analysis of RMST was used to identify risk factors of recurrent stroke.

Participants Patients hospitalised with first-ever ischaemic stroke were eligible for this study. Patients with severe cognitive impairment were excluded.

Results We included 641 surviving patients who were followed up for 3 years. Stroke recurrence occurred in 115 patients, including 16 patients who died of stroke recurrence. The cumulative risk of stroke recurrence rate was 11.51% (9.20%–14.35%) at 1 year, 16.76% (13.96%–20.05%) at 2 years and 20.07% (17.00%–23.61%) at 3 years. Modified Rankin Scale (mRS) score ≥3 thus resulted in the recurrence time loss, which was 0.22 months (p=0.008) at 6 months, 0.61 months (p=0.004) at 1 year, 1.49 months (p=0.007) at 2 years and 2.46 months (p=0.008) at 3 years. It is similar with the effects of drug adherence after stroke. The recurrence time of patients ≥75 years at 3 years was 2.02 months (p=0.220) less than that of those aged <55 years.

Conclusion In China, the time of first recurrence varies among different patients with ischaemic stroke. The mRS and the level of drug adherence after stroke are important risk factors of stroke recurrence.

INTRODUCTION

Stroke is the second most common cause of death,[1] the third most common cause of disability-adjusted life years (DALYs) worldwide in 2010,[2] and the most heavy burden in low-income and middle-income countries.[3][4] Ischaemic stroke, mainly secondary to arterial occlusion, accounts for above

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Strengths and limitations of this study

► The main strength of this study was the introduction of restricted mean survival time, which is a useful measure, especially in the case that the proportional hazards assumption is not met.

► Limitations are that follow-up for outcome variables was performed by telephone interviews rather than by face-to-face contact.

► In addition, the possibility that the stroke recurrence information was biased could not be excluded. The recurrence of stroke was gathered from interviews with patients or their proxies, rather than from examinations and reviews of the medical records done by all of us.

► Due to the limitation of the reality, it may be inaccurate for using Modified Rankin Scale instead of National Institute of Health Stroke Scale to evaluate the severity of stroke.

85% of all strokes.[5][6] In China, the annual stroke mortality rate, approximately 157 per 100 000, has exceeded heart disease to become the leading cause of death and adult disability.[7] Stroke survivors are often at significantly increased risk of stroke recurrence,[8] even in spite of appropriate treatment, which in turn further increase the risk of disability and death.[9] In Chinese population, the recurrent rate (11.2%) remains high.[7] With ageing of the population, China is under great pressure to meet further increased demands on the healthcare system due to stroke in the future.[10] Secondary stroke prevention remains a top priority in treating patients after the first stroke.[11–15]

Statements on the risk of stroke recurrence are invariably based on the hazard ratio (HR), which rely on the proportional hazards (PHs) assumption to estimate the treatment effect and implicitly. However, formal verification of this assumption is rarely. Some studies[16–18] argued that when the PH assumption is

invalid, it is misleading to report the treatment effect through the estimated HR, since it depends on study-specific follow-up time.

Even when PH holds, we are dissatisfied with the HR as a universal summary measure.[17] Without appropriate background information about the absolute hazard, the summary ratio fails to convey a more transparent clinical value of a treatment, such as the prolonged survival time.[16] Moreover, the precision of the HR estimator depends primarily on the observed number of events, resulting in that confidence intervals (CIs) for the HR estimate can be quite large when the event rates are low for both groups, which ostensibly suggesting that the information is not enough to properly assess the between-group difference.

The mean survival time is another parameter of great interest, which gives the expected time until some events occur. However, the mean survival time is often ill determined beyond a certain range because of the right censored data. The restricted mean survival time (RMST) can be understood as the average survival time over a period of time and can quantify the difference between the survival time caused by different factors, which is less sensitive to right censoring. Moreover, from a practical point of view, one is often interested in the effect of the risk factors. Differences between patients' RMST of different risk factor can be interpreted as the number of months lost due to the risk factor.[16]

Therefore, we aimed to conduct a prospective hospital-based study by a cohort of patients of first-ever ischaemic stroke to estimate the time of recurrent ischaemic stroke events among the first 3 years of follow-up after discharge, and introduce a regression analysis of RMST based on pseudo-observation to determine the risk factors, namely assessing the gain or loss in the event-free recurrence time owing to given risk factors.

MATERIALS AND METHODS
Patient and public involvement
The patients and the public were not involved in the design or planning of the study.

Study population
This was a prospective study conducted in the Department of Neurology in No 1 West China Hospital of Sichuan University, the largest tertiary hospital in Sichuan, China. Patients who were diagnosed with first-ever ischaemic stroke by a neurologist according to WHO criteria[19] and CT or MRI were eligible for this study. Patients with severe cognitive impairment were excluded. Consecutive enrolment started in January 2010 and ended in June 2016. All participants provided written informed consents.

Study design
Trained interviewers conducted face-to-face interviews at the hospital to collect data at baseline. Basic sociodemographic characteristics and some potential predictors of stroke recurrence were recoded using a standardised

and semistructured questionnaire and supplemented by medical records review. Follow-up questionnaires were completed via telephone interviews every 3 months after discharge. We administered the semistructured questionnaires by expert consultation based on the pilot study, and experts of Neurology have reviewed their availability. Previous studies have shown that both the Chinese version of the 3-level EuroQol five dimensions (EQ-5D-3L) and the 12-items Short Form Health Survey (SF-12) Questionnaires are valid measurements for assessing quality of life in Chinese population.[20–23] Although this study does not cover the content of quality of life, the reliability and validity of this part of the questionnaire can also reflect the availability of the overall questionnaire to a certain extent. The questionnaires collected information on death, self-dependency (Modified Rankin Scale (mRS) score) and stroke recurrence. For subjects who had cognitive or language impairment, proxies were interviewed. The start point of follow-up was the incident date of first-ever stroke, and the endpoint event was the first recurrence or die of recurrence after first-ever stroke. Patients who die of other causes or without stroke recurrent were censored at either the date of death or their last follow-up interview.

Variable definition
After the initial stroke, a subsequent claim with any type of ischaemic stroke diagnosis at readmission was identified as a recurrence. Time between the initial event and recurrent event was calculated in months. If a patient did not have any recurrent stroke within the 3-year study period, he or she was censored and 36 months was used as censored time. As potential predictors of stroke recurrence, the following variables were selected. Demographic factors included age (categorised as <55 years, 55–64 years, 65–74 years, ≥75 years), gender, marital status, degree of education, occupation and annual household income. We also documented family stroke history, the history of hypertension, diabetes mellitus, hyperlipidaemia, cardiac vascular disease (CVD) and peripheral vascular disease (PVD), drug adherence after ischaemic stroke, drinking status, smoking status and weekly exercise time before ischaemic stroke.

Poststroke functional status was assessed using the mRS, with a score >2 as meeting the criteria for disability.[24] The initial stroke preventive drug prescribed after stroke was considered the index drug. Drug adherence was estimated using the proportion of days covered (PDC), which was calculated by dividing the number of days of index drug supplied by the number of days of observation.[25] A PDC ≥80% was considered optimal.[26] We made notes of those who added another drug as doctor said and kept them in the adherence cohort. Switching to another drug or discontinued the drug without medical advice was classified as non-adherence. We estimated the drug adherence at their every follow-up interval, categorised it as always (optimal adherence at every interval), never (no optimal adherence happened) and sometimes over their entire

study period. The body mass index (BMI) at hospital admission was calculated as the ratio of body weight and squared height, given as kilogram per squared metre in all patients with available weight and height assessment.

Statistical analysis

Data were tested for normality using the Kolmogorov-Smirnov test and presented as mean (SD) or median (IQR) as appropriate. In non-normally distributed data, Mann-Whitney U tests were used. Unadjusted statistical analyses were performed using χ^2 analysis for dichotomous results. To identify predictors associated with recurrence time within 3-year follow-up, generalised linear regression analysis of RMST based on pseudo-observation was performed. All tests were two-tailed and statistical significance was determined at α level of 0.05. Analyses were performed using STATA 13 (Stata, College Station, Texas, USA).

The method is based on the pseudo-values from a jackknife statistics constructed from integrated Kaplan-Meier estimators for the probability in question.[27] These pseudo-values are used as outcome variables in a generalised estimating equation to obtain estimates of model parameters. And in cases where this estimator is adequate, regression analysis based on pseudo-observations turned out to work well.[28] We can interpret the RMST difference as the mean event-free survival time up to a prespecified, clinically important point[16 29] and robustness of the estimator to the PHs assumption.[17]

RESULTS

Out of 764 patients with ischaemic stroke who met the study inclusion criteria at baseline, 641 surviving patients were all followed up to 3 years.

Within 3 years after discharge, 115 recurrent strokes were documented including 16 patients died of stroke recurrence. Four hundred and ninety-one patients were not recurrent or dead within 3 years, of whom 278 patients completed the 3-year assessment, 110 patients did not complete it but we could acquire the recurrence information from later follow-up, and we did not obtain 103 patients any information at all, namely that they were lost to follow-up. Figure 1 shows how we obtained our cohort.

As summarised in table 1, the study population was primarily male (59.91%), Han (97.04%), married/cohabited (87.36%), retired (42.90%), BMI <25 (65.05%) and most commonly had hypertension (63.34%). The mean±SD age of the cohort was 61.8±12.6 years.

Recurrence rates of stroke

Within 3 years, 115 recurrent strokes after the first-ever ischaemic stroke were documented. The cumulative risk of stroke recurrence was 11.51% (9.20%–14.35%) at 1 year, 16.76% (13.96%–20.05%) at 2 years and 20.07% (17.00%–23.61%) at 3 years. The 3-year cumulative hazard for recurrence by different levels of three risk factors were evaluated by Kaplan-Meier analysis (figure 2A–C).
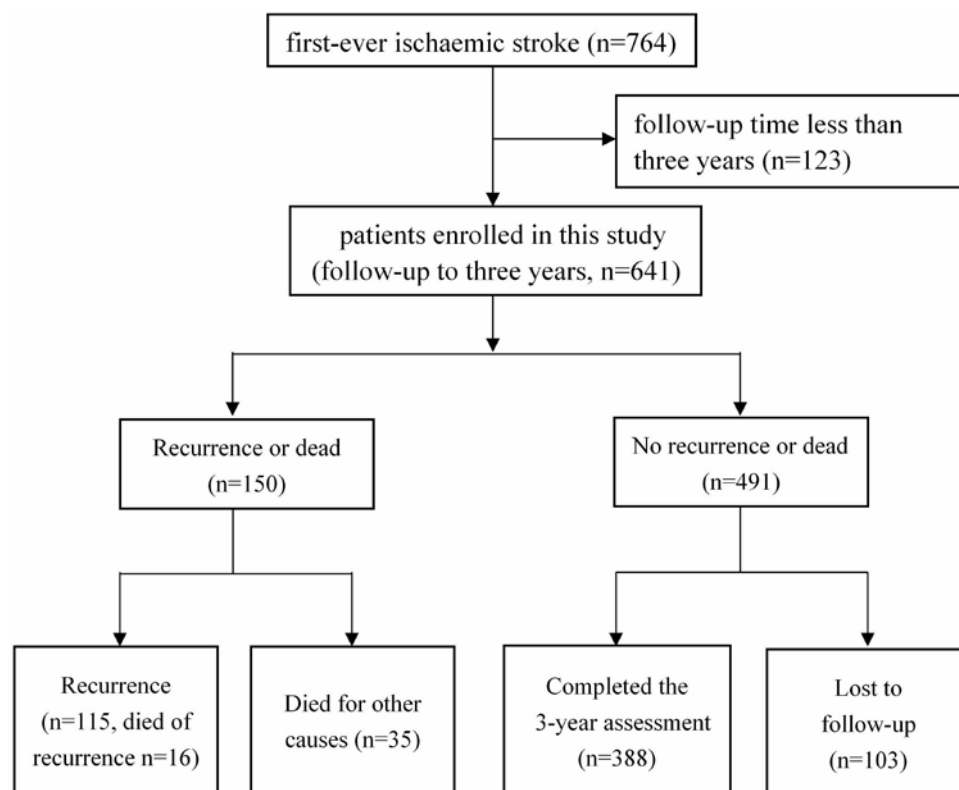

Figure 1 Flow chart of the recruitment.

Table 1 Baseline characteristics of patients with and without stroke recurrence

	Stroke recurrence (n=115)	No recurrence (n=526)	P value*
Demographics (%)			
Age, median (IQR), year	65 (57–75)	62 (52–71)	0.002
Age group			0.007
<55 years	20 (17.5)	146 (28.4)	
55–64 years	35 (30.7)	148 (28.7)	
65–74 years	29 (25.4)	146 (28.4)	
≥75 years	30 (26.3)	75 (14.6)	
Male	63 (54.8)	321 (61.0)	0.248
Han nationality	113 (98.3)	509 (96.8)	0.550
Married/cohabited	101 (87.8)	459 (87.3)	0.869
Occupation			0.068
Farmer	28 (24.4)	134 (25.5)	
No-farmer worker	19 (16.5)	143 (27.2)	
Unemployed	8 (7.0)	34 (6.5)	
Retired	60 (52.2)	215 (40.9)	
Education			0.393
Primary school and below	47 (40.9)	194 (37.2)	
Middle school	24 (20.9)	141 (27.0)	
High school and above	44 (38.3)	187 (35.8)	
Annual family income (RMB)			0.608
<20 000	46 (40.4)	187 (36.2)	
20000–40 000	40 (35.1)	181 (35.1)	
>40 000	28 (24.6)	148 (28.7)	
BMI, mean±SD	23.6±3.8	23.6±3.7	
BMI			0.965
<25	73 (66.4)	344 (66.7)	
25–30	31 (28.2)	147 (28.5)	
≥30	6 (5.4)	25 (4.8)	
Risk factors and medical history (%)			
Stroke family history	22 (19.1)	106 (20.2)	0.804
Hypertension	73 (63.5)	333 (63.3)	0.973
Diabetes mellitus	32 (27.8)	143 (27.2)	0.889
Hyperlipidaemia	42 (36.5)	199 (37.8)	0.770
CVD	36 (31.3)	120 (22.8)	0.055
PVD	3 (2.6)	14 (2.7)	0.974
mRS at 3 months			0.015
0–2	63 (54.8)	351 (66.7)	
3–5	52 (45.2)	175 (33.3)	
Drug adherence after stroke			<0.001
Always	36 (31.3)	301 (57.2)	
Never	21 (18.3)	59 (11.2)	
Sometimes	58 (50.4)	166 (31.6)	
Smoking status			0.086
Non-smoker	80 (69.6)	310 (58.9)	

Continued

Table 1 Continued

	Stroke recurrence (n=115)	No recurrence (n=526)	P value*
Current-smoker	23 (20.0)	155 (29.5)	
Ex-smoker	12 (10.4)	61 (11.6)	
Drink	32 (27.8)	190 (36.1)	0.090
Exercise	56 (48.7)	217 (41.3)	0.144

The total numbers of missing values by risk factors are the following: age 12, education 4, annual family income 11, BMI 15 and hyperlipidaemia 2.

*Comparison of proportions with versus without recurrence using χ^2 test.

BMI, body mass index; CVD, cardiac vascular disease; mRS, Modified Rankin Scale; PVD, peripheral vascular disease.

Recurrence predictors

mRS and drug adherence after stroke remained significantly associated with time of stroke recurrence in a regression analysis of RMST based on pseudo-observation. Table 2 shows the adjusted coefficient for relevant risk factors of stroke recurrence. RMST differences between different characteristics of patients with other risk factors in control can be interpreted as the number of months lost due to this characteristic. mRS ≥3 thus resulted in the stroke recurrence time loss, which was 0.22 months (p=0.008) at 6 months, 0.61 months (p=0.004) at 1 year, 1.49 months (p=0.007) at 2 years and 2.46 months (p=0.008) at 3 years. With the observation time increased, the RMST difference increased. Compared with the patients who always adhere to medication prescription, those never had RMST decline of 2.14 months and those sometimes had 1.73 months over the next 2 years. The never and sometimes adherence over the next 3 years pushes recurrence time point earlier to 4.21 months and 4.15 months relatively. The recurrence time of patients aged ≥75 years at 3 years was 2.02 months (p=0.220) less than that of those aged <55 years. With CVD, the recurrence time was 2.03 months less than those without, though even not reached a significant difference (p=0.070).

DISCUSSION

In this study, the RMST difference for stroke recurrence up to 3 years after initial ischaemic stroke was estimated. The results showed that in a 3-year follow-up period, 17.94% of the patients had suffered from an ischaemic stroke recurrence; moreover, 0.16% of patients died as a consequence of the recurrence. MRS and drug adherence after stroke were found to have significant roles in predicting stroke recurrence up to 3 years.

This study found that the cumulative risk of recurrence was 11.51% (9.20%–14.35%) at 1 year, 16.76% (13.96%–20.05%) at 2 years and 20.07% (17.00%–23.61%) at 3 years. At 1 year, the annual risk of stroke recurrence reported in many studies is widely ranging from 4% in Perth, Western Australia,[30] 8.0% in South Carolina,[31] to 17.7% in China.[32] Our result 11.51% is within the range described above. Studies differ in the study population.

Yilong Wang *et al* enrolled patients with consecutive stroke (≥18 years) in South Carolina within 14 days after stroke onset. In our study, we excluded patients with severe cognitive impairment at baseline, in which population the stroke recurrence rate was higher.[33] By 3 years, the risk of stroke recurrence reported in other studies lies between 14.1% in South London Stroke Register[34] and 20.80% in control community of Beijing, China,[35] close to 20.07% in this study. Whereas more than 90% of residents in the Beijing intervention communities were influenced by the health education and promotion implemented, thus leading to a reduction of stroke recurrence rate of nearly 12%.[35]

RMST is a useful measure, especially in the case that the PHs assumption is not met, but it is still rarely used in neurology. Comparison of covariates is more clearly interpreted as a quantity of months gained or lost with the RMST than as a survival probability or HR. Taking the RMST of the patients into account allows us to discuss various ways of presenting the results.

Omori *et al*[33] followed up to 1087 first-time ischaemic stroke survivors and found that the higher mRS score of discharge (the more severe the condition) patients had, the higher risk of recurrence patients would have. The data agreed and extended previous studies by reporting an inverse relation between mRS, recurrence rate and time difference at 6 months, 1 year, 2 years and 3 years. We have tried to evaluate patients' disability level in hospital, for the time span of evaluation is very large and mRS at the time of discharge correlated with the disability level after discharge,[33] so we just examined the effect of mRS at 3 months after discharge on stroke recurrence. A small difference in 3-month disability leads to important differences in long-term recurrence. Patients with ischaemic stroke with mRS at 3 months ≥3 may be told that their stroke recurrence time over the next 6 months will be shorten by 0.22 months, over the next 1 year shorten by 0.61 months, over the next 2 years shorten by 1.49 months, over the next 3 years shorten by 2.46 months, compared with those patients with mRS at 3 months <3. These results suggested that the impact of mRS may be more obvious over a longer period of time. Researches of Kawajiri *et al*[36–38] indicate that physical activity (PA) which
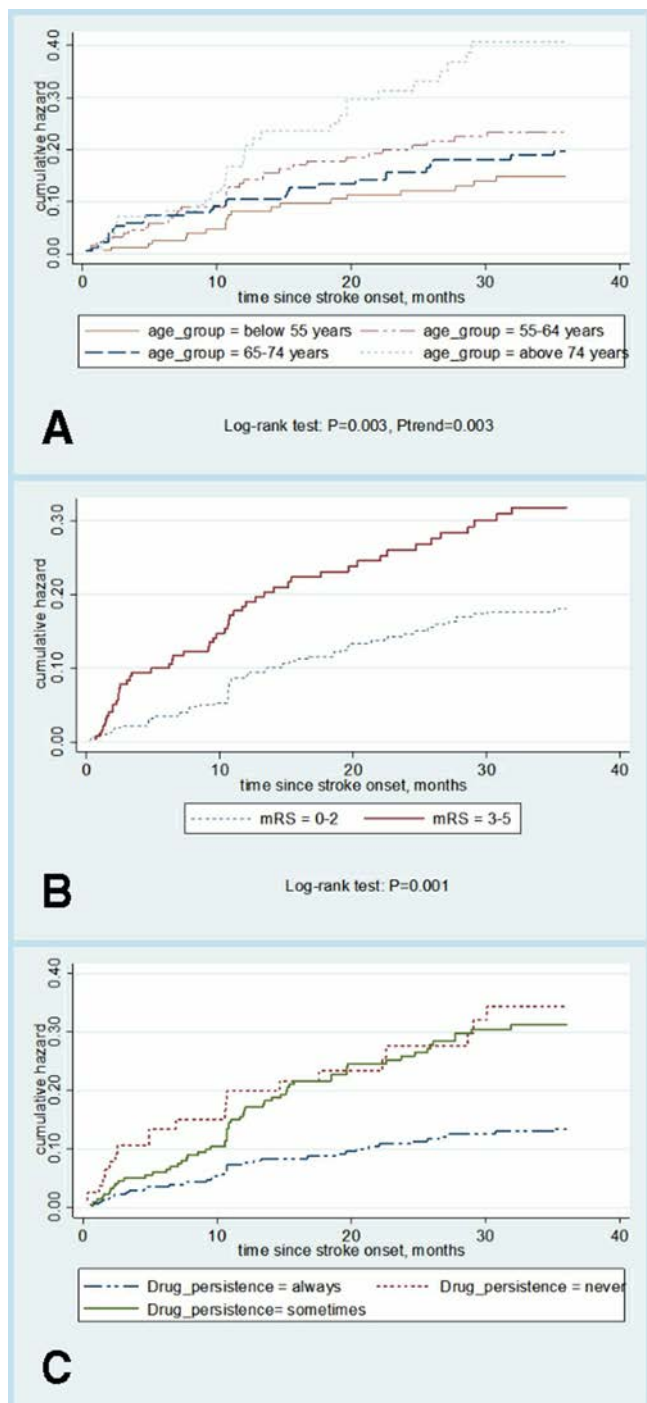
Figure 2 (A–C) Cumulative risk of stroke recurrence. mRS, Modified Rankin Scale.

is assessed by maximum walking speed at discharge may predict future vascular events in mild ischaemic stroke (MIS), and PA-related factors measured during hospitalisation are likely to predict stroke or cardiovascular events after MIS. Because of the disability, those patients with mRS at 3 months ≥3 may show longer time of lying in bed, sitting, lack of exercise, thus lead to lower PA. This may promote the occurrence of cardiovascular events after stroke. As mRS was a predictive indicator for stroke recurrence, persistent long-term care for patients poststroke,

especially for patients with low functional level or severe disability, comes to be more important.[33]

Low adherence to initial stroke preventive medication taken after the first-ever ischaemic stroke is a significant risk factor for recurrence time. When drug adherence was never or sometimes, the survival curve crossed and always adherence had the lowest recurrence rate. Also, for this reason, we choose the RMST difference to explore the related factors associated with time of stroke recurrence. This study measured adherence to specific pill prescription, including antiplatelet agents and anticoagulants. For the reason that the RMST difference could be proposed to explain the association between high adherence and lengthened recurrence time, we may consider great antithrombotic effects and also that patients with high adherence to antithrombotic therapy are more likely to adhere to other recommended treatments, such as antidiabetic agents. Unfortunately, we failed to adjust all those covariates because of lacking data, in the next future, we can analyse these medications' effect separately and mutually.

One of the strengths of this study was the introduction of RMST, which is comparable to PH in detecting differences between arms when hazards are proportional, but better when hazards are not proportional.[17] Based on pseudo-observations, taking the RMST difference into account allows us to discuss various ways of presenting the results and it is easy to interpret for clinicians. Nonetheless, the results of this study must be discussed while bearing in mind the following limitations. First, follow-up for outcome variables was performed by telephone interviews rather than by face-to-face contact. To minimise the impact of this factor on our results, the follow-up was managed centrally and performed by specially trained interviewers using a structured interview protocol. It has been demonstrated previously, thus the use of structured interviews can improve the validity of the results[39] and a centrally managed interviewing procedure may reduce bias and inter-rater variability.[40] Moreover, studies on the reliability of structured telephone interviews have confirmed a high agreement with face-to-face assessments.[41] Next, the possibility that the stroke recurrence information was biased could not be excluded. The recurrence of stroke was gathered from interviews with patients or their proxies, rather than from examinations and reviews of the medical records done by all of us. Patients who reported that they had a stroke recurrence usually went to the hospital for medical diagnosis after the onset of symptoms. Hence, this part of information is considered to be correct, to a certain extent, and it is still applicable.

After the first-ever stroke occurrence, the stroke recurrence rate is expected to rise with the proportion of elderly population increasing. Various factors were assumed to affect the recurrence of stroke, in which the disability level of patients discharged after 3 months evaluated by mRS and drug adherence throughout the course of treatment appear to be important predictors of recurrence. Providing estimates based on months gained or lost of expected RMST may improve the accuracy of the stroke recurrence estimates that influences clinical decisions and advice given

Table 2 Influence of various predictors on recurrence time of first-ever stroke

	6-month recurrence		1-year recurrence		2-year recurrence		3-year recurrence	
	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value
Age group								
<55 years	Ref.		Ref.		Ref.		Ref.	
55–64 years	−0.14 (−0.33 to 0.05)	0.146	−0.36 (−0.86 to 0.14)	0.155	−0.81 (−2.19 to 0.56)	0.247	−1.48 (−3.81 to 0.84)	0.212
65–74 years	−0.15 (−0.37 to 0.07)	0.193	−0.28 (−0.85 to 0.30)	0.346	0.01 (−1.53 to 1.54)	0.995	0.17 (−2.44 to 2.78)	0.899
≥75 years	−0.10 (−0.39 to 0.18)	0.475	−0.23 (−0.94 to 0.48)	0.519	−0.67 (−2.54 to 1.21)	0.484	−2.02 (−5.24 to 1.20)	0.220
CVD								
No	Ref.		Ref.		Ref.		Ref.	
Yes	−0.18 (−0.39 to 0.03)	0.083	−0.47 (−0.99 to 0.05)	0.075	−1.29 (−2.58 to 0.01)	0.052	−2.03 (−4.23 to 0.17)	0.070
mRS at 3 months								
0–2	Ref.		Ref.		Ref.		Ref.	
≥3	**−0.22 (−0.38 to 0.06)**	**0.008***	**−0.61 (−1.03 to −0.19)**	**0.004***	**−1.49 (−2.57 to 0.41)**	**0.007***	**−2.46 (−4.28 to 0.65)**	**0.008***
Drug adherence after stroke								
Always	Ref.		Ref.		Ref.		Ref.	
Never	−0.17 (−0.38 to 0.04)	0.119	−0.55 (−1.18 to 0.07)	0.083	**−2.14 (−3.93 to 0.36)**	**0.019***	**−4.21 (−7.18 to 1.26)**	**0.005***
Sometimes	−0.13 (−0.36 to 0.09)	0.245	−0.20 (−0.60 to 0.20)	0.337	**−1.73 (−2.84 to 0.62)**	**0.002***	**−4.15 (−6.07 to 2.23)**	**<0.001***

Adjusted for sex, BMI, occupation, annual family income, smoking status, drinking, exercise, PVD.

Bold values with "" indicate the significant risk factors.

Bold values with "" indicate the significant risk factors.

BMI, body mass index; CVD, cardiac vascular disease; mRS, Modified Rankin Scale; PVD, peripheral vascular disease.

to patients. Therefore, adequate disease control and risk factor management from early stroke onset are required to prevent the recurrence of stroke. Further research is needed to evaluate whether RMST improves patients' understanding and influences treatment decision.[42]

CONCLUSIONS

Though difficult to predict with absolute certainty when stroke will recur, estimating based on months gained or lost of RMST may improve the understanding of the prognostic estimates which may influence clinical decisions and advice given to patients. In China, the time of first recurrence varies among different patients with ischaemic stroke. The mRS and the level of drug adherence after stroke are important risk factors of stroke recurrence.

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