Predictor Naïve Temporal Baseline Hazard of Recurrent Ischemic Stroke

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Abstract

There are established correlation between risk factors and the recurrence of ischemic stroke (IS), however does the hazard of recurrent IS change although without the influence of established risk factors? This study aimed to quantify the hazard of recurrent IS at different time points after the index IS. This was a population cohort study extracted data of 7697 patients with a history of first IS attack registered with National Neurology Registry of Malaysia. A repeated time to recurrent IS model was developed using NONMEM version 7.5. Three baseline hazard models were fitted into the data. The best model was selected using maximum likelihood estimation, clinical plausibility and visual predictive checks. Three hundred and thirty-three (4.32%) patients developed at least one recurrent IS within the maximum 7.37 years follow-up. In the absence of significant risk factors, the hazard of recurrent IS was predicted to be 0.71 within the first month after the index IS and reduced to 0.022 between the first to third months after the index attack. The hazard of IS recurrence accelerated with the presence of typical risk factors such as hyperlipidaemia (HR, 2.64 [2.10-3.33]), hypertension (HR, 1.97 [1.43-2.72], and ischemic heart disease (HR, 2.21 [1.69-2.87]). In conclusion, the absence of significant risk factors, predicted hazard of recurrent IS was prominent in the first month after the index IS and was non-zero even three months after the index IS or later. Optimal secondary preventive treatment should incorporate the 'nature risk' IS recurrence.

Introduction

Stroke is the world's second leading cause of death and mortality (1–4). The risk of recurring strokes is much greater for survivors of acute ischemic stroke (IS). For survivors of acute ischemic stroke (IS), the risk of repeated strokes is significantly larger (5–7). Nearly 33% of the IS population experienced a recurring stroke in Malaysia (8). Recurrence neurological damage is usually severe, harder to deal with and higher mortality compared with the first stroke (9). Therefore, secondary prevention is crucial to reduce IS recurrence events (9).

The prognosis of recurrent IS has been widely studied. The probability of recurrent IS after the index attack was predicted to varies over time which was predicted to occur by 11.2–30% within the first 24 months(10, 11) and 9.5% within 5 years after the IS attack (12). While the most recent study reported IS recurrence rate was 1.2% in the first 30 days, 3.4% within 90 days, 7.4% within one year, and 19.4% within 5 years (13). Moreover, the reported risk factors of recurrent stroke vary (14–16) in which hypertension (HTN), atrial fibrillation (AF), diabetes mellitus (DM), hyperlipidaemia (HPLD), ischemic heart diseases (IHD), and smoking were the most common reported predictors of recurrent stroke (17, 18). Despite improvement in recurrent IS risk classification and prevention measures of recurrent IS over the last decades, IS remains a devastating disease. Currently, most of the secondary prevention of IS are focusing on reducing and controlling the risk factors lead to recurrent IS. Nevertheless, does the probability of recurrent IS different in the absence of these risk factors influence?

The majority of the previous prognosis studies of recurrent stroke involved the use of the most common semi-parametric survival analysis method; Cox-regression analysis. The Cox model incorporates the

effect of covariates on the hazard without quantifying the form of recurrent stroke hazard at baseline and distribution of hazard function. The hazard of event at baseline is defined as the hazard of having the interest event when all the risk factors or covariates are set to zero. Thus, in the case of recurrent IS, the baseline hazard should be defined as the hazard of having recurrent IS after the index event in the absence of risk factors. While distribution hazard function quantifies the probability of IS recurrence during a very small-time interval, assuming that the individual has survived to the beginning of the interval. Nevertheless, unlike cox regression, the parametric approach of survival analysis quantifies the baseline hazard and distribution hazard function of the event. This permits more time-dependent prognostic information that better reflects the expected 'natural history' of the disease. Moreover, information on the recurrent IS distribution after the index IS is limited and the studies using the parametric approach on this topic are still lacking (19, 20). Moreover, validated prognostic model of recurrent IS is limited. Thus, this study aimed to quantify the hazard of recurrent IS at different time points after the index IS when the influence of significant risk factors was absent and to develop a validated parametric prognostic model of recurrent IS.

Method

Patients and data acquisition

This was a population cohort study involves a secondary analysis of data from the National Neurology Registry (NNEUR) of Malaysia. Data of all Malaysian patients with a history of index IS from August 2009 to December 2016 were extracted from the NNEUR of Malaysia. The details on the National Stroke Registry of Malaysia were published previously (21-23). The stroke was diagnosed according to the World Health Organization's criteria (24). All diagnoses were confirmed using brain computed tomography or magnetic resonance imaging. Index IS was defined as the first stroke registered into the NNEUR for the patients from 2009 to 2016. Recurrent IS was defined as any IS event recorded by involving hospitals after the index IS for a specific patient in the NNEUR database. Malaysian adults aged above 18 years with the history of IS and registered with NNEUR was included. Non-Malaysian citizen and diagnosis other than IS was excluded from the study. Minimum events needed to develop this prognostic model was calculated as 228. [Sample size – Survival analysis | Sample Size Calculators \(sample-size.net\)](#)

Stroke Registry in Malaysia

The NNEUR in Malaysia was established in 2009. The NNEUR has recorded data from multi-ethnic involving stroke cases from 13 states in the country. The NNEUR aims to provide comprehensive epidemiological data on the country's stroke statistics, trends, and management, representing a multicentre, hospital-based registry. The registry development is funded by the Ministry of Health, Malaysia (MOH). A comprehensive explanation of the NNEUR has been previously published(25).

Ethics Approval

Ethical approval for this study was obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health, Malaysia (Research ID: NMRR-08-1631-3189). All methods were performed according to the guidelines of the Declarations of Helsinki. Informed consent was obtained from all subjects that included into this study.

Collected variables

Demographic data and concomitant diseases including DM, HTN, HPLD, IHD, and hyperuricemia were tested. They were defined either by physician diagnosis, patients' electronic records, or deduced from the medication history, and the medications prescribed during discharge.

Data for external validation

Data on demographic and significant covariates identified in the final model of all Malaysian patients with a history of index IS registered in NNEUR from January 2017 until December 2020, were extracted to perform external validation of the developed model.

Analysis

Repeated time to the recurrent events of IS and factors predicting the recurrent IS were quantified and determined using NONMEM version 7.5 software and Perl speaks NONMEM (PsN) version 4.1.0. The event was described as having recurrent IS events after the index IS. All event times were treated as exact time models, in which the event assumed to occur at the time of observation time. Three models, which were exponential, Gompertz, and Weibull investigated for the baseline hazard model.

Model development

The model was developed in the following two steps: (i) a base model without any explanatory factors and (ii) exploration of covariates.

Development of the base model

A parametric survival function according to Equation 1 was used to describe the repeated time to the recurrent IS.

$$S(t) = e^{-\int_0^t h(t) dt} \quad (1)$$

where $S(t)$ is the time course of the probability of survival, or the survivor function calculated from the time-varying hazard $h(t)$. The hazard is $h(t)$, and the survival $S(t)$ is a function of the cumulative hazard within the time interval between the time zero and the time t describing the probability of not experiencing any recurrent IS within this interval.

The base model was developed by exploring different functions for the hazard $h(t)$, starting from a simple time-independent constant hazard and then gradually progressing to more complex functions, including Gompertz and Weibull according to Equations (2), (3), and (4) respectively (26).

$$h = \lambda_0 \times e^0 \quad (2)$$

$$h(t) = \lambda_0 \times e^{\beta t} \quad (3)$$

$$h(t) = \lambda_0 \times e^{\beta \ln(t)} \quad (4)$$

Hazard of recurrent IS at baseline or baseline hazard function at different time point after the index was quantified based on Equation 5. Equation 5 gives an example of the baseline hazard $h_0(t)$ changes depending during different time t intervals.

$$h_0(t) = \begin{cases} \theta_1, & \text{if } 0 < t < t_1 \\ \theta_2, & \text{if } t_1 < t \leq t_2 \\ \dots & \dots \dots \dots \\ \theta_{nt}, & \text{if } t(n-1) < t \leq tn \end{cases} \quad (5)$$

Between-subject variability around the hazard was estimated, assuming an exponential distribution for the random effect.

Development of the covariate model

Possible explanatory variables that may influence or predict the changes in hazard were explored by including each explanatory variable in the hazard function. A parameter, β_n , for each of the n explanatory variables, X_n , was estimated using the following equation.

$$h(t) = h_0(t) * \exp^{\beta_1 X_1 + \beta_2 X_2 + \dots + \beta_n X_n}$$

Where h_0 is the baseline hazard, β_n is the coefficient for the explanatory variable, X_n , describing how the hazard varies with the explanatory variable. Exponentiation of the explanatory variable coefficient

provides the hazard ratio (HR), which reflects the influence of the explanatory variables relative to the hazard when the explanatory variable is not present.

Initially, the covariates were tested in a univariate manner, i.e. each covariate relationship was evaluated on the base hazard individually. Then, based on the results, covariate relationships were identified for a systematic covariate search by applying stepwise analysis approach, i.e. with stepwise forward inclusion followed by backward elimination (27).

In the forward inclusion, the statistical significance level was set to $P < 0.05$, which corresponds to a reduction of the OFV of at least 3.84, for one degree of freedom (addition of one covariate parameter). While in the backward deletion, the significant value was set to $P < 0.01$, corresponding to an increase of the OFV of at least 6.64 to be kept in the model for one degree of freedom.

Model evaluation

Parameters were estimated using the LAPLACE method (ADVAN=6 TOL=9 NSIG=3) in NONMEM to obtain maximum likelihood estimates of time-to-event parameters. The parametric repeated time-to-event (RTTE) analysis was performed using NONMEM v7.5, and Perl speaks NONMEM (PsN) version 4.1.0.7. Model selection was based on comparing the OFV between models, bootstrap confidence intervals for parameter estimates, and biological plausibility. The improvement in the fit was measured by a decrease (28) in the OFV generated by NONMEM. The difference in OFV between two hierarchical models is approximately χ^2 distributed and can be tested for significance with $\chi^2_{1,0.052}=3.84$

To evaluate the predictive performance of the model throughout model building, Kaplan-Meier visual predictive checks (VPCs) for internal and external validation, Xpose4 (version 4.7.1) function (29, 30) in RStudio software (version 1.1.456, RStudio, Inc., Boston, MA, <http://www.rstudio.com/>) was utilized. The plots were based on simulations of 1000 simulated dataset. To enable simulations for time points where no clinical observations had been made, extra dummy time points were added to the dataset until 7.37 years in all individuals for the to allow for VPC simulation. The parameter certainty was evaluated through relative standard error (RSE) produced from the sampling importance resampling (SIR) method (31).

External validation

Data from 2692 patients with and without recurrent IS were used to validate the developed final model externally. The parameters estimate obtained from the final model were used to simulate 1000 replicates of the dataset and to plot the VPC. The predictive performance of the final developed model was then evaluated on the ability of the model to predict the probability of not having recurrent IS from the validation data by overlaying the VPC plot on the Kaplan-Meier curve of the validation data.

Clinical application of the developed model

An online prognosis IS recurrent risk calculator was developed based on the developed final model. The probability of early (within a year) and late (2-year, and after 4-years after the index IS) IS recurrent for two clinical scenarios were predicted using the calculator. The scenarios were as the following:

Scenario 1: A patient with a history of IHD, HTN and HPLD had the first IS attack. The probability of recurrent IS was calculated.

Scenario 2: A patient with no concomitant diseases had the first IS attack. The probability of recurrent IS was calculated.

Results

Out of 7697 subjects, 333 patients (4.32%) developed a recurrent IS within the maximum 7.37 years follow-up. The median time to the first recurrent IS was 1.2 years, while the time to the 2nd recurrent IS was 2.2 years. The study population included all age groups from young to elderly, with a median age of 63.47 years at the time of index IS. As shown in Table 1, most of the patients were females (4289, 55.72%). The percentage of smokers in this study population was 48%. Of 7697 subjects, 3493 (45.38%) were diabetics before index IS, while patients with HTN before index IS were 5506 (71.5%). The number of subjects with HPLD before index IS was 2028 (26.34%), patients who had IHD before index IS was (879, 11.4%), and patients who had AF before index IS was 3.4%.

Baseline hazard model

The hazard function that gave the best result with regard to OFV, clinical plausibility, and Kaplan–Meier plots was a Gompertz model, defining the hazard for four-time intervals (Table 2). Without the influence of any significant predictors, the risk of having recurrent IS within a month, between 1-3 months after the index were IS 0.71, 0.0224 respectively, while the risk of having a recurrent IS after 3 months of index IS was small but non-zero (0.0002) (Figure 1).

Table 3 represented the required half-life for developing recurrent IS after the index IS during different time intervals. The risk of IS recurrence increased 2-folds at 0.4 month after the index IS. This risk further increased steadily by 2-folds at 7-month, 1.2-year, 2.4-year, and 4-year time-points, after the index IS.

Concurrent diseases influencing the risk of having recurrent IS after index IS.

Table 4 showed the final covariates retained in the final model. These results reported that the recurrent IS rate in those with HPLD before index IS was 2.65 times higher than that in those without HPLD prior to index IS (HR, 2.64; 95% CI [2.10-3.33]). While having HTN prior to index IS increased the rate of recurrent IS by 97.9% compared to the patients without HTN prior index IS (HR, 1.97; 95% CI [1.43-2.72]). The recurrent IS rate in those with IHD before index IS was 121% of that in those without HTN prior to index IS (HR, 2.21; 95%CI [1.69-2.87]) (Figure 2). Kaplan-Meier VPCs for recurrent IS after index IS showed good predictions (Figure 3). Recurrent IS events shown in Figure 3 indicated that the final model described the observed data adequately for the internal (a) and external (b) validation. While (c), (d), and (e) compared the VPCs between IS patients who had HPLD, IHD, HTN respectively, versus those who did not have these concurrent diseases.

Clinical application of the developed model

A calculator tool (MyReCuRIS) has been developed for this model and can be accessed via this link <https://www.calconic.com/calculator-widgets/recurrent-stroke-cal/60e3a89aa17c7c002c61f655?layouts=true>. The probability of IS recurrent after a certain period was estimated using the calculator based on the two clinical scenarios.

Scenario 1: A patient with a history of IHD, HTN and HPLD had the first IS attack. The probability of IS recurrence was calculated as 2.48%, 6.32%, and 3.23% after 1, 2 and 4 years of first IS, respectively.

Scenario 2: A patient with no concomitant diseases had the first IS attack. The probability of IS recurrence was calculated as 0.2%, 0.5%, and 0.28% after 1, 2 and 4 years of first IS, respectively.

Discussion

To our knowledge, this is the first study incorporating the predicted hazard of recurrent IS in the absence of risk factor at different time points after the first IS as one of component of recurrent IS prognostic model. Previous study (32) reported a constant baseline hazard of recurrent IS over time which assuming the hazard of recurrent IS in the absence of risk factors constant throughout the study period. In our population, after the first IS attack, the baseline hazard of recurrent IS was predicted as non-zero even three months after the first IS attack. This indicates that, in the absence of any risk factors, the hazard of recurrent IS present and change at different time-points after the first attack. The 'natural history' of the stroke is postulated to play a role in the recurrent IS. In addition to reducing the risk factor of recurrent IS, the factor of this 'natural history' of IS should be taken into consideration when identifying an optimal secondary preventive treatment.

In addition to baseline hazard of recurrent IS, influence of time was incorporated to predict the recurrent IS. The hazard of having recurrent IS during the first 30 days after index IS was nearly twice the subsequent intervals. These results are consistent with previous findings reported that the maximum incidence of recurrent stroke occurred in the first 30 days after the initial stroke (33, 34).

Recurrent stroke is associated with increased disability and mortality compared to the index stroke(35). Even with appropriate secondary prevention, the risk of recurrence after IS is high, especially in the early phase after stroke (36). It has been reported that within the first year after the initial stroke, the risk of stroke recurrence is higher (between 6-14%) as opposed to risk in subsequent years (4% annually) (37-39). A more recent study showed that the incidence of stroke recurrence was the highest during the first year after index stroke, 12.8% with a declining annual rate, 6.3% during the second year and 5.1% (95% CI, 4.0-6.5) during the third year after the index stroke (15). In the current model, the hazard of recurrent IS was estimated as increasing exponentially with time, which is in concordance with previous reports (13). This may suggest the disease progression over time may influence the prognosis and other risk factors, which require further studies to investigate any preventive measures to alter the progression over time and minimise the hazard of recurrent IS.

Moreover, this study reported also that the recurrent hazard increased by half in the first 6 months after index IS. These findings may guide the clinicians to keep close monitoring and intervention, especially for the first month, and suggest a need for more intensive patients follow up to ensure adherence and efficacy of secondary preventive drugs given for IS patients during the first 6 months after index IS.

In this study, IHD, HPLD, and HTN were identified as independent predictors for recurrent IS. These findings are consistent with data reported previously (20-23). Additionally, this model quantified the hazard of having recurrent IS between the patients who have a history of HPLD, IHD, and HTN.

Having HPLD, IHD or HTN were found to increase the hazard of developing recurrent IS by 2.64, 2.21, 1.97, respectively. Effective management of these co-morbidities is necessary to reduce the risk of recurrent IS.

The developed TTE model for the hazard of having recurrent IS during different time intervals after index IS may allow comprising a description of hazard during different time intervals and with the presence of concurrent diseases, as well as the simulation of RTTE data based on the final model. The developed tool may aid physician to stratify patients at high risk of recurrent stroke through the estimated risk, which may help in planning a personalised care post index IS to prevent recurrence.

Limitations

This study was a retrospective study based on the available data from the National Stroke Registry of Malaysia. Therefore, the first stroke captured from the NNEUR from 2009 to 2016 was assumed to be the first-ever stroke experienced by the patient. Any data on the prior TIA or stroke before the NNEUR establishment was not available and not considered in the current study. Due to the nature of the data captured from registry database, the comorbidities were analysed independently. Nevertheless, this study was a population-based study and large samples representing various ethnic groups across the country. This model may provide and insight on the importance of frequent follow up especially in the early days (examples within the first 6 months to one year), thus perhaps may made a positive shift in Malaysian population follow up schedules during the management to prevent recurrent IS.

Conclusion

Incorporating time in predicting the risk of recurrent IS may attribute positively in predicting the prognosis of recurrent IS. In the absence of significant risk factors, predicted hazard of recurrent IS was prominent in the first month after the index IS and was non-zero even three months after the index IS or later. Optimal secondary preventive treatment should not be only focusing on reducing the common established risk factors yet should incorporate the 'nature risk' IS recurrence. Future study determines which secondary prevention alter the baseline hazard of IS recurrence is vital. In addition to concomitant diseases, time also plays a vital predictor of the risk of recurrent IS population. Future studies are required to determine drugs that could alter the changes in hazard of recurrent IS over time. These results may add to the knowledge related to patient follow up schedules during the management to prevent recurrent IS.

Declarations

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Disclosure

The authors report no conflicts of interest in this work.

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Tables

Table 1. Characteristic of patients with recurrent IS during different time intervals that included into the study (*N* = 333)

Variable	Patients with recurrent IS within 1 st month after index IS N=19(%)	Patients with recurrent IS within the 1 st to 3 rd month after index IS N=37(%)	Patients with recurrent IS within the 3 rd months to 3 years after index IS N=215(%)	Patients with recurrent IS 3years after the index IS N=62(%)
Age group				
<60	7(36.84)	17(45.94)	99(46.04)	27(43.54)
≥60	12(63.15)	20(54.05)	116(53.95)	35(56.45)
Female	7(36.84)	21(60)	121(56.27)	37(59.67)
2nd Recurrent stroke	-	-	24(11.16)	12(19.35)
Ethnicity				
Malay	9(52.94)	12(32.43)	86(40)	48(77.41)
Chinese	-	1(2.70)	5(2.32)	2(3.22)
Indian	-	-	2(0.93)	1(1.61)
Others	10(58.8)	24(64.86)	122(56.74)	11(17.74)
Smoker	11(64.7)	22(59.45)	127(59.06)	42(67.74)
DM	11(64.7)	21(56.75)	124(57.67)	39(62.90)
Duration of diabetes (years)				
<1	1(5.88)	-	9(4.18)	2(3.22)
1-5	2(11.76)	11(29.72)	69(32.09)	19(30.64)
6-10	5(29.41)	4(10.81)	27(12.55)	7(26.92)
>10	4(23.52)	6(16.21)	21(9.76)	13(20.96)
Unknown	7(36.84)	16(43.24)	89(41.39)	21(33.87)
Family history of stroke	-	1(2.70)	22(10.23)	4(6.45)
HTN	17(100)	29(78.37)	184(85.58)	58(93.54)
HTN Duration (years)	6(35.29)	20(54.05)	107(49.76)	30(48.38)
≤5	11(64.7)	9(24.32)	77(35.81)	28(45.16)

>5	2(11.76)	8(21.62)	31(14.41)	4(6.45)
IHD	2(11.76)	9(24.32)	45(20.93)	21(33.87)
HPLD	8(47.05)	17(45.94)	106(49.30)	28(45.16)
Atrial fibrillation	1(5.88)	1(2.70)	1(0.46)	1(1.61)
Hyperuricemia	-	3(8.10)	9(4.18)	4(6.45)

Abbreviations; DM: Diabetes mellitus; IHD: Ischemic heart disease; HTN: Hypertension; HPLD: Hyperlipidemia N: Number of patients.

Table 2. Baseline hazard during different time intervals after index IS.

Parameter (Years)	Description	Typical value	RSE%
λ (<0.08)	Baseline hazard during first month	0.71	27.77
λ (≥ 0.08 -<0.25)	Baseline hazard after first month until 3months	0.0224	24.14
λ (≥ 0.25 -<3)	Baseline hazard after 3months until 3years	0.0002	27.43
λ (≥ 3)	Baseline hazard after 3yrs	0.0001	27.05

Abbreviations: λ , baseline hazard; Δ OFV, change in objective function value; RSE, relative standard error; 95% CI, 95% confidence intervals.

Table 3. Time for developing recurrent IS after index IS during different time intervals.

Parameter	Description	Typical value	Half-life ($\ln 2/\lambda$)	RSE%
λ (<0.5)	Shape parameter (<0.5 year)	19.7	0.035	3.31
λ (≥ 0.5 -<1)	Shape parameter (0.5-1 year)	8.27	0.083	4.34
λ (≥ 1 -<2)	Shape parameter (1-2 year)	3.55	0.195	4.76
λ (≥ 2 -<3)	Shape parameter (2-3 year)	1.97	0.351	6.36
λ (≥ 3)	Shape parameter (≥ 3 year)	0.681	1.017	7.93

Abbreviations: λ , shape parameter; RSE, relative standard error.

Table 4. Significant covariates after backward elimination.

Parameter	Description	Δ OFV	Typical value	aHR 95%CI	RSE%
Θ HPLD	Effect of baseline HPLD on hazard	47.418	0.974	2.648 (2.1-3.33)	10.94
Θ HTN	Effect of baseline HTN on hazard	27.145	0.683	1.979 (1.43-2.72)	22.25
Θ IHD	Effect of baseline IHD on hazard	26.846	0.793	2.21 (1.69-2.87)	15.25

Abbreviations: Δ OFV, change in objective function value; aHR, adjusted hazard ration; HPLD, hyperlipidemia; HTN, hypertension; IHD, ischemic heart disease; RSE, relative standard error; 95% CI, 95% confidence intervals.

Figures

Figure 1

Baseline hazard during different time intervals after index IS; First month, after first month until 3 months, after 3months until 3 years, after 3 years.

Figure 2
Effect of concurrent diseases on hazard of having recurrent IS after index IS.

Figure 3

Kaplan-Meier plots showing the IS survivor function (probability of not having recurrent ischemic stroke) throughout different time intervals. **(a)** the final time-to-event model of the internal data, **(b)** external validation of the final time-to-event model. The final time-to-event for patients **(c)** with hyperlipidaemia (HPLD) versus non HPLD, **(d)** with ischemic heart disease (IHD) versus non IHD, and **(e)** with hypertension (HTN) versus non HTN. The observed data survivor function is described by a solid blue line with 95%

confidence interval (CIs). Shaded areas represent the 95% prediction interval from 1000 simulated datasets.

Supplementary Files

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- [supplementary2.docx](#)