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ASSOCIATED FACTORS OF MORTALITY IN FIRST-EVER STROKE PATIENTS

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ABSTRACT

The aim of this study was to determine the associated factors of mortality in first-ever stroke patients receiving care in a suburban hospital setting in Malaysia. A retrospective record review study was conducted among 432 first-ever stroke patients in Hospital Universiti Sains Malaysia, Kelantan, Malaysia. Information on demographic characteristics, past medical history, clinical characteristics, medications prior to stroke and symptoms and signs of first-ever stroke patients were retrieved from medical records. Multiple logistic regression was used for data analysis. At the study endpoint, 101 (23.4%) death was identified and 331 patients (76.6%) were still alive till data collection was completed. The significant prognostic factors included male, patients with seizure/ fit, marital status, Glasgow coma scale score, fasting blood sugar, smoking status, patients with rheumatic heart disease, level of urea and patients with subarachnoid haemorrhage. The findings of this study highlighted the key clinical parameters of associated factors of mortality in first-ever stroke patients in a predominantly suburban setting in Malaysia.

Keywords: Multiple logistic regression, mortality, first-ever stroke

INTRODUCTION

Cerebrovascular disease is a disease of the blood vessels supplying the brain including stroke. According to WHO criteria, stroke is defined as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin". This definition includes stroke due to both ischaemic stroke and haemorrhagic stroke (intracerebral or subarachnoid) [1].

Stroke events can be divided into four types; first-ever, recurrent, non-fatal and fatal. First-ever stroke is referred to people who never experienced a stroke before as clinically defined. On the other hand, recurrent stroke is referred to a person who had a history of a previous stroke event in the past. Non-fatal event is defined when a person had a stroke and survived at least 28 days after the onset of the symptoms and vice versa for the fatal event [2].

In Malaysia, diseases of the circulatory system which include stroke ranked first in the list of principal causes of mortality [3]. This imposes a significant burden on total health expenditure. Kelantan is one of the states in Malaysia located in Northeast Malaysia. Although population and housing census in Malaysia in 2010 grouped Kelantan among the states with lower urbanization level (42.4%) [4], hospital bed utilization in Kelantan appears to be the second highest bed occupancy rate for public hospitals with 70.6% [5].

No contemporary data on associated factors towards mortality of first-ever stroke patients in Kelantan exists despite high occupancy of hospital beds. Therefore this study was aimed to determine the associated factors of mortality in first-ever stroke patients.

MATERIALS AND METHODS

This study was a retrospective record review which was conducted in Hospital Universiti Sains Malaysia (HUSM), Kelantan, Malaysia among 432 first-ever stroke patients. Data from medical records from 1st January 2005 until 31st December 2011 were reviewed and related information was extracted. The inclusion criteria of the participants were those who were clinically diagnosed as first-ever stroke aged more than 18 years old as confirmed by computed tomography (CT) scan or magnetic resonance imaging (MRI) and neurological examination during admission. Participants with recurrent stroke or having any neurological deficits secondary to an infection, epilepsy, tumour or traumatic causes were excluded from the study. Stroke patients whose records had variables with more than 30% of missing value were excluded from the final analysis. From the list of stroke patients for the period of 84 months, systematic random sampling was applied. The study received approval from the Human Ethics Committee of Universiti Sains Malaysia (USMKK/PPP/JEPeM [256.4(2.9)].

A standardized data collection sheet was designed and verified by another researcher to record all the related

information from patients' medical records. Information on demographic characteristics, past medical history, clinical characteristics, medications prior to stroke and symptoms and signs of first-ever stroke patients were retrieved by a single researcher. The dependent variable was dichotomous which were alive and dead.

The variables included in the demographic characteristics were age in years, age at the time of diagnosis in years, gender, race, religion, citizenship, marital status, employment status, smoking status, alcohol status, weight, height and body mass index. For past medical history, the variables included were family history of stroke, high blood pressure, diabetes mellitus, hyperlipidaemia, hyperhomocycteinemia, ischaemic heart disease, atrial fibrillation, rheumatic heart disease, anaemia, history of clinical depression, history of migraine, tuberculosis, transient ischaemic attack and amaurosis fugax (retina ischemia).

The variables included in clinical characteristics were types of stroke, Glasgow Coma Scale (GCS) during admission, NIH stroke scale, Barthel index score, modified Rankin Scale (mRS), fasting blood sugar, low-density lipoprotein, high-density lipoprotein, triglycerides, total cholesterol, haemoglobin, white blood count, platelet count, sodium, potassium, urea, systolic blood pressure and diastolic blood pressure. The medications prior to stroke included aspirin, clopidogrel, dypridamole, warfarin, statin, ACE inhibitor, angiotensin II receptor antagonists, beta blocker, calcium channel blocker, diuretic, oral hypoglycaemic drug and insulin.

The variables included in symptoms and signs were headache at admission, vertigo, gait disturbance, seizure or fit, speech deficit, hemianopia, diplopia, difficulty in swallowing, bladder dysfunction, bowel dysfunction, confusion, memory impairment, paresis, sensory deficit, vomiting and giddiness.

Statistical analysis

The data were entered and analysed by using Stata/SE 11 [6]. The potential associated factors of mortality among first-ever stroke patients were analysed by using multiple logistic regression. After univariable analysis, the variables were chosen for the multivariable analysis based on pre-determined criteria. The preliminary main effect model was obtained upon completion of the variables selection. This was followed by checking linearity of continuous variables, then followed by two-way interaction and multicollinearity in order to obtain the preliminary final model. The preliminary final model was then checked for its specification error.

The next step was checking overall fit of the model using four methods namely Hosmer-Lemeshow test, Pearson chi-square test, classification table and area under the ROC curve. Then regression diagnostic was performed. Plot of leverage versus the estimated logistic probability was performed to detect the outlier covariate patterns. While for influential cases, the plots consisted of ΔX^2, ΔD and $\Delta\beta$ versus the estimated logistic probability. The covariate patterns identified as influential were then further assessed for its percent changes in the regression coefficient. The percent changes equal and more than 20.0% indicated that the covariate pattern was influential to the model.

The model was refitted after removing the influential covariate pattern and was compared to the full model without removing the influential covariate pattern. The new refitted model was then checked for the overall fit of the model. The decision to select which model depend on which model gave lower values of Akaike information criteria (AIC) and Bayesian information criteria (BIC) and the better statistical model. The final model was expressed based on determined variables, adjusted regression coefficient (b), adjusted odds ratio (OR) with 95% confidence interval (CI), Wald statistic and its corresponding *P*-values. The level of significance was set at 0.05. From this study, two influential covariate patterns were detected and were removed from the final model.

RESULTS

At the study endpoint, 101 (23.4%) death was identified and 331 patients (76.6%) were still alive till data collection was completed. The mean age at the time of diagnosis of overall patient was 59.16 years old with standard deviation of 13.47. More than half of the patients were male (n=233, 53.9%) and Malays (n=391, 90.5%). Most patients reported not smoking (n=245, 56.7%) followed by current smoker (n=121, 28.0%) and ever-smoker (n=66, 15.3%). The overall mean of GCS was 11.91 (SD=3.44).

The final model of the associated factors of mortality among first-ever stroke patients admitted in HUSM using multiple logistic regression was shown Table-1. The significant associated factors included male (Adjusted OR=0.361; 95% CI: 0.141, 0.923; *P*=0.033), patients with seizure/ fit (Adjusted OR=0.302; 95% CI: 0.119, 0.766; *P*=0.012), married patients (Adjusted OR=0.195; 95% CI: 0.065, 0.588; *P*=0.004), widowed patients (Adjusted OR=0.150; 95% CI: 0.036, 0.630; *P*=0.010), Glasgow coma scale score (Adjusted HR=0.714; 95% CI: 0.654, 0.780; *P*<0.001), fasting blood sugar (Adjusted HR=1.125; 95% CI: 1.051, 1.205; *P*=0.001), ever-smoker patients (Adjusted OR=4.015; 95% CI: 1.397, 11.541; *P*=0.010), current smoker patients (Adjusted OR=4.753; 95% CI: 1.844, 12.247; *P*=0.001), patients with rheumatic heart disease (Adjusted OR=13.362; 95% CI: 2.291, 77.921; *P*=0.004), level of urea (Adjusted HR=1.095; 95% CI: 1.043, 1.150; *P*<0.001) and patients with subarachnoid haemorrhage (Adjusted OR=3.773; 95% CI: 1.469, 9.690; *P*=0.006).

Table-1. Associated factors of mortality in first-ever stroke patients admitted to HUSM using multiple logistic regression (n=430).

Variable	b	Adjusted OR (95% CI)	Z-statistic	*P*-value
Gender				
Female	0	1		
Male	-1.020	0.361 (0.141, 0.923)	-2.13	0.033
Seizure/ fit				
No	0	1		
Yes	-1.197	0.302 (0.119, 0.766)	-2.52	0.012
Marital status				
Never married	0	1		
Married	-1.636	0.195 (0.065, 0.588)	-2.90	0.004
Widowed	-1.895	0.150 (0.036, 0.630)	-2.59	0.010
Divorced	0.613	1.846 (0.109, 31.307)	0.42	0.671
Glasgow coma scale (GCS)	-0.337	0.714 (0.654, 0.780)	-7.48	<0.001
Fasting blood sugar (FBS)	0.118	1.125 (1.051, 1.205)	3.39	0.001
Smoking status				
Never smoker	0	1		
Ever-smoker	1.390	4.015 (1.397, 11.541)	2.58	0.010
Current smoker	1.559	4.753 (1.844, 12.247)	3.23	0.001
Rheumatic heart disease				
No	0	1		
Yes	2.592	13.362 (2.291,77.921)	2.88	0.004
Urea	0.091	1.095 (1.043, 1.150)	3.63	<0.001
Types of stroke				
Ischaemic stroke	0	1		
Intracerebral haemorrhage	0.344	1.411 (0.757, 2.628)	1.08	0.278
Subarachnoid haemorrhage	1.328	3.773 (1.469, 9.690)	2.76	0.006

b-Regression coefficient OR-Odds ratio CI-Confidence interval

Backward stepwise multiple logistic regression model applied

Linearity of continuous variable was checked and reported to be linear

Two-way interaction and multicollinearity were unlikely

The preliminary final model was properly specified (_hat: ***P***<0.001; _hatsq: ***P***=0.065)

Overall fit of the model was checked and reported to be Hosmer-Lemeshow test (***P***=0.270), Pearson chi-square test (***P***=0.926), overall correctly classified percentage (82.1%) and area under ROC curve (0.855 (95% CI: 0.816, 0.894); ***P***<0.001)

Akaike information criteria (AIC): 358.87; Bayesian information criteria (BIC): 415.76

Regression diagnostic was performed by estimated logistic probability, leverage, Hosmer and Lemeshow Delta chi-squared influence statistic, Hosmer and Lemeshow Delta-D influence statistic and Pregibon Delta-Beta influence statistic

Influential covariate patterns were identified by checking percent changes in regression coefficient set at 20%

A total of 22 potential influential covariate patterns were detected and two covariate patterns were confirmed as influential. Model after deleting influential covariate patterns was chosen as the final model.

DISCUSSIONS

Worldwide, stroke comes second after ischaemic heart disease as leading causes of death over the past decade [7]. In Malaysia, stroke represents the ten principal causes of hospitalization and death in Malaysian hospitals [3]. This current study is a retrospective study which aimed to identify the significant determinants of mortality among first-ever stroke patients receiving care at a 700-bed hospital servicing a predominantly rural area in Northeast Malaysia. There is also a nearby secondary referral centre, namely Hospital Raja Perempuan Zainab II that serves the surrounding areas, data from which were not included in this retrospective study.

Being a male was a protective towards mortality in this study, male patient was 71.2% less likely to die compared to female patient. This result was supported by statistics in 2008, from Department of Statistics, Malaysia which reported deaths due to cerebrovascular disease were higher in female [8]. However, this data appears to be in contrast with European studies. A Norwegian study reported that male stroke patients was 1.69 times more likely to die for long-term mortality for acute stroke (95% CI: 1.40, 2.05) [9]. Nevertheless, other studies including in Malaysia did not regard gender as an important determinant for mortality of stroke patients [10-12].

Hyperglycaemia was found to be one of the prognostic factors of mortality among first-ever stroke patients in this study which demonstrated an increase in one mmol/L of fasting blood sugar had 9.3% higher risk towards mortality. Recent study among older stroke patients in a tertiary hospital in Taiwan reported similar result with the risk of dying by 8% (95% CI: 1.01, 1.20) [13]. A prospective study in Korea which aimed to see the effects of glucose level on mortality among stroke patients demonstrated the same result that glucose level during admission was an independent risk factor for mortality (adjusted HR: 1.10; 95% CI: 1.01, 1.19) [14].

The Glasgow coma scale (GCS) in this study was a general guide to the stroke severity that is routinely documented in this case notes. Stroke specific scales such as National Institutes of Health Stroke Scale (NIHSS), the Canadian Stroke Scale (CSS), the Scandinavian Stroke Scale (SSS) and the Oxfordshire Classification to assess stroke severity were not used routinely in the hospital. We found that low GCS during admission was a significant determinant of mortality among first-ever stroke patients. A patient with an increase in one unit of GCS has 26.7% lesser risk towards mortality (AdjHR=0.733; 95% CI: 0.687, 0.782; p-value<0.001). The finding was also supported by previous study in Malaysia [15].

Smoking was one of the important associated factors of mortality in this study. First-ever stroke patients who ever-smoked and currently smoked were four times more likely to die compared to non-smokers. Similarly, the Danish National Indicator Project had reported that in the multivariable survival analysis, one of the risk factors related to death was smoking [16]. However, a prospective study involving Japanese patients demonstrated that smoking was not associated with death following stroke. It was likely that the smokers quit smoking due to deteriorating health, while smokers in good health may have continued smoking [17].

By stroke subtype, subarachnoid haemorrhage was found to be significant associated factors of mortality among first-ever stroke patients in this study. Similar finding was reported in previous study in Malaysia, haemorrhagic stroke had 3.5 higher odds towards one-month mortality compared to ischaemic stroke (adjusted OR=3.45; 95% CI: 1.09, 10.87; P=0.035) [15]. The finding was also supported in other previous studies [16, 18-20].

CONCLUSIONS

In conclusion, this study though being retrospective in nature revealed insights with the effect of key clinical parameters on associated factors of mortality in first-ever stroke patients in a predominantly suburban setting in Malaysia. The application of advanced multiple logistic regression analysis permits the identification of significant associated factors of mortality among first-ever stroke patients in our data. This analysis allowed the control of covariates. However, there are several limitations to our study. As the data was retrospectively extracted from the secondary data, data likely to have information bias that influenced the data quality. Additional information such as assessment using stroke-specific scale cannot be deduced from this retrospective data.

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