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Modeling Survival in Patients With Brain Stroke in the Presence of Competing Risks

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Objectives: After heart disease, brain stroke (BS) is the second most common cause of death worldwide, underscoring the importance of understanding preventable and treatable risk factors for the outcomes of BS. This study aimed to model the survival of patients with BS in the presence of competing risks.

Methods: This longitudinal study was conducted on 332 patients with a definitive diagnosis of BS. Demographic characteristics and risk factors were collected by a validated checklist. Patients' mortality status was investigated by telephone follow-up to identify deaths that may be have been caused by stroke or other factors (heart disease, diabetes, high cholesterol, etc.). Data were analyzed by the Lunn-McNeil approach at alpha=0.1.

Results: Older age at diagnosis (59-68 years: adjusted hazard ratio [aHR], 2.19; 90% confidence interval [CI], 1.38 to 3.48; 69-75 years: aHR, 5.04; 90% CI, 3.25 to 7.80; ≥76 years: aHR, 5.30; 90% CI, 3.40 to 8.44), having heart disease (aHR, 1.65; 90% CI, 1.23 to 2.23), oral contraceptive pill use (women only) (aHR, 0.44; 90% CI, 0.24 to 0.78) and ischemic stroke (aHR, 0.52; 90% CI, 0.36 to 0.74) were directly related to death from BS. Older age at diagnosis (59-68 years: aHR, 21.42; 90% CI, 3.52 to 130.39; 75-69 years: aHR, 16.48; 90% CI, 2.75 to 98.69; ≥76 years: aHR, 26.03; 90% CI, 4.06 to 166.93) and rural residence (aHR, 2.30; 90% CI, 1.15 to 4.60) were directly related to death from other causes. Significant risk factors were found for both causes of death.

Conclusions: BS-specific and non-BS-specific mortality had different risk factors. These findings could be utilized to prescribe optimal and specific treatment.

Key words: Stroke, Risk factors, Survival analysis, Models

INTRODUCTION

Brain stroke (BS) is the second most common cause of mortality in the world after heart disease [1]. In the United States, 795 000 people have strokes each year affecting the brain [2,3]. The annual number of strokes in Unite States is forecast to rise to 3.4 million between 2012 and 2030 [2,4]. It is also estimated that the cost of treating this disease is US$34 billion annually [2,5].

More than 80% of mortality caused by BS occurs in develop-

ing countries [6]. The risk of mortality due to BS is increasing in most developing countries because of low awareness of its risk factors, a failure to follow the principles of prevention, the lack of stroke-screening tools, and the weakness of prevention programs. Recent reports have shown that the rate of BS in Iran, a developing country, is significantly higher than that of Western countries [7,8]. On average, the annual rate in Iran 139 out of every 100 000 people had a new stroke [7]. Therefore, it is necessary to find ways to reduce stroke-specific mortality in Iran, especially by targeting relevant risk factors [9,10]. Therefore, due to the prevalence and the burden of BS in Iran, it is necessary to study BS-specific mortality and its risk factors.

Studying modifiable risk factors can provide insights into appropriate treatment and prevention measures to enhance the survival of patients with BS [11-13]. The risk factors of BS are divided into 2 groups: the more important risk factors are age, high blood pressure, and heart disease, while second-degree risk factors that are less important include a high blood lipid levels, obesity, smoking, neurological stress, and a history of BS [14]; some of these factors are modifiable, while others are non-modifiable [15]. Understanding the distribution of these factors is of particular importance.

In studies of mortality due to BS, several causes of death have consistently been found, only one of which is the real cause of death. Death in patients with BS may occur due to stroke or other causes. This raises the question, what is the leading cause of death in these patients? Therefore, it is necessary to investigate mortality in patients with BS according to the presence of competing risks [16]. In the presence of competing risks, conventional statistical methods cannot be used because simple survival analysis (Cox model) censors deaths due to other causes, leading to biased estimates [17]. Therefore, to better understand the causes of death in patients with BS, we investigated the causes of death in 2 groups of BS patients (death from stroke and death from other causes) by modeling competing risk with the Lunn-McNeill (L-M) approach.

METHODS

Study Design and Procedure

In this longitudinal study, data were obtained from Imam Khomeini Ardabil Hospital, the only referral center in Ardabil Province in northwestern Iran. A total of 332 patients were enrolled in a 10-year follow-up study (June 2008 up to June 2018)

[18]. The inclusion criteria to join the study were patients who experienced BS for the first time and voluntarily provided informed consent to participate in the study. The exclusion criteria were transient ischemic attack patients and patients with a previous history of BS. All patients' diagnoses were classified using International Classification of Diseases, 10th revision codes according to computed tomography and magnetic resonance imaging scans. For all patients, data on demographic characteristics and major clinical risk factors were extracted from hospital records and utilized in the analyses. Patients' outcome status was ascertained by making telephone calls to their relatives. For patients who died during the period of the study, the exact date of death and cause of death (death from BS or death from other causes, such as diabetes, and heart disease) were recorded and analyzed.

Main Variables and Measures

For all patients, the following demographic variables were analyzed based on hospital records: age group at diagnosis (1: ≤58 years; 2: 59-68 years; 3: 69-75 years; 4: ≥76 years), sex (1: male; 2: female), employment status (1: employed; 2: unemployed), education level (1: secondary school diploma or lower; 2: at least some college/university), place of residence (1: urban; 2: rural), a history of cerebrovascular accident (1: yes; 2: no), a history of myocardial infarction (1: yes; 2: no), heart disease (1: yes; 2: no), a history of diabetes (1: yes; 2: no), a history of high blood pressure (1: yes; 2: no), a history of high cholesterol (1: yes; 2: no), smoking (1: yes; 2: no), past smoking (1: yes; 2: no), passive smoking(1: yes; 2: no), oral contraceptive pill (OCP) use (female only) (1: yes; 2: no), physical activity (1: yes; 2: no), water pipe smoking (1: yes; 2: no), and cerebrovascular accident type (1: ischemic; 2: hemorrhagic).

Statistical Analysis

Data were summarized and reported as frequency and percentage for categorical variables and as mean (standard deviation; SD) or median for continuous variables. The survival time of patients was calculated by month. Significant risk factors ($p < 0.1$) in the univariate analysis were entered into the multivariate analysis. The L-M model was used to generate results for the cause-specific assessment of death by modifying the Cox proportional hazard (PH) model [19]. Based on the selected model, and for each of the factors entered in the model, an unadjusted hazard ratio (HR) and an adjusted hazard ratio (aHR) were presented along with their 90% confidence inter-

vals. The interaction L-M model was used to compare BS and other causes of death. The Schoenfeld residual test was used to assess the PH assumption for each variable. Power analyses were also conducted to evaluate the power of the tests in all L-M models. All analyses were performed using Stata version 16 (StataCorp., College Station, TX, USA).

Ethics Statement

The Ethics Committee of Zanjan University of Medical Sciences approved the protocol of this study (approval No. IR.ZUMS.REC.1399.221). At the beginning of the study, patients were informed that they were free to participate in the research and informed consent was obtained from patients or their relatives. The personal information of the patients was kept safe and confidential. No therapeutic or educational intervention was performed in this study. Each patient's address and two contact numbers were recorded.

RESULTS

The median follow-up time was 20.68 months (range, 0.53 to 80.91) for patients who died due to BS and 68.50 months (range, 60.00 to 107.69) for patients who died due to other causes. The average age at diagnosis for patients who died due to BS and due to other causes was 69.08 ± 11.82 years and 69.37 ± 10.01 years, respectively. Of the BS patients, 208 (86.7%) died from BS, while 32 (13.3%) died from other causes. Furthermore, 37.3% of those who died from BS and 90.4% in those who died from other causes were censored. Tables 1 and 2 provide more details on the demographic characteristics and the percentage of those who were censored.

Age at diagnosis and sex were significantly associated with death from BS, while age and place of residence were significantly associated with death from other causes ($p < 0.01$) (Table 3). Regarding clinical features, heart disease, diabetes, high blood pressure, high cholesterol, OCP use (female only), and

Table 1. Participants' demographic and clinical characteristics, and percentage of patients who were censored

Characteristics	n (%)	Brain stroke, %	Other causes, %
Age (y)			
≤58	88 (26.7)	84.6	93.7
59-68	77 (23.3)	63.0	65.6
69-75	102 (30.9)	51.0	68.7
≥76	63 (19.1)	76.0	71.9
Sex (male)	164 (49.4)	44.2	43.7
Employment status (employed)	107 (32.2)	70.7	59.4
Education level (≤secondary school diploma)	322 (97)	1.9	3.1
Place of residence (rural)	131 (39.5)	59.6	43.7
History of cerebrovascular accident	80 (24.1)	78.8	68.7
History of myocardial infarction	24 (7.2)	94.2	96.9
Heart disease	85 (25.8)	72.1	78.1
History of diabetes	59 (17.9)	79.8	87.5
History of blood pressure	196 (59.2)	33.7	53.1
History of high cholesterol	61 (18.5)	85.1	84.4
Smoking (yes)	64 (19.3)	80.8	75.0
Water pipe smoking (yes)	11 (3.3)	95.7	100
Past smoking (yes)	43 (16)	85.1	87.5
Passive smoking (yes)	60 (18.1)	82.2	90.6
Oral contraceptive pill use (female only)	60 (18.1)	90.9	87.5
Physical activity (yes)	46 (13.9)	87.0	84.5
Cerebrovascular accident type (Ischemic)	257 (79.6)	25.5	21.9

Table 2. Participants' demographic and clinical characteristics for risk factors of death from brain stroke and other causes

Characteristics	Brain stroke	Other causes
Age (y)		
≤58	32 (94.1)	2 (5.9)
59-68	44 (80.0)	11 (20.0)
69-75	80 (88.9)	10 (11.1)
≥76	50 (84.7)	9 (15.3)
Sex (male)	116 (86.6)	18 (13.4)
Employment status (employed)	61 (82.4)	13 (17.6)
Education level (≤secondary school diploma)	204 (86.8)	31 (13.2)
Place of residence (rural)	84 (82.4)	18 (17.7)
History of cerebrovascular accident	44 (81.9)	10 (18.6)
History of myocardial infarction	12 (92.3)	1 (7.7)
Heart disease	58 (89.2)	7 (10.8)
History of diabetes	42 (91.3)	4 (8.7)
History of blood pressure	138 (90.2)	15 (9.8)
History of high cholesterol	31 (86.1)	5 (13.9)
Smoking (yes)	40 (83.3)	8 (16.7)
Water pipe smoking (yes)	9 (100)	0 (0.0)
Past smoking (yes)	31 (88.6)	4 (11.4)
Passive smoking (yes)	37 (92.5)	3 (7.5)
Oral contraceptive pill use (female only)	19 (82.6)	4 (17.4)
Physical activity (yes)	27 (84.4)	5 (15.6)
Cerebrovascular accident type (Ischemic)	155 (86.1)	25 (13.9)

Values are presented as number (%).

type of stroke were significant risk factors for death from BS ($p<0.1$). For death from other causes, only OCP use (female only) was significant ($p<0.1$) (Table 3).

The multivariate L-M model showed that age at diagnosis (years), heart disease, OCP use (female only), and type of stroke were significant risk factors for death from BS ($p<0.1$). In pa-

Table 3. Results of univariate Lunn-McNeil modeling for risk factors of death from brain stroke and other causes

Characteristics	Brain stroke (n=208)	*p*-value	Other causes (n=32)	*p*-value
Age (y)				
≤58	1.00 (reference)	-	1.00 (reference)	-
59-68	2.26 (1.45, 3.51)	0.002	16.91 (3.01, 94.98)	0.007
69-75	4.85 (3.27, 7.21)	<0.001	14.51 (2.52, 83.41)	0.012
≥76	5.27 (3.46, 8.04)	<0.001	27.06 (4.71, 155.34)	0.002
Sex (male)	1.41 (1.10, 1.80)	0.021	1.43 (0.76, 2.72)	0.352
Employment status (employed)	0.77 (0.59, 1.01)	0.106	1.26 (0.66, 2.41)	0.547
Education level (≤secondary school diploma)	2.05 (0.78, 5.33)	0.219	NA	-
Place of residence (rural)	1.20 (0.95, 1.55)	0.203	2.61 (1.37, 4.99)	0.014
History of cerebrovascular accident	0.74 (0.55, 1.01)	0.106	1.21 (0.60, 2.42)	0.651
History of myocardial infarction	0.78 (0.47, 1.27)	0.395	0.41 (0.07, 2.20)	0.384
Heart disease	1.33 (1.01, 1.74)	0.082	1.01 (0.47, 2.16)	0.988
History of diabetes	1.39 (1.03, 1.87)	0.067	1.03 (0.42, 2.50)	0.959
History of blood pressure	1.53 (1.18, 1.98)	0.006	0.69 (0.36, 1.30)	0.336
History of high cholesterol	0.66 (0.46, 0.93)	0.047	0.64 (0.26, 1.56)	0.410
Smoking (yes)	0.95 (0.69, 1.30)	0.784	1.21 (0.57, 2.60)	0.675
Past smoking (yes)	0.96 (0.67, 1.38)	0.868	0.83 (0.30, 2.32)	0.768
Passive smoking (yes)	0.92 (0.66, 1.26)	0.654	0.53 (0.19, 1.46)	0.306
Oral contraceptive pill use (female only)	0.25 (0.16, 0.42)	<0.001	0.28 (0.09, 0.83)	0.055
Physical activity (yes)	0.71 (0.49, 1.04)	0.146	1.21 (0.54, 2.74)	0.695
Water pipe smoking (yes)	1.57 (0.87, 2.85)	0.209	NA	-
Cerebrovascular accident type (Ischemic)	0.64 (0.48, 0.86)	0.011	2.25 (0.67. 7.60)	0.271

Values are presented as hazard ratio (90% confidence interval).
NA, not applicable.

Table 4. Results of multivariate Lunn-McNeil modeling for risk factors of death from brain stroke and other causes

Characteristics	Brain stroke	*p*-value	Other causes	*p*-value
Age (y)				
≤58	1.00 (reference)		1.00 (reference)	
59-68	2.19 (1.38, 3.48)	0.005	21.42 (3.52, 130.39)	0.005
69-75	5.04 (3.25, 7.80)	<0.001	16.48 (2.75, 98.69)	0.010
≥76	5.30 (3.40, 8.44)	<0.001	26.03 (4.06, 166.93)	0.004
Sex (male)	1.13 (0.84, 1.52)	0.490	NA	-
Place of residence (rural)	NA	-	2.30 (1.15, 4.60)	0.047
History of cerebrovascular accident	0.78 (0.56, 1.11)	0.449	1.33 (0.63, 2.79)	0.532
History of myocardial infarction	1.18 (0.73, 1.91)	0.564	0.75 (0.14, 3.94)	0.781
Heart disease	1.65 (1.23, 2.23)	0.005	1.76 (0.77, 4.03)	0.263
History of diabetes	1.34 (0.94, 1.92)	0.180	1.11 (0.40, 3.07)	0.866
History of blood pressure	1.21 (0.90, 1.61)	0.271	0.54 (0.25, 1.14)	0.173
History of high cholesterol	0.75 (0.49, 1.14)	0.260	1.16 (0.41, 3.26)	0.816
Oral contraceptive pill use (female only)	0.44 (0.24, 0.78)	0.020	0.81 (0.25, 2.68)	0.775
Cerebrovascular accident type (Ischemic)	0.52 (0.36, 0.74)	0.002	NA	-

Values are presented as adjusted ratio (90% confidence interval).
NA, not applicable.

tients with other causes of death, age at diagnosis and place of residence were significant risk factors ($p<0.05$) (Table 4).

Comparison of Mortality Risk Factors Between Brain Stroke and Other Causes of Death

Significant differences were found between BS and other causes of death for the age category of 59-68 years, place of residence (rural), a history of high blood pressure, and type of stroke ($p<0.1$) (Table 5).

Assessment of the Proportional Hazard Assumption

Testing the PH assumption demonstrated that all predictors satisfied the PH assumption in all L-M models ($p>0.1$).

Power Analysis

The power analysis showed that some variables in the models satisfied the minimum power required for modeling in all L-M models (range, 0.86 to 0.99). However, the power was low for some risk factors such as age group at diagnosis (power, 0.11), smoking (power, 0.09), past smoking (power, 0.44), and passive smoking (power, 0.06).

Table 5. Comparison between brain stroke and other causes of death using the interaction Lunn-McNeil model

Characteristics	HR (90% CI)	*p*-value
Age (y)		
≤58	1.00 (reference)	-
59-68	7.49 (1.26, 44.48)	0.063
69-75	2.99 (0.50, 17.96)	0.315
≥76	5.13 (0.85, 30.99)	0.135
Sex (male)	1.02 (0.51, 2.02)	0.965
Employment status (employed)	0.61 (0.30, 1.22)	0.239
Place of residence (rural)	2.16 (1.08, 4.32)	0.066
History of cerebrovascular accident	1.63 (0.76, 3.47)	0.289
History of myocardial infarction	0.53 (0.09, 3.05)	0.551
Heart disease	0.76 (0.34, 1.70)	0.573
History of diabetes	0.74 (0.29, 1.89)	0.596
History of blood pressure	0.45 (0.23, 0.89)	0.056
History of high cholesterol	0.97 (0.37, 2.54)	0.964
Smoking (yes)	0.78 (0.34, 1.78)	0.622
Past smoking (yes)	0.86 (0.29, 2.56)	0.824
Passive smoking (yes)	0.58 (0.20, 1.68)	0.402
Oral contraceptive pill use (female only)	1.10 (0.34, 3.63)	0.891
Physical activity (yes)	1.70 (0.69, 4.19)	0.331
Cerebrovascular accident type (Ischemic)	3.50 (1.01, 12.19)	0.099

HR, hazard ratio; CI, confidence interval; NA, not applicable.

DISCUSSION

The risk factors for mortality in patients with a BS diagnosis were compared between death from BS and death from other causes in the context of competing risks. We overcame the problem raised in the classical analysis (i.e., Cox regression) by utilizing the L-M approach. In classical analyses, it is usually assumed that competing risks are independent. Considering the competing risks as the censor and ignoring the risks incurred by other causes are the most crucial problems faced by the Cox model when analyzing data in the presence of competing risks. This leads to biased estimates [20]. The L-M model is a useful tool for analyzing data in the context of competing risks, in which the event occurs for several reasons. In this form of modeling, it is possible to compare the effect of each variable on competing causes of an event [21]. Therefore, in this study, the univariate and multivariate L-M approach was used, considering the risk of death from BS and death from other causes as competing risks.

Out of the 332 patients with a BS diagnosis, 208 died from BS and 32 died from other causes. The rate of mortality after BS was 69%, of which 60% were deaths due to stroke and 9% were deaths due to other causes. In line with our study, Hardie et al. [22] assessed long-term (10-year) mortality after BS in Australia and reported a mortality rate of 79%.

The results of the univariate L-M analysis showed that an older age at diagnosis and male sex were directly and significantly related to death from BS, while an older age at diagnosis and place of residence (rural) were directly and significantly related to death by other causes. These results align with those reported by studies conducted in Europe and the United States, according to which the highest mortality rate is found in the ninth decade of life [23]. Furthermore, in a study conducted in Farshchian Hospital in Hamedan, patients under the age of 50 years had a lower died from BS, and the risk of BS increased with age [24]. Males were at a higher risk of death than females, which is consistent with the results of studies conducted in the United States, Europe [23], and Arab countries [25]. However, in some other studies, such as in the Copenhagen cohort study [26], females were 1.49 times more likely to have died than males 10 years after a stroke. This discrepancy may be due to physiological differences between male and female.

In the study by Madsen et al. [27], risk factors such as diabetes, metabolic syndrome, and migraine were found to in-

crease the risk of stroke in female more than male, and hypertension was found to be associated with age and ethnicity. In the present study, the incidence of stroke was higher in urban areas than in rural areas (60.5%). However, place of residence was not a significant predictor of death from BS ($p > 0.1$). Still, the mortality rate due to other causes was higher in people with BS who lived in urban areas than in rural areas. Similar to our study, Javor et al. [28] and Ferri et al. [29] in Egypt, United States. Latin, India, China [30], and Europe [28], and our country [24] showed that the prevalence of BS was higher in urban than in rural areas. In the present study, the risk of attenuation due to other causes of patients living in the rural was higher.

In this study, a history of high cholesterol, heart disease, a history of high blood pressure, a history of diabetes, OCP use, and type of stroke were significantly associated with death from BS, and OCP use was significantly associated with other causes of death. The results of our study showed that of the patients who died due to BS, 89.2% had heart disease, 90.2% had high blood pressure, 91.3% had diabetes. 86.1% had high cholesterol, and 82.6% had a history of OCP use. Hardie et al. [22], in a study of 10-year survival after stroke, found that 79% of patients died within 10 years, and the leading cause of mortality was initial stroke and cardiovascular disease (27%). Another study showed that the overall mortality rate was 29%, and the mortality rate in those 70+ years of age was 57.1% [31]. OCP use is affected by age, blood pressure, smoking, and migraine [32]. A meta-analysis by Gillum et al. [33] found that people on OCP had a higher risk of BS.

Stroke is divided into ischemic and hemorrhagic at the most basic level. In this study, approximately 79.6% of people had ischemic stroke, while 20.4% had hemorrhagic stroke. Although the majority of patients had ischemic stroke, the mortality rate of hemorrhagic stroke was higher. In line with our research, in a long-term attenuation study of stroke among people aged 18 years to 50 years in the Netherlands in 2013 by Rutten-Jacobs et al. [34], 606 of 959 (63%) patients had ischemic stroke. In a 2016 study in Brazil, Goulart et al. [35] found that the risk of death from hemorrhagic stroke was higher than that of ischemic stroke.

According to the results of the multivariate L-M model, the significant risk factors for mortality due to BS were age, heart disease, OCP, and cerebrovascular accident type. In contrast, the significant risk factors for mortality due to other causes were age at diagnosis and place of residence. Finally, according to the interaction L-M model, age at diagnosis (59-68 years), place of residence, and a history of high blood pressure were significantly different between the 2 causes of death. The results of our study align with those of Mogensen et al. [36], who studied the long-term (10 years) outcomes of stroke in 988 patients and concluded that stroke death was related to old age, sex (male), diabetes, a history of stroke, heart disease and non-vascular disease, and type of stroke (hemorrhagic).

This study has some limitations. First, it did not take into account a series of conditions; for instance, there was a lack of correlation between observations and additional dispersion may have been caused by unexpected factors. In this regard, it is suggested to use the competing risk model with frailty. Another limitation of this study is that the number of cases in some subgroups was less than 5. Studies with a larger sample size, especially for other causes of death, are urgently required. Specifically, studies with a greater number of patients are needed to increase the reliability of the statistical tests.

Differences were found between the 2 causes of death (BS and other causes) for some risk factors. The hypothesis that some risk factors (demographic, clinical, and hereditary) may have different effects on the cause of death (BS and other causes) was confirmed based on the findings of this study. Significant differences were found between death from BS and death from other causes for age (59-68), place of residence (rural), a history of high blood pressure, and cerebrovascular accident type. Age at diagnosis, sex, heart disease, a history of high cholesterol, high blood pressure, diabetes, OCP use, and stroke type showed significant relationships with death from BS, while age at diagnosis and place of residence showed significant relationships for death from other causes. These findings should be considered for prevention, planning, health policy-making, and prescribing optimal and specific treatment in order to increase survival in patients with BS.

CONFLICT OF INTEREST

FUNDING

AUTHOR CONTRIBUTIONS

Conceptualization: SN, MAJ, SMS, FF, RF. Data curation: SN, MAJ, FF. Formal analysis: SN, MAJ. Funding acquisition: None. Methodology: SN, MAJ. Writing – original draft: SN, MAJ, SMS, FF, RF. Writing – review & editing: SN, MAJ, SMS, FF, RF.

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