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Original Article

Survival Analysis of Patients with Brain Stroke in the Presence of Competing Risks: A Weibull Parametric Model

Solmaz Norouzi[1], Ramazan Fallah[1], Ahmad Pourdarvish[2], Seyed Morteza Shamshirgaran[3], Farshid Farzipoor[4], Mohammad Asghari Jafarabadi[1,5*]

[1]Department of Statistics and Epidemiology, School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran.
[2]Department of Statistics, University of Mazandaran, Babolsar, Iran.
[3]Department of Statistics and Epidemiology, School of Health Sciences, University of Neyshabur, Neyshabur, Iran.
[4]Department of Health Education and Promotion, School of Health, Tabriz University of Medical Sciences, Tabriz, Iran.
[5]Center for the Development of Interdisciplinary Research in Islamic Sciences, and Health Sciences Tabriz University of Medical Sciences, Tabriz, Iran.

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ABSTRACT

Introduction: This study aimed to assess the association between the survival of patients and outcomes in Brain Stroke (BS) in the presence of competing risks utilizing a Weibull parametric model.
Methods: In this longitudinal study, 332 patients with BS were attended from Imam Khomeini Hospital in Ardabil, Iran. The stroke was diagnosed according to the medical history, current symptoms, and brain imaging during June 2008 and 2018. The survival of the patients, as the primary outcome, was modeled utilizing the best-chosen Weibull model in the presence of competing risks, including stroke and other factors (heart disease, blood pressure, etc.).
Results: Older age at diagnosis (59-68 years: hazard ratio [HR]=2.27; 90% confidence interval [CI]: 1.65 to 3.12; 69-75 years: HR=4.79; 95% CI: 3.56 to 6.44; ≥76 years: HR, 4.92; 95% CI: 3.55 to 6.80), being a male (HR, 1.39; 95% CI: 1.11 to 1.75), being unemployed (HR, 1.44; 95% CI: 1.39 to 1.82), having heart disease (HR, 1.68; 95% CI: 1.38 to 2.06), and hemorrhagic stroke (HR, 2.21; 95% CI: 1.378to 2.75) were directly related to death from BS. Older age at diagnosis (59-68 years: HR, 18.01; 90% CI, 5.33 to 64.92; 75-69 years: HR, 18.56; 95% CI: 6.97 to 86.57; ≥76 years: HR, 28.90; 95% CI: 15.77 to 218.49), and urban residence (HR, 0.46; 90% CI, 0.28 to 0.77) were directly related to death from other causes.
Conclusion: The recognition of the influential factors on the mortality of BS patients can allow increasing their survival.

Introduction

Brain stroke is considered one of the leading causes of mortality globally, which affects individuals' performance in many daily activities.[1] Recent epidemiological studies show that the BS rate is growing in western countries[2-4] and Iran.[5, 6] Further, its mortality

*.Corresponding Author: m.asghari862@gmail.com

rate in Asia is more than in North America and Europe.[7] Therefore, it is raised as an essential issue in the public health of countries. Evaluating prognostic factors and classification of patients in each disease, mainly BS, help clinical researchers significantly. Therefore, conducting a study with the competing risk approach is vital for finding the influential risk factors on stroke patient mortality due to BS and other causes.

The survival-competing risks are frequently raised in the different fields of sciences such as medicine and engineering. The competing risk data arise when more than one event affects patients' survival time.[8] In the framework, the subject may experience events other than the intended one.[9] Obtaining the parametric distribution of survival time is essential in the survival analysis so that survival and hazard probability can be precisely calculated at all times. In the cases where a reasonable parametric distribution can be considered for the survival function understudy, estimation is relatively easy, usually based on the maximum-likelihood attitude. Weibull distribution is the most widely-used parametric survival analysis model. Today, the Weibull model introduced by Weibull, a Swedish physicist,[10] is commonly employed in different fields such as medicine and engineering. The model is essential due to its application for modeling failure times and the distribution of data lifetime function and behavior of its hazard rate function, which can be ascending, descending, or fixed by changing parameters. In addition, the Weibull distribution is flexible for modeling different data since the behavior of its hazard function is not fixed over the time and has an additional parameter called shape. So aim of the present study was Survival Analysis of Patients with BS in the Presence of Competing Risks using Weibull Parametric Model.

Materials and Methods

Study design and procedure

In this prospective longitudinal study,[11] data were obtained from Imam Khomeini Ardabil hospital, Iran. A total of 332 patients were entered in the 10-year follow-up study (June 2008 up to June 2018). The inclusion criteria for joining the study were patients who experienced BS for the first time and voluntarily provided informed consent to participate. The exclusion criteria were patients with a previous history of BS. In the present study, a neurologist definitively diagnosed brain stroke using the medical history, current symptoms, and brain imaging results. Data on demographic characteristics and significant clinical risk factors were extracted from hospital records and analyzed for all patients. Patients' outcome status was ascertained by making telephone calls to their relatives. Patients who became unavailable after enrollment for various reasons were considered as censored data (right censoring). For patients who died during the study period, the exact date and cause of death (death from BS or death from other causes, such as (heart disease, blood pressure, etc.) were recorded and analyzed.

Ethical Considerations

The Ethics Committee of Tabriz University of Medical Sciences approved the protocol of this study (Project no: 67813, Ethics code: IR.TBZMED.REC.1400.296).

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), place of residence (1: urban; 2: rural), a history of cerebrovascular accident (1: yes; 2: no), heart disease (1: yes; 2: no), smoking (now smokers) (1: yes; 2: no), and cerebrovascular accident type (1: ischemic; 2: hemorrhagic).

Statistical modeling

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. In recent follow-ups, it is found that about 13.33% of Patients with Brain Stroke died of other causes of death, such as heart disease, blood pressure, etc., so we analyzed the data by using competing-risks models and because of some benefits of parametric models, we have used parametric competing risks.

The optimal model was chosen based on the Akaike information criteria (AIC) and Bayesian information criteria (BIC). We decided on the Weibull model: First, there was no considerable difference between the Weibull model and other models in AIC and BIC (less than 5%). Second, in both BS and other causes data, we had required the same model, and we choose the Weibull model accordingly.

Weibull distribution has two parameters, shape (α) and location (λ). The Weibull distribution density function with the parameters λ and α$f(t \mid \alpha,\lambda) = \lambda \alpha t^{\alpha-1} \exp(-\lambda t^{\alpha})$; $t>0$, $\alpha>0$, $\lambda>0$. The simultaneous establishment of accelerated failure time and proportional hazard assumptions is the unique feature of the model.[9] The model was fitted on stroke data by considering the AIC criterion and the advantages of the distribution. All analyses were performed using Stata version 14 (StataCorp., College Station, TX, USA). A P-value lower than 0.1 was defined as significant.

Based on the Weibull model, a hazard ratio (HR) was presented along with their 90% confidence intervals for each factor entered in the model. The covariates identified as significant throughout the univariate analysis (P<0.1) were selected to attend the multivariate Weibull model.

Results

A total number of 332 patients with BS were included in the study. After recent follow-ups, 92 cases were alive, 208 cases had died due to BS, and 32 cases were other causes. There were 49.4% male cases. The age ranges were from 23 to 90 years at the time of diagnosis, but most patients (31%) were between 69 and 75 years old. The average age at diagnosis for patients who died due to BS and other causes was 69.08 years (SD, 11.82 years) and 69.37 years (SD, 10.01 years), respectively. The median follow-up time was 20.68 months (range, 0.53-80.91 months) for patients who died due to BS and 68.5 months (range, 60-107.69 months) for patients who died due to other causes. See Table 1 for more results.

Additionally, according to the values for AIC and BIC of the models, finally, we choose the Weibull distribution as the same distribution for deaths caused by brain stroke and other causes (Table 2).

In the Weibull model, and in univariate analysis, age at diagnosis (P<0.001), sex (male)

(P<0.001), Employment status (unemployed) (p=0.025), history of cerebrovascular accident (p=0.025), Heart disease (p=0.010), history of blood pressure (P<0.001), Cerebrovascular accident type (P<0.001) were significantly associated with death from BS, and age at diagnosis (P<0.001) and place of residence (P<0.001) were significantly associated with death from other causes (Table 3).

According to the results of the multivariate Weibull model (Table 4), age at diagnosis (P<0.001), Sex (male) (p=0.016), Employment status (unemployed) (p=0.010), Heart disease (P<0.001), and Cerebrovascular accident type(P<0.001) were significant risk factors for death from BS. In patients with other causes of death, age at diagnosis (P<0.001) and place of residence (p=0.012) were statistically significant.

Table 1. Participants' demographic and clinical characteristics, and percentage of patients with censoring

Characteristic	Number of persons (%)	Number of deaths due to Brain stroke (%)	Number of deaths due to other causes (%)
Age category (years)			
≤ 58	88 (26.7)	32 (13.44)	2 (0.84)
59- 68	77 (23.3)	44 (18.48)	11 (4.62)
69-75	102 (30.9)	80 (33.61)	10 (4.20)
≥76	63 (19.1)	50 (21.01)	9 (3.78)
Sex (male)	164 (49.4)	116 (86.6)	18 (13.4)
Employment status (unemployed)	225 (67.8)	147 (88.65)	19 (11.5)
Place of residence (urban)	201 (60.5)	1244(89.9)	14 (10.1)
History of cerebrovascular accident (yes)	80 (24.1)	44 (81.9)	10 (18.1)
Heart disease (yes)	85 (25.8)	58 (89.2)	7 (10.8)
History of blood pressure (yes)	196 (59.2)	138 (90.2)	15 (9.8)
Smoking (yes)	64 (19.3)	40 (83.3)	8 (16.7)
Cerebrovascular accident type (hemorragic)	66 (20.4)	49 (92.5)	4 (7.5)

Table 2. Akaike information criterion and Bayesian information criterion values for parametric models

Distribution	AIC	BIC	Distribution	AIC	BIC
Brain Stroke			Other Causes		
Exponential	2793.4	2838.3	Exponential	354.7	399.2
Weibull	2259.1	2308.1	Weibull	350.1	399.1
Log-Normal	2253.1	2302.1	Log-Normal	352.9	401.9
Log-Logistic	2260.4	2309.4	Log-Logistic	349.8	398.8

AIC, Akaike information criterion; BIC, Bayesian information criterion

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

Characteristic	Brain stroke Hazard ratio (90% CI)	p-value	Other causes Hazard ratio (90% CI)	p-value
Age category (years)				
≤ 58				
59- 68	2.21 (1.62-3.02)	<0.001	17.56 (5.18-59.50)	<0.001
69-75	4.53 (3.44-5.98)	<0.001	16.73 (4.85-57.62)	<0.001
≥76	5.01 (3.73-6.75)	<0.001	31.61 (9.18-108.87)	<0.001
Sex (male)	1.39 (1.17-1.65)	<0.001	1.46 (0.93-2.29)	0.166
Employment status (unemployed)	1.29 (1.07-1.56)	0.025	0.79 (0.50-1.25)	0.402
Place of residence (urban)	0.85 (0.71-1.01)	0.113	0.38 (0.24-0.59)	<0.001
History of cerebrovascular accident (yes)	0.75 (0.60-0.93)	0.025	1.20 (0.74-1.97)	0.532
Heart disease (yes)	1.35 (1.11-1.63)	0.010	0.99 (0.58-1.70)	0.983
History of blood pressure (yes)	1.52 (1.27-1.82)	<0.001	0.70 (0.45-1.11)	0.201
Smoking (yes)	0.94 (0.75-1.17)	0.649	1.22 (0.71-2.10)	0.535
Cerebrovascular accident type (hemorrhagic)	1.60 (1.31-1.95)	<0.001	0.45 (0.19-1.08)	0.132

*p<0.1; CI, Confidence interval

Table 4. Results of multivariate Weibull modeling for risk factors of death from brain stroke and other cause

Characteristic	Brain stroke Hazard ratio(90% CI)	p-value	Other causes Hazard ratio(90% CI)	p-value
Age category (years)				
≤ 58				
59- 68	2.27 (1.65-3.12)	<0.001	18.01 (5.33-64.92)	<0.001
69-75	4.79 (3.56-6.44)	<0.001	18.56 (6.97-86.57)	<0.001
≥76	4.92 (3.55-6.80)	<0.001	28.90 (15.77-218-49)	<0.001
Sex (male)	1.39 (1.11-1.75)	0.016	NA	
Employment status (unemployed)	1.44 (1.39-1.82)	0.010	NA	
Place of residence (urban)	NA		0.46 (0.28-0.77)	0.012
History of cerebrovascular accident (yes)	0.83 (0.66-1.04)	0.181	1.10 (0.62-1.96)	0.790
Heart disease (yes)	1.68 (1.38-2.06)	<0.001	1.74 (0.94-3.24)	0.140
History of blood pressure (yes)	1.21 (0.99-1.48)	0.121	0.61 (0.36-1.03)	0.125
Cerebrovascular accident type (hemorragic)	2.21 (1.78-2.75)	<0.001	0.56 (0.23-1.37)	0.288

*p<0.1; CI, Confidence interval

Discussion

The purpose of the study was to assess the association between the survival of patients with BS and prognosis factors using Weibull parametric models in the Presence of Competing Risks.

The competing risk survival analysis is appropriate in Weibull parametric models because of smoothing the fluctuations produced by the sampling error and providing better estimates. In addition, another advantage of the modeling includes no need to establish the assumption of the proportionality of hazards.[12, 13] Considering the benefits of the Weibull model, the model was fitted on the data to find the factors influencing the long-term mortality of brain stroke patients with the competing risk approach.

After BS, the mortality rate was 69%, of which 60% were deaths due to stroke, and 9% were deaths due to other causes. In line with our study, Hardy et al. assessed long-term (10-year) mortality after BS in Australia and reported a mortality rate of 79%.[14]

The multivariate Weibull Parametric Model results showed that older age at diagnosis, male sex, unemployed, having heart disease, and hemorrhagic stroke were directly and significantly related to death from BS. Older age at diagnosis and place of residence were directly and significantly associated with death by other causes.

Age at diagnosis was a prognostic factor, and our findings in multivariate analysis were similar to those of previous reports.[15-17] The present study results showed that with increasing age, the mortality of patients in both causes (BS and others causes) increases. Due to the significance of rising age in the death of BS and other reasons, more attention should be paid to the health of community members after brain stroke, especially older individuals.

Based on the results, sex was determined as another factor affecting mortality in the stroke-caused death, which was insignificant in the end for other causes. Further, men were 39% more at risk to die of stroke compared to the women, which is in line with the results of the research conducted in Europe,[16] the US,[17] and Arabic countries,[18] as well as those obtained by Mogensen et al.[19] However, some studies reported higher mortality due to BS and other causes among women.[1, 20-23] The conflict may be related to the physiological difference between men and women.

Among the individuals who died of BS, the mortality of the unemployed was 29% greater than that of employees, which is consistent with the result of Kivimäki.[24] According to Marshall, Cox, and Kimball, lower socioeconomic status groups survive less and have a more severe stroke.[25-27] In general, the mechanisms related to the effect of employment status on stroke mortality are ambiguous. The studies should be conducted using prospective population-based methods, and better control the confounding factors to confirm or reject these relationships.

Furthermore, heart disease was detected as another significant risk factor in death for stroke so that those with heart disease were 68% more at risk for dying of stroke compared to the others, which is in line with the results obtained by Mogensen et al.,[19] Ekker et al.,[28] and Hardie et al. regarding the evaluation of 10-year survival after BS.[14] The results indicated that heart diseases failed to be effectively controlled after the first BS attack, which requires more assessments.

BS mortality among those who experienced hemorrhagic stroke was 2.21 times higher than that in the individuals with ischemic one, which is in line with the results of some studies.[19, 20, 29] Physicians referred to higher mortality among patients diagnosed with hemorrhagic stroke than those with ischemic one because of rupturing blood vessels in the brain.

Regarding the death for other causes, the subjects living in rural died more, which is consistent with the results of the previous studies.[15, 30]

Indeed, inequality is observed among patients, and villagers have less access to post-disease care than the citizens.

Given that the number of subjects who died of other causes was low in the present study, the results of some factors were provided with caution. Thus, conducting studies with larger sample size is suggested to reveal all mortality-related clinical aspects. The high-income countries possess the systems for collecting death cause data, while the systems are not found in many low- and moderate-income ones. An improvement in the quality of death cause data is considered vital for enhancing health and decreasing the predictable mortality rate in the countries.

Conclusion

In general, the present study assessed the long-term mortality of BS patients in terms of dying due to BS and other causes as the competing risk. Some of the factors included high age, employment status, sex (men), heart diseases, and Cerebrovascular accident type (hemorrhagic) in the BS-caused death, as well as high age and residence, in the end, other causes. The recognition and awareness of the risk factors affecting the long-term mortality of stroke patients by the case of death allow interventions to be targeted and assessed appropriately.

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Author Contributions

All authors studied and confirmed the manuscript. Conceptualization: SN, MAJ, SMS, FF, RF. Data curation: SN, MAJ. 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.

Competing interests

The authors declare no competing interests.

References

1. Feigin VL, Norrving B, Mensah GA. Global burden of stroke. Circulation research. 2017;120(3):439-48.
2. Boehme AK, Esenwa C, Elkind MS. Stroke risk factors, genetics, and prevention. Circulation research. 2017;120(3):472-95.
3. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, et al. Heart disease and stroke statistics—2011 update: a report from the American Heart Association. Circulation. 2011;123(4):e18-e209.
4. Ovbiagele B, Goldstein LB, Higashida RT, Howard VJ, Johnston SC, Khavjou OA, et al. Forecasting the future of stroke in the United States: a policy statement from the American Heart Association and American Stroke Association. Stroke. 2013;44(8):2361-75.
5. Azarpazhooh MR, Etemadi MM, Donnan GA, Mokhber N, Majdi MR, Ghayour-Mobarhan M, et al. Excessive incidence of stroke in Iran: evidence from the Mashhad Stroke Incidence Study (MSIS), a population-based study of stroke in the Middle East. Stroke. 2010;41(1):e3-e10.

6. Delbari A, Roghani RS, Tabatabaei SS, Lökk J. A Stroke Study of an Urban Area of Iran: Risk Factors, Length of Stay, Case Fatality, and Discharge Destination. Journal of Stroke and Cerebrovascular Diseases. 2010;19(2):104-9.

7. Cho J, Choi YJ, Suh M, Sohn J, Kim H, Cho S-K, et al. Air pollution as a risk factor for depressive episode in patients with cardiovascular disease, diabetes mellitus, or asthma. Journal of affective disorders. 2014;157:45-51.

8. Klein JP, Bajorunaite R. Inference for competing risks. Handbook of statistics. 2003;23:291-311.

9. Kleinbaum DG, Klein M. Survival analysis: Springer; 2010.

10. Weibull W. The phenomenon of rupture in solids. IVA Handlingar. 1939;153.

11. Someeh N, Jafarabadi MA, Shamshirgaran SM, Farzipoor F. The outcome in patients with brain stroke: A deep learning neural network modeling. Journal of Research in Medical Sciences: The Official Journal of Isfahan University of Medical Sciences. 2020;25.

12. Iraji Z, Koshki TJ, Dolatkhah R, Jafarabadi MA. Parametric survival model to identify the predictors of breast cancer mortality: An accelerated failure time approach. Journal of Research in Medical Sciences. 2020;25(1):38.

13. Baghfalaki T. Interpretation of exposure effect in competing risks setting under accelerated failure time models. Journal of Biostatistics and Epidemiology. 2018;4(2):91-8.

14. Hardie K, Hankey GJ, Jamrozik K, Broadhurst RJ, Anderson C. Ten-year survival after first-ever stroke in the Perth Community Stroke Study. Stroke. 2003;34(8):1842-6.

15. Norouzi S, Jafarabadi MA, Shamshirgaran SM, Farzipoor F, Fallah R. Modeling Survival in Patients With Brain Stroke in the Presence of Competing Risks. J Prev Med Public Health. 2021;54:55-62.

16. Putaala J, Yesilot N, Waje-Andreassen U, Pitkäniemi J, Vassilopoulou S, Nardi K, et al. Demographic and geographic vascular risk factor differences in European young adults with ischemic stroke: the 15 cities young stroke study. Stroke. 2012;43(10):2624-30.

17. Grambauer N, Schumacher M, Beyersmann J. Proportional subdistribution hazards modeling offers a summary analysis, even if misspecified. Statistics in medicine. 2010;29(7-8):875-84.

18. Farghaly WM, El-Tallawy HN, Shehata GA, Rageh TA, Abdel-Hakeem NM, Abd Elhamed MA, et al. Epidemiology of nonfatal stroke and transient ischemic attack in Al-Kharga District, New Valley, Egypt. Neuropsychiatric disease and treatment. 2013;9:1785.

19. Mogensen UB, Olsen TS, Andersen KK, Gerds TA. Cause-specific mortality after stroke: relation to age, sex, stroke severity, and risk factors in a 10-year follow-up study. Journal of stroke and cerebrovascular diseases. 2013;22(7):e59-e65.

20. Rutten-Jacobs LC, Arntz RM, Maaijwee NA, Schoonderwaldt HC, Dorresteijn LD, van Dijk EJ, et al. Long-term mortality after stroke among adults aged 18 to 50 years. Jama. 2013;309(11):1136-44.

21. Andersen MN, Andersen KK, Kammersgaard LP, Olsen TS. Sex differences in stroke survival: 10-year follow-up of the Copenhagen stroke study cohort. Journal of Stroke and Cerebrovascular Diseases.

2005;14(5):215-20.
22. Madsen TE, Howard VJ, Jiménez M, Rexrode KM, Acelajado MC, Kleindorfer D, et al. Impact of conventional stroke risk factors on stroke in women: an update. Stroke. 2018;49(3):536-42.
23. de Rivero Vaccari JP, Bramlett HM, Perez-Pinzon MA, Raval AP. Estrogen preconditioning: a promising strategy to reduce inflammation in the ischemic brain. Conditioning medicine. 2019;2(3):106.
24. Kivimäki M, Vahtera J, Virtanen M, Elovainio M, Pentti J, Ferrie JE. Temporary employment and risk of overall and cause-specific mortality. American journal of epidemiology. 2003;158(7):663-8.
25. Marshall IJ, Wang Y, Crichton S, McKevitt C, Rudd AG, Wolfe CD. The effects of socioeconomic status on stroke risk and outcomes. The Lancet Neurology. 2015;14(12):1206-18.
26. Cox AM, McKevitt C, Rudd AG, Wolfe CD. Socioeconomic status and stroke. The Lancet Neurology. 2006;5(2):181-8.
27. Kimball MM, Neal D, Waters MF, Hoh BL. Race and income disparity in ischemic stroke care: nationwide inpatient sample database, 2002 to 2008. Journal of Stroke and Cerebrovascular Diseases. 2014;23(1):17-24.
28. Ekker MS, Verhoeven JI, Vaartjes I, Jolink WMT, Klijn CJM, de Leeuw F-E. Association of stroke among adults aged 18 to 49 years with long-term mortality. Jama. 2019;321(21):2113-23.
29. Liu C-H, Lin J-R, Liou C-W, Lee J-D, Peng T-I, Lee M, et al. Causes of death in different subtypes of ischemic and hemorrhagic stroke. Angiology. 2018;69(7):582-90.
30. Koifman J, Hall R, Li S, Stamplecoski M, Fang J, Saltman AP, et al. The association between rural residence and stroke care and outcomes. Journal of the neurological sciences. 2016;363:16-20.