Journal of Biostatistics and Epidemiology

J Biostat Epidemiol. 2022;8(3):248-257

Original Article

Competing Risks and Analysis of Patients with Brain Stroke: Cumulative Incidence Function and Cause-Specific Hazard Approach

Solmaz Norouzi[1, 2], Mohammad Asghari -Jafarabadi[3,4,5], Seyed Morteza Shamshirgaran[6], Farshid Farzipoor[7], Ramazan Fallah[2]

[1]Department of Biostatistics, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran.
[2]Department of Statistics and Epidemiology, Faculty of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran.
[3]Cabrini Research, Cabrini Health, VIC 3144, Australia.
[4]School of Public Health and Preventative Medicine, Faculty of Medicine, Nursing and Health Sciences, Monash University, VIC 3800, Australia.
[5]Road Traffic Injury Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.
[6]Department of Statistics and Epidemiology, Faculty of Health Sciences, Neyshabur University of Medical Sciences, Iran.
[7]Department of Health Education and Promotion, Faculty of Health, Tabriz University of Medical Sciences, Tabriz, Iran.

ARTICLE INFO

Received 19.02.2022
Revised 27.04.2022
Accepted 28.04.2022
Published 15.10.2022

Key words:
Competing risks;
Cumulative incidence function;
Cause-specific hazard;
Brain stroke

ABSTRACT

Introduction: In the presence of competing risks, patients with brain stroke (BS) experience death by various causes, such as diabetes, and heart disease, and other causes in the follow-up.
This study aimed to model the survival in patients with BS in the presence of these competing risk of death using cumulative incidence function (CIF) and cause-specific hazard (CSH) models.
Methods: In the study, 332 patients with the definitive diagnosis of BS were followed up for 10 years, and their mortality status due to BS or other causes was evaluated. In addition, significance tests and parameters were estimated by using STATA 14 software by considering the CIF and CSH model.
Results: The median follow-up time was 20.68 months for patients who died due to BS and 68.50 months for patients who died due to other causes. In the CIF model, Sex [BS: cumulative incidence hazard ratio (SHR) = 2.35, 90% confidence interval (CI) = (1.76-3.14)], Employment status [BS: 2.04(1.50-2.75)], History of blood pressure[BS: 1.64(1.25-2.14)], Heart disease[BS: 1.47(1.13-1.94)], Cerebrovascular accident type[BS: 0.77(0.69-0.87)]; age [Other case: 59-68 years, 2.61 (1.13-6.06) and ≥76 years: 3.03 (1.32-6.92)] were directly related to hazard of death. The CSH model resulted in similar estimates except for age [BS: 69-75 years; 1.31(1.18-1.45), ≥76 years; 1.37(1.23-1.53); other case: age 59-68 years 1.91 (1.22-2.99) and 69-75 years; 1.89 (1.21-2.96) and ≥76 years: 2.14 (1.36-3.37)], Sex[BS: 1.38(1.07-1.79)], History of blood pressure [BS: 1.57(1.20-2.05)], Heart disease [BS:1.44(1.09-1.91)] were directly related to hazard of death.
Conclusion: The estimation of CIF analysis, along with CSH one for the competing risks, is suggested to provide more precise information about patients' status in order to support adopted clinical decisions when aiming at assessing health related to a specific cause economically and determining the probability of occurring an intended event among other causes.

*.Corresponding Author: rfv@zums.ac.ir

Introduction

Finding risk factors affecting diseases in medicine is of particular importance because if such factors are found, provided they are modifiable, these factors can be eliminated or modified or their impact can be reduced. Due to the high prevalence of BS[1, 2] and the increase in the number of survivors of this disease, which leads to an increase in economic and social burden in society,[3] a better understanding of the factors affecting the long-term damping of the disease, as well as the prescription of optimal and specific treatment, information from the specific assessment of the cause of death, can be of great help to patients with BS. The occurrence time of various events such as death and disease relapse has a large share among abundant medical data. A part of science which deals with such data is called as survival. Survival analysis is a set of statistic methods for analyzing the data with the variable of the time required for an event to occur.[4] In many follow-up studies in the medical sciences field, the event may happen due to the reasons other than the main reason for the study.

Regarding the evaluation of brain stroke (BS) long-term mortality, the BS-caused death is considered as the main event, while patient may die during following-up for other causes such as heart disease and blood pressure etc., which are named as the competing risks.[5]

In the traditional analysis of survival data, researchers were mainly interested in understanding the distribution of survival times observed under a particular failure factor and considered all other factors as censored data. In 1972, cause-specific hazard model (CSH) that has been widely used since then to investigate the effects of explanatory (independent) variables affecting survival time.[6] The CSH is semi-parametric and does not require a special distribution for survival times.[7] It is necessary to check the assumption of proportional hazard (PH) (risk ratio is constant at all times) to use the CSH so that if this assumption is not met, the results of CSH are not reliable.[8]

But in recent years, with the development of models, the survival time of a particular risk in the presence of other competing risk factors has been assessed. One of the most widely used functions in competitive risk data analysis is the cumulative occurrence function. There are several methods for estimating and evaluating the effect of auxiliary variables using the CIF in competing risk data. And the effect of covariate variables on competing risk data is assessed using CIF modeling.[9] In conventional methods of survival analysis, CSH and CIF is estimated based on these hazards. This study aims to directly model the CIF and CSH with a competing risk approach and its application in BS data.

Methods

Design

A total of 332 patients with a definitive diagnosis of BS were entered from Imam Khomeini Ardabil Hospital, Iran. The duration of data collection was from June 2008 up to June 2018 and the follow-up period of patients from the time of diagnosis was ten- years.

Diagnosis of BS

Out of 332 patients with BS were included in the study. After recent follow ups it is confirmed that 92 patient were alive, 208 patient had died due to BS, 32 patient were other causes.

Inclusion criteria to join the study were the first-time BS, informed, and voluntary consent to participate in the study. Exclusion criteria were Transient Ischemic Attack (TIA) patients and patients with a previous history of BS. All patients complied with the International Coding System ICD-10 according to the Computerized Tomography (CT) scan and Magnetic Resonance Imaging (MRI).

Main variables

We collected the data on demographic and clinical
information, including: age (≤58 years; 59-68 years; 69-75 years; ≥76 years), employment status (employed; unemployed), sex (male; female), place of residence (urban; rural), a history of cerebrovascular accident (yes; no), heart disease (yes; no), now smokers (yes; no), and cerebrovascular accident type (ischemic; hemorrhagic).

Main outcome

The primary outcome of interest was death from BS, and competing risks were death from other causes. After ten years of follow-up, a total of 332 patients with BS, the number of patients who died due to BS was 208 (86.7%) and the number of patients who died due to other causes was 32 (13.3%). Patients' outcome status (The date of BS diagnosis, date of death, the cause of death) was ascertained by making documents or telephone calls to their relatives.

Statistical modeling

The total survival time of BS patients was calculated in months. Data were reported using mean (SD), median (min–max) for continuous variables and frequency (percent) for categorical variables. This study considers two types of risks: the death of patients with BS due BS and death due to other causes (heart disease, blood pressure, etc.). If death in patients with BS occur due to other causes, it is impossible to observe the death due to BS. Therefore, this study was performed using two models of cumulative incidence function (CIF) and cause-specific hazard (CSH) models.in determining the risk factors of competing risk of death due to BS and death from other causes in patients with BS. This part of statistical analyses was conducted by STATA software [ver.14] (StataCorp, College Station, Texas, USA).
Considering the existence of competing risks and using CSH and CIF models, the effect of each covariate variable was tested separately, the results of which are as follows.

Results

In this study, the mortality of 332 BS patients in two sections of death due to BS and death due to other causes during 10 years was investigated. The mean age at diagnosis was 69.08±(SD 11.82) years for patients who died of BS and 69.37±(SD 10.01) for patients who died of other causes. The mean follow-up time was 46.86±(SD 51.94) months for patients who died of BS and 78.98±(SD 37.72) for patients who died of other causes, respectively. The highest diagnosis of BS was between the ages of 69 and 75 years (30.9%) and the lowest was over 76 years (19.1%). Also, 50.6% of patients were female and 49.4% were male. In the death section due to BS, 86.8% were female and 86.6 were male, and in the death due to

other causes, 13.2% were female and 13.4% were male. See Table 1 for more results.
Nelson Allen's cumulative hazard for BS patients by cause of death is shown in Figure 1. The rate was about 50 percent for deaths due to BS in the 60th month and about 25 percent for deaths from other causes during the same period, indicating a higher risk of death from BS.

Assessing the PH assumption

The results of testing the PH assumption indicated that all predictors had satisfied the PH assumption in all CIF and CSH models ($p>0.1$).

Multivariate Analyses

The results related to the multivariate analysis of generalized CSH reflected the significance of age at diagnosis, sex, history of blood pressure and heart disease for the BS-caused death, as well as age at diagnosis at diagnosis for dying for other causes. Considering the effect of other variables, the results of the multivariate analysis concerning generalized CIF represented that sex and employment status, as well as the heart disease and history of blood pressure, and Cerebrovascular accident type were significant in the patients died of BS. However, only age at diagnosis was significantly related to death risk among those died for other causes.

Death due to BS

The results of both CSH and CIF models showed that BS was significantly related to Sex, blood pressure, and heart disease to the hazard of death. In the CSH model, males had 38% more hazard than Females did, and in the CIF model, men had 2.35 times more hazard of death by BS. The history of blood pressure was

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

Characteristic	N (%)	Brain stroke N (%)	Other causes N (%)
Age category (years)			
≤ 58	88 (26.7)	32 (94.12)	2 (5.88)
59- 68	77 (23.3)	44 (80)	11 (20)
69-75	102 (30.9)	80 (88.9)	10 (11.1)
≥76	63 (19.1)	50 (84.7)	9 (15.3)
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 (18.6)
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)
now smokers	64 (19.3)	40 (83.3)	8 (16.7)
Cerebrovascular accident type (hemorrhagic)	66 (20.4)	49 (92.5)	4 (7.6)

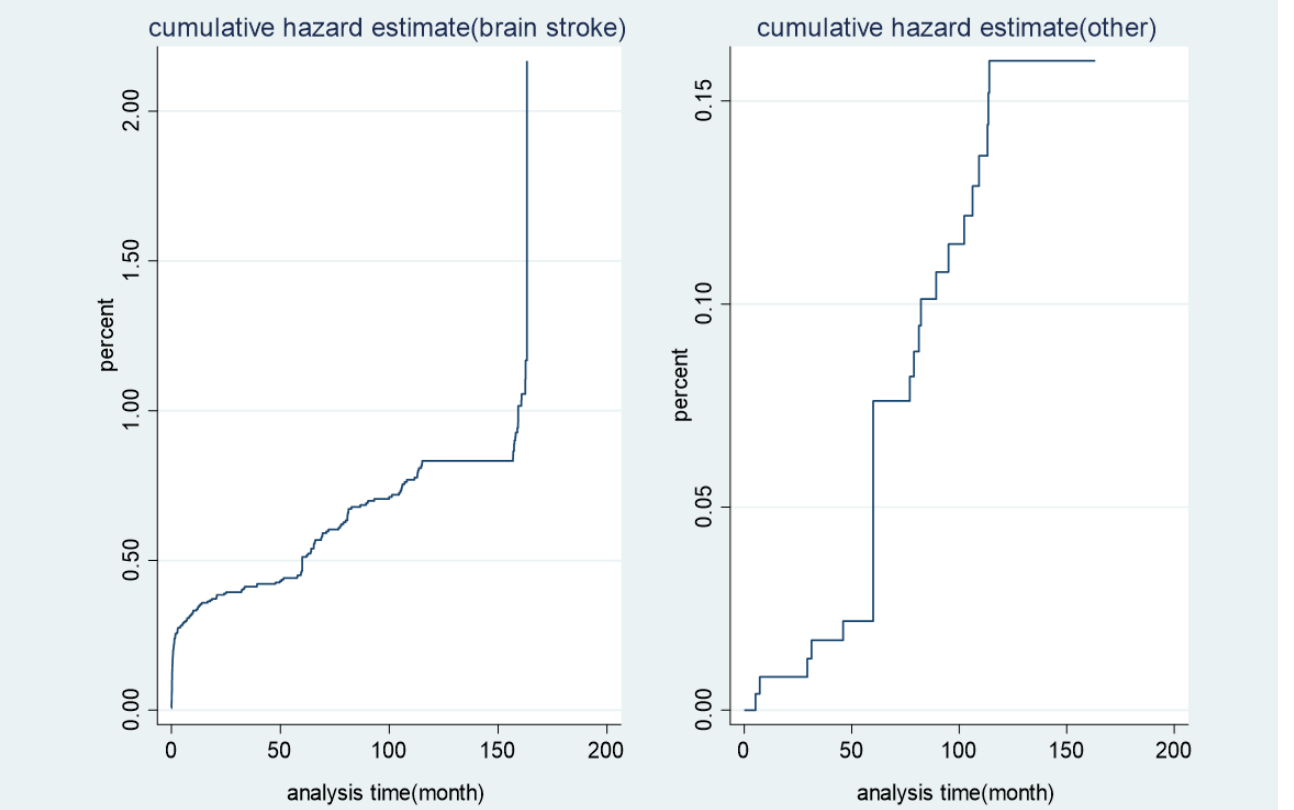

Figure 1. Nelson Allen Cumulative Risk for patients with BS by Cause of Death

Table 2. Results of multivariate CSH and CIF modeling for risk factors of death from brain stroke

Characteristic	CSH		CIF	
	HR (90% CI)	p-value	SHR (90% CI)	p-value
Age category (years)				
≤ 58	Reference	Reference	Reference	Reference
59- 68	1.09 (0.98-1.21)	0.155	0.96 (0.85-1.07)	0.526
69-75	1.31 (1.18-1.45)	<0.001*	0.97 (0.86-1.10)	0.730
≥76	1.37 (1.23-1.53)	<0.001	0.95 (0.83-1.08)	0.511
Sex (male)	1.38 (1.07-1.79)	0.039*	2.35 (1.76-3.14)	<0.001*
Employment status (unemployed)	NA	NA	2.04 (1.50-2.75)	<0.001*
History of cerebrovascular accident (yes)	0.77 (0.57-1.05)	0.167	0.78 (0.57-1.06)	0.181
History of blood pressure (yes)	1.57 (1.20-2.05)	0.005*	1.64 (1.25-2.14)	0.003*
Heart disease (yes)	1.44 (1.09-1.91)	0.029*	1.47 (1.13-1.94)	0.018*
Cerebrovascular accident type (hemorrhagic)	0.91 (0.81-1.03)	0.237	0.77 (0.69-0.87)	<0.001*

*p<0.1

CIF, Cumulative incidence function; CSH, Cause-specific hazard; HR, Hazard Ratio; SHR, Sub-distribution hazard ratio; CI, Confidence interval

associated with hazard ratios 1.57(1.20-2.05) and 1.64(1.25-2.14) in CSH and CIF models, respectively. Also, the heart disease was associated with hazard ratios 1.44(1.09-1.91) and 1.47(1.13-1.94) in CSH and CIF models, respectively (Table 2).

Death due to other causes

Regarding the death due to other causes, only age at diagnosis was obtained as significant in two models. The hazard ratio for the age at diagnosis range of 59-68 years old was respectively estimated as 1.91(1.22-2.99) and 2.61(1.13-6.06) in CSH and CIF models. In the range of 69-75 years was associated with hazard ratios 1.89(1.21-2.96) and 2.14(0.91-5.02) in CSH and CIF models, respectively. In the ≥76 years, this ratio was estimated 2.14 and 3.03 times the hazard of death by other causes than ≤ 58 years in CSH and CIF models, respectively (Table 3).

Discussion

In the present study, the common classic models in the competing risks problem were presented in two parts of inference based on the CIF and CSH hazards. The above-mentioned models were performed by considering the assumption of the independence of hazards, in each of which the results of estimating and comparing the quantity of interest were provided by the cause of death.

Each of the CSH and CIF-based analyses responds to different research questions. The CSH hazard analysis is applied when aiming to assess a special cause independently in the presence of the competing risks. The results of the analysis disregard the effect of other competing risks. The CSH analysis aims at examining the biological relationship between a specific factor and event occurrence by the intended cause, and the effect of other causes is ignored. During the CIF-based one, the probability of happening an event by the intended cause is compared by considering the

Table 3. Results of multivariate CSH and CIF modeling for risk factors of death from other causes

Characteristic	CSH		CIF	
	HR (90% CI)	p-value	SHR (90% CI)	p-value
Age category (years)				
≤ 58	Reference	Reference	Reference	Reference
59- 68	1.91 (1.22-2.99)	0.017*	2.61 (1.13-6.06)	0.061*
69-75	1.89 (1.21-2.96)	0.019*	2.14 (0.91-5.02)	0.141
≥76	2.14 (1.36-3.37)	0.006*	3.03 (1.32-6.92)	0.027*
Place of residence (urban)	0.89 (0.74-1.07)	0.300	0.83 (0.53-1.27)	0.470
History of cerebrovascular accident (yes)	0.99 (0.81-1.23)	0.996	1.24 (0.81-1.89)	0.399
History of blood pressure(yes)	0.66 (0.33-1.32)	0.329	0.53 (0.27-1.02)	0.110
Heart disease (yes)	1.06 (0.84-1.33)	0.667	0.71 (0.81-1.89)	0.319
Cerebrovascular accident type (hemorrhagic)	0.99(0.75-1.28)	0.931	0.74 (0.39-1.39)	0.431

*p<0.1

CIF, Cumulative incidence function; CSH, Cause-specific hazard; HR, Hazard Ratio; SHR, Sub-distribution hazard ratio; CI, Confidence interval

effect of other competing risks from a general perspective.[10] The simplicity of interpreting these models clinically by the users of life sciences field is important in selecting these two approaches.[11] The hazard ratio or survival rate and 90% confidence interval can be interpreted easily in clinical situations.

In this regard, the effect of each covariate variable was evaluated by the cause of death through CSH and CIF models in the present study in order to estimate the survival of BS patients more precisely. The estimated values, as well as the severity of the effect of variables were different in two models. The results obtained from CSH and CIF analyses were similar in the significance of the risk factors affecting mortality except for employment and BS type although these analyses respond to different questions.[5, 12] In both models, sex, as well as the heart disease and history of blood pressure was significant, and age at diagnosis was determined as the risk factor influencing long-term mortality in death due to other causes. Additionally, mortality hazard increased by rising age at diagnosis in death caused by other causes.

The data related to BS mortality have been analyzed through CSH method in most of the previous studies worldwide,[13-16] while estimating the CIF of the competing risks has been rarely utilized in this regard. Mogensen et al. evaluated the long-term mortality (10 years) of BS through CSH method among 988 BS patients and found that 310(31%) individuals died of BS, 201 (21%) heart disease, and 289 (29%) non-vascular diseases, respectively. However, 180 (18%) ones were alive after 10 years of follow-up.[17] Further, Ekker et al. assessed mortality and Kaplan-Meier analysis among BS patients.[18]

Regarding diabetes disease, Lim et al. reported that CSH can be only utilized when the frequency of hazards is rare; otherwise, two models can be applied.[19] Furthermore, Hyun et al. conducted a study among diabetic patients, which indicates the usability of both models in the presence of high competing risks, as well as the more appropriateness of CSH one compared to proportional CIF when the number of hazards is low.[20] Some of the studies estimated the effect of auxiliary variables in the presence of the competing risks by using CSH. In the model, the interpretation of the hazard ratio obtained from auxiliary variables in the presence of the competing risks is complex and ambiguous, which clarifies by using proportional subdistribution hazards.[21, 22] Based on comparing CSH and proportional subdistribution hazard models concerning pediatric cancer by Tai et al., analyzing the effect of various treatments without considering the competing risks leads to different results.[23] Wolbers et al. fitted Cause-specific hazard and proportional subdistribution hazard models in the presence of the competing risks among heart patients. In addition, the CSH estimated the hazard ratio of the intended event greater than the proportional subdistribution hazard one by ignoring and censoring the competing risks.[24] Jason and Gray estimated the effect of auxiliary variables in the competing risk data by using CSH hazard and proportional subdistribution models among breast cancer patients. The values estimated by two models were different, and the effect was significant in CSH hazard model, while no significant effect was observed in the other model.[9] Some researchers pointed out that considering hazards as censorship in the competing risk data could lead to skewed results.[25-27]

Limitations and suggestions

The need to conduct further studies among BS patients for collecting more precise results is considered as one of the limitations of the present study. Given that the sample size related to the patients died of other causes was small in one center, performing multi-center studies are suggested at macro level. Further, The Bayesian modeling of CIF is suggested as an alternative method for considering the limitations of the study. In the study, the analysis was performed based on the independence between hazards. Thus, it is suggested to evaluate the results by examining the dependence between hazards by using frailty model.

Conclusion

The present study sought to find the risk factors influencing the long-term mortality of BS patients with the competing risk approach. In this regard, the competing risks were inferred through CSH and CIF approaches based on the estimable quantities. The results of two analyses were similar in the variables of sex, heart disease, and history of blood pressure in BS-caused death, as well as age at diagnosis in death for other causes. Fitting an appropriate model in the presence of the competing risks was considered as important in the study. Based on the results, CIF and CSH models were more efficient in the death caused by BS and other causes, respectively. In general, CIF analysis can be further interpreted and discussed, and is more interesting clinically and epidemiologically. As already mentioned, the selection of a proper analysis is dependent on the research question under study.

Acknowledgements

The authors thank the Vice Chancellor for Research of Zanjan University of Medical Sciences. The study protocol was supported by the Research Deputy of Zanjan University of Medical Sciences [Ethic code: IR.ZUMS.REC.1399.221].

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.

Conflict of Interest

The authors declared no conflicts of interest.

References

1. Boehme AK, Esenwa C, Elkind MS. Stroke risk factors, genetics, and prevention. Circulation research. 2017;120(3):472-95.

2. 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.

3. Popa-Wagner A, Petcu E, Capitanescu B, Hermann D, Radu E, Gresita A. AGEING AS A RISK FACTOR FOR CEREBRAL

ISCHEMIA. UNDERLYING MECHANISMS AND THERAPY IN ANIMAL MODELS AND IN THE CLINIC. Mechanisms of Ageing and Development. 2020:111312.

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

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

6. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. Journal of the American statistical association. 1958;53(282):457-81.

7. Fox J. Cause-specific hazard proportional-hazards regression for survival data. An R and S-PLUS companion to applied regression. 2002;2002.

8. Ray S, Dacosta-Byfield S, Ganguli A, Bonthapally V, Teitelbaum A. Comparative analysis of survival, treatment, cost and resource use among patients newly diagnosed with brain metastasis by initial primary cancer. Journal of neuro-oncology. 2013;114(1):117-25.

9. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. Journal of the American statistical association. 1999;94(446):496-509.

10. Asghari Jafarabadi M, Mohammadi SM, Hajizadeh E, Fatemi SR. An evulation of 5-year survival of metastatic colon and rectal cancer patients using cumulative incidence models. Koomesh journal. 2013;14(2):207-14.

11. Zhang MJ, Fine J. Summarizing differences in cumulative incidence functions. Statistics in Medicine. 2008;27(24):4939-49.

12. Dignam J, Bryant J, Wieand HS. Analysis of Cause-Specific Events in Competing Risks Survival Data. Handbook of Statistics. 2003;23:313-29.

13. Thorvaldsen P, Asplund K, Kuulasmaa K, Rajakangas A-M, Schroll M. Stroke incidence, case fatality, and mortality in the WHO MONICA project. Stroke. 1995;26(3):361-7.

14. Koton S, Tanne D, Green MS, Bornstein NM. Mortality and predictors of death 1 month and 3 years after first-ever ischemic stroke: data from the first national acute stroke Israeli survey (NASIS 2004). Neuroepidemiology. 2010;34(2):90-6.

15. 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.

16. Kimura K, Minematsu K, Kazui S, Yamaguchi T. Mortality and cause of death after hospital discharge in 10,981 patients with ischemic stroke and transient ischemic attack. Cerebrovascular diseases. 2005;19(3):171-8.

17. 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.

18. 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.

19. Lim HJ, Zhang X, Dyck R, Osgood N. Methods of competing risks analysis of end-stage renal disease and mortality among people with diabetes. BMC medical research methodology. 2010;10(1):97.

20. Hyun J, Lim J, editors. Comparison of Three Different Approaches for Competing Risks Analysis of Patients with Diabetes. Canada-Korea Conference on Science and Technology; 2011.

21. 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.

22. Andersen PK, Geskus RB, de Witte T, Putter H. Competing risks in epidemiology: possibilities and pitfalls. International journal of epidemiology. 2012;41(3):861-70.

23. Tai B-C, Grundy RG, Machin D. On the importance of accounting for competing risks in pediatric cancer trials designed to delay or avoid radiotherapy: I. Basic concepts and first analyses. International Journal of Radiation Oncology* Biology* Physics. 2010;76(5):1493-9.

24. Wolbers M, Koller MT, Witteman JC, Steyerberg EW. Prognostic models with competing risks: methods and application to coronary risk prediction. Epidemiology. 2009:555-61.

25. Tai BC, Machin D, White I, Gebski V. Competing risks analysis of patients with osteosarcoma: a comparison of four different approaches. Statistics in medicine. 2001;20(5):661-84.

26. Huang X, Zhang N. Regression survival analysis with an assumed copula for dependent censoring: a sensitivity analysis approach. Biometrics. 2008;64(4):1090-9.

27. Chin C-C, Wang J-Y, Yeh C-Y, Kuo Y-H, Huang W-S, Yeh C-H. Metastatic lymph node ratio is a more precise predictor of prognosis than number of lymph node metastases in stage III colon cancer. International journal of colorectal disease. 2009;24(11):1297-302.