Functional dependence and mortality after stroke: long-term prognosis by age group

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Directed by Professor Deog Young Kim

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ABSTRACT

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Introduction: The prognosis after stroke according to onset age have been dealt in many studies. However, previous studies had limitations in that data was gathered with a relatively short total follow-up period, fewer participants, and fewer assessment iterations. The purpose of this study was to define the specific ages of stroke-onset, which determine the prognosis after stroke, and to elucidate the relationship between the age at stroke onset and long-term poststroke functional dependence and risk of death using large-scale, multi-center longitudinal cohort data.

Methods: Of the total 10,636 patients registered in the Korean Stroke Cohort for Function and Rehabilitation from August 2012 to May 2015, patients who completed follow-ups for four-year follow-up after stroke and met inclusion criteria were enrolled. To classify all patients into one to three groups with similar prognostic trajectories of Functional Independence Measure (FIM) and modified Rankin Scale (mRS) scores, and mortality risk, models adjusted for covariates were constructed with all possible combinations. Of these, the models with the best goodness-of-fit were selected for each dependent variable. Then, to investigate the time points with the most abrupt change in the effect of age groups on the FIM, mRS, and mortality risk, among the all possible adjusted model combinations with one to three time-intervals (zero to two time points) based on every time point in 30-day units, the models with the best goodness-of-fit were

selected.

For mortality analysis, the Kaplan-Meier method with log-rank tests was used to estimate mortality risk according to age group and associations between age groups and death were summarized with hazard ratios and 95% confidence intervals, estimated using the Cox proportional hazards model.

For all kinds of statistics, adjustment was applied for following variables: sex, stroke type (ischemic/hemorrhagic), initial National Institutes of Health Stroke Scale score, and stroke risk-factors.

Results: Of the 10,636 candidate patients, 7,805 patients met the inclusion criteria and consented to the long-term follow-up. For the analyses of FIM, mRS, and mortality, 5,247, 5,744, and 7,795 patients met the criteria for longitudinal analyses, and were included in the analyses, respectively.

In FIM and mRS, the models with the best goodness-of-fit revealed three age groups (≤70, 71-81, and 82≤ years old in FIM; ≤68, 69-80, and ≥81 years old in mRS) based on the age of stroke onset, and also did three time-intervals (<90, 90-390, 390< days in FIM; <60, 60-210, and 210< days in mRS) based on post-stroke durations.

In mortality, the model for age groups with the best goodness-of-fit revealed three groups (≤66, 67-82, 83≤ years old) based on the age of stroke onset, but the best model for post-stroke duration from onset did not divide time-intervals.

Conclusion: Based on the 70 and 80 years of age at the onset of stroke, the functional dependence and the risk of death after stroke significantly increased. Age-related differences in functional dependence increased over time after stroke onset; however, the difference in the risk of death according to stroke onset age groups did not increase significantly over time.

Key words: stroke, functional outcome, disability, mortality, onset age, longitudinal analysis, cohort study

Functional dependence and mortality after stroke: long-term prognosis by age group

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I. INTRODUCTION

The nature and etiology of stroke differ with age. Therefore, determining the age-group differences in patterns of long-term poststroke functional recovery and mortality is important to establish targeted management and rehabilitation treatment. A previous study found that age is a significant inverse predictor of excellent functional outcome after ischemic stroke, regardless of stroke severity, characteristics, or complications [1]. Previous studies have defined the "young age stroke" and "oldest-old age stroke" populations as those with first-in-life stroke at <45–49 years [2,3] and >80–90 years, respectively [4,5]; however this classification excludes a large proportion of the total stroke population. Moreover, different treatments are required depending on the age at stroke onset because the outcomes are age dependent [1]. Therefore, the classification criteria for stroke onset age are lacking. Furthermore, previous studies, had a relatively short total follow-up period (1 week–3 years) [1,6-10], limited number of participants (236–2,000 patients) [8,10,11], and limited assessment iterations (1–3 follow-up assessments) [3,4,6-11].

We hypothesized that the trajectories of changes in functional dependence and risk of death after stroke onset would be divided into several groups according to specific onset-age values. We further hypothesized that the disparity in the likelihood of the dependent variables increases over time among the age groups. We aimed to identify the specific ages of stroke-onset determining the prognosis post-stroke and the post-stroke periods, when the

difference of the dependent variables between the specific age groups rapidly increases.

II. MATERIALS AND METHODS

1. Design and study population

This study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement. An interim data analysis of KOSCO, a 10-year longitudinal follow-up, multi-center, prospective cohort study for all acute first-ever stroke patients admitted to participating hospitals in nine distinct areas of Korea was performed. The study protocol was approved by the ethics committees of each hospital, and the detailed protocol is available online [12]. From August 2012 to May 2015, 10,636 patients aged 19–100 years with first-ever stroke were recruited. Four-year longitudinal data of all patients were analyzed. The following are the criteria for inclusion in the KOSCO study: (1) first-ever acute stroke (ischemic stroke or intracerebral hemorrhage) with corresponding lesion and/or evidence of acute arterial occlusion on computed tomography brain imaging or magnetic resonance imaging, (2) age ≥ 19 years at stroke onset, and (3) onset of symptoms within seven days prior to inclusion. The exclusion criteria were as follows: (1) transient ischemic attack, (2) history of stroke, (3) traumatic intracerebral hemorrhage, and (4) non-Korean nationality. Patients who provided informed consent were enrolled in the study. If a patient was unable to provide informed consent, it was obtained from the patient's legally authorized representative. The Korean Stroke Cohort for Functioning and Rehabilitation (KOSCO) is an ongoing study. Therefore, in accordance with the internal regulations of the Korean National Institute of Health, the data used in this study was not publicly accessible.

Among the patients enrolled in the KOSCO study, those who met any of the following conditions were additionally excluded: (1) never been collected for dependent variable with exact date of assessment for corresponding analysis,

(2) in case of longitudinal analysis, if the dependent variable was not collected more than once or received a perfect score on the first assessment date, (3) missing data for any of the covariates for adjustment, and (4) pre-morbid conditions leading to neurologic deterioration, such as Parkinson's syndrome, normal pressure hydrocephalus, and brain tumors.

Of the total 10,636 candidate patients, 7,858 who met the inclusion criteria and consented to the long-term follow-up of the KOSCO study were screened for each dependent variable. Among them, 30 patients with missing data for any of the covariates for adjustment were excluded. Subsequently, an additional 23 patients with pre-morbid conditions, such as Parkinson's syndrome, normal pressure hydrocephalus, and brain tumors, leading to neurologic deterioration were excluded. Therefore, 7,805 patients remained to be screened for the longitudinal analyses of each dependent variable (Figure 1).

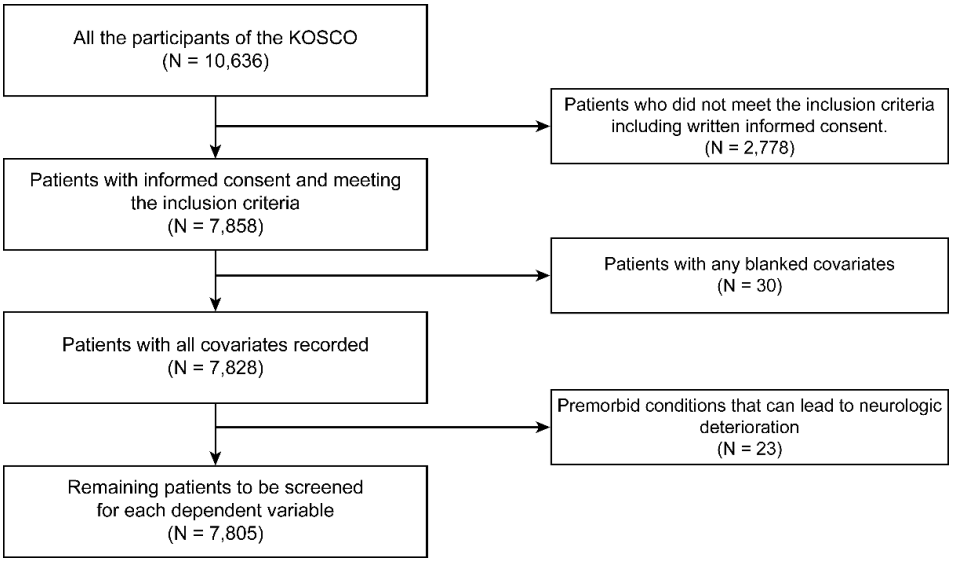

Figure 1. Flow chart of participant enrollment

KOSCO, Korean Stroke Cohort for Functioning and Rehabilitation. N, number.

Of the 7,805 patients, 56 without a Functional Independence Measure (FIM) total score at any time point and 2,502 with incomplete FIM scores (missing assessment dates, missing scores immediately after acute neurological treatment, or only one assessment) or perfect scores were excluded. Finally, 5,247 patients met the criteria for longitudinal analysis and were included in the longitudinal analysis of FIM. The nine time points of FIM assessment were as follows: immediately after completion of acute phase neurological treatment, 3 months, 6 months, 12 months, 18 months, 24 months, 30 months, 3 years, and 4 years. For the nine time points, 5,247, 4,482, 4,157, 3,936, 3,849, 3,786, 3,721, 3,626, and 3,417 patients were followed up.

Among the 7,805 patients, those without any modified Rankin Scale (mRS) total score or recorded assessment dates were excluded. Additionally, patients with blank mRS score, no disability, or without ≥2 assessments were further excluded. As a result, 5,744 patients who showed disability (mRS>0) a week post-stroke onset but did not die (6>mRS) until 4 years after onset were included in the longitudinal analysis of mRS. There were ten assessment time points for mRS: 1 week from onset, immediately after completion of acute phase neurological treatment, 3 months, 6 months, 12 months, 18 months, 24 months, 30 months, 3 years, and 4 years. At each of the ten time points, 5,744, 3,744, 4,440, 4,134, 3,976, 3,872, 3,843, 3,752, 3,645, and 3,448 patients were followed up.

The date of death was identified in each patient's KOSCO database entry, and censorship was based on the available last follow-up date. After screening 7,805 patients, 10 were excluded owing to the absence of any survival record, and 7,795 remained.

2. Outcome measure

For all patients, all the dependent variables were assessed based on specific time points (such as immediately after completion of acute phase neurological

treatment, and 3 months post-onset), and the precise assessment date was slightly different for each patient; all dates were recorded. The primary outcomes were the Functional Independence Measure (FIM) total score and modified Rankin scale (mRS) score. The FIM is an 18-item measurement tool aimed at assessing an individual's physical, psychological, and social function following a stroke, traumatic brain injury, spinal cord injury, or cancer, with a perfect score of 126 [13].

The mRS is a 6-point ordinal scale, with a perfect score of 0 indicating no disability and a worst-case score of 6 indicating death; it measures the impairment or independence of daily activities in people with stroke or other nervous system disorders [14]. Only patients who did not die in the primary outcome analysis were enrolled; therefore, no one had an mRS score of 6. For mRS, when acute phase treatment was terminated within 1 week of onset, only mRS measured at the termination of acute phase treatment was included in the analysis instead of mRS measured at 1 week of onset. For the secondary outcome, the date of death in the case of the deceased and the last follow-up date or follow-up loss in the case of survivors were collected.

3. Statistical modeling

Linear mixed model was used to evaluate the effects of age groups on FIM over follow-up period of study. We also used ordinal mixed model to examine the effect of age groups on mRS score changes from baseline, assuming proportional odds.

First, to classify all patients (19–100 years) into groups with similar prognostic trajectories of FIM, mRS, and mortality risk, respectively, models adjusted for covariates were constructed for 3,404 possible combinations (one [$_{82}C_0$], two [$_{82}C_1$], and three [$_{82}C_2$] age groups). The models with the best goodness-of-fit were selected using the Akaike (AIC) and Bayesian Information Criteria (BIC). To calculate the odds ratios (ORs) for the deterioration of FIM

score by age group, scores were classified into the following ordinal categories: mild (>90), moderate (54~90), and severe (<54) dependences [15].

Second, to investigate the time points with the most abrupt change in the effect of age groups on the FIM, mRS, and mortality, respectively, among the adjusted models of total 1,177 possible combinations (one [$_{48}C_0$], two [$_{48}C_1$], and three [$_{48}C_2$] time-intervals, respectively) based on 48 time points (30, 60, 90, …, 1,410, and 1,440 days from stroke onset) in 30-day units, the models with the best goodness-of-fit were selected using the AIC and BIC. For every time interval determined for each dependent variable, the ORs of FIM and mRS score deterioration, the hazard ratios (HRs) of mortality, and 95% confidence intervals among the age groups were estimated.

The Kaplan–Meier method with log-rank tests was used to estimate the mortality risk by age group. Associations between age groups and death were summarized with HRs and 95% confidence intervals and estimated using the Cox proportional hazards model. The proportional hazards assumption was checked using the Shoenfeld residuals method. When the proportional hazard assumption of covariates was violated, a time-dependent coefficient analysis was then considered.

To analyze the FIM, mRS, and mortality, adjustments for sex, stroke type (ischemic/hemorrhagic), initial National Institutes of Health Stroke Scale (NIHSS) score, and risk factors of stroke (hypertension, diabetes mellitus, coronary heart disease, atrial fibrillation, hyperlipidemia, obesity, smoking history, alcohol consumption, left ventricular hypertrophy, peripheral artery disease, low cholesterol, unruptured intracranial aneurysm, arteriovenous malformation, moyamoya disease, and family history of stroke) were performed. All covariates except the NIHSS score were dichotomous variables (see Supplementary Table S1, S2, and S3 for all covariates statistics).

4. Statistical analysis

Continuous variables were expressed as means (standard deviations), and categorical variables were expressed as numbers (percentages). A two-tailed *P* value of <0.05 was considered statistically significant. One-way analysis of variance for continuous variables and the chi-square test or Fisher's exact test for categorical variables were used to compare patient characteristics. All data analyses were performed using the R Statistical Package, version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

III. RESULTS

1. Baseline demographic and clinical characteristics

Although slight differences were observed in the mean or percentage values of baseline demographic and clinical characteristics depending on the dependent variable type, the mean age at onset was 64–65 years, the percentage of women was 42–43%, the rate of ischemic type stroke was 80–82%, and the mean initial NIHSS score was 4.4–4.9 (see Table 1 for baseline characteristics of each dependent variable for all patients and each age group).

Table 1. Baseline characteristics of each dependent variable for age groups and all patients

	Age Groups			Total	*P* value
	Group 1	Group 2	Group 3		
Functional Independence Measure					
Onset age range	19–70	71–81	82–100	19–100	
n		1,658	439	5,247	
Onset age	56.8 (9.6)	75.6 (3.0)	85.1 (3.1)	65.1 (13.0)	<0.001
Female sex§	1,136 (36.1)	836 (50.4)	298 (67.9)	2,270 (43.3)	<0.001
Ischemic type§	2,405 (76.3)	1,483 (89.5)	405 (92.3)	4,293 (81.8)	<0.001
Initial NIHSS score	3.9 (5.6)	5.1 (6.5)	6.9 (7.2)	4.5 (6.1)	<0.001
modified Rankin Scale					
Onset age range	19–68	69–80	81–100	19–100	
n	3,199	1,946	599	5,744	
Onset age	55.2 (9.3)	74.4 (3.3)	84.5 (3.3)	64.8 (13.2)	<0.001
Female sex§	1,094 (34.2)	929 (47.7)	391 (65.3)	2,414 (42.0)	<0.001
Ischemic type§	2,374 (74.2)	1,734 (89.1)	543 (90.7)	4,651 (81.0)	<0.001
Initial NIHSS score	3.6 (5.5)	4.9 (6.5)	7.1 (7.6)	4.4 (6.2)	<0.001
Mortality analysis					
Onset age range	19–66	67–81	82–100	19–100	
n	4,013	3,092	690	7,795	
Onset age	54.0 (9.1)	73.9 (4.0)	85.4 (3.3)	64.7 (13.4)	<0.001

Female sex§	1,359 (33.9)	1,465 (47.4)	457 (66.2)	3,281 (42.1)	<0.001
Ischemic type§	2,900 (72.3)	2,684 (86.8)	617 (89.4)	6,201 (79.6)	<0.001
Initial NIHSS score	4.0 (6.4)	5.3 (7.4)	8.2 (8.6)	4.9 (7.13)	<0.001

Continuous variables are expressed as mean (standard deviation).

§ Categorical variables are expressed as number (percentage).

NIHSS, National Institutes of Health Stroke Scale.

2. Classified age groups and segmented post-stroke time intervals in functional outcome and disability

Among all combinations of one to three age groups, FIM and mRS had the best goodness-of-fit when they were divided into three age groups(Groups 1, 2, and 3 in ascending order). Regarding FIM, when the stroke onset age was divided at 71 and 82 years, the model showed the best goodness-of-fit according to the AIC and BIC. Similar, mRS showed the best goodness-of-fit when the stroke onset age was divided at 69 and 81 years. Of all combinations with one to three time-intervals models, FIM and mRS showed the best goodness-of-fit when they were all divided into three periods.

Based on the constructed models for longitudinal analysis of FIM scores including interactions of 1-month interval timepoints and age groups, the selected model showed that differences among three age-groups in functional outcomes were significantly increased at 90 and 390 days post-stroke onset. Based on Group 1, in the three intervals, the adjusted ORs for FIM score deterioration were 3.5, 10.5, and 29.2 in Group 2, and 9.5, 94.8, and 338.4 in Group 3, respectively. A statistically significant (P<0.001) difference was observed in all comparisons in all intervals. As the time interval progressed, the adjusted ORs for FIM score deterioration among the age groups increased (Table 2 (A), Figure 2, and 3 (A)).

Table 2. Longitudinal analysis of **(A)** Functional Independence Measure, and **(B)** modified Rankin Scale

(A) Odds ratios (95% confidence intervals) for FIM			
	Periods from stroke onset		
Age group	onset – 90 days	90 – 390 days	390 days – 1,440 days
Age<71	1 (reference)	1 (reference)	1 (reference)
71≤Age<82	3.5 (2.8, 4.4)‡	10.5 (8.6, 12.8)‡	29.2 (24.3, 35.0)‡
Age≥82	9.5 (6.8, 13.3)‡	94.8 (68.6, 130.9)‡	338.4 (247.2, 463.3)‡

(B) Odds ratios (95% confidence intervals) for mRS			
	Periods from stroke onset		
Age group	onset – 60 days	60 – 210 days	210 days – 1,440 days
Age<69	1 (reference)	1 (reference)	1 (reference)
69≤Age<81	1.6 (1.4, 1.8)‡	3.7 (3.2, 4.1)‡	7.4 (6.7, 8.2)‡
Age≥81	4.0 (3.3, 5.0)‡	20.7 (16.8, 25.4)‡	67.9 (57.4, 80.3)‡

All values are adjusted for sex, stroke type, initial National Institutes of Health Stroke Scale score, and risk factors of stroke. FIM, Functional Independence Measure. mRS, modified Rankin Scale.

‡ $P < 0.001$.

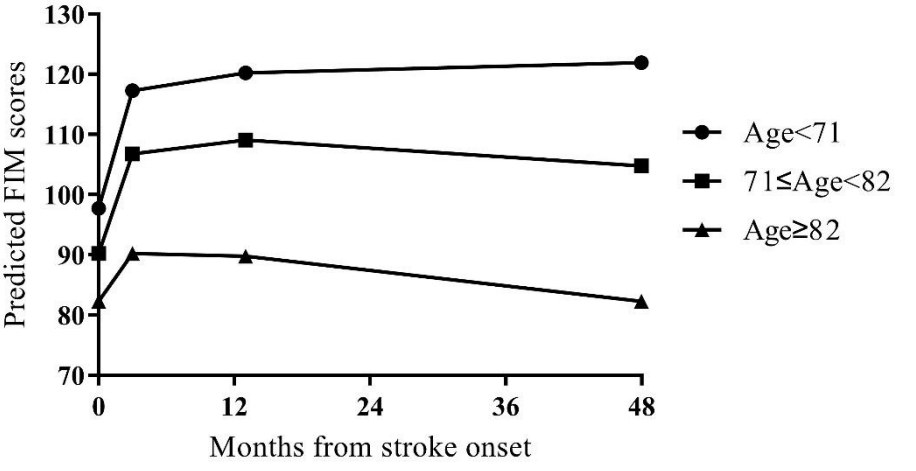

Figure 2. Longitudinal trends for each age group in predicted mean Functional Independence Measure scores adjusted for covariates

FIM, Functional Independence Measure.

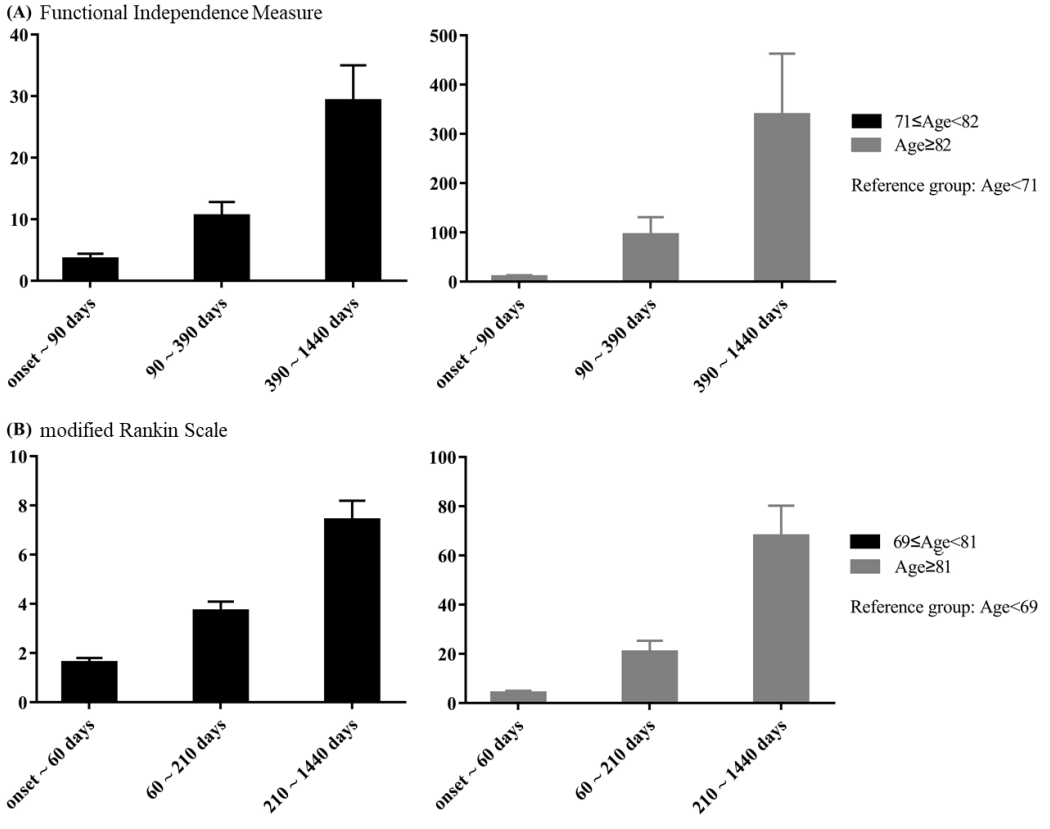

Figure 3. Adjusted odds ratios and 95% confidence intervals of predicted scores adjusted for covariates (A) Functional Independence Measure and (B) modified Rankin Scale

The selected mRS model showed that age-group differences in disability were statistically significantly widened at 60 and 210 days after stroke onset. When using Group 1 as a reference, in order of three intervals, the adjusted odds ratios were 1.6, 3.7 and 7.4 in Group 2, and 4.0, 20.7, and 67.9 in Group 3, respectively. There were statistically significant ($p < 0.001$) differences in every interval. As with FIM, the adjusted odd ratios of mRS score deterioration between age groups increased with time (Table 2 (B), Figure 3 (B), and 4).

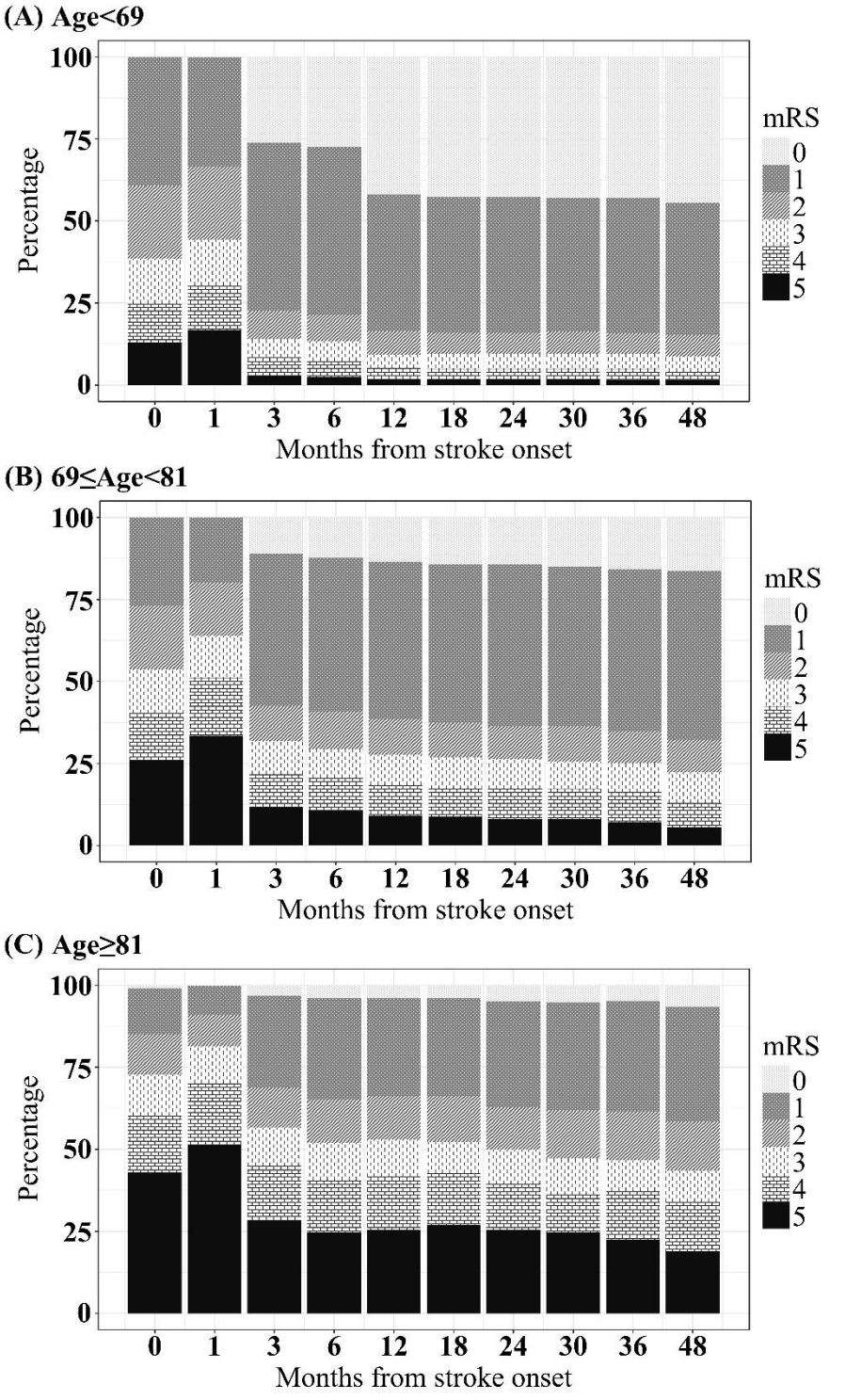

Figure 4. Longitudinal trends in predicted proportions of modified Rankin Scale scores adjusted for covariates

(A) <69 Age group, (B) ≥69 Age group, and (C) ≥81 Age group

mRS, modified Rankin Scale

3. Classified age groups and segmented post-stroke time intervals in mortality risk

Mortality trajectory showed the best goodness-of-fit when patients were divided at 67 and 82 years of stroke onset age. The number of intervals was one for mortality risk, because the assumption of the proportional HR for the age group was satisfied over the entire 4-year period post-stroke. Table 3 shows that the HR for death increased with age. Compared with Group 1, Groups 2 and 3 showed HRs of 0.3 and 2.5, respectively, at ≤4 years post-stroke onset (all P < 0.001; Table 3 and Figure 5). The unadjusted Kaplan-Meier curves for each age group are shown in Figure 6.

Table 3. Adjusted hazard ratios hazard ratios and 95% confidence intervals for mortality analysis using Cox proportional hazards model

Age group	Periods from stroke onset
	onset ~ 4 years
Age<67	1 (reference)
67≤Age<82	3.4 (2.9, 4.0)‡
82≤Age	8.4 (6.9, 10.2)‡

All values are adjusted for sex, stroke type, initial National Institutes of Health Stroke Scale score, and risk factors of stroke.

‡ *P* < 0.001.

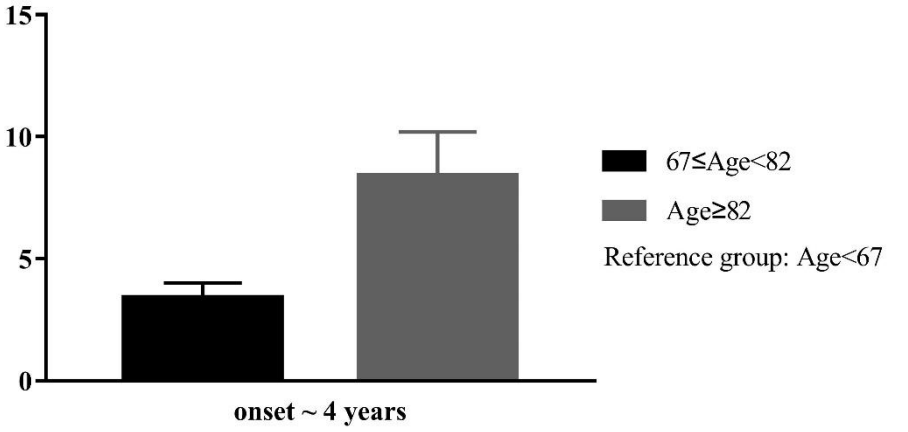

Figure 5. Adjusted hazard ratios and 95% confidence intervals of mortality analysis using Cox regression

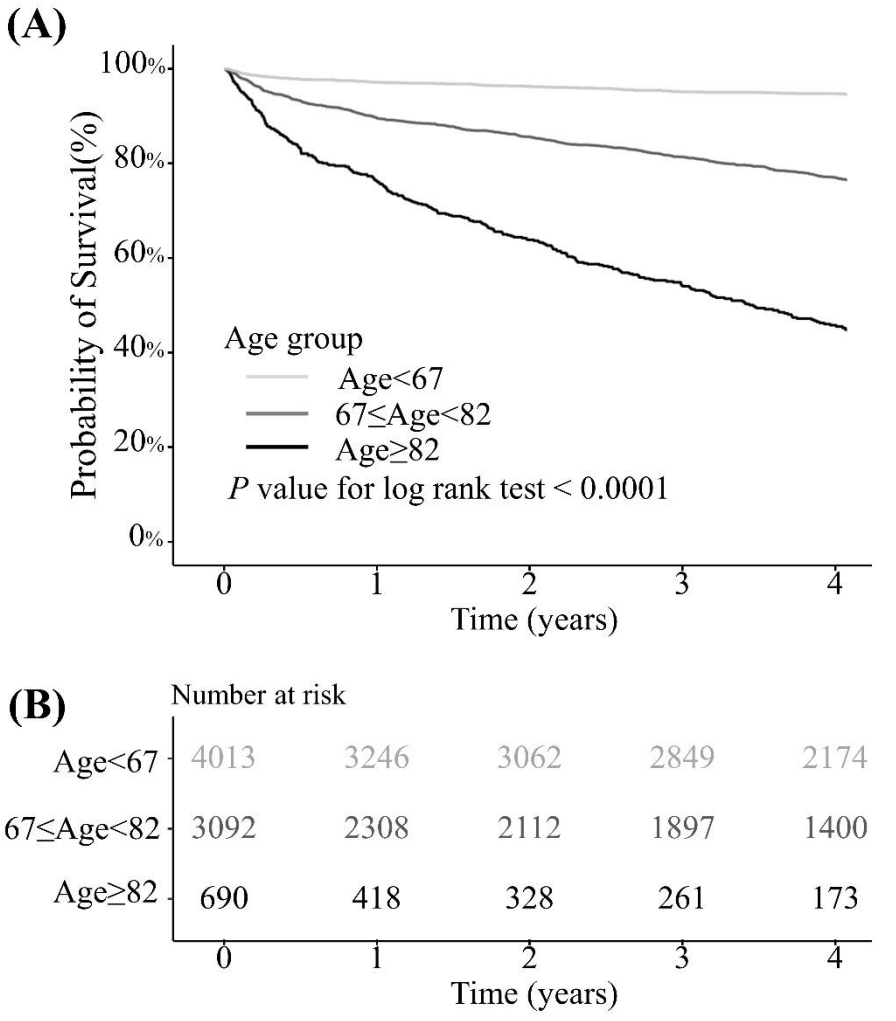

Figure 6. Unadjusted (A) Kaplan–Meier survival curves and (B) the number of patients at risk for each age group

IV. DISCUSSION

This is the first study to statistically clarify the age criteria with different longitudinal trajectories in terms of functional dependence and death risk after first-ever stroke, using multi-center large-scale prospective cohort data with multiple follow-ups. Furthermore, the difference in the likelihood of recovery by onset age gradually increased as the post-stroke period progressed. Conversely, the relatively high mortality risk after stroke due to higher age at stroke onset remained relatively constant over time. These associations were independent of various demographic characteristics, initial stroke severity, and stroke-related risk factors.

Although a previous study reported that functional outcomes at discharge were not statistically significantly affected by age [8], worse recovery in older stroke patients is not unexpected. While previous studies have shown that aging reduces the expected degree of functional recovery and increases the risk of death after stroke [1,16,17], our study has revealed that the aging effect on functional recovery and disability post-stroke increases differentially at certain time points.

Multiple comorbidities, defined as the presence of two or more chronic diseases, are common in elderly patients with stroke. The prevalence of multiple comorbidities was shown to be 89% and 60% for patients aged > 65 and < 65 years, respectively [18]. The same study showed that in patients hospitalized with stroke and transient ischemic attack, these comorbidities affect subsequent hospital readmission, functional recovery, and mortality. Moreover, the number of comorbidities in older stroke patients increased over time. Therefore, the difference in the likelihood of recovery gradually increases with age.

The available neuropathological findings attribute the decline in recovery potential to aging. Age-related microcirculatory changes are associated with impaired endothelial function and cerebral autoregulation; these promote neuroinflammation, microvascular damage, and decoupling of the neurovascular

bundle, leading to cortical dysfunction [19]. Recurrence of cerebrovascular disease without obvious symptoms may also explain our findings. Silent stroke and white matter hyperintensity have a reported prevalence of 20–90% depending on age, and cerebral microbleeding has been reported in up to 40% of the elderly aged >80 years [20]. Additionally, if the degree of sequelae from the first symptomatic stroke is severe, it is hardly detectable, even if an additional stroke onset occurs.

The findings on the prognosis of stroke patients by age group are consistent with experimental animal models: the degree of functional recovery after stroke is lower in older than in younger mice [21,22]. To date, this age-dependent differentiated recovery has been described as enhanced regenerative capacity in the brain as well as an age-dependent deregulation of neuronal and glial repair and impaired angioneogenesis [23,24].

To determine the change in the ability of human brain neuroplasticity due to aging, a gene expression regulation study harvested RNA from postmortem samples of 30 frontal lobes aged 26–106 years and analyzed it using the Affymetrix gene chip [25]. In this study, DNA damage that adversely affected synaptic function and plasticity was the most prominent in all genes after age 70, which is consistent with our clinical findings, and the relevant evidence helps interpret our results.

Here, the HRs for mortality by age group were not notable because aging increases the risk of life-threatening comorbidities indirectly induced by stroke. However, the mortality rate did not change differentially at certain time points in terms of model fit, unlike the FIM and mRS. Thus, the HR for death by age group post-stroke may remain relatively constant over time. Our results are supported by a previous study comparing the long-term mortality of individuals aged >70 and <70 years at stroke onset; the intergroup rate of standardized mortality ratio was maintained at approximately 1.3 over 1, 5, 10, and 15 years after stroke onset [26]. Another longitudinal study conducted 8–20 years follow-up of 13,481 patients aged <50 years at stroke onset. The patients survived >30 days after index stroke,

and the main cause of death was malignancy (32.7%), followed by infection, trauma, and other miscellaneous causes (34.9%)[27]. These results may be attributed to the fact that stroke mortality after the acute phase is indirectly related to neurological deterioration. Conversely, functional outcome or degree of disability is directly related to neurological sequelae.

This study has some limitations. First, variables, such as cognitive function or level of consciousness, potentially affecting the functional level and degree of disability were not reflected in the analyses. In a previous study, return to work was possible in only approximately 40% of young stroke patients, in contrast to a relatively good recovery of function in elderly patients [28]. This discrepancy may be attributed to the fact that measurement methods, including those of the mRS and FIM, did not measure high-level cognitive functions necessary for work life. Second, data were collected only at tertiary hospital level or higher; patients who visited small- and medium-sized community hospitals in the acute phase were not included. Thus, the cohort included patients with relatively high initial severity and may not reflect the outcomes of minor strokes. Third, the deterioration of function due to recurrence after discharge from the first hospital was not reflected in the analysis. Therefore, the results of this study reflect only the influence of first-ever stroke because we considered that the recurrence of stroke itself is inextricably linked with aging and should not be considered as a separate factor from senescence [29]. Fourth, although adjustments for risk factors assigned as covariates were reflected in the results, other comorbidities increasing with age, not entered as covariates in this study, may have also affected the results. Fifth, regarding the cause of death, we did not analyze direct death due to stroke because the cause of death was not recorded in a significant percentage of the deceased patients.

After the 10-year follow-up observation of the KOSCO, the cohort data used in this study will be complete. Therefore, it is necessary to confirm whether the results of this study are reproducible, even in the analysis using longer follow-

up period data. Furthermore, as human life expectancy and the percentage of young age stroke increase, future studies based on data collected from changed demographic and healthcare settings are warranted.

V. CONCLUSION

At the age of approximately 70 and 80 years at stroke onset, the functional dependence and the risk of death after stroke significantly increased. Particularly, onset age-related differences in functional dependence increased over time after stroke onset. Additionally, the risk of death in stroke patients was affected by the age at stroke onset; however, the difference in the risk of death according to stroke onset age did not increase significantly over time. Our results provided a rationale for stratified treatment goal setting according to the age at stroke onset.

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ABSTRACT(IN KOREAN)

뇌졸중 후 기능적 의존성 및 사망률 : 연령별 장기 예후

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서론: 발병 연령에 따른 뇌졸중 후 예후는 많은 연구에서 다루어져 왔다. 그러나 선행 연구들은 상대적으로 짧은 총 추적 기간, 적은 수의 연구대상자, 적은 수의 반복평가라는 한계점들이 있었다. 이 연구의 목적은 대규모의 다기관 종단 코호트 데이터를 사용하여 뇌졸중 후 예후를 결정하는 뇌졸중 발병시의 구체적인 연령을 정의하고, 발병시 연령과 뇌졸중 후 장기간 기능적 의존성 및 사망 위험 간의 장기적 관계를 밝히는 것이었다.

방법: 2012년 8월부터 2015년 5월까지 Korean Stroke Cohort for Function and Rehabilitation에 등록된 총 10,636명의 환자 중 뇌졸중 후 4년 추적 관찰을 완료하고 선정 기준을 충족한 환자를 대상으로 분석하였다. 모든 환자를 FIM(Functional Independent Measure) 및 mRS(Modified Rankin Scale) 점수 및 사망위험도에서 유사한 예후 궤적을 가진 1~3개 그룹으로 분류하기 위해 가능한 모든 조합으로 공변량에 대해 조정된 모델들을 구성했다. 이 중 각 종속변수에 대해 적합도가 가장 좋은 모델들을 선택했다. 이후, 그런 다음, FIM, mRS 및 사망 위험에 대한 연령 그룹의 영향측면에서 가장 급격한 변화가 있는 시점을 조사하기 위해 1-3 시간 간격(0-2 시점)을 기반으로 하는 모든 가능한 수정 모델 조합 중 30일 단위의 모든 시점에서 적합도가 가장 좋은 모델을 선택했다.

사망위험 분석을 위해 로그 순위 검정을 포함하는 Kaplan-Meier 방법을 사용하여 연령 그룹에 따른 사망 위험도를 추정하고 연령 그룹과 사망 간의 연관성을 Cox 비례 위험 모델을 사용하여 추정 위험비 및 95% 신뢰 구간으로 요약했다.

모든 종류의 통계에 대해 성별, 뇌졸중 유형(허혈성/출혈성), 초기 National Institutes of Health Stroke Scale 점수 및 뇌졸중 위험 인자들에 대해 조정이 적용되었다.

결과: 10,636명의 후보 환자 중 7,805명의 환자가 포함 기준을 충족하고 장기 추적 관찰에 동의했다. FIM, mRS, 사망률 분석을 위해 5,247명, 5,744명, 7,795명의 환자가 종단 분석의 기준을 충족하여 각 분석에 포함되었다.

FIM과 mRS에서 가장 좋은 적합도를 가진 모델은 뇌졸중 발병 연령에 따라 세 가지 연령 그룹(FIM에서 ≤70세, 71-81세 및 82세≤; mRS에서 ≤68세, 69-80세 및 81세≤), 뇌졸중 후 기간에 따라 세 구간의 시간 간격 (FIM에서 <90일, 90-390일, 390일<, mRS에서 <60일, 60-210일 및 210일<) 을 밝혀냈다.

사망률에서 연령 그룹에 대한 가장 적합도가 가장 좋은 모델은 뇌졸중 발병 연령을 기준으로 세 그룹 (≤66세, 67-82세, 83세 ≤)을 나타냈지만, 뇌졸중 발병 이후 기간에 대한 가장 적합도가 좋은 모델은 시간 간격을 나누지 않았다.

결론: 뇌졸중 발병 시 약 70세 및 80세 연령을 기준으로 기능적 의존성과 뇌졸중 후 사망 위험이 유의미하게 증가했다. 기능적 의존성의 발병 연령에 따른 차이는 뇌졸중 발병 후 시간이 지남에 따라 증가했지만, 뇌졸중 발병 연령군에 따른 사망 위험의 연령군간 차이는 시간이 지남에 따라 유의미하게 증가하지 않았다.

핵심되는 말: 뇌졸중, 기능적 결과, 장애, 사망률, 발병 연령, 종단 분석, 코호트 연구

APPENDICES

Supplementary Table S1. Baseline characteristics of covariates for analysis for Functional Independence Measure

All patients	
n	5,247
Female sex	2,270 (43.3)
Ischemic type	4,293 (81.8)
Initial NIHSS score§	4.5 (6.1)
hypertension	2,994 (57.1)
diabetes mellitus	1,264 (24.1)
coronary heart disease	376 (7.2)
atrial fibrillation	548 (10.4)
left ventricular hypertrophy	61 (1.2)
peripheral artery disease	40 (0.8)
hyperlipidemia	770 (14.7)
low cholesterol	155 (3.0)
unruptured intracranial aneurysm	68 (1.3)
arteriovenous malformation	19 (0.4)
moyamoya disease	25 (0.5)
obesity	596 (11.4)
family history of stroke	460 (8.8)
smoking history	1,359 (25.9)
alcohol consumption	1,981 (37.8)

	Age Groups			
	Group 1	Group 2	Group 3	*P* value
Onset age range	19~70	71~81	82~100	
n	3,150	1,658	439	
Female sex	1,136 (36.1)	836 (50.4)	298 (67.9)	<0.001
Ischemic type	2,405 (76.3)	1,483 (89.5)	405 (92.3)	<0.001
Initial NIHSS score§	3.9 (5.6)	5.1 (6.5)	6.9 (7.2)	<0.001
hypertension	1,581 (50.2)	1,103 (66.5)	310 (70.6)	<0.001
diabetes mellitus	705 (22.4)	476 (28.7)	831 (18.9)	<0.001

coronary heart disease	170 (5.4)	160 (9.7)	461 (10.5)	<0.001
atrial fibrillation	214 (6.8)	276 (16.6)	581 (13.2)	<0.001
left ventricular hypertrophy	33 (1.1)	19 (1.2)	9 (2.1)	0.185
peripheral artery disease	17 (0.5)	18 (1.1)	5 (1.1)	0.061
hyperlipidemia	468 (14.9)	246 (14.8)	561 (12.8)	0.494
low cholesterol	87 (2.8)	54 (3.3)	14 (3.2)	0.6
unruptured intracranial aneurysm	47 (1.5)	17 (1)	4 (0.9)	0.301
arteriovenous malformation	15 (0.5)	2 (0.1)	2 (0.5)	0.097
moyamoya disease	21 (0.7)	3 (0.2)	1 (0.2)	0.049
obesity	406 (12.9)	159 (9.6)	31 (7.1)	<0.001
family history of stroke	315 (10)	124 (7.5)	21 (4.8)	<0.001
smoking history	1,076 (34.2)	245 (14.8)	38 (8.7)	<0.001
alcohol consumption	1,475 (46.8)	443 (26.7)	631 (14.3)	<0.001

All variables are categorical and expressed as numbers (percentages), except for initial NIHSS score§.
NIHSS, National Institutes of Health Stroke Scale.

Supplementary Table S2. Baseline characteristics of covariates for analysis for modified Rankin Scale

All patients	
n	5,744
Female sex	2,414 (42.0)
Ischemic type	4,651 (81.0)
Initial NIHSS score§	4.4 (6.2)
hypertension	3,219 (56.0)
diabetes mellitus	1,352 (23.5)
coronary heart disease	375 (6.5)

atrial fibrillation	567 (9.9)
left ventricular hypertrophy	60 (1.0)
peripheral artery disease	43 (0.8)
hyperlipidemia	850 (14.8)
low cholesterol	117 (2.0)
unruptured intracranial aneurysm	70 (1.2)
arteriovenous malformation	20 (0.4)
moyamoya disease	31 (0.5)
obesity	669 (11.7)
family history of stroke	497 (8.7)
smoking history	1,522 (26.5)
alcohol consumption	2,220 (38.6)

	Age Groups			
	Group 1	Group 2	Group 3	*P* value
Onset age range	19~68	69~80	81~100	
n	3,199	1,946	599	
Female sex	1,094 (34.2)	929 (47.7)	391 (65.3)	<0.001
Ischemic type	2,374 (74.2)	1,734 (89.1)	543 (90.7)	<0.001
Initial NIHSS score§	3.6 (5.5)	4.9 (6.5)	7.1 (7.6)	<0.001
hypertension	1,510 (47.2)	1,286 (66.1)	423 (70.6)	<0.001
diabetes mellitus	661 (20.7)	575 (29.6)	116 (19.4)	<0.001
coronary heart disease	146 (4.56)	172 (8.84)	57 (9.52)	<0.001
atrial fibrillation	191 (5.97)	281 (14.4)	95 (15.9)	<0.001
left ventricular hypertrophy	29 (0.91)	20 (1.03)	11 (1.84)	0.121
peripheral artery disease	17 (0.53)	20 (1.03)	6 (1)	0.084
hyperlipidemia	452 (14.1)	313 (16.1)	85 (14.2)	0.145
low cholesterol	58 (1.81)	51 (2.62)	8 (1.34)	0.061
unruptured intracranial aneurysm	42 (1.31)	23 (1.18)	5 (0.83)	0.609
arteriovenous malformation	15 (0.47)	3 (0.15)	2 (0.33)	0.162

moyamoya disease	27 (0.84)	3 (0.15)	1 (0.17)	0.001
obesity	417 (13)	204 (10.5)	48 (8.01)	<0.001
family history of stroke	322 (10.1)	146 (7.5)	29 (4.84)	<0.001
smoking history	1,150 (36)	321 (16.5)	51 (8.51)	<0.001
alcohol consumption	1,577 (49.3)	554 (28.5)	89 (14.9)	<0.001

All variables are categorical and expressed as numbers (percentages), except for initial NIHSS score§.
NIHSS, National Institutes of Health Stroke Scale.

Supplementary Table S3. Baseline characteristics of covariates for analysis for mortality

All patients	
n	7,795
Female sex	3,281 (42.1)
Ischemic type	6,201 (79.6)
Initial NIHSS score§	4.9 (7.13)
hypertension	4,350 (55.8)
diabetes mellitus	1,811 (23.2)
coronary heart disease	527 (6.8)
atrial fibrillation	771 (9.9)
left ventricular hypertrophy	78 (1.0)
peripheral artery disease	53 (0.7)
hyperlipidemia	1,090 (14.0)
low cholesterol	247 (3.2)
unruptured intracranial aneurysm	106 (1.4)
arteriovenous malformation	28 (0.4)
moyamoya disease	45 (0.6)
obesity	922 (11.8)
family history of stroke	637 (8.2)
smoking history	2,045 (26.2)
alcohol consumption	2,987 (38.3)

	Age Groups			
	Group 1	Group 2	Group 3	*P* value
Onset age range	19~66	67~81	82~100	
n	4,013	3,092	690	
Female sex	1,359 (33.9)	1,465 (47.4)	457 (66.2)	<0.001
Ischemic type	2,900 (72.3)	2,684 (86.8)	617 (89.4)	<0.001
Initial NIHSS score§	4.0 (6.4)	5.3 (7.4)	8.2 (8.5)	<0.001
hypertension	1,834 (45.7)	2,033 (65.8)	483 (70.0)	<0.001
diabetes mellitus	776 (19.3)	898 (29.0)	137 (19.9)	<0.001
coronary heart disease	174 (4.3)	286 (9.3)	67 (9.7)	<0.001
atrial fibrillation	209 (5.2)	454 (14.7)	108 (15.7)	<0.001
left ventricular hypertrophy	33 (0.8)	32 (1.0)	13 (1.9)	0.034
peripheral artery disease	20 (0.5)	25 (0.8)	8 (1.2)	0.072
hyperlipidemia	549 (13.7)	455 (14.7)	86 (12.5)	0.222
low cholesterol	101 (2.5)	125 (4.0)	21 (3.0)	0.001
unruptured intracranial aneurysm	60 (1.5)	40 (1.3)	6 (0.9)	0.39
arteriovenous malformation	19 (0.5)	6 (0.2)	3 (0.4)	0.116
moyamoya disease	40 (1.0)	4 (0.1)	1 (0.1)	<0.001
obesity	535 (13.3)	337 (10.9)	50 (7.3)	<0.001
family history of stroke	381 (9.5)	224 (7.2)	32 (4.6)	<0.001
smoking history	1,471 (36.7)	515 (16.7)	59 (8.6)	<0.001
alcohol consumption	1,993 (49.7)	892 (28.9)	102 (14.8)	<0.001

All variables are categorical and expressed as numbers (percentages), except for initial NIHSS score§.

NIHSS, National Institutes of Health Stroke Scale.