Predicting risk of fracture after stroke diagnosis in Korean Adults

Yeunsoo Yang

The Graduate School

Yonsei University

Department of Public Health

Predicting risk of fracture after stroke diagnosis in Korean Adults

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Yeunsoo Yang

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This certifies that the Dissertation of ***Yeunsoo Yang*** is approved.

Heejin Kimm: Thesis Supervisor

Sun Ha Jee: Thesis Committee Member #1

Chung Mo Nam: Thesis Committee Member #2

Hyeon Chang Kim: Thesis Committee Member #3

Kem Ji Jung: Thesis Committee Member #4

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LIST OF ABBREVIATION

Abbreviation	Description
AIC	Akaike information criterion
BMI	Body mass index
BMD	Bone mineral density
CI	Confidence interval
DBP	Diastolic blood pressure
DF	Degree of freedom
DM	Diabetes mellitus
FRAX	Fracture Risk Assessment Tool
FBS	Fasting blood sugar
FRS	Fracture risk after stroke
FRSE	Fracture risk after stroke extended
HIRA	Health Insurance Service Review & Assessment service
HR	Hazard ratio
ICD-10	International Classification of Diseases
IDI	Integrated Discrimination Improvement
LOS	Length of Stay
mRS	modified Ranking Score
NHIS-KCPS	National Health Insurance Service-Korean Cancer Prevention Study
NRI	Net Reclassification Improvements
SBP	systolic blood pressure
SD	Standard deviation
SE	Standard error
TC	Total Cholesterol

ABSTRACT

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Yang, Yeunsoo

Department of Public Health

The Graduate School

Yonsei University

(Directed by Professor Heejin Kimm)

Background: Post-stroke comorbidities associated with stroke patients include pneumonia, deep venous thrombosis, pressure ulcers, and urinary tract infections. They also have an increased risk of future low-trauma fractures, such as those caused by falls to the ground. A prior study found that the likelihood of low-trauma fractures in stroke patients was greater than 30 percent higher than in the general population. In that study, independent fracture risk variables were discovered, however, the accuracy of fracture prediction and the most predictive risk factors were not determined. For low-trauma fracture screening, prediction criteria for general population have been devised and verified. World Health Organization Fracture Risk score tool (FRAX) is the best verified and most extensively used assessment. However, the FRAX was obtained from a broad community sample, does not account for unique stroke-related variables, and has not been validated in a stroke patient group. Therefore, research is required to predict fracture risk in stroke patients.

Methods: This study utilized cohort data from the National Insurance Health Service-Koran Cancer Prevention Study (NHIS-KCPS). To determine if the fracture score (FRAX) formation variable was appropriate for stroke patients, we randomly separated them into two groups. Subjects were randomly separated into two groups: 50% for model creation and 50% for model validation. The association between

risk factors and the incidence of fractures was analyzed using a cause-specific hazard model. In the NHIS-KCPS, the FRAX variables used to predict the 5-year fracture risk equation were validated using a discrimination and calibration method. Integrated discrimination improvement (IDI) and net reclassification improvement (NRI) were used to evaluate the improvement in fracture prediction by adding osteoporosis, total cholesterol (TC), and length of hospital stay (LOS), respectively. The variable LOS, which can indicate the severity of a stroke, was selected as a replacement variable; TC is defined as a variable influencing stroke; and, osteoporosis is a risk factor for fracture; thus, these three factors were selected as additional variables.

Results: Using a large prospective cohort study, a predictive model for fracture risk after stroke (FRS) was developed and validated in a Korean population. The mean ages of the participants in the data used to create the fracture risk prediction model were 67.8 years for men and 72.9 years for women, and 67.9 years and 72.8 years, respectively, in the verification data. The FRS model was used to predict fractures in both men and women following a diagnosis of stroke. In the validation set, the C-statistic for the FRS model after stroke generated in the Korean cohort was 0.7001 (95% CI, 0.69-0.71) for men and 0.6370 (95% CI, 0.63-0.65) for women. When osteoporosis, total cholesterol, and duration of stay were used to evaluate the

improvement in the predictive capacity of the extended FRS model (FRSE), the addition of total cholesterol resulted in a C-statistic of 0.6371 (95% CI, 0.63-0.65) and the model increased predictive ability by IDI 0.015848 (p<.0001), NRI 0.041350 (p<.0001) in women. For the FRSE model in men, the length of stay led to a C-statistic of 0.7035 (95% CI, 0.69-0.72) and increased the ability to predict by IDI 0.015848 (p=.0001) and NRI 0.041350 (p=.0001).

Conclusion: This study assessed the applicability of FRAX factors except for bone mineral density(BMD) test and family history for predicting fracture risk in the Korean population following a diagnosis of stroke. The FRS model appears suitable as predictor for this group. Since the FRS model does not require a BMD test nor parent hip fracture history information, it might be more useful for clinical usage as a screening test and is therefore expected to contribute to prevention by finding a post-stroke fracture risk group.

Keywords: Fracture, Stroke, FRAX, Fracture prediction

I. INTRODUCTION

1. Study background

In 2019, The top global causes of death, in order of total number of lives lost, are associated with three broad topics: cardiovascular (ischemic heart disease, stroke), respiratory (chronic obstructive pulmonary disease, lower respiratory infections) and neonatal conditions which include birth asphyxia and birth trauma, neonatal sepsis and infections, and preterm birth complications.[1] The World's biggest killer is ischemic heart disease, responsible for 16% of the world's total deaths. Since 2000, the largest increase in deaths has been for this disease, rising by more than 2 million to 8.9 million deaths in 2019. Stroke and chronic obstructive pulmonary disease are the 2nd and 3rd leading causes of death, responsible for approximately 11% and 6% of total deaths respectively.[1]

Stroke refers to a disease in which a blood vessel supplying blood to the brain is blocked or ruptured, leading to death or physical disability due to brain damage.[2] Cerebrovascular disease in Korea ranks 4th among the top 10 causes of death, including stroke.[3] According to the statistical data of the Health Insurance Review and Assessment Service, the number of patients receiving treatment for stroke

(cerebral hemorrhage and cerebral infarction) is increasing every year.[4] Most of the strokes are ischemic stroke,[5] and the number of patients with cerebral infraction increased from 2015 to 2020, and the number of patients has increased sharply after the age of 40.

1-1. The risk of facture after stroke diagnosis

The risk of fracture increased by 1.5 to 4 times after a stroke,[6] and fractures complicate the post-stroke course, leading to functional decline and impeding rehabilitation.[7] The number of patients experiencing a fracture after a stroke diagnosis is 1.7 times the hip fracture rate of the general population and 2.3 times that of myocardial infarction patients. The fracture tends to occur most frequently less than 6 months (46.6%) after stroke diagnosis, and 13.7% in patients longer than 6 months and less than 1 year. It shows that about 60% of stroke patients experience a fracture within 1 year after stroke diagnosis.[8] The risk of low trauma fracture in stroke patients was increased compared with matched controls from the general population,[9] and the Cumulative Incidence Functions (CIFs) of fractures are about 8% at 2 years and 13% at 4 years after acute ischemic stroke in Korea.[10] The hemiplegic side of the femur was reported to be the site most affected by slipping.[8] In 2012, Korea reported changes in the characteristics of stroke patients, focusing

on increasing age, increasing frequency of dyslipidemia and heart embolism, increasing thrombolytic treatment, decreasing stroke severity, and decreasing stroke onset time.[11] Despite the declining severity of a stroke, complications and aftereffects of stroke diagnosis continue to be an issue, and managing the quality of life of stroke patients has become a crucial duty.

1-2. Major factors contributing to adult disability

Stroke is the main cause of disability in adults, and more than half of sufferers have limited mobility.[12, 13] After discharge, individuals with a stroke experience a diminished quality of life due to cognitive impairment, depression, pain, and fatigue,[14-16] as well as a variety of sequelae and consequences including sarcopenia, falls, and fractures.[17-19] For instance, a stroke in particular vascular regions of the brainstem can result in certain stroke syndromes[20] that impair balance function and increase the risk of falls. Moreover, impairments in vision, motor, sensory, or cognitive function[21] following a stroke may result in injuries resulting from falls. In addition to falls, a rapid decrease in bone mineral density[22, 23] after stroke may contribute to fractures among stroke patients. Following a stroke, weakness inevitably leads to limited weight bearing on the affected leg, resulting in a loss of bone mass.[24] Additionally, social isolation, hunger, decreased sun exposure, and the

resulting vitamin D deficiency[25] exacerbate bone loss in stroke patients. Finally, typical therapies for stroke, such as oral anticoagulants, are associated with an increased risk of osteoporosis and fracture.[26, 27] Recognizing risk factors for post-stroke fractures and identifying high-risk patients is crucial for preventing post-stroke fractures and improving patients' prognoses by targeted medication therapy.[28] In a previous study, 37% of patients reported at least one fall within six months following a stroke, and 37% of patients who fell experienced an injury requiring medical attention, including 8% who fractured.[29] Two years following stroke, 60.7% of those who fell experienced at least two falls, and 23.4% sustained fractures.[30]

1-3. Genetic factors for decreased bone mineral density

The of the bone mineral density (BMD) in affected sides was highly correlated with the duration of hemiplegia, but the correlation was not shown in the case of those in unaffected sides.[31] MicroRNA-378 Suppressed Osteogenesis of MSCs and Impaired Bone Formation via Inactivating Wnt/β-Catenin Signaling. The abnormal bone tissues and impaired bone quality were observed in the miR-378 TG mouse, and moreover, the bone-fracture healing was delayed in the femoral fracture model of this TG mouse.[32] Zhu’s group reported that skeletal muscle mass was

significantly reduced in TGmiceglobally overexpressing miR-378 (TG) compared with that in the WT mice.[33] The levels of microRNA-378f were significantly increased among the patients with osteoporosis and maximal total SVD score and positively correlated with parathyroid hormone and osteocalcin.[34]

Few studies have identified a relationship between fractures and stroke. Nevertheless, the majority of the cited studies were cross-sectional. Only four out of eighteen prospective studies had longer than ten-year follow-up periods, and fracture as an endpoint was uncommon.[35] Stroke is a high-risk factor for fractures; however, this fact is not acknowledged. It is difficult to locate research on the prediction of fractures in stroke patients, particularly research on Korean stroke patients. Between 1990 and 2017, the absolute number of people who died of a stroke or survived with a disability nearly doubled.[36] It is vital to identify fracture risk factors following a stroke for focused intervention and prevention of primary fractures. Importance is attached to the development of a predictive model for these interventions and preventive measures. However, there are few research on fracture prediction in people with a stroke. A recent study conducted on Korean stroke patients was an epidemiological investigation regarding fractures that addressed individuals with acute ischemic stroke and was not a prediction model study.[10] Although it was a fracture prediction model study in other countries, it was designed

for Canadians and is difficult to apply to Koreans due to racial variations.[37]

Predicting the occurrence of an adverse event or outcome over time is an important issue in clinical medicine, health services research, and in population and public health. Estimating the incidence of adverse events over time provides clinicians, patients, and policy-makers with important evidence necessary for medical decision making and for making informed policy decisions.[38]

2. Study Objectives

The objectives of this study, which utilized data from two large prospective cohorts, are as follows:

(1) To determine whether FRAX variables are suitable fracture predictors in stroke patients without BMD.

(2) To develop the predictive model which can identify stroke patients with a high risk of low trauma fractures within 5-year after stroke diagnosis.

(3) To determine whether the model is improved by adding osteoporosis or total cholesterol (TC) or length of stay (LOS) using NRI and IDI

II. MATERIALS AND METHODS

1. Data used

This study was based on Korean Cohort Study to predict a model of fracture after a stroke diagnosis. The National Insurance Health Service-Korean Cancer Prevention Study (NHIS-KCPS) is used in the derivation and validation of the fracture after stroke diagnosis prediction model.

1-1. NHIS-KCPS cohort

The National Insurance Health Service-Koran Cancer Prevention Study (NHIS-KCPS) is a prospective cohort study that has undergone 28 years of follow-up (1992-2020). The study includes the insured, who were government employees and private school staff, who were enrolled in Korean Medical Insurance Corporation (currently the National Health Insurance Service [NHIS] as Government Employees' Union and Private School Staff Union), and who underwent regular physical examinations at least once between 1992 and 1999, between the ages of 20 and 95.[39, 40]

1-3. Study population

In NHIS-KCPS cohort includes 2,384,045 participants and used a detailed health and lifestyle questionnaire between 1997 and 1999 as the baseline data. The participant in this study was tracked until December 31, 2020. The mean duration of fracture incidence time is 6.2 years (6.4 years for men and 5.9 years for women).

Within the total sample size of 2,384,045, only 158,078 participants who had a stroke were included. We excluded from this study were 584 individuals under the age of 40 and 2,478 individuals above the age of 90 and excluded 6,554 individuals diagnosed with cancer within two years prior to and after stroke diagnosis. Also, 16,957 individuals with missing information on exercise status, body mass index (BMI), or who had an extremely high (>100 kg/m^2) or low BMI (<16 kg/m^2) were excluded. To identify the severity of stroke, 14,655 patients with missing length of stay (LOS) were excluded, and 5,706 patients with LOS equal to the survival duration were classified as having died upon discharge and excluded. In addition, 142 patients with the same dates for their stroke and fracture diagnoses were ruled out. None of the participants were classified as accidents. Finally, 2,316 patients those who died within 30 days after a stroke diagnosis were also excluded. The final study participants were 108,686 individuals, of which 63,857 and 44,829 are men and women, respectively.

To develop and validate a risk model for predicting Fracture, we selected a derivation set consisting of fifty percent of all participants and sampled them at random. 54,483 participants (31,864 men and 22,619 women) were included in the derivation set, while 54,203 participants (31,993 men and 22,210 women) were included in the validation set. Below is a concise description of each cohort that participated (Figure 1).

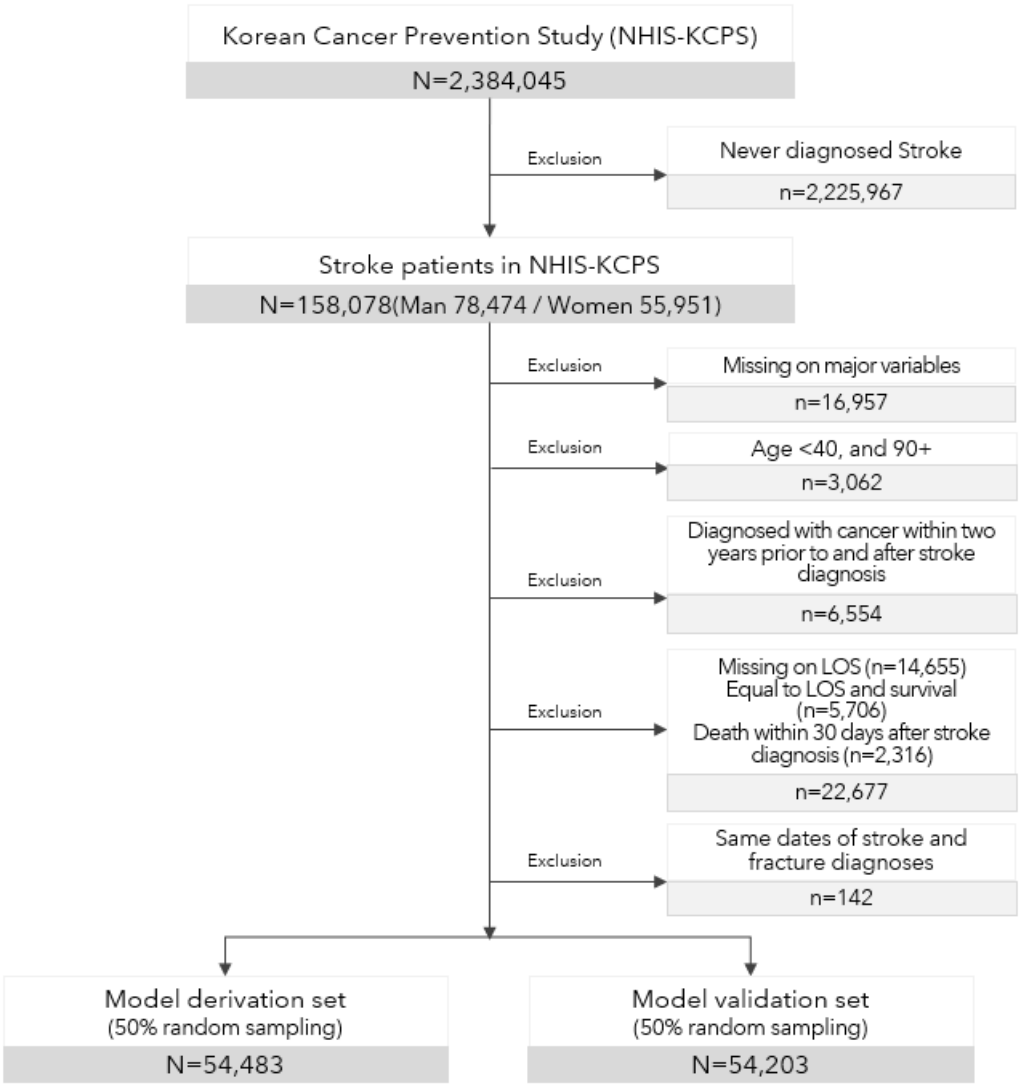


Figure 1. Flowchart of study population, NHIS-KCPS

2. Data collection

2-1. NHIS-KCPS cohort data

The participants were instructed to self-report their lifestyle, including a history of smoking (never, former, current), alcohol amount (g/day: ethanol), exercise participation (yes, no), and medical history, including hypertension (yes, no), diabetes (yes, no), and family medical history (yes, no). Height and weight were measured directly in light clothing with shoes removed. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. Blood pressure was measured while the participants remained seated using a standard mercury sphygmomanometer or an automatic manometer.[39, 41] Standard mercury sphygmomanometers or automatic manometers were used to measure BP in a seated position. Fasting serum samples were collected to determine the total cholesterol and fasting blood glucose. Diabetes was defined by a self-reported past history of diabetes or detected hyperglycemia (fasting glucose ≥126 mg/dl) as a result of the health examination. Hypertension was defined as having blood pressure ≥ 140/90 mmHg.[39, 41]

3. Variables

3-1. Outcome variables

The outcome of the study was the occurrence of a new low-trauma fracture within the 5-year after stroke diagnosis. Outcomes were captured using linked all outpatient and hospital records from 1996 to 2020 were collected by NHIS. Because NHIS is a national institution, follow-up was expected to be 100% complete.

A low-trauma fracture was defined as any fracture of the femur, forearm, humerus, pelvis or vertebrae, including ground-level falls but excluding fractures resulting from trauma, motor vehicle accidents, falls from a height. The codes for variables derived from NHIS data were coded using the International Classification of Disease, 10th edition (ICD-10) specified in the Table 1.

3-2. Independent variables

Based on the variables utilized in FRAX, independent variables were developed for this investigation. BMD and a parent's hip fracture were not accounted for in the data and were therefore not utilized. Age was determined as age at the time of stroke diagnosis and usage of glucocorticoids within one year of stroke diagnosis. In Table 2 are offered descriptions of additional variables (Table 2, Figure 2).

Table 1. ICD-10 code for variables and Code for drugs from HIRA*

Variables	ICD-10 Code
Stroke	ICD-10 codes: I60, I61, I62, I63, ICD-9 codes: 430, 431, 432, 433, 434
Osteoporosis	ICD-10 codes: M80-M82, ICD-9 code: 733
Parkinson's disease	ICD-10 codes: F02.3, G20, G21.0-G21.4, G21.8, G21.9, G22, ICD-9 code: 322
Second osteoporosis	ICD-10 codes: E21, ICD-9 code 252-, K90, ICD-9 code: 579, K70, K701-K709, E10, E10.0-E10.9, E23.0, E29.1
Rheumatoid arthritis	ICD-10 codes: M05, M06, ICD-9 code 714
Ischemic heart disease	ICD-10 codes: I20, I21, I22, I23, I24, I25
Atrial fibrillation	ICD-10 codes: I48.0, I48.1, I48.2, I48.9
Dementia	ICD-10 codes: G30, F00, F01, F02, F03, ICD-9 codes: 290, 294, 331
Malabsorption syndromes	ICD-10 code: K90, ICD-9 code: 579
Hyperparathyroidism	ICD-10 codes: E21, ICD-9 code 252-
Renal disease	ICD-10 codes: E102, E112, E132, E142, I12, I13, N08, N18, N19, ICD-9 codes: 403.0, 403.1, 403.9, 404.0, 404.1, 404.9, 585.x, 586.x, 588.8, 588.9
Hyperlipidemia	ICD-10 codes: E78, E78.0, E78.1, E78.2, E78.3, E78.4, E78.5, E78.00, E78.08
Falls	ICD-10 codes: W00-W19, ICD-9 codes: E880 to E888
Low-trauma fracture	ICD-10 codes: S72.0-72.2 (hip), S52 (forearm), S42.2 (upper arm), S32.1-32.5, S32.7, S32.8 (pelvis), S22.0, S22.1, S32.0 (vertebrae), ICD-9 codes: 820-821 (hip), 810-812 (upper arm), 813 (forearm), 805.6, 805.7, 808 (pelvis), 805-806 (vertebrae)
Death	All-cause mortality

Name of drug	Code
Beclomethasone	114507CSI, 114508CSI, 114509CLQ, 114509CSI, 114510CSI, 114511ATE, 502000CSI
Betamethasone	116401ATB, 296900ATB, 344900CCM, 345000CCM, 346400CCM, 346400COM, 490500CCM, 490500COM
Budesonide	119401CLQ, 119402CAE, 119403CAE, 119403CCM, 119404CSI, 119405CLQ, 119406ACH, 119407CAE
Deflazacort	140801ATB
Desonide	141501CCM, 141501CLT
Dexamethasone	141901ATB, 141902CCO, 141902COS, 141903ATB, 141904ATB, 141906CIM, 331500COO, 331500COS
Fludrocortisone	160201ATB
Hydrocortisone	170901ATB, 170901CCM, 170901CLT, 170901COM, 170901CSS, 170902CLT, 170902CSS, 170903CLQ, 170905ATB, 170906ATB, 171001CCM, 171101CCM, 171101CLT, 171201BIJ, 171202BIJ, 171301CCM
Methylprednisolone	193301ATB, 193302ATB, 193305ATB, 193304ATB, 193401CCM, 193401COM, 193401CLT, 193401COM
Prednisolone	217001ATB, 217002CCM, 217002CLT, 217003ASY, 217004ASY, 217102COS, 217103COS, 217302BIJ
Triamcinolone	243201ATB, 243202ATB, 243203ATB, 243301BIJ, 243302COM, 243302CPA, 243303BIJ, 243304CCM

* HIRA, Health Insurance Service Review & Assessment service

Table 2. Comparing the definitions of independent variables

Variables	Definition	Modify definition
Age	Ages between 40 and 90 years	Identical
Sex	Male or female	Identical
Weight	kg	Conversion to BMI and application
Height	cm	Conversion to BMI and application
History of Fracture	A previous fracture denotes more accurately a previous fracture in adult life occurring spontaneously, or a fracture arising from trauma which, in a healthy individual, would not have resulted in a fracture. (yes, no)	Low-trauma fractures before to stroke diagnosis, excluding accident-related fractures. (yes, no)
Parent Fractured Hip	history of hip fracture in the patient's mother or father. (yes, no)	No variable
Current smoking	Whether the patient currently smokes tobacco. (yes, no)	Identical
Presence of rheumatoid arthritis	Whether a confirmed diagnosis of rheumatoid arthritis. (yes, no)	Identical
Use of glucocorticoid medications	currently exposed to oral glucocorticoids or has been exposed to oral glucocorticoids for more than 3 months at a dose of prednisolone of 5mg daily or more (or equivalent doses of other glucocorticoids). (yes, no)	Use of glucocorticoids within a year of stroke diagnosis (yes, no)
Having secondary osteoporosis	patient has a disorder strongly associated with osteoporosis. (yes, no) These include type I (insulin dependent) diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (<45 years), chronic malnutrition, or malabsorption and chronic liver disease	These include type I (insulin dependent) diabetes, hyperthyroidism, hypogonadism, malabsorption and chronic liver disease. * Unused diseases are factors that are not included in the data or are only researched for a single period and hence cannot be applied to all participants.
Drinking three or more units of alcohol per day	Takes 3 or more units of alcohol daily. (yes, no) A unit of alcohol varies slightly in different countries from 8-10g of alcohol.	Identical Based on soju, one unit is defined as 10 grams.
Bone mineral density	Bone Mineral Density (BMD)	No variable

4. Statistical analysis

This study predicts the risk of fracture after stroke diagnosis using Cause-specific hazard analysis.

A 50% random sample of NHIS-KCPS cohort data is used to build a derivation set, 50% of the remaining NHIS-KCPS data is used for internal validation as the validation set (Figure 3).

The variables used were the closest to the time of stroke diagnosis. Those diagnosed with cancer within the 2-year interval preceding and following a stroke diagnosis were considered active cancer patients and excluded. Glucocorticoids use was defined as the use of drugs within a year after stroke diagnosis (Figure 2).

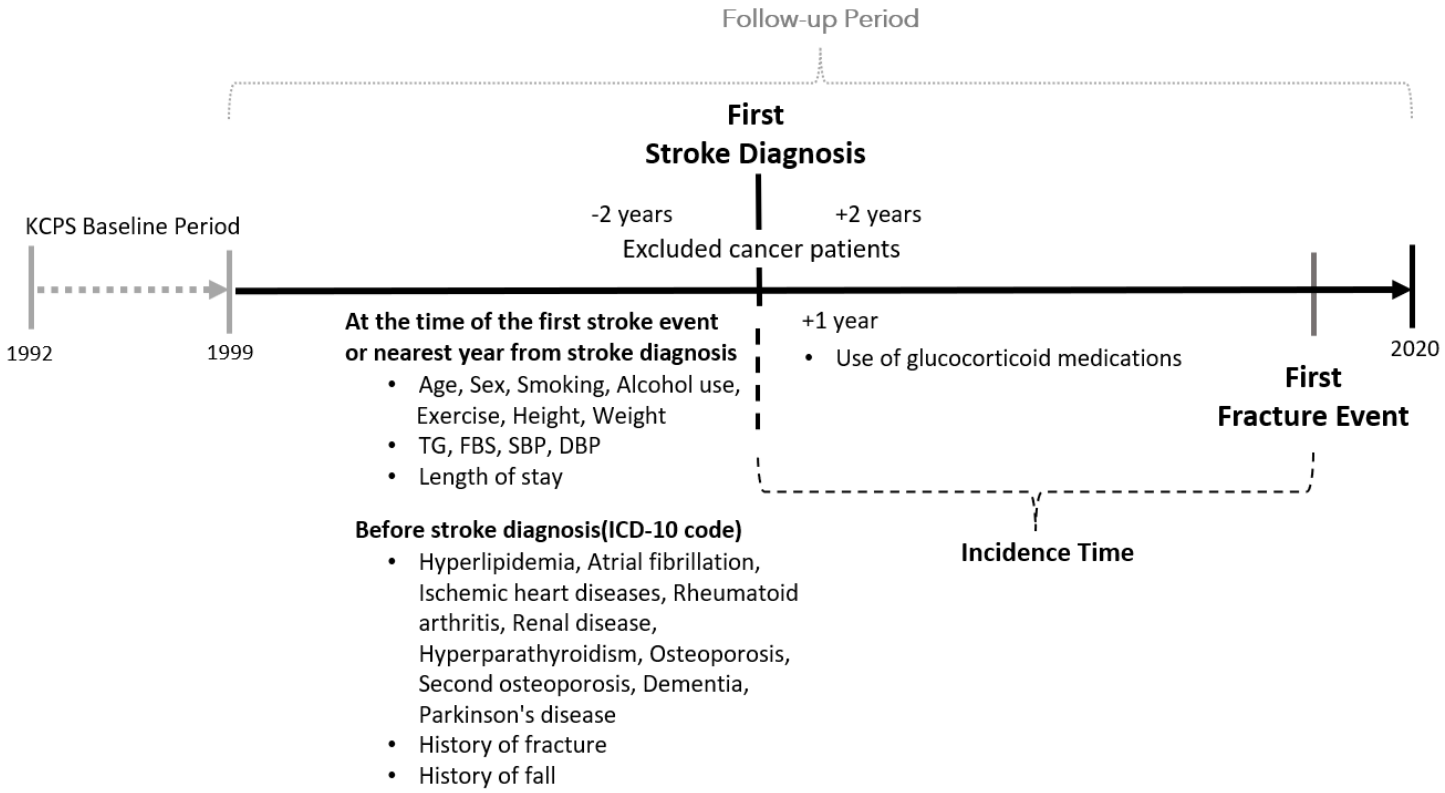


Figure 2. Variables used in the study

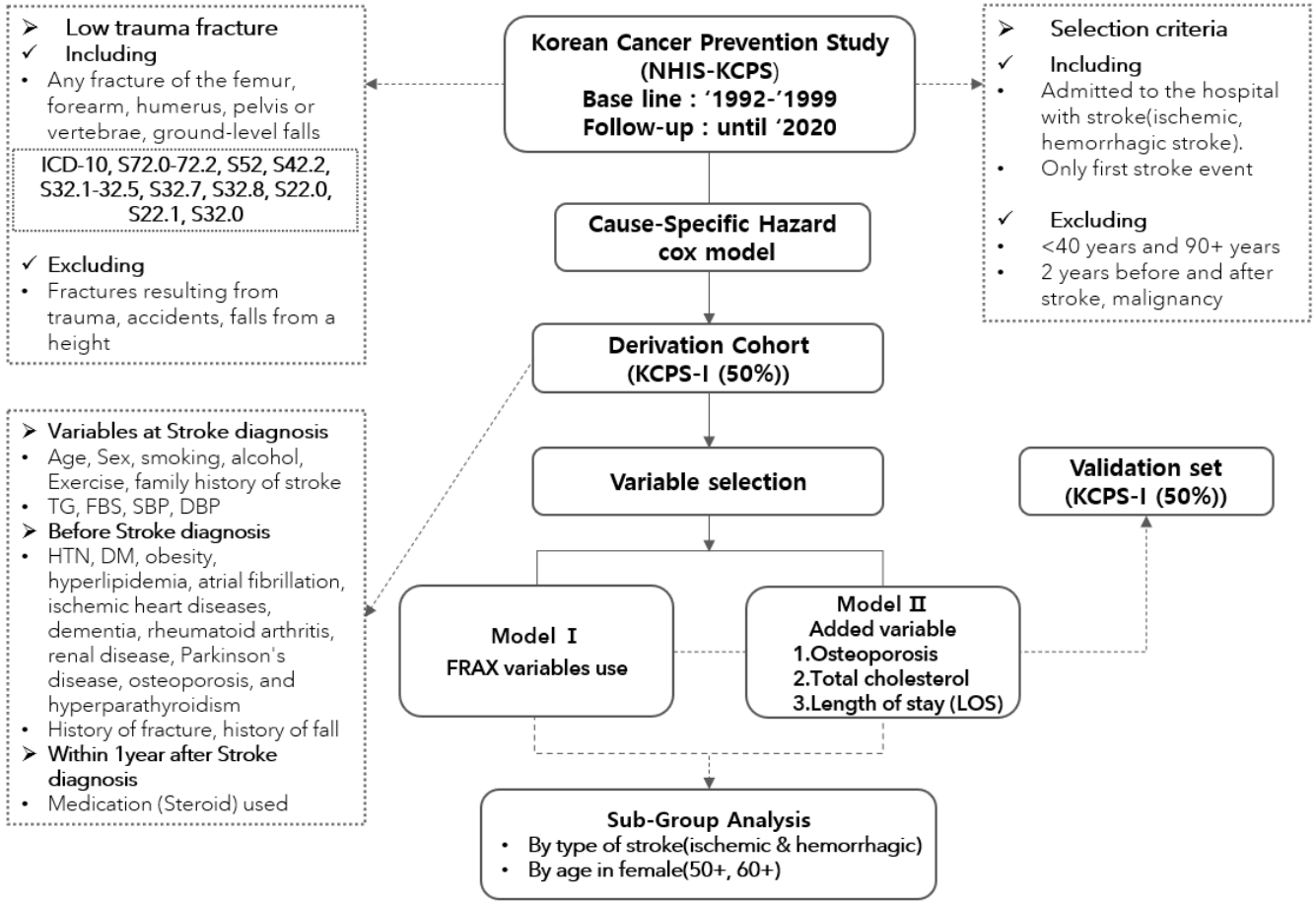


Figure 3. Schematic diagram of the study

4-1. Derivation of the predictive model using Cause Specific Hazard model

For the NHIS-KCPS cohort model, 50% of the cohort was used as random samples for model development, and the remaining 50% for data testing. To develop the Fracture risk after stroke diagnosis model, we used cause specific cox proportional hazard models to evaluate the association between risk factors and the incidence of Fracture.

A model of the 5-year fracture risk was developed,

where,

$$P(t) = 1 - S(5\ year)^{\exp(f[x,M])}$$

$$f[x, M] = \beta_1(x_1 - M_1) + \cdots + \beta_p(x_p - M_p)$$

Here, P is the 5-year Fracture risk, $\beta_1,\ldots,\beta_p$ are the regression coefficients, $x_1,\ldots,x_p$ represent an individual's risk factors, $M_1,\ldots,M_p$ represent the mean values of the risk factors in the cohort, and $S(t)$ is the survival rate at the mean values of the risk factors at time t (t = 5 years).

4-2. Validation analysis

On the basis of discrimination and calibration of the models in the validation sets, the diagnostic capacity of the fracture after stroke was evaluated. The fracture risk factors following a diagnosis of a stroke in Koreans included age, BMI, second osteoporosis, rheumatoid arthritis, prior fracture, current smoking, alcohol amount, and the use of glucocorticoids.

Discrimination is the ability to categorize diseased and healthy individuals based on predicted values. Calibration is a measurement of how well the projected risk matches the observed risk. In all analyses, the follow-up period was censored for 5 years. Using the area under the receiver operating characteristic curve (AUROC) or C-statistic, the discriminatory power in predicting Fracture after stroke diagnosis was determined.

The calibration analysis, which analyzes how closely the projected risk is measured to the actual risk, was performed by splitting the participants into quintiles based on their expected risk. Using the Hosmer–Lemeshow test, the observed and projected 5-year Fracture risks following a stroke diagnosis were compared for each decile. The calibration was also determined graphically by showing the observed and projected Fracture occurrences organized by quintiles of predicted probability.

The improvement in fracture prediction was evaluated by integrated discrimination improvement (IDI) and net reclassification improvements (NRI) after the addition of osteoporosis, total cholesterol (TC), and length of stay (LOS) variables, respectively.

There are no variables such as the Korean-National Institute of Health Stroke Scale (NIHSS) to evaluate neurological impairment or the modified Ranking Score (mRS) established to measure status upon hospital discharge among the scales used to assess the severity of stroke patients in this data set. The variable LOS, which can indicate the severity of a stroke, was selected as a replacement variable; TC is defined as a variable influencing stroke; and, osteoporosis is a risk factor for fracture; thus, these three factors were selected as additional variables.

IDI is a method for measuring how accurately the new model predicted events in the event group and non-events in the non-event group by computing the mean using the prediction probability of the initial model and the new model. NRI separates the event group and the non-event group into a reclassification table and determines the accuracy with which the new model predicts events in the event group and non-events in the non-event group. It is a technique for assessing the predictive power of biomarkers.[42]

III. RESULTS

PART I. The developed and validated a risk model for the prediction of fracture after stroke (FRS) using FRAX (Fracture Risk Assessment Tool) variables

1. Baseline characteristic of the study population

The characteristics of the derivation and validation sets of the participants' initial health assessment at baseline are detailed in Table 3-4. The mean age of the participants in the derivation set was 69.94 years and, in the validation set, it was 69.95 years. Moreover, 58.48% of the derivation set and 59.02% of the validation set were men.

The NHIS-KCPS derivation set and validation set had essentially comparable characteristics. 41.52% of the derivation set and 40.98% of the validation set were women, and rates of ischemic stroke was higher than those of hemorrhagic stroke, with 79.52% of the derivation set and 79.34% of the validation set. Approximately 58% of the participants were non-smokers, and about 25% were current smokers. Additionally, around 12% of the participants had a fracture prior to the diagnosis

of stroke. After the diagnosis of stroke, 13.36% of the derivation set and 13.21% of the validation set experienced fracture (Table 3).

Compared to the general features of men and women in each data set, the mean age of women was greater than that of men: 67.83 years for men and 72.90 years for women in the derivation set; 67.96 years for men and 72.81 years for women in the validation set. Women had greater total cholesterol levels, while more than 90 percent of women were non-smokers (Table 4). Women had a greater frequency of dementia, osteoporosis, and prior fractures. Women had a higher incidence of fractures following a diagnosis of stroke than men. The percentage of men who responded that they exercised was higher than that of women. Other overall traits of men and women were comparable (Table 4).

Table 3. Baseline characteristics of study subjects in the derivation and validation sets (N, %)

Variables		Derivation set (NHIS-KCPS, n=54,483)	Validation set (NHIS-KCPS, n=54,203)
		N (%)	N (%)
Sex			
	men	31,864(58.48)	31,993(59.02)
	women	22,619(41.52)	22,210(40.98)
Age			
	40-49	2,521(4.70)	2,476(4.57)
	50-59	7,225(13.26)	7,323(13.51)
	60-69	13,993(25.68)	13,910(25.66)
	70-79	19,608(35.99)	19,387(35.77)
	80-89	11,096(20.37)	11,107(20.49)
Stroke Type			
	Ischemic	43,324(79.52)	43,003(79.34)
	Hemorrhagic	11,159(20.48)	11,200(20.66)
Smoking status			
	None	32,093(58.90)	31,863(58.78)
	Former	8,617(15.92)	8,912(16.44)
	Current	13,719(25.18)	13,428(24.77)
Exercise			
	yes	31,127(57.13)	31,329(57.80)
Alcohol use			
	No	50,174(92.09)	49,924(92.11)
	less than 3units	3,492(6.41)	3,444(6.35)
	More than 3units	817(1.50)	835(1.54)
Fracture		7,278(13.36)	7,161(13.21)
Prior	falls	18(0.03)	23(0.04)
	fracture	6,428(11.80)	6,520(12.03)
Hypertension		6,764(12.41)	6,800(12.55)
Diabetes		8,897(16.33)	8,841(16.31)
Hyperlipidemia		84(0.15)	85(0.16)
Dementia		1,331(2.44)	1,300(2.40)
Osteoporosis		615(1.13)	580(1.07)
Second Osteoporosis		1,294(2.38)	1,268(2.34)
Parkin's disease		494(0.91)	411(0.76)
Rheumatoid arthritis		149(0.27)	163(0.30)
Hyperparathyroidism		6(0.01)	9(0.02)
Ischemic heart disease		4,188(7.69)	4,314(7.96)
Atrial fibrillation		400(0.73)	341(0.63)
Drugs(steroid)		2,697(4.95)	2,971668(5.01)

* Data are expressed as number (%)

Table 3-1. Baseline characteristics of study subjects in the derivation and validation sets

Variables	Derivation set (NHIS-KCPS, n=54,483)	Validation set (NHIS-KCPS, n=54,203)
	Mean (SD)	Mean (SD)
Age, years	69.94(10.74)	69.95(10.72)
Length of Stay, days	12.68(12.63)	12.70(13.24)
Height, cm	160.05(9.47)	160.13(9.45)
Weight, kg	61.86(10.66)	61.96(10.70)
BMI, kg/m^2	24.06(3.05)	24.08(3.06)
SBP, mmHg	133.94(19.06)	133.89(19.18)
DBP, mmHg	81.85(12.23)	81.84(12.93)
Total cholesterol, mg/dl	198.56(45.86)	198.53(42.41)
FBS, mg/dl	108.55(40.74)	108.38(40.47)

* Data are expressed as means standard deviation

Table 4. Baseline characteristics of study subjects by sex in the derivation and validation sets

Variables	Derivation set (n=54,483)			Validation set (n=54,203)		
	Men (n=31,864)	Women (n=22,619)	p-value	Men (n=31,993)	Women (n=22,210)	p-value
Age, years	67.83(10.93)	72.90(9.72)	<.0001	67.96(10.92)	72.81(9.72)	<.0001
40-49	2,011(6.31)	550(2.43)	<.0001	1,971(6.16)	505(2.27)	<.0001
50-59	5,501(17.26)	1,724(7.62)		5,495(17.18)	1,828(8.23)	
60-69	9,024(28.32)	4,969(21.97)		9,053(28.3)	4,857(21.87)	
70-79	10,492(32.93)	9,116(40.3)		10,473(32.74)	8,914(40.14)	
80-89	4,836(15.18)	6,260(27.68)		5,001(15.63)	6,106(27.49)	
Height, cm	166.23(6.00)	151.33(5.97)	<.0001	166.22(5.99)	151.35(5.98)	<.0001
Weight, kg	66.27(9.64)	55.64(8.77)	<.0001	66.37(9.69)	55.61(8.74)	<.0001
BMI, kg/m^2	23.93(2.86)	24.26(3.3)	<.0001	23.97(2.91)	24.23(3.27)	<.0001
SBP, mmHg	134.00(18.67)	133.86(19.59)	0.3876	133.94(18.89)	133.82(19.59)	0.5036
DBP, mmHg	82.30(12.14)	81.23(12.34)	<.0001	82.28(13.40)	81.20(12.19)	<.0001
Total cholesterol, mg/dl	193.28(40.48)	205.99(51.62)	<.0001	193.55(40.84)	205.70(43.58)	<.0001
FBS, mg/dl	110.31(41.50)	106.07(39.53)	<.0001	110.46(42.13)	105.38(37.75)	<.0001
Length of Stay, days	12.31(12.30)	13.21(13.06)	<.0001	12.41(12.93)	13.11(13.66)	<.0001
Stroke Type						
Ischemic	25,483(79.97)	17,841(78.88)	0.0018	25427(79.48)	17576(79.14)	0.3400
Hemorrhagic	6,381(20.03)	4,778(21.12)		6566(20.52)	4634(20.86)	
Smoking status						
None	10,825(33.97)	21,268(94.03)	<.0001	11,039(34.50)	20,824(93.76)	<.0001
Former	8,301(26.05)	370(1.64)		8505(26.58)	407(1.83)	
Current	12,738(39.98)	981(4.34)		12,449(38.91)	979(4.41)	
Exercise						
yes	20,848(65.43)	10,279(45.44)	<.0001	21,095(65.94)	10,234(46.08)	<.0001
Alcohol use						
No	29,569(92.50)	20,605(91.51)	<.0001	29,550(92.66)	20,374(91.31)	<.0001
less than 3units	1,619(5.06)	1,873(8.32)		1,545(4.84)	1,899(8.51)	
More than 3units	779(2.44)	38(0.17)		795(2.49)	40(0.18)	
Glucocorticoids used	1,526(4.79)	1,171(5.18)	0.0416	1,606(5.02)	1,110(5.00)	0.9236

Variables	Derivation set (n=54,483)			Validation set (n=54,203)		
	Men (n=31,864)	Women (n=22,619)	p-value	Men (n=31,993)	Women (n=22,210)	p-value
Fracture	2,493(7.82)	4,785(21.15)	<.0001	2,596(8.11)	4,565(20.55)	<.0001
Prior						
falls	12(0.04)	6(0.03)	0.6416	14(0.04)	9(0.04)	1.0000
fracture	2,091(6.56)	4,337(19.17)	<.0001	2,167(6.77)	4,353(19.60)	<.0001
Hypertension	4,070(12.77)	2,694(11.91)	0.0027	4,207(13.15)	2,593(11.67)	<.0001
Diabetes	5,710(17.92)	3,187(14.09)	<.0001	5,801(18.13)	3,040(13.69)	<.0001
Hyperlipidemia	46(0.14)	38(0.17)	0.5605	43(0.13)	42(0.19)	0.1409
Dementia	526(1.65)	805(3.56)	<.0001	509(1.59)	791(3.56)	<.0001
Osteoporosis	95(0.30)	520(2.30)	<.0001	99(0.31)	481(2.17)	<.0001
Second Osteoporosis	904(2.84)	385(1.70)	<.0001	918(2.87)	355(1.60)	<.0001
Parkin’s disease	225(0.71)	269(1.19)	<.0001	223(0.70)	188(0.85)	0.0546
Rheumatoid arthritis	48(0.15)	101(0.45)	<.0001	42(0.13)	121(0.54)	<.0001
Hyperparathyroidism	2(0.01)	4(0.02)	0.4031	6(0.02)	3(0.01)	0.8987
Ischemic heart disease	2,550(8.00)	1,638(7.24)	0.0011	2,653(8.29)	1,661(7.48)	0.0006
Atrial fibrillation	220(0.69)	180(0.80)	0.1711	168(0.53)	173(0.78)	0.0003

* Data are expressed as means standard deviation and number (%); BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar

2. Fracture incidence after stroke diagnosis

Table 5 displays the incidence of events and incidence rate by Fracture occurrence year (2000 - 2020) in the derivation set. The fracture incidence rate grew from 1.84 per 100,000 persons in 2000 to 2,079.2 per 100,000 persons in 2020. (Table 5, Figure 4).

In the derivation set, 7,278 Fracture occurrences occurred throughout the 21 years of follow-up (2,493 men and 4,785 women). The age-adjusted fracture incidence rates per 100,000 person-years for men and women were 17.56 and 31.81, respectively (Table 6).

Table 5. Incidence events and incidence rates of fracture by occurrence year in the derivation set from the NHIS-KCPS

Year	n/at risk	Fracture after stroke diagnosis			
		Incidence event (n)	**Cumulative event** (n)	**Annual death** (n)	**Incidence rate** Per 100,000 persons
2000	54,483	1	1	4	1.84
2001	54,478	25	26	149	45.89
2002	54,304	75	101	290	138.11
2003	53,939	114	215	399	211.35
2004	53,426	172	387	512	321.94
2005	52,742	186	573	576	352.66
2006	51,980	201	774	703	386.69
2007	51,076	228	1,002	842	446.39
2008	50,006	333	1,335	885	665.92
2009	48,788	314	1,649	953	643.60
2010	47,521	409	2,058	1,109	860.67
2011	46,003	394	2,452	1,218	856.47
2012	44,391	451	2,903	1,310	1,015.97
2013	42,630	458	3,361	1,396	1,074.36
2014	40,776	523	3,884	1,440	1,282.62
2015	38,813	507	4,391	1,571	1,306.26
2016	36,735	562	4,953	1,614	1,529.88
2017	34,559	581	5,534	1,777	1,681.18
2018	32,201	604	6,138	1,921	1,875.72
2019	29,676	575	6,713	1,927	1,937.59
2020	27,174	565	7,278	2,052	2,079.19

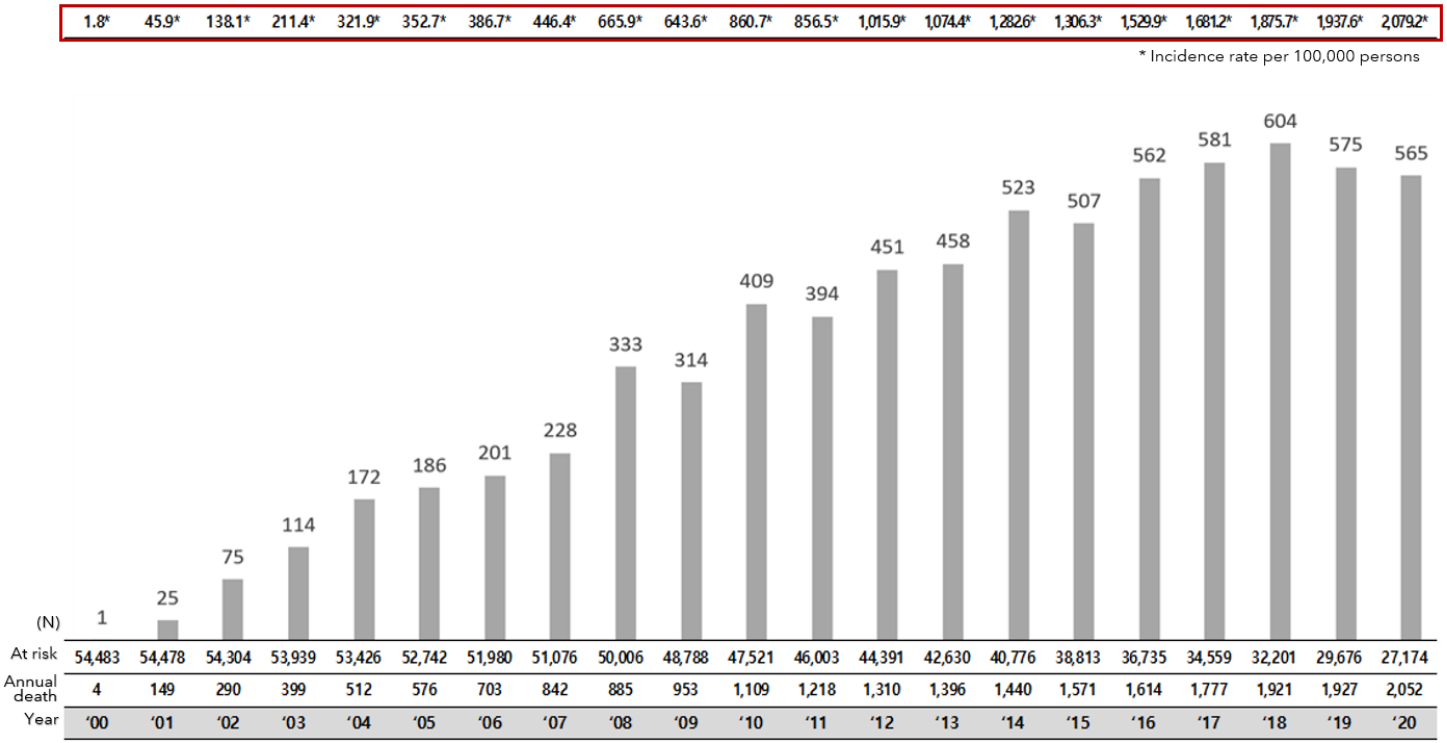


Figure 4. Incidence of fracture after stroke diagnosis by occurrence year in the derivation set from the NHIS-KCPS

Table 6. Person-years of follow-up and fracture events by age and sex in the derivation set (n=54,483)

Age group (years)	**Population** (n)	**Person-years of follow-up**	**No. of event**	**Incidence per** 100,000 person-years
Men (N=31,864)				
40-49	2,011	8073283	71	0.88
50-59	5,501	17798508	285	1.60
60-69	9,024	25049740	752	3.00
70-79	10,492	19444752	1,004	5.16
80-89	4,836	4993607	381	7.63
Total	31,864	75359890	2,493	3.31
Age-adjusted rate*				17.56
Women (N=22,619)				
40-49	550	1946688	31	1.59
50-59	1,724	6643249	212	3.19
60-69	4,969	15092329	1,185	7.85
70-79	9,116	18222449	2,295	12.59
80-89	6,260	6967510	1,062	15.24
Total	22,619	48872225	4,785	9.79
Age-adjusted rate*				31.81

* Incidence was standardized to the age distribution in the 2021 Korean population

3. Development of a risk model for the prediction of fracture by Cause specific hazard model

The association between each possible variable and the incidence of Fracture in the NHIS-KCPS cohort is displayed in Tables 7-8. The association between each potential variable and the fracture incidence in the NHIS-KCPS cohort is presented. Age, BMI, prior fracture, current smoking, arthritis, and second osteoporosis were found to be associated with fracture in both models in men and women.

The table 9 presents the model coefficients of the derivation set for FRAX variables. The FRAX variables are Age, BMI, prior fracture, current smoking, glucocorticoids use, arthritis, second osteoporosis and alcohol amount. The addition of the FRAX variables produced the most accurate prediction model with the least Akaike information criterion (AIC) in both FRAX of stroke patients' models in men and women.

Table 7. Hazard ratios for risk of fracture events after stroke derivation set in men (n = 31,864)

Variables	Model 1		Model 2		Model 3	
	HR	95% CI	HR	95% CI	HR	95% CI
Age, years	1.06	(1.06-1.07)	1.06	(1.06-1.07)	1.06	(1.06-1.07)
BMI	0.93	(0.91-0.94)	0.93	(0.92-0.95)	0.93	(0.92-0.95)
Rheumatoid arthritis	2.40	(1.08-5.34)	2.33	(1.04-5.18)	2.33	(1.04-5.19)
Second Osteoporosis	2.13	(1.75-2.58)	2.04	(1.67-2.30)	2.03	(1.67-2.47)
Prior fracture			2.01	(1.75-2.30)	2.00	(1.75-2.29)
Alcohol amount			0.83	(0.70-0.99)	1.10	(0.81-1.50)
Current smoking			1.19	(1.10-1.29)	1.21	(1.12-1.32)
Exercise			0.88	(0.81-0.95)		
Glucocorticoids use					0.96	(0.81-1.13)
DF	4		8		8	
AIC	46704.92		46591.22		46605.29	

*HR, hazard ratio; 95% CI, 95% confidence interval; DF, degree of freedom; AIC, Akaike information criterion; BMI, body mass index

Table 8. Hazard ratios for risk of fracture events after stroke from derivation set in women (n = 22,619)

Variables	Model 1		Model 2		Model 3	
	HR	95% CI	HR	95% CI	HR	95% CI
Age, years	1.05	(1.05-1.06)	1.05	(1.05-1.06)	1.05	(1.05-1.05)
BMI	0.98	(0.97-0.99)	0.98	(0.97-0.99)	0.98	(0.97-0.99)
Rheumatoid arthritis	0.97	(0.61-1.55)	0.92	(0.58-1.49)	0.91	(0.57-1.44)
Second Osteoporosis	1.08	(0.85-1.37)	1.07	(0.84-1.35)	1.07	(0.84-1.35)
Prior fracture			1.45	(1.38-1.60)	1.48	(1.37-1.59)
Alcohol amount			0.87	(0.79-0.97)	1.02	(0.33-3.16)
Current smoking			1.16	(1.02-1.32)	1.18	(1.04-1.34)
Exercise			0.99	(0.93-1.05)		
Glucocorticoids use					0.93	(0.82-1.04)
DF	4		8		8	
AIC	87463.14		87352.42		87357.31	

*HR, hazard ratio; 95% CI, 95% confidence interval; DF, degree of freedom; AIC, Akaike information criterion; BMI, body mass index

Table 9. Risk of incident fracture within 5-year of Fracture Risk after Stroke (FRS) model in men and women

Variables	Men (n = 31,864)					Women (n = 22,619)				
	β-coefficient	SE	HR	95% CI	p-value	β-coefficient	SE	HR	95% CI	p-value
Age, years	0.06044	0.00233	1.06	(1.06-1.07)	<.0001	0.04777	0.00180	1.05	(1.05-1.05)	<.0001
BMI	-0.07014	0.00752	0.93	(0.92-0.95)	<.0001	-0.02076	0.00452	0.98	(0.97-0.99)	<.0001
Rheumatoid arthritis	0.84476	0.40883	2.33	(1.04-5.19)	0.0388	-0.09559	0.23632	0.91	(0.57-1.44)	0.6859
Second Osteoporosis	0.70979	0.09968	2.03	(1.67-2.47)	<.0001	0.06526	0.11964	1.07	(0.84-1.35)	0.5854
Prior fracture	0.69172	0.06901	2.00	(1.75-2.29)	<.0001	0.39017	0.03683	1.48	(1.37-1.59)	<.0001
Alcohol amount	0.09309	0.15754	1.10	(0.81-1.50)	0.5546	0.01868	0.57761	1.02	(0.33-3.16)	0.9742
Current smoking	0.19237	0.04196	1.21	(1.12-1.32)	<.0001	0.16715	0.06490	1.18	(1.01-1.34)	0.0100
Glucocorticoids use	-0.046325	0.08552	0.96	(0.81-1.13)	0.5879	-0.07795	0.06059	0.93	(0.82-1.04)	0.1983

*SE, Standard error; HR, hazard ratio; 95% CI, 95% confidence interval; BMI, body mass index

4. Validation of a risk model for the prediction of Fracture by cause specific hazard model

To verify the FRS model for fracture prediction, further tests were conducted using NHIS-KCPS validation sets. The validity of the prediction for fracture in the NHIS-KCPS was validated in the validation sets. The graphs illustrate the predicted and actual risks of fracture by quintile of predicted hazards.

4-1. Validation of a FRS model for the prediction of Fracture in NHIS-KCPS

Figure 5 illustrates the performance curves of the NHIS-KCPS cohort (validation set). Appendix 1 has the algorithm. Using the coefficients estimated from the derived set, the AUROCs for men and women were 0.7001 (95% CI: 0.69–0.71) and 0.6370 (95% CI: 0.63-0.65), respectively, indicating a decent ability to differentiate situations. In terms of calibration, the Hosmer-Lemeshow x^2 value was 13.54 for men (p=.1396) and 167.43 for women (p <.0001). In the women's FRS model, the C-statistic was enhanced by the addition of the agesq variable with age effect correction (Table 10).

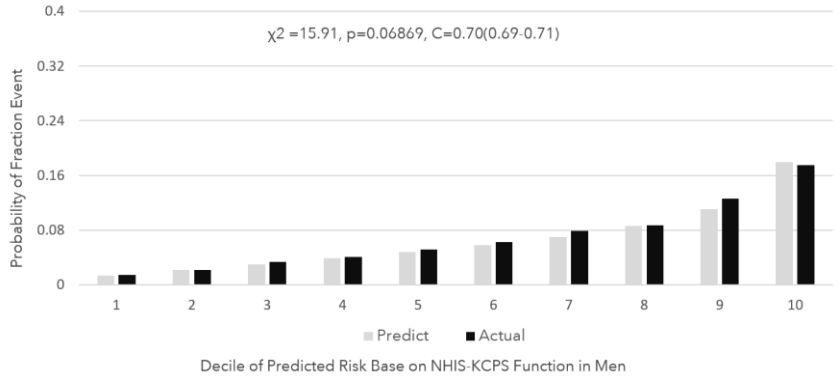
Table 10. Discrimination and calibration of the FRS models in the validation sets

Validation set	C-statistic, 95% CI	Calibration χ^2 (p-value)
FRS_Men	0.7001 (0.69-0.71)	15.91 (p 0.0687)
FRS_Women	0.6370 (0.63-0.65)	167.43 (p <.0001)
FRS_Women_agesq**	0.6415 (0.63-0.65)	38.00 (p <.0001)

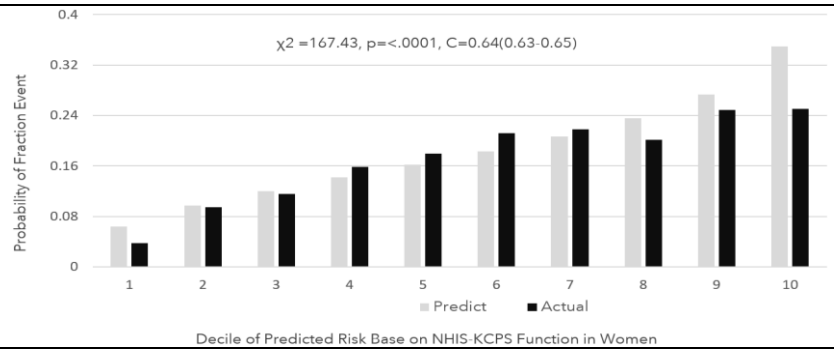
* 95% CI, 95% confidence interval

** agesq=age*age

Men



Women



Women_agesq

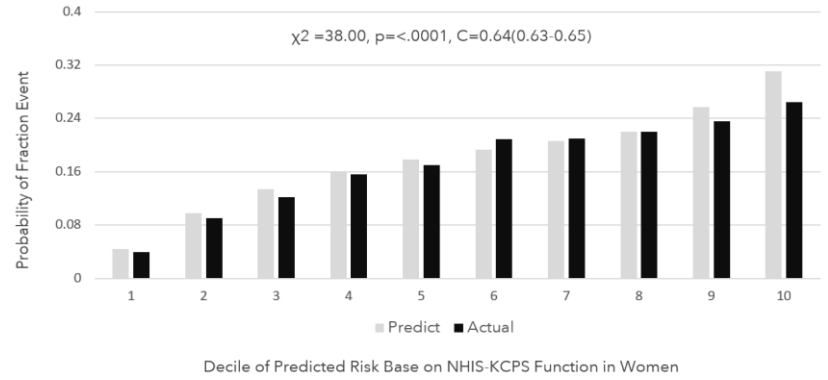


Figure **5. The 5-year probability of predicted and actual fracture events after stroke**

PART II. The developed and validated a risk model for the prediction of fracture after stroke with additional variables (FRSE)

On the basis of clinical plausibility, candidate model variables were selected, including variables related to FRAX score components, fracture risk factors, and stroke severity. This study used an integrated Net Reclassification Index (NRI) and discrimination improvement (IDI) to determine the added predictive value of including osteoporosis or total cholesterol (TC) or length of stay (LOS) versus not including them.

NRI evaluated the predictive ability of the novel biomarker by reclassifying the fracture group and the non-fracture group. The relative IDI was calculated as -1 plus the ratio of the difference in the mean estimated probability between events and nonevents under the model with osteoporosis or total cholesterol (TC) or length of stay (LOS) to the difference in the mean estimated probability between events and nonevents without them.

1. NRI and IDI for the prediction of fracture based on FRS model including osteoporosis or total cholesterol (TC) or length of stay (LOS) variable

The FRSE model was derived from the FRS model by adding osteoporosis, total cholesterol, and length of hospital stay one at a time, and the model was compared using NRI and IDI in men and women models (Table 11, Table 12).

The coefficients of the derivation set of the TC model in women and LOS model in men with the lowest AIC among models to which each variable was included are presented in Table 13.

Table 11. Hazard ratios of the FRS model, with osteoporosis or total cholesterol (TC) or length of stay (LOS) variable in the derivation set in men (n = 31,864)

Variables	Model 1		Model 2		Model 3	
	HR	95% CI	HR	95% CI	HR	95% CI
Age, years	1.06	(1.06-1.07)	1.06	(1.06-1.07)	1.06	1.06-1.07
BMI	0.93	(0.92-0.95)	0.93	(0.92-0.95)	0.93	0.92-0.95
Rheumatoid arthritis	2.06	(0.92-4.64)	2.31	(1.04-5.15)	2.37	1.06-5.27
Second Osteoporosis	2.02	(1.66-2.46)	2.02	(1.66-2.45)	2.02	1.66-2.45
Prior fracture	1.96	(1.71-2.25)	1.99	(1.74-2.28)	1.99	1.74-2.27
Alcohol amount	1.10	(0.81-1.49)	1.09	(0.81-1.13)	1.11	0.81-1.51
Current smoking	1.21	(1.12-1.32)	1.22	(1.13-1.33)	1.21	1.11-1.31
Glucocorticoids use	0.95	(0.81-1.13)	0.96	(0.81-1.13)	0.95	0.81-1.13
Osteoporosis	2.00	(1.18-3.35)				
Total cholesterol			0.99	(0.99-1.00)		
Length of stay (LOS)					1.01	1.01-1.01
DF	9		9		9	
AIC	46601.79		46563.27		46581.91	

*HR, hazard ratio; 95% CI, 95% confidence interval; DF, degree of freedom; AIC, Akaike information criterion; BMI, body mass index

Table 12. Hazard ratios of the FRS model, with osteoporosis or total cholesterol (TC) or length of stay (LOS) variable in the derivation set in women (n = 22,619)

Variables	Model 1		Model 2		Model 3	
	HR	95% CI	HR	95% CI	HR	95% CI
Age, years	1.05	(1.05-1.05)	1.05	(1.05-1.05)	1.05	1.05-1.05
BMI	0.98	(0.97-0.99)	0.98	(0.97-0.99)	0.98	097-099
Rheumatoid arthritis	0.89	(0.56-1.42)	0.91	(0.57-1.44)	0.91	(0.58-1.45)
Second Osteoporosis	1.06	(0.84-1.35)	1.07	(0.84-1.35)	1.07	(0.85-1.35)
Prior fracture	1.43	(1.33-1.54)	1.47	(1.37-1.58)	1.48	(1.38-1.59)
Alcohol amount	1.03	(0.33-3.20)	1.01	(0.33-3.14)	1.02	(0.33-3.17)
Current smoking	1.18	(1.04-1.34)	1.18	(1.04-1.35)	1.18	(1.04-1.34)
Glucocorticoids use	0.92	(0.82-1.04)	0.93	(0.82-1.05)	0.93	(0.82-1.04)
Osteoporosis	1.60	(1.36-1.89)				
Total cholesterol			1.00	(0.99-1.00)		
Length of stay (LOS)					0.99	0.99-1.00
DF	9		9		9	
AIC	87331.96		87298.56		87357.64	

*HR, hazard ratio; 95% CI, 95% confidence interval; DF, degree of freedom; AIC, Akaike information criterion; BMI, body mass index

Table 13. Risk prediction of incident fracture within 5-year in extended FRS model with additional variables

Variables	Men (n = 31,864)					Women (n = 22,619)				
	β-coefficient	SE	HR	95% CI	p-value	β-coefficient	SE	HR	95% CI	p-value
Age, years	0.06343	0.00233	1.07	(1.06-1.07)	<.0001	0.04777	0.00180	1.05	(1.05-1.05)	<.0001
BMI	-0.07343	0.00754	0.93	(0.92-0.94)	<.0001	-0.02055	0.00454	0.98	(0.97-0.99)	<.0001
Rheumatoid arthritis	1.43677	0.57814	4.21	(1.36-13.07)	0.0129	-0.09589	0.23632	0.91	(0.57-1.44)	0.6849
Second Osteoporosis	0.19312	0.04197	1.21	(1.12-1.32)	<.0001	0.06512	0.11964	1.07	(0.84-1.35)	0.5862
Prior fracture	-0.05165	0.08551	0.95	(0.80-5.41)	0.5459	0.38789	0.03687	1.47	(1.37-1.58)	0.0001
Alcohol amount	0.68668	0.40891	2.43	(1.09-1.12)	0.0301	0.01184	0.57764	1.01	(0.33-3.14)	0.9837
Current smoking	0.73040	0.09963	2.08	(1.71-2.52)	<.0001	0.16922	0.06492	1.18	(1.04-1.35)	0.0091
Glucocorticoids use	0.11652	0.15754	1.12	(0.83-1.53)	0.4595	-0.07465	0.06065	0.93	(0.82-1.05)	0.2184
Length of stay	0.00794	0.00142	1.01	(1.01-1.01)	<.0001					
Total cholesterol						-0.0002954	0.000284	1.00	(0.99-1.00)	0.2975

*SE, Standard error; HR, hazard ratio; 95% CI, 95% confidence interval; BMI, body mass index

2. Validation of an extended FRS model (FRSE) and evaluate NRI and IDI for the prediction of fracture

In the men the FRSE model, when the length of stay variable was included, the C-statistic was 0.7035 and Hosmer-Lemeshow x^2 was 16.07 (p=.06551). The addition variable improved NRI and IDI by 0.006186 and 0.045350 respectively, which was statistically significant (p<.0001 and p<.0001). The highest C-statistic was 0.7035 and Hosmer-Lemeshow x^2 was 18.76 (p=.02729) when the variables osteoporosis, total cholesterol, and length of stay were added. The improvements of 0.002041 in NRI and 0.000162 in IDI were not statistically significant (p=.5998, p=.1152, respectively), and lower than the length of stay (Table 14).

In the women the FRSE model, when the total cholesterol variable was included, the C-statistic was 0.6371 and Hosmer-Lemeshow x^2 was 163.82 (p<.0001). The addition of the TC variable improved NRI and IDI by 0.041350 and 0.015848 respectively, which were statistically significant (p<.0001, p<.0001). The highest C-statistic was 0.6386 and Hosmer-Lemeshow x^2 was 165.27 (p<.0001) when the variables osteoporosis, total cholesterol, and length of stay were added. The improvements of 0.002758 in NRI and 0.007576 in IDI were statistically significant (p<.0001, p=.00035), but lower than the total cholesterol (Table 14).

Table 14. Discrimination and calibration of the extended FRS models by including variables

Validation set	Calibration χ^2 (p-value)	C-statistic (95% CI)	IDI (95% CI, p-value)	NRI (95% CI, p-value)
Men				
FRS model	15.91(p .06869)	0.7007(0.69-0.71)		
+ Osteoporosis	14.59(p .10296)	0.7014(0.69-0.71)	0.000057 (-0.0001-0.0002; p .4116)	0.000850 (-0.0019-0.0036; p .5495)
+ Toral cholesterol	15.77(p .07192)	0.7005(0.69-0.71)	0.000071 (0.0000-0.0002; p .1097)	0.000560 (-0.0054-0.0065; p .8522)
+ Length of stay	**16.07(p .06551)**	**0.7035(0.69-0.72)**	**0.006186 (0.0045-0.0079; P <.0001)**	**0.045350 (0.0314-0.0593; P <.0001)**
+ Osteoporosis, TC, LOS	18.76(p.02729)	0.7040(0.69-0.72)	0.000162 (0.0000-0.0004; P .1152)	0.002041 (-0.0056-0.0097; P .5998)
Women				
FRS model	167.43(p<.0001)	0.6370(0.63-0.65)		
+ Osteoporosis	169.64(p<.0001)	0.6383(0.63-0.65)	0.000720 (0.0003-0.0011; p .0004)	0.005015 (0.0017-0.0083; p .0033)
+ Toral cholesterol	**163.82(p<.0001)**	**0.6371(0.63-0.65)**	**0.015848 (0.0138-0.018; p <.0001)**	**0.041350 (0.034-0.0487; p <.0001)**
+ Length of stay	157.30(p<.0001)	0.6368(0.63-0.65)	0.015060 (0.0091-0.0119; P <.0001)	0.014880 (0.0105-0.0193; P <.0001)
+ Osteoporosis, TC, LOS	165.27(p<.0001)	0.6386(0.63-0.65)	0.002758 (0.0021-0.0034; P<.0001)	0.007576 (0.0035-0.0117; P .00035)

* 95% CI, 95% confidence interval

PART III. validation of the FRS model for the fracture after stroke in subgroups in NHIS-KCPS

In subgroup analyses, calibration and discrimination were assessed independently in individuals 50 years older, as well as in ischemic stroke patients using the derivation cohort (Table 15, Table 16).

Figure 6 illustrates the performance curves of the age 50 year and older in NHIS-KCPS cohort (validation set). Appendix 2 has the algorithm. Using the coefficients estimated from the derived set, the AUROCs for men and women were 0.6900 (95% CI: 0.68–0.70) and 0.6280 (95% CI: 0.62-0.64), respectively, indicating a decent ability to differentiate situations. In terms of calibration, the Hosmer-Lemeshow x^2 value was 15.60 (p = .0756) for men and 142.94 (p <.0001) for women (Table 15). Figure 7 illustrates the performance curves of the ischemic stroke patient in NHIS-KCPS cohort (validation set). Appendix 2 has the algorithm. Using the coefficients estimated from the derived set, the AUROCs for men and women were 0.7016 (95% CI: 0.69–0.72) and 0.6275 (95% CI: 0.62-0.64), respectively, indicating a decent ability to differentiate situations. In terms of calibration, the Hosmer-Lemeshow x^2 value was 6.33 (p=.7062) for men and 103.63 (p <.0001) for women (Table 16).

Table 15. Hazard ratios for risk of fracture events after stroke from derivation set in age 50 and older in men and women

Variables	Men					Women				
	β-coefficient	SE	HR	95% CI	p-value	β-coefficient	SE	HR	95% CI	p-value
Age, years	0.05970	0.00260	1.06	(1.06-1.07)	<.0001	0.04524	0.00190	1.05	(1.04-1.05)	<.0001
BMI	-0.06923	0.00765	0.93	(0.92-0.95)	<.0001	-0.02257	0.00455	0.98	(0.97-0.99)	<.0001
Rheumatoid arthritis	0.84549	0.40891	2.33	(1.05-5.19)	0.0387	-0.09724	0.23632	0.91	(0.57-1.44)	0.6807
Second Osteoporosis	0.67393	0.10257	1.96	(1.61-2.40)	<.0001	0.06762	0.11965	1.07	(0.85-1.35)	0.5719
Prior fracture	0.69909	0.06940	2.01	(1.76-2.31)	<.0001	0.39613	0.03685	1.49	(1.38-1.60)	<.0001
Alcohol amount	0.16360	0.16360	1.11	(0.81-1.53)	0.5256	0.00549	0.57763	1.01	(0.32-3.12)	0.9924
Current smoking	0.19601	0.04259	1.22	(1.12-1.32)	<.0001	0.16401	0.06502	1.18	(1.04-1.34)	0.0116
Glucocorticoids use	-0.05055	0.08701	0.95	(0.80-1.13)	0.5612	-0.07921	0.06070	0.92	(0.80-1.04)	0.1919
DF	8					8				
AIC	46794.74					86618.19				
Calibration χ^2 (p-value)	15.60(0.0756)					142.94(<.0001)				
C-statistic (95% CI)	0.6900(0.68-0.70)					0.6280(0.62-0.64)				

*HR, hazard ratio; 95% CI, 95% confidence interval; DF, degree of freedom; AIC, Akaike information criterion; BMI, body mass index

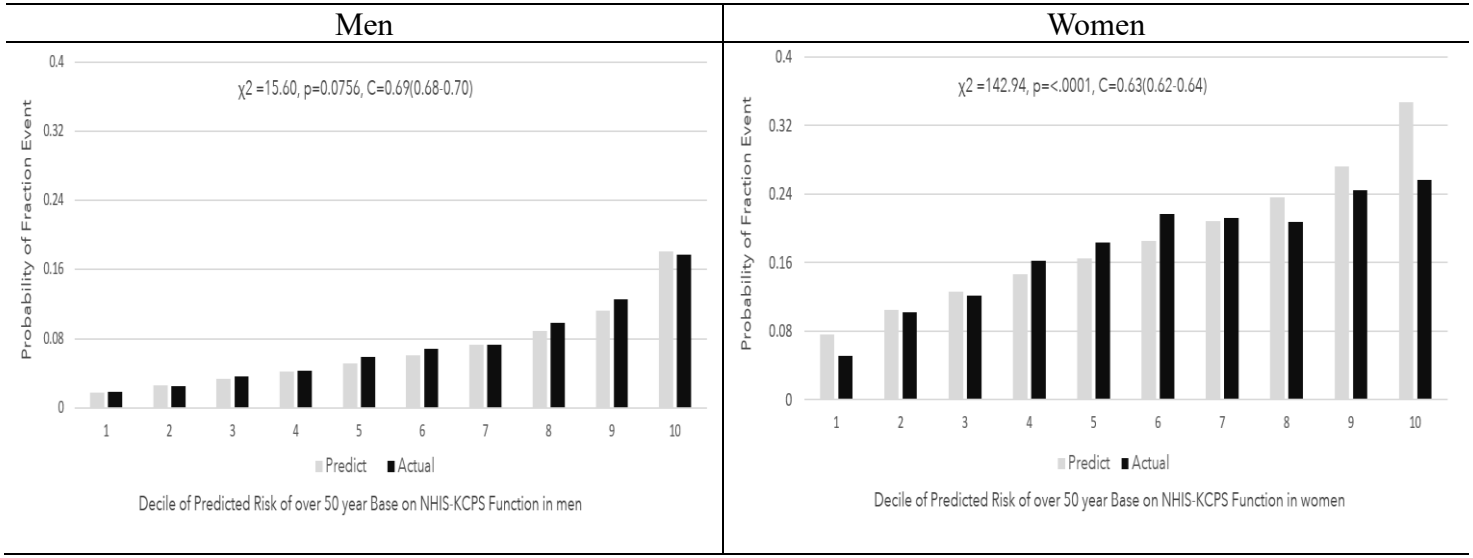


Figure 6. The 5-year probability of predicted and actual fracture events in ages 50 and older

Table 16. Hazard ratios for risk of fracture events from derivation set in ischemic stroke patients in men and women

Variables	Men					Women				
	β-coefficient	SE	HR	95% CI	p-value	β-coefficient	SE	HR	95% CI	p-value
Age, years	0.06263	0.00264	1.07	(1.06-1.07)	<.0001	0.04483	0.00205	1.05	(1.04-1.05)	<.0001
BMI	-0.06835	0.00824	0.93	(0.92-0.95)	<.0001	-0.01687	0.00498	0.98	(0.97-0.99)	0.0007
Rheumatoid arthritis	0.91618	0.40838	2.50	(1.12-5.57)	0.0249	0.03929	0.23031	1.04	(0.66-1.63)	0.8645
Second Osteoporosis	0.55275	0.12103	1.74	(1.37-2.20)	<.0001	0.17271	0.12514	1.19	(0.93-1.52)	0.1675
Prior fracture	0.66884	0.07377	1.95	(1.69-2.26)	<.0001	0.35280	0.04026	1.42	(1.32-1.54)	<.0001
Alcohol amount	0.32205	0.15246	1.38	(1.02-1.86)	0.0347	0.28041	0.57782	1.32	(0.43-4.11)	0.6275
Current smoking	0.17104	0.04590	1.19	(1.08-1.30)	0.0002	0.12893	0.07017	1.14	(0.99-1.31)	0.0661
Glucocorticoids use	0.03088	0.09020	1.03	(0.86-1.23)	0.7321	-0.00176	0.06413	0.99	(0.88-1.13)	0.9781
DF	8					8				
AIC	38647.29					71107.16				
Calibration χ^2 (p-value)	6.33(.7062)					103.63(<.0001)				
C-statistic (95% CI)	0.7016(0.69-0.72)					0.6275(0.62-0.64)				

*HR, hazard ratio; 95% CI, 95% confidence interval; DF, degree of freedom; AIC, Akaike information criterion; BMI, body mass index

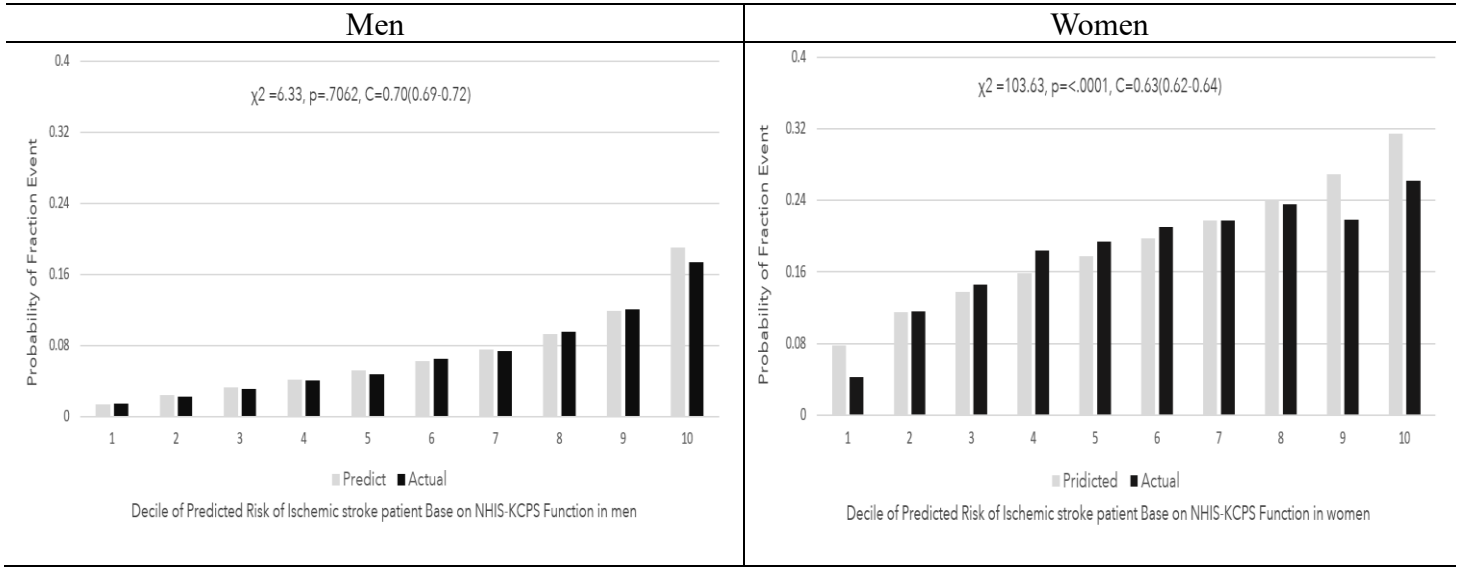


Figure 7. The 5-year probability of predicted and actual fracture events in ischemic stroke patients

IV. DISCUSSION

Fracture following stroke diagnosis-related prediction models were constructed and internally verified in the Korean population using large prospective cohort study. The fracture prediction model used FRAX variables as predictors. In the validation sets (men and women), this prediction model discrimination was shown by C-statistic of 0.70 and 0.64, respectively. A C-statistic (AUC) of 0.5 implies no discrimination, 0.7 to 0.8 is considered acceptable, 0.8 to 0.9 is considered excellent, and greater than 0.9 is considered remarkable.[43] On the basis of this evidence, both the men's and women's fracture prediction models after a diagnosis of stroke were rated acceptable.

Few studies have substantiated the association between fractures and stroke, and the majority of these research were cross-sectional. According to prior research, fractures with a follow-up length of more than 10 years are uncommon. There are a limited number of studies focusing on the Asian population, and there are studies that have examined osteoporotic fracture risk using small community cohorts,[44-46] but it is difficult to locate long-term follow-up studies focusing on stroke patients.

In this research, the HR between the ages of 80 and 89 was 10.32 for men and 10.21 for women, which were higher than in other age groups, as verified by a

meta-analysis of cohorts from various demographic groups.[46-52] Age increases fracture risk irrespective of BMD, and age-related changes are approximately seven times more important than BMD-related changes in a different ethnic group.[51]

BMI was identified as a significant independent risk factor for fracture.[47,48] Below 18.5 kg/m^2 and between 18.5 and 22.9 kg/m^2 are considered "underweight" and "normal" by the World Health Organization for the Asia-Pacific region. The mean BMI of the study participants was within the overweight BMI range for adult Asians, at 23.9 kg/m^2 for men and 24.3 kg/m^2 for women.[53]

The most prevalent kind of secondary osteoporosis is caused by corticosteroids.[54] According to meta-analysis, the risk of fracture increases immediately with the initiation of oral corticosteroid therapy (within 3 to 6 months) and decreases following the cessation of therapy.[55] The all ages (50 to 85 years) of RR for osteoporotic fracture is 1.66 in Western societies.[56] In our study population, the hazard ratio was lower (HR, 0.96; 95% CI, 0.81-1.13 in men and HR, 0.93; 95% CI, 0.823-1.04 in women) and was not statistically significant.

High alcohol intake confers a significant risk of future fracture. Alcohol use was positively associated with the risk of total fractures,[50] and any fractures and that drinking more than four units of alcohol per day increased the incidence of

osteoporotic fractures in a Caucasian study.[50] In this study, high alcohol intake (more than 3 units/day) had a similar risk (HR, 1.10; 95% CI, 0.81-1.50 in men and HR, 1.03; 95% CI, 0.33-3.16 in women), but was not significant.

In terms of fracture risk, smoking has a significant increase the risk for both men and women.[57] The result of this study is similar to previous research. Previous study has identified rheumatoid arthritis as a significant risk factor for any fracture,[56] but it was significant only in men in this study. This result is the same as previous research.[47] Discrepancies between the results of this study and those of previous studies in other cohorts may be attributable to ethnic group differences and other population-specific characteristics.

This study did not include BMD as a result because it was not captured in the registry data. The results of this study demonstrate that clinical risk variables are sufficient for predicting fracture risk. Incorporating bone mineral density into the evaluation of risk factors would improve fracture prediction, particularly for osteoporosis fractures. According to recent research of the performance of osteoporosis absolute fracture risk assessment instruments without a BMD component, their calibration is comparable to that of the fraction of devices with a BMD component.[58] When comparing the bone density on the paretic side with the non-paretic side in stroke patients, a recent study indicated that the bone

density on the paretic side decreased significantly.[59] In addition, despite the bone loss, increased fracture risk, and poor prognosis after fractures in stroke patients,[60,61] only seven out of twenty-five international stroke management recommendations contain the phrase "bone, fracture, or osteoporosis." A bone density test is essential to prevent fracture risk after a diagnosis of stroke, and the prediction model presented in this research that excludes bone density can be used to screen initial individuals.

It is difficult to locate a Korean-specific study on fracture prediction in stroke patients. Nonetheless, in a study that built a fracture model for the general Korean population, the men model's C-statistic was 0.68 and the women model's C-statistic was 0.65.[46] In a Canadian study of ischemic stroke patients, the C-statistic was 0.68 (95% CI: 0.66 to 0.71) for women and 0.70 (95% CI: 0.66 to 0.73) for men, these studies are comparable to the results of this study.[37]

The FRS model C-statistic is a good model in this study, considering the fact that its analysis method differs from previous studies and, the Canadian study includes a variable that can measure status upon hospital discharge of stroke patients, modified Ranking Score (mRS). Based on these results, fracture can be predicted with FRS model which used just FRAX variables, eliminating BMD, and although there are no “BMD” and “parent fractured hip” variables in the

model in this study, it may be more clinically applicable.

This cohort study's strength is that it was done using a big sample size, a broad age range, and a countrywide sample. Second, more than 20 years of long-term follow-up data were utilized. Thirdly, it is difficult to identify a research that predicts fractures after a diagnosis of stroke in Asians. However, this research focused on Asians, namely Koreans.

This study has some limitations. First, this study included possible measurement errors, and clinical data from the health promotion centers included one-time measurements of blood pressure and other medical outcomes. Second, the results were likely to be affected by unmeasured and residual confounding factors. Third, not all FRAX variables were included in the model used for this investigation. A future study including the parent fractured hip variable is needed. Fourth, the majority of participants in this study are of Korean descent, which may restrict the generalizability of the results to persons of other races/ethnicities. In order to generalize the outcomes of this model, it will be necessary to do more practical research on several populations.

In this study, the FRS model's prediction ability for women in the 10^{th} decile was relatively low. This result may be owing to the under detection of vertebral fractures because they were misunderstood as ordinary back pain or aging, or to the

inclusion of accident-related participants among hemorrhagic stroke patients. In this study, accidents were defined and excluded based on the ICD-10 codes, however they might not have been excluded if they had been classified according to sub-diagnosis. In addition, among the characteristics predicting fractures, the absence of the "parent fractured hip" may have had an influence.

Vertebral compression fractures (VCF) are considered as the hallmark of osteoporosis;[62,63] Many patients and family confuse back pain symptoms for "arthritis" or natural aging, therefore only around one-third of vertebral fractures are properly identified.[64-65] The predicted prevalence of vertebral fracture continuously increases with age, reaching 40% in women aged 80 years old.[66]

VCF non-modifiable risk variables include old age, female gender, Caucasian race, vulnerability to falling, dementia, history of adult fractures, and family history of fractures.[67] The FRS model does not account for the parent fractured hip, which is a fracture history in the family. Additional research is required to determine the origin of the findings of this study's 10th decile of women and to enhance the prediction of fractures in stroke patients. The appendix 3-4 presents the overall features of women in the 10th decile. They are, on mean, 82.1 years old. Compared to the participants in this study, the average LOS was slightly longer at 13.82 days, the incidence of fractures prior to the diagnosis of stroke was extremely high at

99.9%, and the incidence of osteoporosis was similarly high at 8.1%. In contrast, the mean weight was 49.2 kg, and the BMI was relatively low at 22.2 kg/m^2. In these groups, the FRS model's predictive value may be low, it may be unpredictable, hence it should be used with caution.

V. CONCLUSION

This study suggests a predictive model that is comparable to or slightly superior to the fracture prediction model for stroke patients in Canadian and the study of the general Korean population.

This study assessed the applicability of FRAX factors except for bone mineral density(BMD) test and family history for predicting fracture risk in the Korean population following a diagnosis of stroke. The FRS model appears suitable as predictor for this group. Since the FRS model does not require a BMD test nor parent hip fracture history information, it might be more useful for clinical usage as a screening test and is therefore expected to contribute to prevention by finding a post-stroke fracture risk group.

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Appendix 1. Risk profile in the NHIS-KCPS study

For men, its general form in NHIS-KCPS cohort is

FRS_M = 0.06044×(AGE-67.8332) - 0.07014×(BMI-23.9314)

+0.69172×(Prior_Fracture-0.065623) + 0.19237×(Current_smok-0.39976)

- 0.04635×(Glucocorticoids-0.04789) - 0.84476×(Arthritis-0.00151)

+ 0.70979×(Second_Osteoporosis-0.02837) + 0.09309×(Alco-0.01384)

The function FRS_M is then exponentiated, and this function is designated KFRSM1.

KFRSM1=EXP(FRS_M)

Finally, KFRSMP is the absolute 5-year risk of Fracture.

KFRMSP =1-0.94942**(KFRSM1)

Where 0. 94942 is the survival rate, S(t), for participants.

For women, its general form in NHIS-KCPS cohort is

FRS_W = 0.04777 × (AGE-72.9005) - 0.02076 × (BMI-24.2567)

+ 0.39017 × (Prior_Fracture -0.19174) + 0.16715 × (Current_smok-0.04337)

- 0.07795 × (Glucocorticoids-0.05177) - 0.09559 × (Arthritis-0.00447)

+ 0.06526 × (Second_Osteoporosis-0.01702) + 0.01868 × (Alco-0.00088)

KFRSW1=EXP(FRS_W); KFRSWP =1-0.83367**(KFRSW1)

Appendix 2. Risk profile of age 50 year and older in NHIS-KCPS

For men in age 50 and older, its general form in NHIS-KCPS cohort is

FRS_M50 = 0.05970×(AGE-69.3258) - 0.06923×(BMI-23.8628)

- 0.69909×(Prior_Fracture-0.068636) + 0.19601×(Current_smok-0.38884)

- 0.05055×(Glucocorticoids-0.047231) - 0.84549×(Arthritis-0.001607879)

+ 0.67393×(Second_Osteoporosis-0.028573) + 0.10383×(Alco-0.013064)

KFRSM1=EXP(FRS_M50); KFRMP =1-0.94436**(KFRSM1)

For women in age 50 and older, its general form in NHIS-KCPS cohort is

FRS_W50 = 0.04777 × (AGE-72.9005) - 0.02076 × (BMI-24.2567)

+ 0.39017×(Prior_Fracture -0.19174) + 0.16715×(Current_smok-0.043371)

- 0.07795×(Glucocorticoids-0.051771) - 0.09559×(Arthritis-0.004465273)

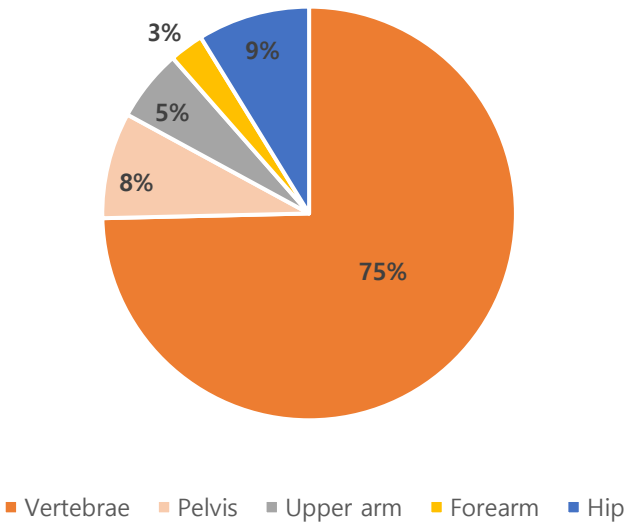
+ 0.06526×(Second_Osteoporosis-0.017021) + 0.01868 × (Alco-0.000884212)

KFRSW1=EXP(FRS_W50); KFRSWP =1-0.83367**(KFRSW1)

Appendix 3. 10th decile women's characteristics of the validation set in NHIS-KCPS

Variables		Women in Validation set- NHIS-KCPS (n=2,220)	
		Mean / N	SD / %
Age, years (mean, sd)		82.06	3.73
Length of Stay, days		13.82	2.80
Height, cm		148.61	5.95
Weight, kg		**49.15**	**6.80**
BMI, kg/m^2		**22.21**	**2.41**
SBP, mmHg		133.06	18.50
DBP, mmHg		79.93	11.72
Total cholesterol, mg/dl		202.13	38.69
FBS, mg/dl		103.78	33.82
Age, years			
	70-79	569	25.61
	80-89	1,653	74.39
Stroke Type			
	Ischemic	1,871	84.20
	Hemorrhagic	351	15.80
Smoking status			
	Non-smoker	1,992	89.65
	Ex-smoker	52	2.34
	Cur-smoker	178	8.01
Exercise			
	yes	958	43.11
Alcohol use			
	No	2,218	99.82
	less than 3units	4	0.18
	More than 3units	0	0.00
Glucocorticoids use		37	1.67
Prior			
	falls	2	0.09
	fracture	2,219	99.86
Fracture		421	18.95
Hypertension		38	9.18
Diabetes		272	12.24
Hyperlipidemia		6	0.27
Dementia		250	11.25
Osteoporosis		180	8.1
Second Osteoporosis		57	2.57
Parkin’s disease		38	1.71
Rheumatoid arthritis		11	0.50
Hyperparathyroidism		0	0.00
Ischemic heart disease		219	9.86
Atrial fibrillation		35	1.58

Appendix 4. 10th decile women's fracture sites of the validation set in NHIS-KCPS



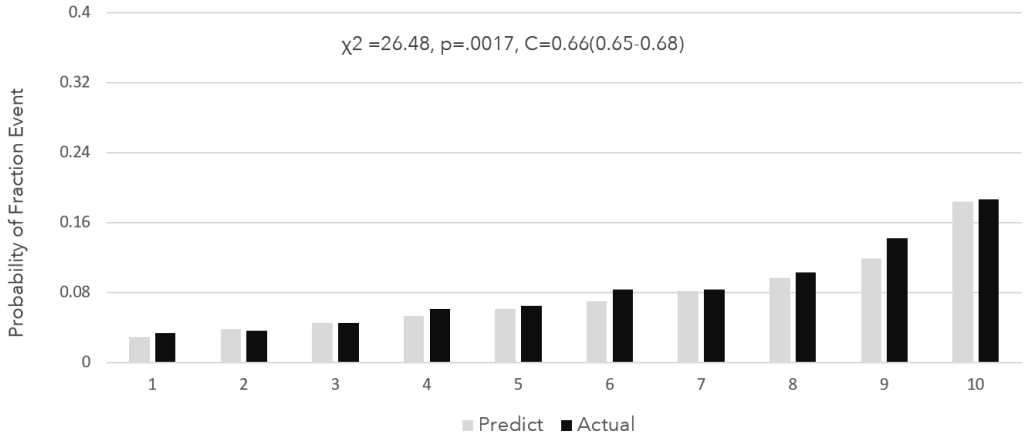
Appendix 5. Sub-group analysis of age 60 year and older in NHIS-KCPS

Supplement Table 1. Hazard ratios for risk of fracture events from derivation set in age 60 year and older by sex

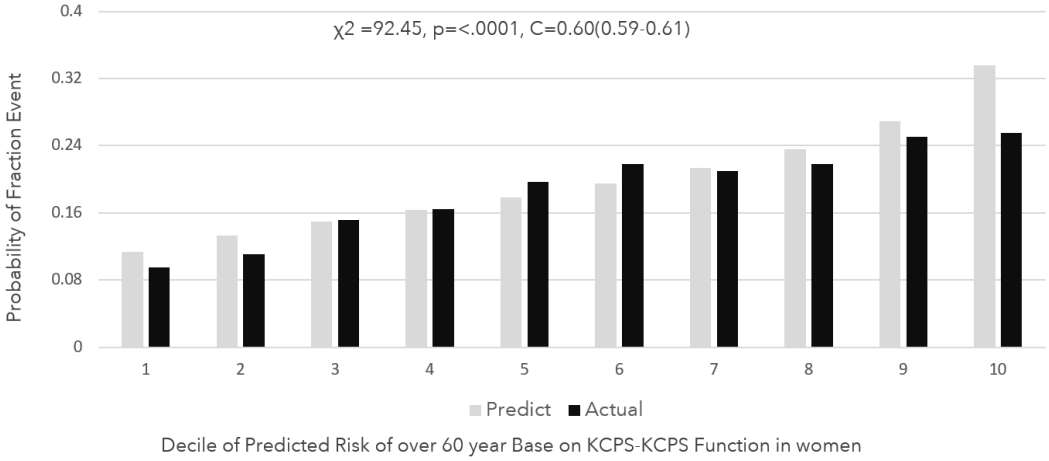
Variables	Men				
	β-coefficient	SE	HR	95% CI	p-value
Age, years	0.05721	0.00341	1.06	(1.05-1.07)	<.0001
BMI	-0.07022	0.00816	0.93	(0.92-0.95)	<.0001
Rheumatoid arthritis	0.90187	0.40902	2.46	(1.11-5.19)	0.0275
Second Osteoporosis	0.60945	0.11510	1.84	(1.47-2.31)	<.0001
Prior fracture	0.67672	0.07195	1.97	(1.71-2.27)	<.0001
Alcohol amount	0.13116	0.17572	1.14	(0.81-1.61)	0.4554
Cu-smoke	0.18879	0.04548	1.21	(1.11-1.32)	<.0001
Glucocorticoids use	0.01029	0.09043	1.01	(0.85-1.21)	0.9094
DF	8				
AIC	38797.34				
Calibration χ^2 (p-value)	26.48(0.0017)				
C-statistic (95% CI)	0.660(0.65-0.68)				
Variables	**Women**				
	β-coefficient	**SE**	**HR**	**95% CI**	**p-value**
Age, years	0.03456	0.00227	1.04	(1.03-1.04)	<.0001
BMI	-0.02489	0.00467	0.98	(0.97-0.98)	<.0001
Rheumatoid arthritis	-0.13317	0.24315	0.88	(0.54-1.41)	0.5839
Second Osteoporosis	0.03422	0.12225	1.04	(0.81-1.32)	0.7796
Prior fracture	0.40733	0.03703	1.50	(1.40-1.62)	<.0001
Alcohol amount	0.01127	0.57766	1.01	(0.33-3.14)	0.9844
Cu-smoke	0.15436	0.06566	1.17	(1.03-1.33)	0.0187
Glucocorticoids use	-0.09814	0.06262	0.91	(0.80-1.03)	0.1171
DF	8				
AIC	82062.23				
Calibration χ^2 (p-value)	92.45(<.0001)				
C-statistic (95% CI)	0.604(0.59-0.61)				

*HR, hazard ratio; 95% CI, 95% confidence interval; DF, degree of freedom; AIC, Akaike information criterion

Men

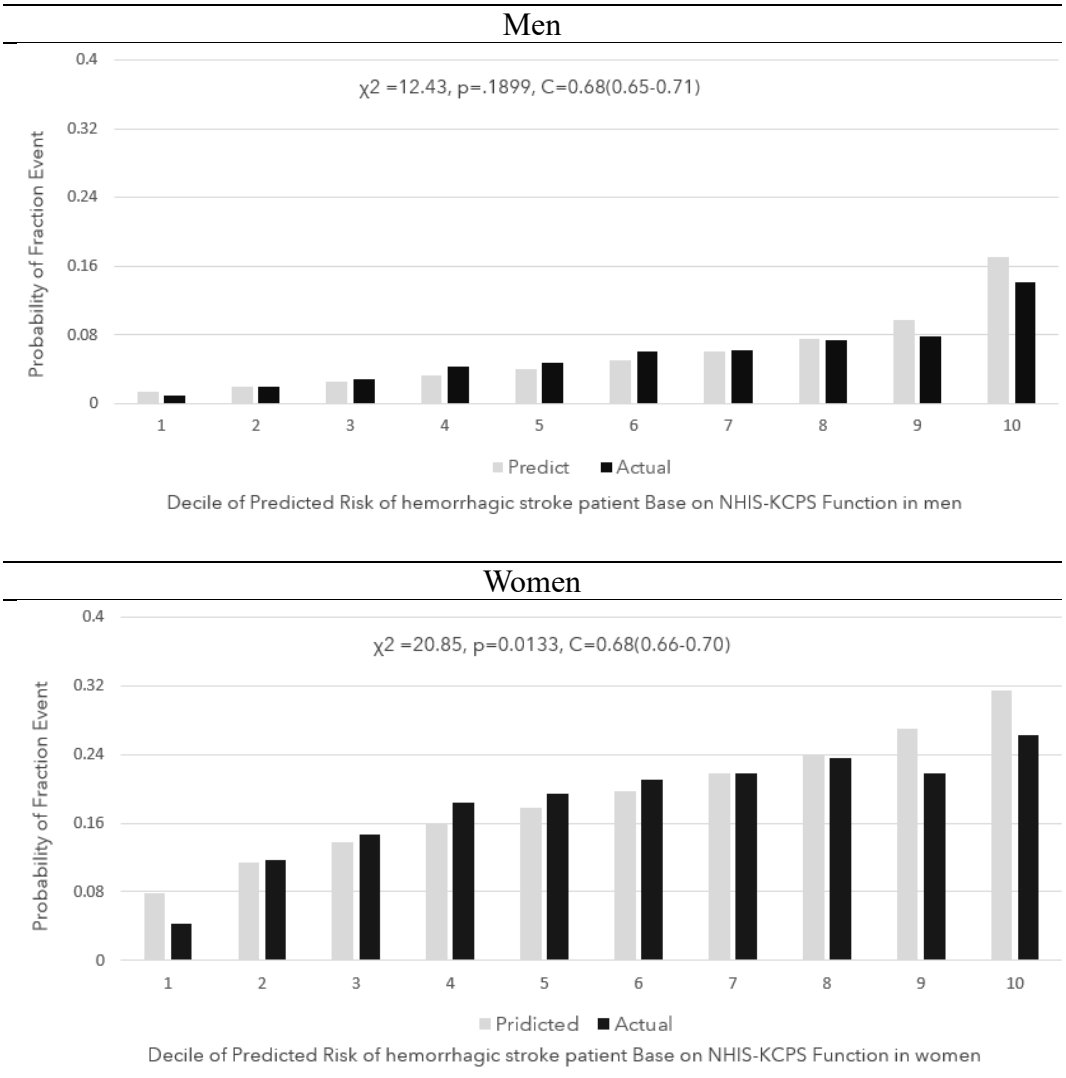


Women



Supplement figure 1. The 5-year probability of predicted and actual fracture events of age 60 and older in the NHIS-KCPS cohort

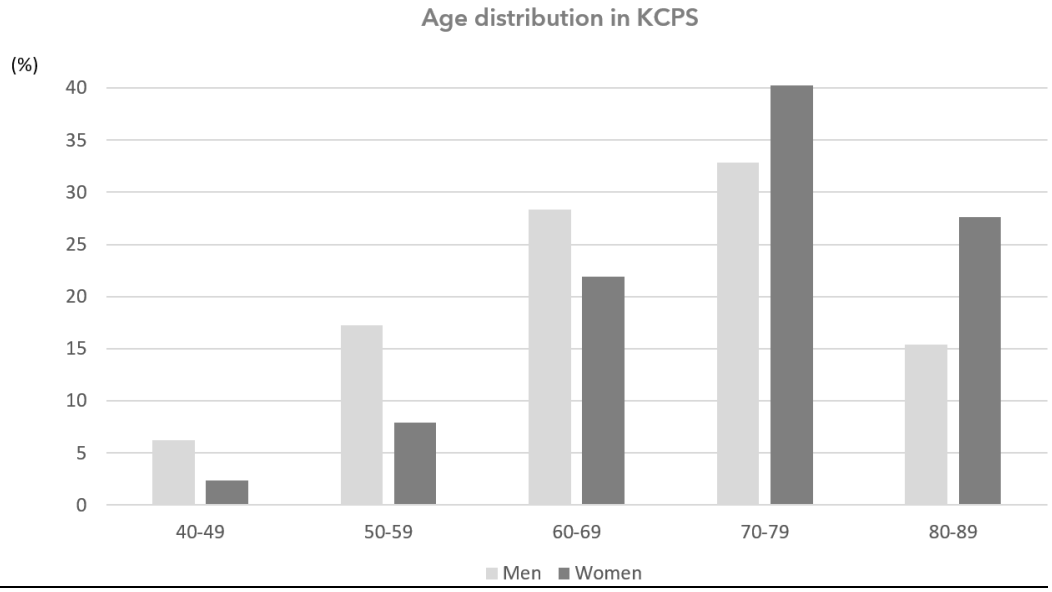
Appendix 6. Sub-group analysis of hemorrhagic stroke in NHIS-KCPS



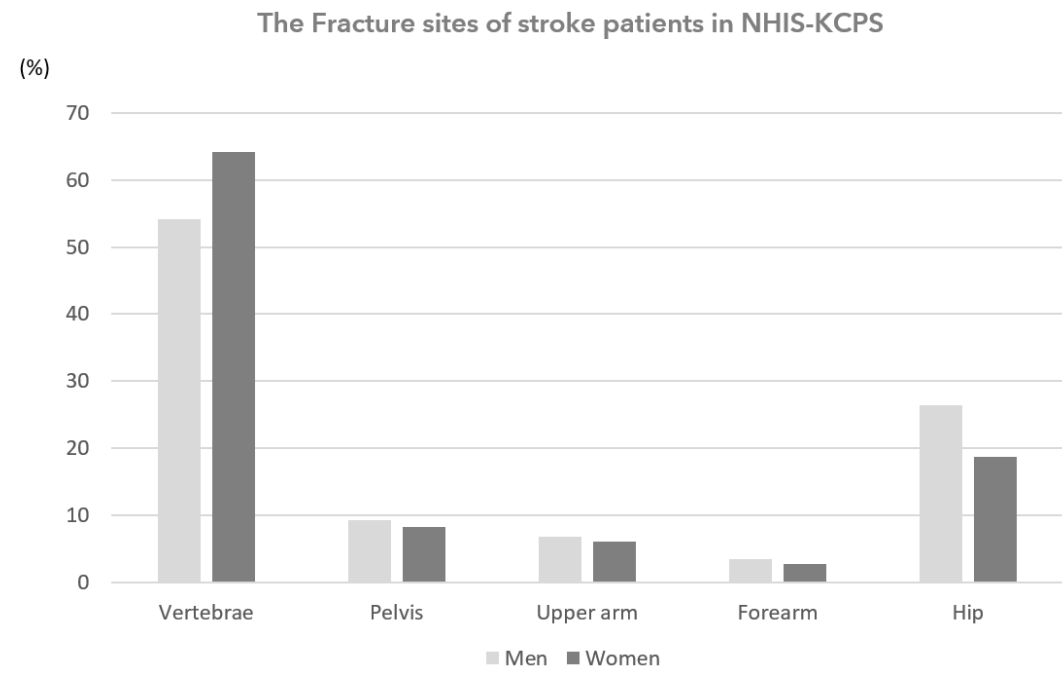
Supplement figure 2. The 5-year probability of predicted and actual fracture events of hemorrhagic stroke in the NHIS-KCPS cohort

Appendix 7. The age distribution in NHIS-KCPS cohort

NHIS-KCPS, n=108,868



Appendix 8. The fracture sites of stroke patients in NHIS-KCPS



국 문 요 약 (Korean Abstract)

한국 성인에서의 뇌졸중 진단 후 골절 위험 예측 분석

연세대학교 대학원 보건학과

양 연 수

연구배경: 뇌졸중 환자는 폐렴, 심부정맥혈전증, 욕창 및 요로 감염을 포함한 뇌졸중 후 동반 질환의 위험이 있으며, 지상에서의 낙상 같은 가벼운 사건으로도 저외상 골절의 위험이 더 높다. 선행연구에 따르면, 일반 인구의 일치된 대조군에 비해 뇌졸중 생존자의 저외상 골절 위험이 30% 이상 증가했다. 여러 선행연구들에서 골절에 대한 독립적인 위험인자가 확인되었으나 골절예측의 적절성과 가장 예측가능한 위험인자는 파악되지 않았다. 골절의 1차 예방을 위해 여러 지침에서는 위험도에 따라 골밀도 측정을 통한 골다공증 검진을 권장한다. 이러한 스크리닝을 안내하기 위해 저외상 골절에 대한 예측 규칙이 도출되고 검증되어 사용되고 있는데, 가장 일반적으로 사용되는 점수는 세계보건기구 골절 위험도(FRAX) 점수이다. 그러나 FRAX 점수는 일반 인구를 대상으로 개발되었으며 고유한 뇌졸중 관련 예측 변수를 고려하지 않아 뇌졸중 생존자 인구에서 검증되지 않았다. 그러므로 뇌졸중 생존자를 대상으로 골절 위험도를 예측하는 연구가 필요하다.

연구방법: 본 연구는 국민건강보험단-한국인 암 예방 연구(National Insurance Health Service-Koran cancer prevention study; NHIS-KCPS) 코호트 자료를 사용하였다. 골절 위험도 (FRAX) 생성 변수가 뇌졸중 환자들에게서도 적합한지를 확인하기 위해 무작위 추출을 통해 두 그룹으로 분류하였다. 무작위 추출을 통해 모델 개발을 위한 50%와 모델 검증을 위한 50%로 대상자를 나누었다. 위험 요인과 골절 발생률 간의 연관성을 평가하기 위해 Cause specific hazard model 분석법을 사용하였다. NHIS-

KCPS 코호트에서 FRAX 변수에 의해 예측된 5년 골절 위험에 대한 방정식을 판별(discrimination) 및 교정(calibration) 방법으로 평가하였으며, 골다공증 및 총콜레스테롤(TC), 입내원일수(LOS) 변수를 모델에 각각 추가하여 IDI(integrated discrimination improvement)와 NRI(net reclassification improvement)로 골절 예측의 개선을 평가하였다.

연구결과: 뇌졸중 진단 후 골절 발생 관련 예측 모델은 대규모 전향적 코호트 연구를 사용하여 한국인 인구에서 구축되고 검증되었다. 골절 위험 예측 모델을 개발하기 위한 파생 데이터에서의 대상자 평균 연령은 남자 67.8세, 여자 72.9세였으며 검증 데이터에서는 각각 67.9세, 72.8세였다. 뇌졸중 진단 후 골절예측 모형 (FRS)은 남, 녀 모두에서 FRAX 변수들을 사용하였다. 한국인 코호트에서 개발된 뇌졸중 후 골절 위험 예측모형은 검증 세트에서 예측 모델의 C-통계량은 여자 0.6370(0.63-0.65), 남자 0.7001(0.69-0.71) 이었다. 예측모형의 예측력 향상을 평가하기 위해 골다공증, 총콜레스테롤, 입내원일수를 각각 적용하였을 때 총콜레스테롤을 포함하였을 때의 모형이 여자에서 C-통계량 0.6371(0.63-0.65)로 약간의 개선을 보였다. 남자에서는 입내원일수를 포함하였을 때, C-통계량 0.7035(0.69-0.72)로 약간의 개선을 보였으며, 이 모델들은 여자 모형에서 IDI 0.015848($p<.0001$), NRI 0.041350($p<.0001$), 남자 모형에서 IDI 0.015848($p<.0001$), NRI 0.041350($p<.0001$) 만큼의 예측력 향상을 보였다.

결과고찰: 본 연구는 한국인 인구집단에서 뇌졸중 진단 후 골절 위험 예측을 위하여 골밀도(BMD)와 부모의 고관절 골절 병력을 제외한 FRAX 변수의 적용 가능성을 평가하였다. FRS 모델은 뇌졸중 환자의 골절 예측 변수로 적합해 보인다. FRS 모델은 골밀도 검사나 부모의 고관절 골절 병력 정보를 필요로 하지 않기 때문에 선별 검사로 임상적 활용에 더 유용할 수 있어, 뇌졸중 진단 후 골절 위험군을 찾아 예방에 기여할 수 있을 것으로 기대할 수 있다.

핵심어: 골절, 뇌졸중, FRAX 점수, 골절 위험 예측