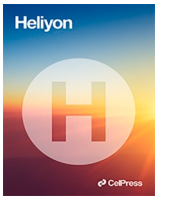
Heliyon 10 (2024) e30196

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Stroke recurrence and osteoporotic conditions in postmenopausal patients with atherosclerotic ischemic stroke

Byeong Jin Ha [1], Sang Mook Kang [1], Bo Mi Choi, Jin Hwan Cheong, Je Il Ryu, Yu Deok Won [**], Myung-Hoon Han [*]

Department of Neurosurgery, Hanyang University Guri Hospital, 153 Gyeongchun-ro, Guri, 471-701, Gyonggi-do, Republic of Korea

ARTICLE INFO

Keywords:
Large-artery atherosclerosis
Small-vessel occlusion
Stroke recurrence
Hounsfield unit
Bone mineral density

ABSTRACT

Recurrence after stroke is common, and associated with a high mortality rate. Degradation of the elastic tissue in the arterial wall has been shown to aggravate atherosclerosis in blood vessels. Considering that type 1 collagen is present in both bone and vascular smooth muscle cells, we explored whether osteoporotic conditions affect the likelihood of stroke recurrence in postmenopausal women following atherosclerotic ischemic stroke. To determine actual bone mineral density (BMD), the Hounsfield unit values in the frontal skull were evaluated using brain computed tomography (CT) scans taken at admission. A multivariate Cox regression analysis was also performed to examine if osteoporosis could independently predict stroke recurrence in postmenopausal patients with large artery atherosclerosis (LAA) or small vessel occlusion (SVO) stroke. This study included 2130 consecutive patients (both males and females aged 50 and older) with acute LAA or SVO strokes. After adjusting for all covariates, hypothetical osteoporosis was identified as an independent predictor of stroke recurrence in female patients ≥50 years with acute LAA or SVO stroke (hazard ratio, 1.84; 95 % confidence interval, 1.05 to 3.24; $p = 0.034$). Our findings showed that osteoporosis could potentially affect the recurrence of ischemic stroke in postmenopausal patients with LAA or SVO stroke.

1. Introduction

The recurrence rate of ischemic stroke ranges from 5.7 % to 51.3 % [1]. A recent study reported that for ischemic stroke, the 1- and 10-year risks of all-cause mortality after the first stroke were 17 % and 56 %, respectively, while the corresponding values after a recurrent stroke were 25 % and 70 %, respectively [2]. Numerous predictors have been reported to increase the risk of stroke recurrence, including male sex, age, diabetes mellitus, etiologic stroke subtype, distribution of brain infarcts, history of transient ischemic attacks, atrial fibrillation, and hypertension [3–5].

Destruction of the elastic tissue in the arterial wall aggravates vascular atherosclerosis [6,7]. Both bone and vascular smooth muscle cells (SMCs) in the tunica media are composed of type 1 collagen [8]. Given that osteoporosis is considered a systemic condition [9],

* Corresponding author. Department of Neurosurgery, Hanyang University Guri Hospital, 153 Gyeongchun-ro, Guri, 471-701, Gyonggi-do, Republic of Korea.
** Corresponding author. Department of Neurosurgery, Hanyang University Guri Hospital, 153 Gyeongchun-ro, Guri, 471-701, Gyonggi-do, Republic of Korea.
E-mail addresses: hidma823@hanmail.net (Y.D. Won), gksmh80@gmail.com (M.-H. Han).
[1] B.J. Ha and S.M. Kang contributed equally.

https://doi.org/10.1016/j.heliyon.2024.e30196
Received 24 December 2023; Received in revised form 20 April 2024; Accepted 22 April 2024
Available online 28 April 2024

we proposed that osteoporotic states may lead to the weakening of blood vessel walls. This could aggravate vascular atherosclerosis, and increase the likelihood of stroke recurrence. Therefore, given the prevalence of osteoporosis in individuals around the age of 50 years, we aimed to determine whether osteoporosis is associated with stroke recurrence in patients aged ≥50 years [10]. We decided that focusing on patients with ischemic stroke subtypes primarily caused by atherosclerosis would be more consistent with our hypothesis. Therefore, we only included patients with large-artery atherosclerosis (LAA) or small-vessel occlusion (SVO) stroke, as defined by the Trial of Org10172 in Acute Stroke Treatment (TOAST) classification. These subtypes are more closely linked to vascular atherosclerosis than other stroke subtypes [11,12].

We previously reported that bone mineral density (BMD) could be predicted by measuring the skull Hounsfield unit (HU) values [13–15]. Therefore, the aim of this study was to determine whether possible osteoporotic conditions, as predicted by skull HU values, would influence stroke recurrence in patients ≥50 years with LAA or SVO stroke.

2. Material and methods

2.1. Study patients

We retrospectively retrieved data from the Registry of Ischemic Stroke Patients at Hanyang University Guri Hospital, South Korea, for the first time at our hospital from January 1, 2009, to December 31, 2020 [16]. The registry was established with the intent of facilitating future research, and was therefore carefully structured to ensure high-quality, consistent, and accurate data gathering. This dependability is derived from the uniform and direct handling of data by a team of trained personnel at a single hospital. The diagnosis of ischemic stroke was made by a neurologist, who used clinical symptoms for the initial assessment and magnetic resonance imaging (MRI) for confirmation.

Patients of all ages and stroke subtypes were selected from the registry, among whom 3772 were included in the analysis

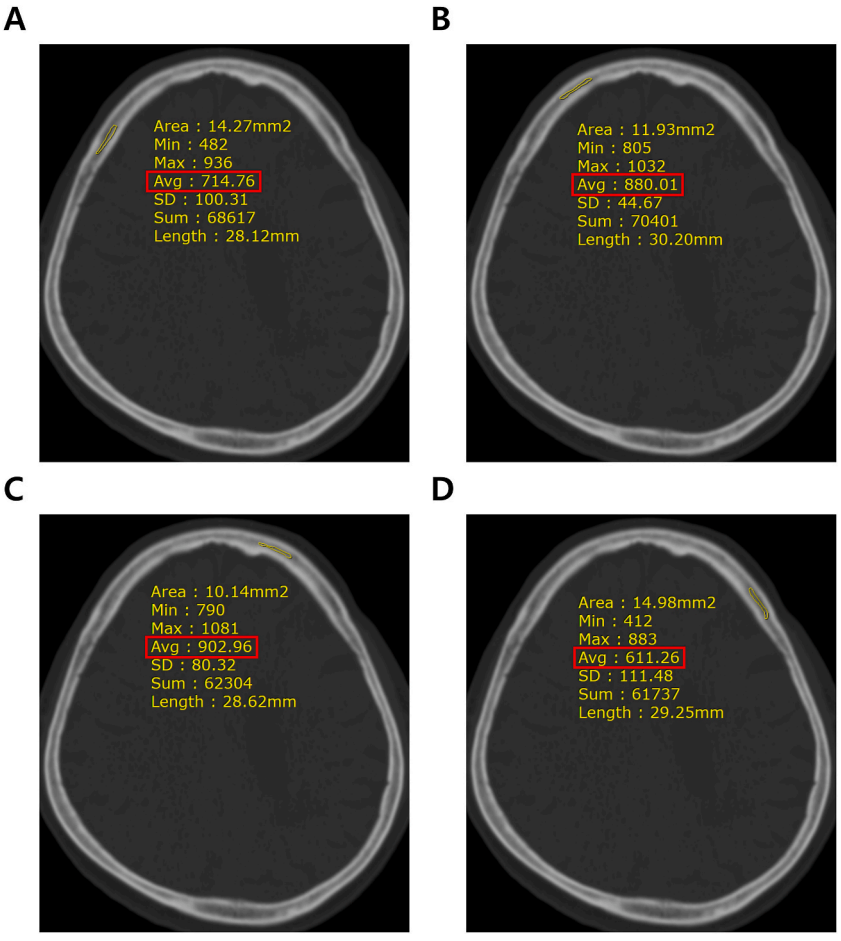


Fig. 1. The process involves the PACS system automatically determining the maximum, minimum, and average HU values across four specific areas of cancellous bone in the frontal skull on brain CT scans. (A) Right lateral; (B) right medial; (C) left medial; (D) left lateral. HU, Hounsfield unit; PACS, picture archiving and communication system.

(Supplementary Fig. 1). We only included patients aged ≥50 years who were diagnosed with LAA or SVO stroke. Altogether, 2190 patients were initially identified. We excluded 33 patients from the study due to the absence of at least one brain computed tomography (CT) scan near the time of their initial diagnosis of ischemic stroke. Furthermore, 27 patients were excluded due to the presence of markedly narrow intercortical spaces in the frontal skull. The remaining 2130 consecutive male and female patients with LAA or SVO strokes were included in the analyses.

The Institutional Review Board of Hanyang University Guri Hospital in South Korea approved this study, which adhered to the principles outlined in the Declaration of Helsinki. The need for informed consent was waived due to the retrospective study design. Prior to analysis, all personal data were anonymized.

2.2. Radiological assessment

All LAA and SVO strokes were diagnosed based on diffusion-weighted (DWI) MRI, brain magnetic resonance angiography, and/or computed tomography (CT) angiography, electrocardiography, laboratory studies, carotid Doppler imaging, and echocardiography, in accordance with the TOAST classification [11]. A diagnosis of intracranial large artery atherosclerosis (LAA) was made in cases of symptomatic stenosis of 50 % or greater in the intracranial arteries, or complete occlusion with no indications of cardioembolic (CE) stroke [17]. SVO stroke was diagnosed when a small (<1.5 cm in diameter) deep lesion was observed on MRI in the absence of potential sources of CE or LAA [17]. Stroke recurrence was defined as neurological deterioration with new infarct development relevant to the clinical symptoms confirmed on brain MRI [18]. Stroke subtypes were confirmed using diffusion-weighted MRI according to the Radiographic Oxfordshire Community Stroke Project (OCSP) classification [19]. An experienced neuroradiologist confirmed all radiological findings.

The HU values of the skull were analyzed using brain CT images acquired at our facility at the time of initial stroke diagnosis. We have previously described the methodology for measuring HU values in the frontal skull [14,15,20]. In summary, the HU values in the frontal skull were recorded at four designated regions of interest in the frontal cancellous bone, specifically between the right and left coronal sutures, at the point where the lateral ventricles were no longer visible on brain CT scans (Fig. 1A–D). To ensure accuracy, all CT images were enlarged during the measurement of HU values to exclude the cortical bone.

The infarct size was determined using the conventional ABC/2 technique [13,21]. The largest area of acute infarction was chosen for measurement using DWI MRI. The methods are detailed in Supplementary Fig. 2.

2.3. Clinical factors

The clinical information (sex, age, National Institutes of Health Stroke Scale (NIHSS) score at admission, use of tissue plasminogen activator (tPA), antithrombotic use after first-ever stroke, hypertension, diabetes, myocardial infarction, smoking, alcohol consumption, and hyperlipidemia) of all patients enrolled in the study was collected from the electronic medical records.

2.4. Concepts and definitions

In all analyses, the average skull HU value was calculated using the following formula: ([mean right lateral HU + mean right medial HU + mean left medial HU + mean left lateral HU]/4. In a previous publication, we introduced the Skull HU and BMD (SHUB) registry, a collection of retrospectively-gathered data from individuals older than 18 years who underwent dual-energy X-ray absorptiometry for BMD measurements and brain CT scans at our hospital between January 1, 2010, and December 31, 2016 [15]. We further analyzed a registry of 1413 patients for whom both skull HU and actual BMD data were available. Using receiver operating characteristic (ROC) curve analysis, we identified an optimal cutoff value of 601.375 for skull HU, which was indicative of osteoporosis (AUC = 0.776; sensitivity = 72.3 %; specificity = 70.5 %; $p < 0.001$). Because the skull HU values are absolute [22,23], we applied the threshold established in our previous study. Patients with values ≤ 601.375 were classified into the hypothetical osteoporosis group, while those with values > 601.375 were categorized into the hypothetical osteopenia or normal groups [15].

2.5. Statistical methods

Kaplan-Meier analysis was used to compute the cumulative hazard of ischemic stroke recurrence based on hypothetical BMD classifications and tertile divisions of skull HU values. In this analysis, patients who showed no stroke recurrence on their most recent brain MRI were censored. Using multivariate Cox regression analysis, hazard ratios (HRs) and 95 % confidence intervals (CIs) were determined to evaluate if osteoporotic conditions may independently predict stroke recurrence among female patients with acute LAA or SVO strokes aged 50 years and older. The multivariate model was adjusted for potential confounders, such as age, hypothetical BMD classification, stroke subtype, infarct volume, stroke location, NIHSS score, tPA use, antithrombotic use, hypertension, diabetes, myocardial infarction, smoking, alcohol consumption, and hyperlipidemia.

The proportionality of the hazard assumption in the Cox regression models was evaluated using the Schoenfeld global test for goodness of fit [24]. A scatterplot with a linear regression line or a line determined by a locally weighted scatterplot smoothing (LOWESS) regression curve was used to visualize the association between age and frontal skull HU values according to ischemic stroke recurrence. The rationale and detailed methodology for using a LOWESS curve have been described previously [25].

Statistical significance was set at $p < 0.05$. All statistical procedures were conducted using R software version 4.2.2 (The R Foundation for Statistical Computing, Vienna, Austria) and SPSS for Windows (version 24.0; IBM, Chicago, IL, USA).

3. Results

3.1. Characteristics of patients in the study cohort

We registered 2130 consecutive patients (≥50 years) who received treatment for acute LAA or SVO stroke at our institution over a period of 12 years. During treatment for acute ischemic stroke, 264 (12.4 %) patients experienced recurrent stroke. The average patient age was 69.8 years, with 854 of the participants being female (40.1 %). Of the female patients, 101 (11.8 %) had recurrent stroke, which was not significantly different from that observed in male patients (p = 0.515) (Table 1). The frontal skull HU values were notably lower in females compared to in males. In addition, 423 women (49.5 %) were classified as having hypothetical osteoporosis. Detailed patient characteristics are presented in Table 1.

3.2. Mean frontal skull HU values according to stroke recurrence in female patients with acute LAA or SVO stroke

Table 2 shows the average frontal skull HU values and stroke recurrence in female patients (≥50 years) with acute LAA or SVO stroke. The average frontal skull HU value was 609.9 for patients who experienced stroke recurrence, compared with 645.3 for those who did not develop stroke recurrence. Although the skull HU values tended to be lower in the group with stroke recurrence than in the group without stroke recurrence, this difference was not statistically significant (Table 2).

3.3. Cumulative hazard of stroke recurrence according to mean frontal skull HU values

Fig. 2A shows the overall cumulative hazard of stroke recurrence in all patients (≥50 years) diagnosed with acute LAA or SVO stroke. When all patients were categorized into groups according to their hypothetical BMD, the difference in stroke recurrence rate between the hypothetical osteoporosis group and the hypothetical osteopenia or normal group was not statistically significant (P = 0.077) (Fig. 2B). However, when we analyzed only female patients aged ≥50 years with acute LAA or SVO stroke, the hypothetical osteoporosis group had a significantly higher stroke recurrence rate during the clinical course of AIS (p = 0.013) (Fig. 2C). In addition, when female patients were categorized into tertile groups based on skull HU values, patients in the lowest tertile had a significantly

Table 1
Characteristics of patients (≥50 years) with acute LAA or SVO stroke categorized by sex.

Characteristics	Male patients	Female patients	Total	p
Number (%)	1276 (59.9)	854 (40.1)	2130 (100)	
Age, mean ± SD, y	67.3 ± 10.1	73.6 ± 10.4	69.8 ± 10.7	<0.001
Stroke recurrence, n (%)	163 (12.8)	101 (11.8)	264 (12.4)	0.515
The time between acute ischemic stroke diagnosis and the last follow-up image, median (IQR), months	42.0 (13.3–79.0)	33.0 (6.0–63.0)	39.0 (9.0–73.0)	<0.001
Mean frontal skull HU, mean ± SD	891.5 ± 274.5	641.1 ± 239.2	791.1 ± 288.3	<0.001
Classification of skull HU according to our previous hypothetical criteria for osteoporosis, n (%)				<0.001
Hypothetical osteopenia or normal group (HU > 601.375)	1086 (85.1)	431 (50.5)	1517 (71.2)	
Hypothetical osteoporosis group (HU ≤ 601.375)	190 (14.9)	423 (49.5)	613 (28.8)	
Etiologic stroke subtypes based on TOAST, n (%)				0.290
LAA	671 (52.6)	469 (54.9)	1140 (53.5)	
SVO	605 (47.4)	385 (45.1)	990 (46.5)	
Infarct volume, mean ± SD, cc	14.2 ± 40.1	13.6 ± 41.8	14.0 ± 40.8	0.732
Stroke subtypes by radiographic OCSP classification, n (%)				0.334
LACI	75 (5.9)	60 (7.0)	135 (6.3)	
TACI	28 (2.2)	20 (2.3)	48 (2.3)	
PACI	741 (58.1)	473 (55.4)	1214 (57.0)	
POCI	329 (25.8)	244 (28.6)	573 (26.9)	
Multiple	103 (8.1)	57 (6.7)	160 (7.5)	
Baseline NIHSS score, median (IQR)	3 (1–5)	3 (1–5)	3 (1–5)	0.276
Received tPA, n (%)	89 (7.0)	44 (5.2)	133 (6.2)	0.088
Antithrombotic use after first-ever stroke, n (%)				0.350
Antiplatelet	1232 (96.6)	814 (95.3)	2046 (96.1)	
Anticoagulant	37 (2.9)	33 (3.9)	70 (3.3)	
Antiplatelet + anticoagulant	7 (0.5)	7 (0.8)	14 (0.7)	
Hypertension, n (%)	741 (58.1)	600 (70.3)	1341 (63.0)	<0.001
Diabetes, n (%)	468 (36.7)	291 (34.1)	759 (35.6)	0.219
Myocardial infarction, n (%)	40 (3.1)	23 (2.7)	63 (3.0)	0.555
Smoking, n (%)	735 (57.6)	72 (8.4)	807 (37.9)	<0.001
Alcohol, n (%)	790 (61.9)	113 (13.2)	903 (42.4)	<0.001
Hyperlipidemia, n (%)	588 (46.1)	432 (50.6)	1020 (47.9)	0.041

LAA, large artery atherosclerosis; SVO, small vessel occlusion; SD, standard deviation; IQR, interquartile range; HU, Hounsfield unit; OCSP, Oxfordshire Community Stroke Project; LACI, lacunar infarction; TACI, total anterior circulation infarction; PACI, partial anterior circulation infarction; POCI, posterior circulation infarction; NIHSS, National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator.

Table 2
Summary data on skull HU values for female patients (≥50 years) with acute LAA or SVO stroke.

Variables	Stroke recurrence (−)	Stroke recurrence (+)	Total	p
Average skull HU value, median (IQR)	608.1 (467.8–779.5)	570.2 (433.8–720.8)	603.8 (464.2–777.5)	0.163
Average skull HU value, mean ± SD	645.3 ± 237.7	609.9 ± 249.2	641.1 ± 239.2	0.163
Average HU value at four locations within the frontal skull, mean ± SD				
Right lateral	603.3 ± 232.6	558.2 ± 238.4	598.0 ± 233.6	0.068
Right medial	687.3 ± 260.3	653.2 ± 277.9	683.3 ± 262.5	0.220
Left medial	684.4 ± 265.1	645.5 ± 268.3	679.8 ± 265.6	0.167
Left lateral	606.2 ± 232.2	582.9 ± 241.7	603.4 ± 233.3	0.347
Average, medial	685.9 ± 257.6	649.4 ± 268.7	681.6 ± 259.0	0.183
Average, lateral	604.7 ± 228.0	570.5 ± 236.3	600.3 ± 221.0	0.159
Classification of skull HU according to our previous hypothetical criteria for osteoporosis, n (%)				0.091
Hypothetical osteopenia or normal group (HU > 601.375)	388 (51.5)	43 (42.6)	423 (49.5)	
Hypothetical osteoporosis group (HU ≤ 601.375)	365 (48.5)	58 (57.4)	431 (50.5)	
Grouping of skull HU values into tertiles, n (%)				
Tertile 1 (HU ≤ 516.25)	N/A	N/A	284 (33.3)	
Tertile 2 (HU 516.25–696.97)			285 (33.4)	
Tertile 3 (HU > 696.97)			285 (33.4)	

HU, Hounsfield unit; LAA, large artery atherosclerosis; SVO, small vessel occlusion; IQR, interquartile range; SD, standard deviation; N/A, not available.

higher stroke recurrence rate than those in the middle and highest tertile groups (p = 0.027) (Fig. 2D). Conversely, when male patients were sorted into hypothetical BMD classifications, there was no significant difference in stroke recurrence rates between the hypothetical osteoporosis group and the hypothetical osteopenia or normal groups (Supplementary Fig. 3A and B).

3.4. Independent predictive factors for stroke recurrence in female patients with acute LAA or SVO stroke

Table 3 shows the findings of univariate and multivariate Cox regression analyses. In the multivariate analysis, after adjustment for age as a continuous variable, it was determined that hypothetical osteoporosis independently predicted stroke recurrence in female patients ≥50 years with acute LAA or SVO stroke (HR, 1.84; 95 % CI, 1.05 to 3.24; p = 0.034). We further observed that baseline infarct volume was an independent predictive factor for stroke recurrence (HR, 1.02; 95 % CI, 1.01 to 1.03; p < 0.001).

The p-values obtained from Schoenfeld's global test to assess the proportional hazard assumption for the Kaplan–Meier curves in Fig. 2B, C, and 2D were 0.151, 0.255, and 0.180, respectively (Supplementary Fig. 4A-C). These findings suggest no significant violation of the proportional hazards assumption across the observed time intervals, as evidenced by the relatively high p-values.

3.5. Interaction analysis between age and skull HU values with respect to stroke recurrence in female patients with acute LAA or SVO stroke

It has been widely recognized that both the likelihood of stroke recurrence, and the incidence of osteoporosis, increase with age. Consequently, although our study initially focused on middle-aged and elderly patients (≥50 years), incorporating age as a continuous covariate in our multivariate analysis, it was nevertheless possible that older age could act as a confounding factor affecting both the rates of stroke recurrence and the occurrence of osteoporosis. As a result, we performed an interaction analysis to examine the relationship between age and frontal skull HU values in relation to stroke recurrence in female patients aged 50 years and older with acute LAA or SVO strokes. Our analysis did not reveal a significant interaction between age, skull HU values, or stroke recurrence in female stroke patients (p = 0.686) as illustrated in Fig. 3A. Moreover, when categorizing patients into tertiles according to their skull HU values, we found no significant variation in age distribution between the stroke recurrence and no-recurrence groups (Fig. 3B).

Given the potential confounding effect of sex on these results, we performed a further interaction analysis between sex and average skull HU values in relation to stroke recurrence. As shown in Supplementary Fig. 4D, our findings revealed no significant interaction between sex and skull HU values with respect to stroke recurrence (p = 0.108).

3.6. Age range at which bone density appears to influence stroke recurrence in female patients with acute LAA or SVO stroke

Interestingly, when the linear regression lines used in the interaction analysis were transformed into smoothed LOWESS curves, we observed that the skull HU values in the group with stroke recurrence tended to be lower than those in the group without stroke recurrence aged between 65 and 80 years of age (Fig. 3C). When female patients were categorized into groups (50y–64y, 65y–79y, and ≥80y) according to the age classification method used in previous studies [26,27], we further observed significantly lower mean skull HU values in the group with stroke recurrence than in the group without stroke recurrence in the 65y–79y age interval (p = 0.030) (Fig. 3D). In addition, we calculated changes in skull HU values with age in male patients. However, unlike in female patients, skull HU showed no significant change as age increased in male patients (Supplementary Fig. 3C and D).

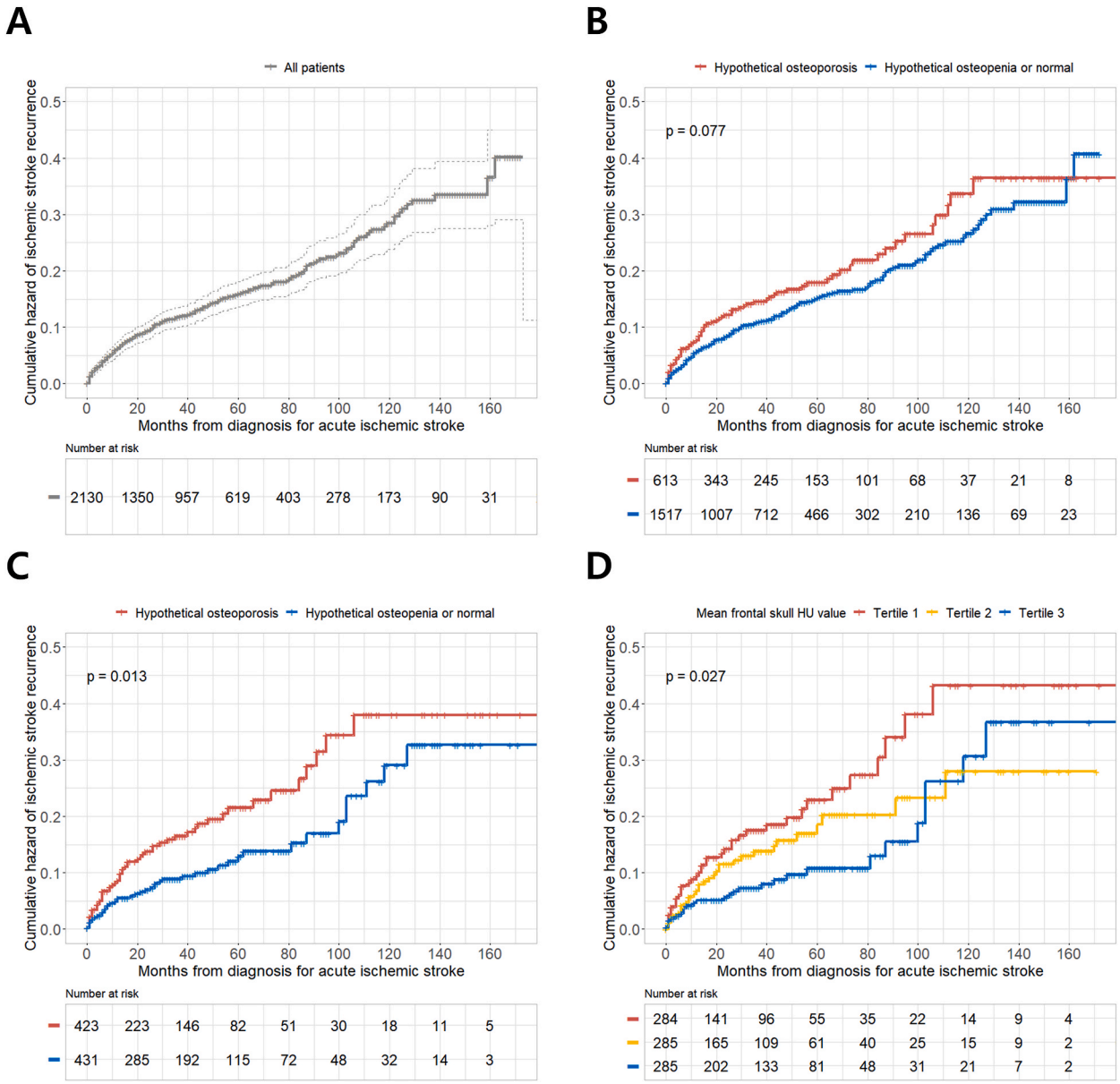


Fig. 2. Kaplan-Meier curves display the cumulative risk for recurrent strokes in patients ≥50 years with acute LAA or SVO stroke. (A) Cumulative risk of stroke recurrence; (B) cumulative risk of stroke recurrence based on hypothetical BMD classification; (C) cumulative risk of stroke recurrence based on hypothetical BMD classification in female patients; (D) cumulative risk of stroke recurrence categorized by tertile groups of skull HU values in female patients. LAA, large-artery atherosclerosis; SVO, small-vessel occlusion; BMD, bone mineral density; HU, Hounsfield units.

4. Discussion

We found that possible osteoporotic conditions were associated with an increased risk of ischemic stroke recurrence after adjusting for predictive risk factors, including age, in female patients aged ≥50 years diagnosed with acute LAA or SVO stroke. According to our findings, the stroke recurrence group showed a significantly lower BMD than the group without stroke recurrence in the approximate age range of 65–80 years. However, at approximately 80 years of age, the significant difference in BMD between the stroke recurrence and nonrecurrence groups disappeared. We attributed this finding to the fact that most patients with stroke do not survive or experience recurrence because of the high stroke mortality rate in patients older than 80 years [28]. In addition, most female patients aged >80 years already have osteoporotic conditions, which could explain the lack of a significant difference in BMD between the stroke recurrence and non-recurrence groups. A previous study showed that the percentage of female patients aged ≥80 years with osteoporosis was twice that of female patients aged 65–69 years [29]. Therefore, we assert that low BMD or osteoporotic conditions independently increase the risk of ischemic stroke recurrence in postmenopausal patients aged >65 years who have been diagnosed

Table 3
Multivariable Cox regression analysis investigating the predictors of ischemic stroke recurrence in female patients (≥50 years) with acute LAA or SVO stroke.

	Univariate analysis		Multivariate analysis	
Variable	HR (95 % CI)	p	HR (95 % CI)	p
Age (per 1-year increase)	**1.04 (1.01–1.06)**	**0.002**	1.01 (0.98–1.04)	0.654
Grouping of average skull HU				
Hypothetical osteopenia or normal	Reference		Reference	
Hypothetical osteoporosis	**1.64 (1.11–2.44)**	**0.014**	**1.84 (1.05–3.24)**	**0.034**
Etiologic stroke subtypes based on TOAST				
LAA	Reference		Reference	
SVO	0.71 (0.48–1.06)	0.096	0.94 (0.53–1.67)	0.826
Infarct volume (per 1 cc increase)	**1.01 (1.00–1.01)**	**0.005**	**1.02 (1.01–1.03)**	**<0.001**
Stroke subtypes by radiographic OCSP classification				
LACI	Reference		Reference	
TACI	2.41 (0.50–11.63)	0.273	0.14 (0.01–1.96)	0.144
PACI	1.13 (0.52–2.49)	0.756	1.08 (0.32–3.67)	0.908
POCI	1.05 (0.46–2.40)	0.903	1.24 (0.35–4.35)	0.737
Multiple	1.13 (0.38–3.36)	0.826	1.55 (0.34–7.01)	0.570
NIHSS (per 1-score increase)	1.02 (0.96–1.09)	0.489	0.93 (0.85–1.02)	0.105
Received tPA				
No	Reference		Reference	
Yes	1.31 (0.57–2.99)	0.524	2.50 (0.95–6.59)	0.063
Antithrombotic use after first-ever stroke				
Antiplatelet	Reference		Reference	
Anticoagulant	0.92 (0.29–2.91)	0.889	0.65 (0.15–2.77)	0.564
Antiplatelet + anticoagulant	**4.08 (1.00–16.61)**	**0.050**	4.36 (0.50–37.89)	0.182
Hypertension				
No	Reference		Reference	
Yes	1.11 (0.72–1.70)	0.648	0.82 (0.47–1.44)	0.493
Diabetes				
No	Reference		Reference	
Yes	1.03 (0.68–1.56)	0.898	1.19 (0.68–2.09)	0.544
Myocardial infarction				
No	Reference		Reference	
Yes	1.99 (0.63–6.30)	0.243	0.63 (0.07–5.39)	0.675
Smoking				
No	Reference		Reference	
Yes	0.94 (0.46–1.94)	0.874	1.36 (0.56–3.30)	0.494
Alcohol				
No	Reference		Reference	
Yes	0.54 (0.27–1.07)	0.079	0.52 (0.21–1.27)	0.150
Hyperlipidemia				
No	Reference		Reference	
Yes	0.81 (0.55–1.21)	0.308	0.70 (0.42–1.19)	0.187

LAA, large artery atherosclerosis; SVO, small vessel occlusion; HR, hazard ratio; CI, confidence interval; HU, Hounsfield unit; OCSP, Oxfordshire Community Stroke Project; LACI, lacunar infarction; TACI, total anterior circulation infarction; PACI, partial anterior circulation infarction; POCI, posterior circulation infarction; NIHSS, National Institutes of Health Stroke Scale.

with acute LAA or SVO stroke. To our knowledge, this is the first study to propose a relationship between possible osteoporotic conditions and stroke recurrence in older female patients with LAA or SVO.

The incidence of osteoporosis has previously been shown to increase after menopause [30]. As such, we conducted the present study to determine whether osteoporosis is associated with stroke recurrence in postmenopausal patients with stroke. We observed that in postmenopausal patients with stroke, recurrence was more likely to occur in those with possible osteoporotic conditions who were aged approximately 65 and older. A previous study further reported that almost one in four female patients aged >65 years had osteoporosis [29]. The incidence of hospital morbidity due to osteoporosis continues to rise in female patients >65 years [31]. The U.S. Preventive Services Task Force recommends BMD screening for osteoporosis to prevent osteoporotic fractures in women aged 65 years and older [32]. The documented increase in the prevalence of osteoporosis and its complications in females aged >65 years supports our finding that stroke recurrence is higher in female patients with possible osteoporosis, beginning at approximately 65 years of age.

Hounsfield unit (HU) measurements on CT scans and BMD T-scores were considered absolute values. Our previous studies have shown that the HU values of cancellous bone in the frontal skull, as determined through brain CT scans, could be used as indicators of osteoporotic conditions [13–15]. The condition of cancellous bone in the frontal skull could also be influenced by osteoporotic states, as osteoporosis is a systemic disease closely associated with genetic factors related to type 1 collagen, such as *COL1A1* and *COL1A2* [9].

Mutations in type 1 collagen, an essential structural component of bones, lead to reduced bone mineral density (BMD) and osteoporosis. Type 1 collagen is also a significant component of the extracellular matrix (ECM) across all three layers of blood vessel walls, particularly the surrounding SMCs in the vascular media [8]. Notably, SMCs are crucial in the formation of the fibrous cap and in maintaining plaque stability, not only in advanced atherosclerosis, but also early in atherogenesis [7]. The SMCs in the arterial media

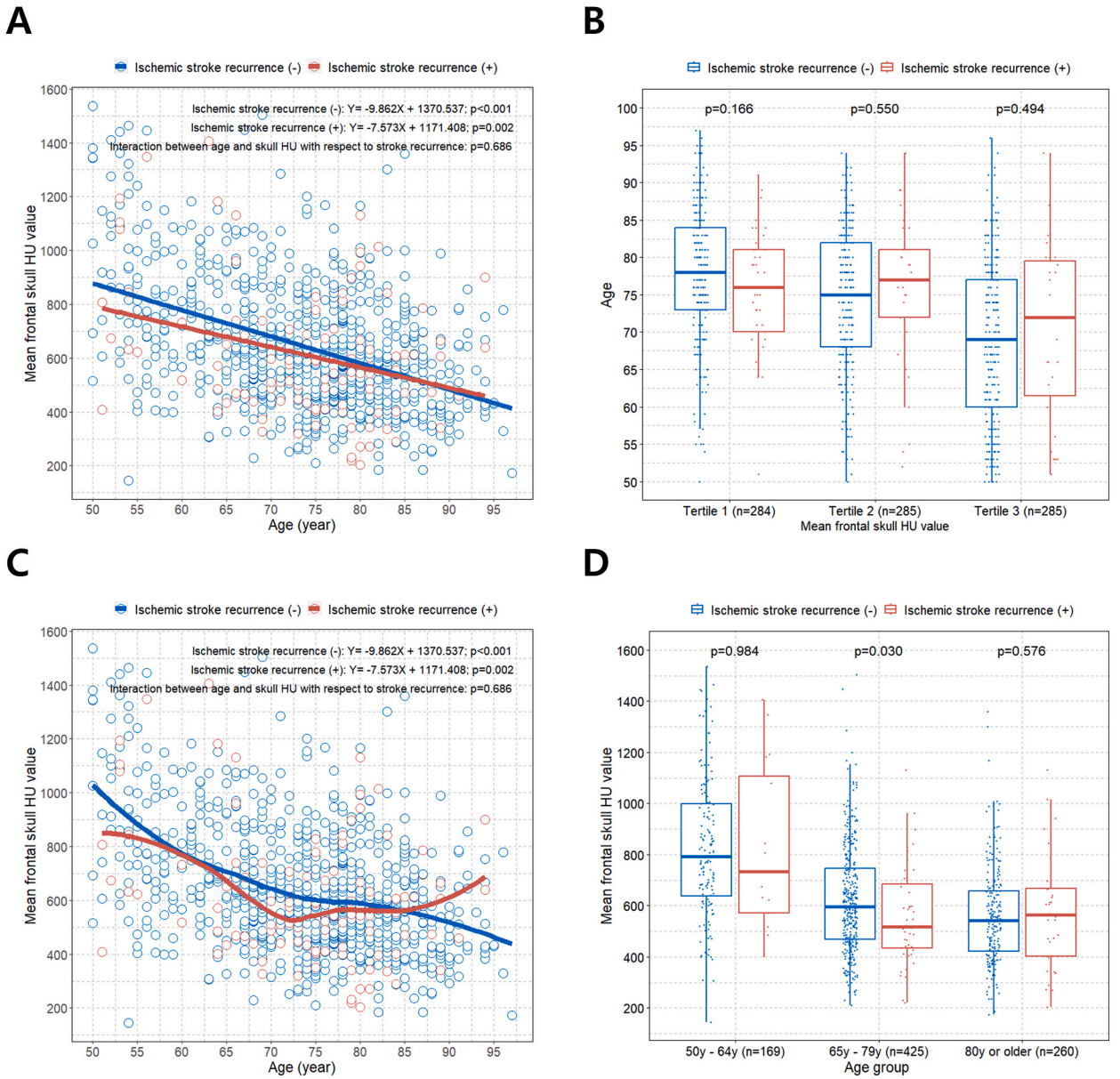


Fig. 3. Interaction plots with linear regression lines, LOWESS curves, and boxplots are used to demonstrate the relationship between age and skull HU values in relation to stroke recurrence among female patients ≥50 years with acute LAA or SVO stroke. (A) Examines the interaction of age with skull HU values regarding stroke recurrence; (B) boxplots showing age distributions sorted into tertiles of skull HU values according to stroke recurrence; (C) LOWESS regression curves between age and skull HU values based on stroke recurrence; (D) boxplots of average frontal skull HU values sorted by age groups and stroke recurrence. LOWESS, locally weighted scatterplot smoothing; HU, Hounsfield unit; LAA, large-artery atherosclerosis; SVO, small-vessel occlusion.

produce various components of the ECM, including elastic fibers, collagen, and proteoglycans [6]. In healthy arterial tissues, the ECM predominantly comprises type 1 and type 3 fibrillar collagens. However, in atherosclerotic arteries, the ECM is primarily characterized by dispersed type 1 collagen fibrils and increased levels of proteoglycans [7]. These changes affect not only the structural integrity of blood vessels, but also their lipid levels and cell proliferation rates, potentially accelerating the progression of atherosclerotic lesions [7]. Aging-induced deterioration of elastic tissues within the arterial walls becomes more pronounced, particularly in the presence of atherosclerosis [6]. This condition is linked to the degradation and reduction of elastic structures in the medial layer of blood vessels, and an associated increase in collagen [6]. These morphological changes cause vascular diseases, including stiffening of the arteries and thickening of the intimal media. We hypothesized that systemic osteoporotic conditions would negatively affect SMCs in the arterial media, based on the knowledge that both bone and SMCs are mainly composed of type 1 collagen, leading to elastin degradation and collagen accumulation, intensifying atherosclerosis of the blood vessels, and creating an environment favorable for stroke.

We only included patients with LAA or SVO stroke, as these stroke subtypes are closely associated with atherosclerosis, making them relevant to our hypothesis. Although SVO is often associated with lipohyalinosis, it also encompasses degenerative alterations in vessel walls, including arteriosclerosis, atherosclerosis, and arteriolosclerosis [33]. Osteogenesis imperfecta, caused by mutations in type 1 collagen genes (*COL1A1/COL1A2*), is associated with atherosclerosis and vascular fragility caused by collagen abnormalities in the cerebral arterial system [34,35].

In our study, no significant association was observed between possible osteoporotic conditions and stroke recurrence in male patients with LAA or SVO. Our study further showed that the rate of hypothetical osteoporosis was more than three times higher in female patients than in males, which is consistent with previous reports showing that women aged ≥50 years are four times more likely to have osteoporosis than men of the same age [30]. We further observed that unlike female patients, male patients showed no significant decrease in skull HU values with increasing age. A rapid decline in BMD correlates with an increased likelihood of vertebral fractures [36]. In addition, it is well known that the role estrogen plays in protecting the cardiovascular system is significantly reduced after menopause, leading to a sharp increase in the risk of atherosclerosis [37,38]. Therefore, we hypothesized that a rapid systemic decline in bone mass would accelerate the destruction of elastic structures of vascular SMCs, leading to a particularly rapid progression of atherosclerosis after menopause.

We further observed that the infarct size was independently associated with ischemic stroke recurrence in postmenopausal patients with LAA or SVO stroke. Worsening arteriopathy in childhood is also associated with recurrent stroke [39,40]. The severity of cerebral arteriopathy correlates with a larger infarct size [41]. This could explain why the LAA and SVO stroke patients with larger infarct sizes in this study had more severe cerebrovascular arteriopathy (arteriosclerosis), leading to an increase in stroke recurrence. A recent study further reported that a larger infarct volume was significantly associated with stroke recurrence [42]. In addition, a meta-analysis reported that a higher risk of recurrent stroke was associated with stroke severity, high NIHSS score, and high modified Rankin Scale score at the time of discharge [1]. Previous studies have further reported a significant association between larger infarction volumes, stroke severity, and NIHSS scores at admission and discharge [43–45]. Therefore, it is reasonable to infer that larger stroke infarct volumes would result in increased stroke severity, thereby increasing the likelihood of stroke recurrence.

Our study has several limitations. First, it was affected by the limitations inherent to all retrospective studies. Second, although frontal skull HU values are strongly correlated with the actual BMD, they may not directly reflect the actual T-scores. Further, exact T-scores were unavailable for the study patients, as patients with ischemic stroke rarely undergo DXA scans. Third, errors in the HU measurements may have occurred; however, as described in the Methods section, we magnified all brain CT images for HU measurements to exclude the cortical bone and ensure accurate determination of HU values in the frontal cancellous bone. Moreover, we minimized measurement errors using the average HU value from the four regions of the frontal skull for the analysis. Finally, longitudinal observations are necessary to establish a direct causal relationship between osteoporosis and the exacerbation of atherosclerosis or weakening of vessel walls. The need for longitudinal observations makes experimental validation challenging. Nevertheless, our findings provide a theoretical framework for future studies in this field. Based on current evidence, we propose that osteoporosis may contribute to the exacerbation of atherosclerosis or weakening of vessel walls. Osteogenesis imperfecta, a condition caused by mutations in type 1 collagen genes, is associated with atherosclerosis and vascular fragility, thus implicating collagen abnormalities in vascular health [34,35]. The ECM compositions of healthy arteries and atherosclerotic lesions underscore the importance of collagen in maintaining vascular integrity [7]. Lastly, the shared composition of type 1 collagen in the bones and SMCs of blood vessels highlights its potential for cross-system effects [8]. These aspects should be explored further in future studies.

5. Conclusions

Overall, our findings indicate that osteoporosis influences the recurrence of cerebral infarction in postmenopausal women with LAA or SVO. In particular, we found that the relationship between osteoporosis and stroke recurrence was significant, beginning at approximately 65 years of age. Furthermore, our findings enhance the understanding of the relationship between ischemic stroke recurrence and BMD in patients with cerebral infarction. This could stimulate interest in screening and treating osteoporosis in postmenopausal stroke patients to prevent stroke recurrence and ensure better outcomes.

Ethical approval and consent to participate

The study received ethical approval and adhered to the regulations and guidelines by Hanyang University Guri Hospital Ethics Committee (approval no. 2023-10-015), South Korea and conformed to the tenets of the Declaration of Helsinki. The need for informed consent was waived due to the retrospective nature of the study by the Institutional Review Board of Hanyang University Guri Hospital Ethics Committee. All individual records were anonymized prior to the analysis. All methods were carried out in accordance with relevant guidelines and regulations.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Funding

This study was funded by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (NRF-2022R1F1A1063739) and the Hanyang University (HY-202200000000911).

CRediT authorship contribution statement

Byeong Jin Ha: Writing – original draft, Validation. **Sang Mook Kang:** Validation, Methodology. **Bo Mi Choi:** Data curation. **Jin Hwan Cheong:** Supervision. **Je Il Ryu:** Supervision. **Yu Deok Won:** Writing – original draft, Funding acquisition. **Myung-Hoon Han:** Writing – original draft, Visualization, Software, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Myung-Hoon Han reports financial support was provided by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (NRF-2022R1F1A1063739). Yu Deok Won reports financial support was provided by Hanyang University (HY-202200000000911). If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e30196.

References

[1] M. Kolmos, L. Christoffersen, C. Kruuse, Recurrent ischemic stroke - a systematic review and meta-analysis, J. Stroke Cerebrovasc. Dis. 30 (2021) 105935, https://doi.org/10.1016/j.jstrokecerebrovasdis.2021.105935.
[2] N. Skajaa, K. Adelborg, E. Horváth-Puhó, K.J. Rothman, V.W. Henderson, L.C. Thygesen, H.T. Sørensen, Risks of stroke recurrence and mortality after first and recurrent strokes in Denmark: a nationwide registry study, Neurology (2021), https://doi.org/10.1212/WNL.0000000000013118, 10.1212/WNL.0000000000013118.
[3] H.S. Jørgensen, H. Nakayama, J. Reith, H.O. Raaschou, T.S. Olsen, Stroke recurrence: predictors, severity, and prognosis. The Copenhagen Stroke Study, Neurology 48 (1997) 891–895, https://doi.org/10.1212/wnl.48.4.891.
[4] J. Pennlert, M. Eriksson, B. Carlberg, P.-G. Wiklund, Long-term risk and predictors of recurrent stroke beyond the acute phase, Stroke 45 (2014) 1839–1841, https://doi.org/10.1161/STROKEAHA.114.005060.
[5] H. Ay, L. Gungor, E.M. Arsava, J. Rosand, M. Vangel, T. Benner, L.H. Schwamm, K.L. Furie, W.J. Koroshetz, A.G. Sorensen, A score to predict early risk of recurrence after ischemic stroke, Neurology 74 (2010) 128–135, https://doi.org/10.1212/WNL.0b013e3181ca9cff.
[6] M.M. Adeva-Andany, L. Adeva-Contreras, C. Fernández-Fernández, M. González-Lucán, R. Funcasta-Calderón, Elastic tissue disruption is a major pathogenic factor to human vascular disease, Mol. Biol. Rep. 48 (2021) 4865–4878, https://doi.org/10.1007/s11033-021-06478-8.
[7] A.C. Doran, N. Meller, C.A. McNamara, Role of smooth muscle cells in the initiation and early progression of atherosclerosis, Arterioscler. Thromb. Vasc. Biol. 28 (2008) 812–819, https://doi.org/10.1161/ATVBAHA.107.159327.
[8] M. Ponticos, T. Partridge, C.M. Black, D.J. Abraham, G. Bou-Gharios, Regulation of collagen type I in vascular smooth muscle cells by competition between Nkx2.5 and δef1/ZEB1, Mol. Cell Biol. 24 (2004) 6151–6161, https://doi.org/10.1128/MCB.24.14.6151-6161.2004.
[9] M.L. Brandi, Microarchitecture, the key to bone quality, Rheumatology 48 (Suppl 4) (2009) iv3–8, https://doi.org/10.1093/rheumatology/kep273.
[10] M.-X. Ji, Q. Yu, Primary osteoporosis in postmenopausal women, Chronic Dis Transl Med 1 (2015) 9–13, https://doi.org/10.1016/j.cdtm.2015.02.006.
[11] H.P. Adams, B.H. Bendixen, L.J. Kappelle, J. Biller, B.B. Love, D.L. Gordon, E.E. Marsh, Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment, Stroke 24 (1993) 35–41, https://doi.org/10.1161/01.str.24.1.35.
[12] J.-W. Chung, B.J. Kim, C.H. Sohn, B.-W. Yoon, S.-H. Lee, Branch atheromatous plaque: a major cause of lacunar infarction (High-Resolution MRI study), Cerebrovasc. Dis. Extra 2 (2012) 36–44, https://doi.org/10.1159/000341399.
[13] Y.-D. Won, J.-M. Kim, J.-H. Cheong, J.-I. Ryu, S.-H. Koh, M.-H. Han, Effect of possible osteoporosis on parenchymal-type hemorrhagic transformation in patients with cardioembolic stroke, J. Clin. Med. 10 (2021) 2526, https://doi.org/10.3390/jcm10112526.
[14] M.K. Na, Y.D. Won, C.H. Kim, J.M. Kim, J.H. Cheong, J.I. Ryu, M.-H. Han, Opportunistic osteoporosis screening via the measurement of frontal skull Hounsfield units derived from brain computed tomography images, PLoS One 13 (2018) e0197336, https://doi.org/10.1371/journal.pone.0197336.
[15] M.-H. Han, Y.D. Won, M.K. Na, C.H. Kim, J.M. Kim, J.I. Ryu, H.-J. Yi, J.H. Cheong, Association between possible osteoporosis and shunt-dependent hydrocephalus after subarachnoid hemorrhage, Stroke 49 (2018) 1850–1858, https://doi.org/10.1161/STROKEAHA.118.021063.
[16] Y.-D. Won, J.-M. Kim, J.-H. Cheong, J.-I. Ryu, S.-H. Koh, M.-H. Han, Effect of possible osteoporosis on parenchymal-type hemorrhagic transformation in patients with cardioembolic stroke, J. Clin. Med. 10 (2021) 2526, https://doi.org/10.3390/jcm10112526.
[17] P. Amarenco, J. Bogousslavsky, L.R. Caplan, G.A. Donnan, M.G. Hennerici, Classification of stroke subtypes, Cerebrovasc. Dis. 27 (2009) 493–501, https://doi.org/10.1159/000210432.
[18] J.H. Han, S.S.Y. Ho, W.W.M. Lam, K.S. Wong, Total cerebral blood flow estimated by color velocity imaging quantification ultrasound: a predictor for recurrent stroke? J Cereb Blood Flow Metab 27 (2007) 850–856, https://doi.org/10.1038/sj.jcbfm.9600392.

[19] N. Asdaghi, T. Jeerakathil, B. Hameed, M. Saini, J.A. McCombe, A. Shuaib, D. Emery, K. Butcher, Oxfordshire community stroke project classification poorly differentiates small cortical and subcortical infarcts, Stroke 42 (2011) 2143–2148, https://doi.org/10.1161/STROKEAHA.111.613752.
[20] Y.D. Won, M.K. Na, C.H. Kim, J.M. Kim, J.H. Cheong, J.I. Ryu, M.-H. Han, The frontal skull Hounsfield unit value can predict ventricular enlargement in patients with subarachnoid haemorrhage, Sci. Rep. 8 (2018) 10178, https://doi.org/10.1038/s41598-018-28471-1.
[21] R.U. Kothari, T. Brott, J.P. Broderick, W.G. Barsan, L.R. Sauerbeck, M. Zuccarello, J. Khoury, The ABCs of measuring intracerebral hemorrhage volumes, Stroke 27 (1996) 1304–1305, https://doi.org/10.1161/01.STR.27.8.1304.
[22] J.J. Schreiber, P.A. Anderson, H.G. Rosas, A.L. Buchholz, A.G. Au, Hounsfield units for assessing bone mineral density and strength: a tool for osteoporosis management, J Bone Joint Surg Am 93 (2011) 1057–1063, https://doi.org/10.2106/JBJS.J.00160.
[23] B.A. Birnbaum, N. Hindman, J. Lee, J.S. Babb, Multi-detector row CT attenuation measurements: assessment of intra- and interscanner variability with an anthropomorphic body CT phantom, Radiology 242 (2007) 109–119, https://doi.org/10.1148/radiol.2421052066.
[24] W.W.M. Abeysekera, M.R. Sooriyarachchi, Use of Schoenfeld's global test to test the proportional hazards assumption in the Cox proportional hazards model:an application to a clinical study. https://dl.nsf.gov.lk/handle/1/6320, 2009. (Accessed 22 March 2024).
[25] W.G. Jacoby, Loess:: a nonparametric, graphical tool for depicting relationships between variables, Elect. Stud. 19 (2000) 577–613, https://doi.org/10.1016/S0261-3794(99)00028-1.
[26] C. Cowan, R. Healicon, I. Robson, W.R. Long, J. Barrett, M. Fay, K. Tyndall, C.P. Gale, The use of anticoagulants in the management of atrial fibrillation among general practices in England, Heart 99 (2013) 1166–1172, https://doi.org/10.1136/heartjnl-2012-303472.
[27] A.K. Buttery, Y. Du, M.A. Busch, J. Fuchs, B. Gaertner, H. Knopf, C. Scheidt-Nave, Changes in physical functioning among men and women aged 50–79 years in Germany: an analysis of National Health Interview and Examination Surveys, 1997–1999 and 2008–2011, BMC Geriatr. 16 (2016) 205, https://doi.org/10.1186/s12877-016-0377-0.
[28] G. Saposnik, R. Cote, S. Phillips, G. Gubitz, N. Bayer, J. Minuk, S. Black, Stroke outcome in those over 80, Stroke 39 (2008) 2310–2317, https://doi.org/10.1161/STROKEAHA.107.511402.
[29] S.S.-T. Lo, Prevalence of osteoporosis in elderly women in Hong Kong, Osteoporos Sarcopenia 7 (2021) 92–97, https://doi.org/10.1016/j.afos.2021.09.001.
[30] K.A. Alswat, Gender disparities in osteoporosis, J. Clin. Med. Res. 9 (2017) 382–387, https://doi.org/10.14740/jocmr2970w.
[31] M.B. Pastor-Robles, A. Mayo-Íscar, R.M. Cárdaba-García, V. Niño-Martín, Quality of life in women over 65 Years of age diagnosed with osteoporosis, Int J Environ Res Public Health 19 (2022) 5745, https://doi.org/10.3390/ijerph19095745.
[32] US Preventive Services Task Force, S.J. Curry, A.H. Krist, D.K. Owens, M.J. Barry, A.B. Caughey, K.W. Davidson, C.A. Doubeni, J.W. Epling, A.R. Kemper, M. Kubik, C.S. Landefeld, C.M. Mangione, M.G. Phipps, M. Pignone, M. Silverstein, M.A. Simon, C.-W. Tseng, J.B. Wong, Screening for osteoporosis to prevent fractures: US preventive Services Task Force recommendation statement, JAMA 319 (2018) 2521–2531, https://doi.org/10.1001/jama.2018.7498.
[33] L.T. Grinberg, D.R. Thal, Vascular pathology in the aged human brain, Acta Neuropathol. 119 (2010) 277–290, https://doi.org/10.1007/s00401-010-0652-7.
[34] S. Albayram, O. Kizilkilic, H. Yilmaz, B. Tuysuz, N. Kocer, C. Islak, Abnormalities in the cerebral arterial system in osteogenesis imperfecta, AJNR Am J Neuroradiol 24 (2003) 748–750.
[35] J. He, Z. Liao, Osteogenesis imperfecta with cerebral atherosclerosis: a family report, Journal of the Endocrine Society 5 (2021) A209, https://doi.org/10.1210/jendso/bvab048.424.
[36] N. Kameyama, S. Chubachi, M. Sasaki, A. Tsutsumi, H. Irie, K. Sakurai, K. Sayama, H. Nakamura, K. Asano, T. Betsuyaku, K. Fukunaga, Predictive and modifying factors of bone mineral density decline in patients with COPD, Respir. Med. 148 (2019) 13–23, https://doi.org/10.1016/j.rmed.2019.01.005.
[37] M.J. Stampfer, G.A. Colditz, W.C. Willett, J.E. Manson, B. Rosner, F.E. Speizer, C.H. Hennekens, Postmenopausal estrogen therapy and cardiovascular disease. Ten-year follow-up from the nurses' health study, N. Engl. J. Med. 325 (1991) 756–762, https://doi.org/10.1056/NEJM199109123251102.
[38] Q. Meng, Y. Li, T. Ji, Y. Chao, J. Li, Y. Fu, S. Wang, Q. Chen, W. Chen, F. Huang, Y. Wang, Q. Zhang, X. Wang, H. Bian, Estrogen prevent atherosclerosis by attenuating endothelial cell pyroptosis via activation of estrogen receptor α-mediated autophagy, J. Adv. Res. 28 (2021) 149–164, https://doi.org/10.1016/j.jare.2020.08.010.
[39] N. Danchaivijitr, T.C. Cox, D.E. Saunders, V. Ganesan, Evolution of cerebral arteriopathies in childhood arterial ischemic stroke, Ann. Neurol. 59 (2006) 620–626, https://doi.org/10.1002/ana.20800.
[40] H.J. Fullerton, G.A. deVeber, N.K. Hills, M.M. Dowling, C.K. Fox, M.T. Mackay, A. Kirton, J.Y. Yager, T.J. Bernard, E.A. Hod, M. Wintermark, M.S.V. Elkind, Inflammatory biomarkers in childhood arterial ischemic stroke: correlates of stroke etiology and recurrence, Stroke 47 (2016) 2221–2228, https://doi.org/10.1161/STROKEAHA.116.013719.
[41] N. Slavova, H.J. Fullerton, N.K. Hills, P.S. Breiding, M.T. Mackay, M. Steinlin, Validation of the focal cerebral arteriopathy severity score (FCASS) in a Swiss cohort: correlation with infarct volume and outcome, Eur. J. Paediatr. Neurol. 28 (2020) 58–63, https://doi.org/10.1016/j.ejpn.2020.07.015.
[42] L. Ding, Z. Li, Y. Wang, Abstract P343: relationship of infarct volume to inflammation and prognostic significance in patients with acute ischemic stroke, Stroke 52 (2021) AP343, https://doi.org/10.1161/str.52.suppl_1.P343. AP343.
[43] S. Payabvash, S. Taleb, J.C. Benson, A.M. McKinney, Acute ischemic stroke infarct topology: association with lesion volume and severity of symptoms at admission and discharge, Am. J. Neuroradiol. 38 (2017) 58–63, https://doi.org/10.3174/ajnr.A4970.
[44] Q. Huang, M. Gu, J. Zhou, T. Jiang, H. Shi, X. Chen, Y. Zhang, Endovascular treatment of acute ischemic stroke due to anterior circulation large vessel occlusion beyond 6 hours: a real-world study in China, BMC Neurol. 21 (2021) 92, https://doi.org/10.1186/s12883-021-02122-x.
[45] L. Braadt, M. Naumann, D. Freuer, T. Schmitz, J. Linseisen, M. Ertl, Novel inflammatory biomarkers associated with stroke severity: results from a cross-sectional stroke cohort study, Neurological Research and Practice 5 (2023) 31, https://doi.org/10.1186/s42466-023-00259-3.