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The Osteoporotic Condition as a Predictive Factor for Hemorrhagic Transformation in Acute Cardioembolic Stroke

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Objective : Hemorrhagic transformation (HT) can be occurred after acute cerebral infarction. HT can worse symptoms in severe cases and adversely affect long-term prognosis. As bone and vascular smooth muscle are composed of type 1 collagen, we aimed to identify a potential relationship between bone mineral density (BMD) and HT after acute cardioembolic stroke.

Methods : As an indicator of BMD, we used mean frontal skull Hounsfield unit (HU) values on brain computed tomography (CT). Multivariative hazard ratios were calculated using Cox regression analysis to identify whether the osteoporotic condition was an independent predictor of HT after acute cardioembolic stroke.

Results : This 11-year analysis enrolled 506 patients who diagnosed as acute cardioembolic infarction. The first tertile of skull HU value was an independent predictor of HT development compared to the third tertile (hazard ratio, 2.12; 95% confidence interval, 1.13–3.98; p=0.020). We observed no interactions between age and skull HU with respect to HT statistically.

Conclusion : The results of this study revealed an association between osteoporotic conditions and HT development after acute cardioembolic stroke. A convenient method to measure the cancellous bone HU value of the frontal skull using brain CT images may be useful for predicting HT in patients with acute cerebral infarction.

Key Words : Bone density · Hemorrhagic transformation · Skull · Embolic stroke.

INTRODUCTION

Hemorrhagic transformation (HT) can be occurred after acute cerebral infarction. Autopsy studies have shown that HT occurs in 18–42% of cases[19,22]. HT can worse symptoms in severe cases and adversely affect long-term prognosis. Therefore, the study of predictive factors of HT is clinically important.

Both bone and vessel smooth muscles are composed of type 1 collagen. Osteoporosis is a systemic disease that is strongly associated with the genetic components of type 1 collagen[11].

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Cancellous bone structures in the skull may be affected by osteoporotic conditions; thus, we assumed that low bone mineral density (BMD) would negatively affect vessel stability. Moreover, this mechanism may be associated with HT after acute cerebral infarction. We hypothesized that, this mechanism may be associated with HT development after acute cerebral infarction. Patients treated for acute cerebral infarction usually do not an examination of BMD during hospitalization, so we needed another way to predict osteoporosis. As we previously showed an association between the mean frontal skull Hounsfield unit (HU) value and T score[13,26], we used the frontal skull HU values instead of the T-score in the present study.

The overall objective of the study was to identify a possible relationship between BMD and HT after acute cerebral infarction. HT frequency and severity are reportedly high in patients with acute cerebral infarction due to cardiac embolism[23]. Therefore, we included only cardioembolic stroke patients in this study to reduce the effects of heterogeneity among the various subtypes of ischemic stroke on our results.

METERIALS AND METHODS

This study was approved by the Institutional Review Board of Hanyang University Guri Hospital (IRB No. 2020-08-032) and conformed to the tenets of the Declaration of Helsinki, which waived the need for informed consent because of the retrospective nature of the study. All individual records were anonymized before the analysis.

Patient selection

We retrospectively collected data on all consecutive patients with acute cerebral infarction due to cardiac embolism from the Registry of Stroke Patients of our institute from January 1, 2009, to December 31, 2019. All stroke subtypes were classified according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification[1]. As we described in the INTRODUCTION, patients with acute cerebral infarction caused by other causes except cardiac embolism, were excluded to reduce the possible effects of heterogeneity on HT after acute cerebral infarction.

Overall, 578 patients were initially selected. Of these, 72 were excluded for 1) absence of follow-up computed tomography (CT) (because we need to measure the HU value using the CT image; 54 patients) and 2) no measurable cancellous bone (too narrow of an intercortical space of the frontal skull; 18 patients). The remaining 506 patients were included in this study. All patients were confirmed to have had a cardiac embolism infarction on brain magnetic resonance imaging (MRI), including diffusion-weighted imaging (DWI), electrocardiogram, laboratory studies, carotid Doppler imaging, and echocardiography.

Baseline and follow-up images

Brain CT images were obtained using CT scanner (Siemens SOMATOM Definition Edge or Siemens SOMATOM Definition AS; Seimens Healthcare, Forchheim, Germany) and DWI with an MRI scanner (Philips Ingenia 3.0T or Philips Achieva 3.0T; Philips Healthcare, Best, The Netherlands). All CT images were obtained with continuous slices, no gap, and 4.0–5.0-mm slice thickness. The duration (days) between the occurrence of acute cerebral infarction and the last follow-up CT images were investigated in all patients. In the patients had HT, we measured the days from acute cardioembolic stroke onset to the CT at which HT was firstly observed.

Measurement of the infarction volume and the skull HU values

The infarction volume was measured using ABCD/2, a method of measuring intracerebral hemorrhage volume[16,28] using DWI images from MRI performed at admission. The DWI image with the largest area of acute infarction was selected. The maximum diameter (A in Fig. 1) of the infarction was measured. The largest diameter perpendicular to A was measured in the same image (B in Fig. 1). Then, the number of images with infarction was counted (C in Fig. 1), and the thickness of the slices was measured (D in Fig. 1) (Fig. 1). We measured the frontal skull HU values in the cancellous bone using the "Linear histogram graph" function as previous described[13,31]. All CT images were magnified for HU measurement to minimize measurement errors, to avoid including cortical bone (Fig. 2). All frontal skull HUs were measured by two faculty neurosurgeons who were blinded to the clinical data of all patients.

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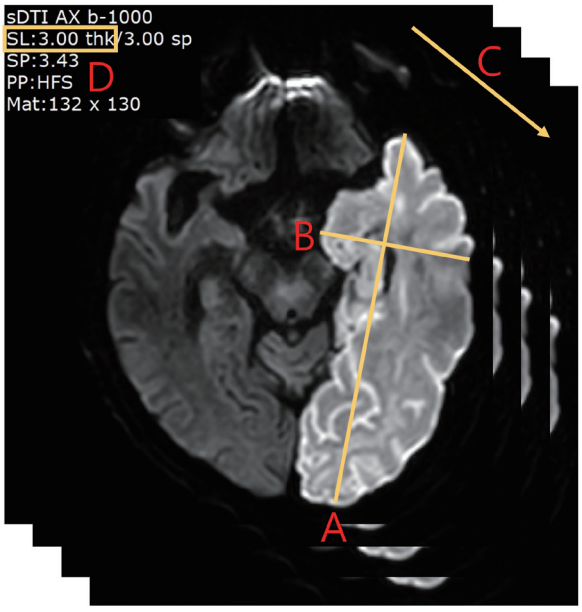

$$\text{Infarction volume} = \frac{A \times B \times C \times D}{2}$$

Fig. 1. Measurement of the infarction volume. A : Maximum infarction diameter. B : The largest diameter perpendicular to A. C : Number of images with infarction. D : Slice thickness.

Clinical factors and definition of HT

Clinical information of all patients, such as sex, age, body mass index, National Institutes of Health Stroke Scale (NIHSS) at admission, use of tissue plasminogen activator (tPA), platelet count, hypertension, diabetes, smoking, hyperlipidemia, and premedication with antithrombotics was investigated from medical records. We define HT as cases in which bleeding was observed in the acute cerebral infarction area on CT, as previously described[9].

Statistical methods

The chi-square and Student's t-tests were conducted to assess clinical differences between the two groups, divided by HT or not. The mean skull HU value was used for all analyses. The skull HU values were classified into tertile groups and analyzed. Box plots with dot plots were used to visualize the infarction volume differences between the HT groups based on sex. To determine the optimal cutoff value of infarction volume associated with HT, we performed receiver operating characteristic (ROC) curve analysis. The cumulative hazards for HT were examined using the Kaplan-Meier method classi-

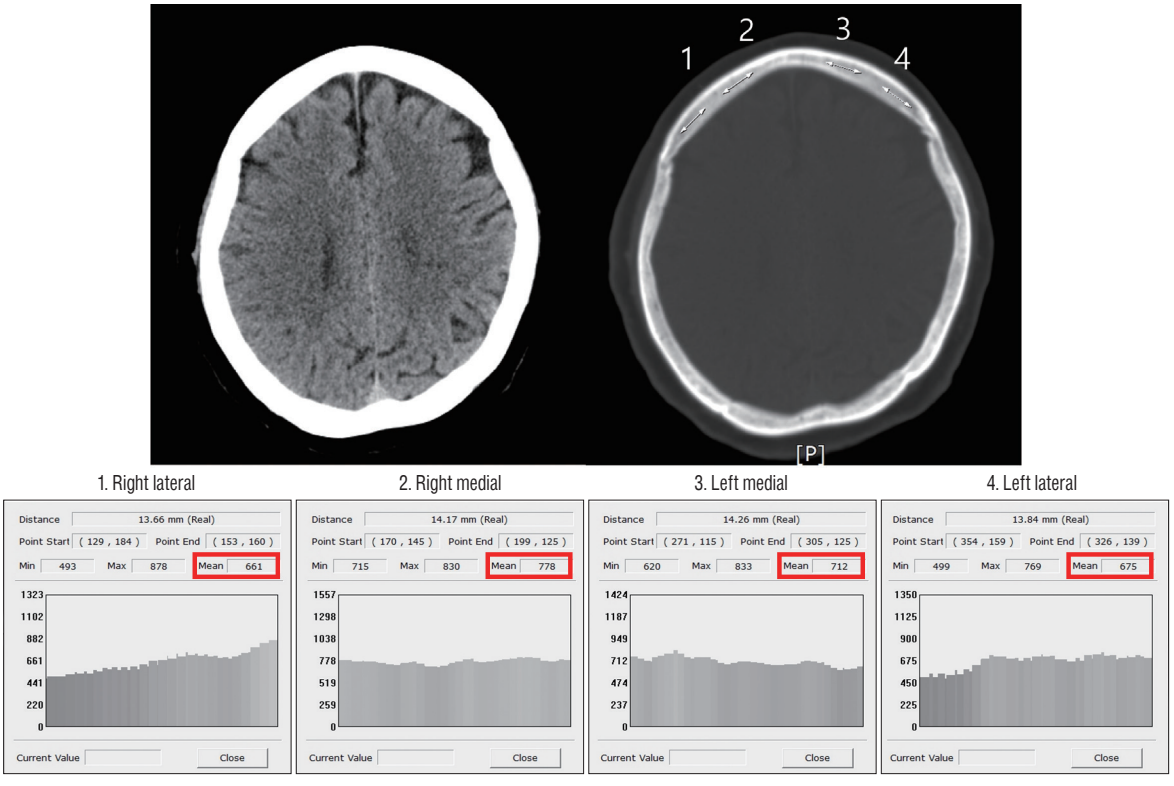

Fig. 2. Measurement of the average frontal skull Hounsfield unit (HU) value. The frontal skull HU values in the cancellous bone is measured using the "Linear histogram graph" function.

fied by tertile groups of skull HU values. Hazard ratios with 95% confidence intervals (CIs) were then estimated using univariate and multivariate Cox regression analyses to evaluate the independent predictive factors for HT in patients with acute cardioembolic stroke. We also performed an interaction analysis between age and skull HU with respect to HT.

Statistical significance was set at $p<0.05$. All statistical analyses were performed using R software, version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria) and IBM SPSS for Windows, version 24.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Patient characteristics

Overall, this 11-year study enrolled 506 patients diagnosed with acute cardioembolic stroke. The HT group included 92 patients (18.2%). The mean age of the patients was 73.6 years, and 269 (53.2%) were female. There was statistical significance in NIHSS score, infarction volume, and use of tPA between the groups. Table 1 shows detailed patients information.

Frontal skull HU values according to HT and sex

Tables 2 and 3 show respectively the descriptive statistics of the detailed frontal skull HU values according to HT and sex.

Table 1. Clinical characteristics of patients after cerebral infarction classified according to HT in the study cohort

Characteristic	HT (-)	HT (+)	Total	*p*-value
Number	414 (81.8)	92 (18.2)	506 (100.0)	
Sex, female	224 (54.1)	45 (48.9)	269 (53.2)	0.367
Age (years)	73.9±10.9	72.3±10.2	73.6±10.7	0.193
BMI	23.5±4.0	23.3±3.9	23.4±4.0	0.640
NIHSS	7.4±7.1	10.9±6.4	8.0±7.1	<0.001
Infarction volume (mL)	36.2±78.5	92.2±87.2	46.4±82.9	<0.001
Infarction volume (mL)	4.6 (0.5–27.5)	74.1 (23.4–134.5)	10.1 (0.7–50.2)	<0.001
Low platelet count	68 (16.4)	20 (21.7)	88 (17.4)	0.224
Use of tPA	64 (15.5)	26 (28.3)	90 (17.8)	0.004
Hypertension	250 (60.4)	64 (69.6)	314 (62.1)	0.101
Diabetes	124 (30.0)	24 (26.1)	148 (29.3)	0.461
Current smoking	56 (13.5)	17 (18.5)	73 (14.4)	0.221
Hyperlipidemia	48 (11.6)	11 (12.0)	59 (11.7)	0.922
Antithrombotics	73 (17.6)	11 (12.0)	84 (16.6)	0.186

Values are presented as mean±standard deviation, median (interquartile range), or number (%). HT : hemorrhagic transformation, BMI : body mass index, NIHSS : National Institutes of Health Stroke Scale, tPA : tissue plasminogen activator

Table 2. Descriptive statistics of frontal HU values in the study cohort classified according to HT

Characteristic	HT (-)	HT (+)	Total	*p*-value
Overall mean frontal skull HU value	673.0 (507.1–872.7)	636.4 (475.6–825.4)	670.4 (503.3–864.3)	0.465
Overall mean frontal skull HU value	688.8±235.8	668.9±235.0	685.2±235.5	0.465
Mean HU value at each of four sites in the frontal skull				
Right lateral	630.5±213.6	611.7±215.1	627.0±213.8	0.447
Right medial	752.4±281.2	738.9±288.9	750.0±282.4	0.679
Left medial	744.9±281.4	716.4±288.1	739.7±282.5	0.382
Left lateral	627.4±215.9	608.7±203.9	624.0±213.7	0.448

Values are presented as mean±standard deviation or median (interquartile range). HU : Hounsfield unit, HT : hemorrhagic transformation

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Table 3. Descriptive statistics of frontal HU values in the study cohort classified according to sex

Characteristic	Male	Female	Total	*p*-value
Overall mean frontal skull HU value	833.5 (683.8–946.9)	538.0 (432.8–676.5)	670.4 (503.3–864.3)	<0.001
Overall mean frontal skull HU value	815.6±195.0	570.3±206.8	685.2±235.5	<0.001
Mean HU value at each of four sites in the frontal skull				
Right lateral	715.5±192.9	549.1±200.8	627.0±213.8	<0.001
Right medial	922.5±228.8	598.0±233.7	750.0±282.4	<0.001
Left medial	911.4±228.4	588.5±235.5	739.7±282.5	<0.001
Left lateral	712.9±202.1	545.7±192.2	624.0±213.7	<0.001
Classification of the skull HU based on tertile groups (HU)				
Tertile 1	≤737.3	≤467.5	≤546.8	
Tertile 2	737.3–907.3	467.5–611.3	546.8–815.0	
Tertile 3	>907.3	>611.3	>815.0	

Values are presented as mean±standard deviation or median (interquartile range). HU : Hounsfield unit

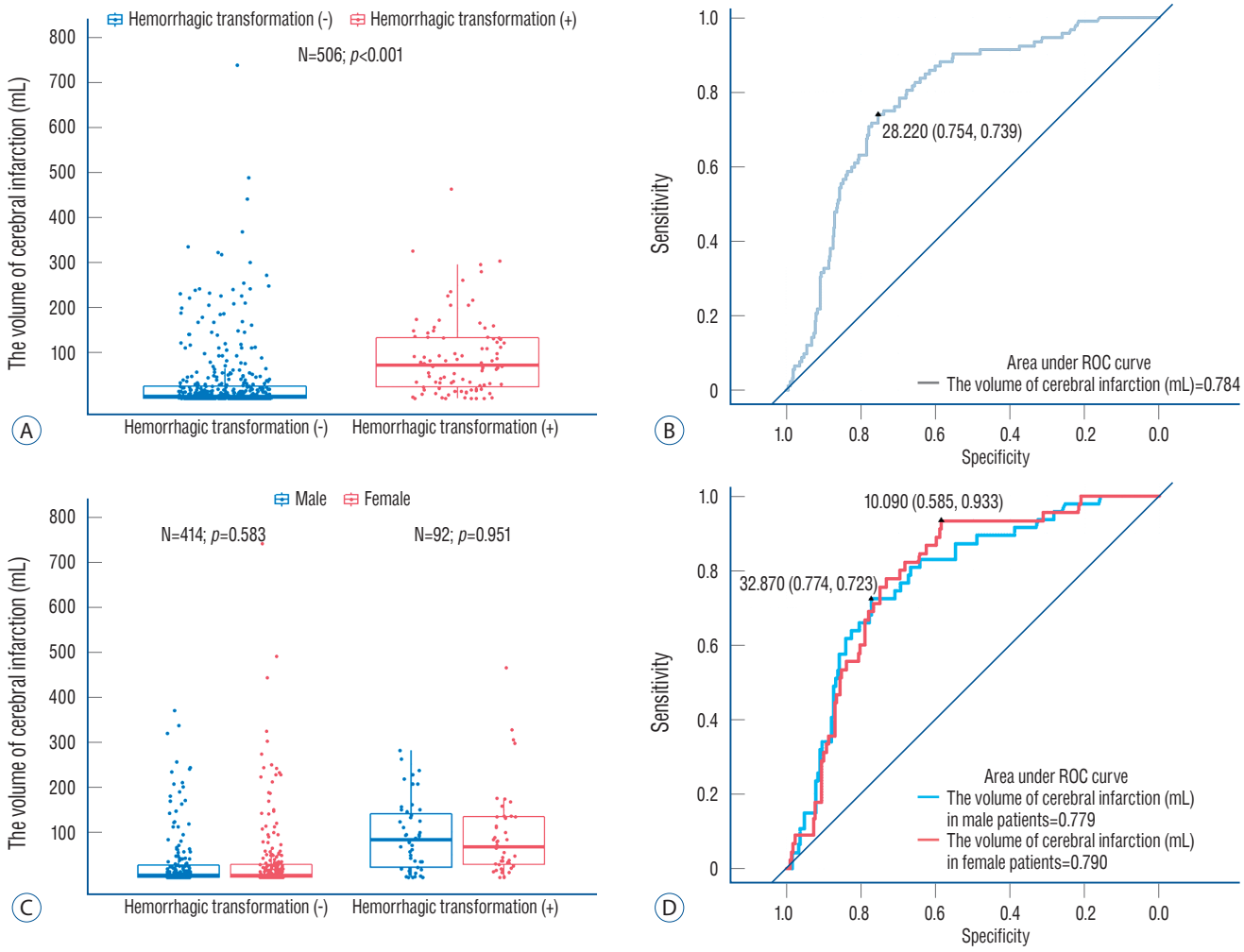

Fig. 3. Trend in infarction volumes according to hemorrhagic transformation (HT). A : Box plot with dot plots showing the trend between HT and infarction volumes. B : Receiver operating characteristic (ROC) curve for HT based on infarction volume. C : Box plot with dot plots showing the trend between HT and infarction volumes divided by sex. D : Receiver operating characteristic curve for HT based on infarction volume divided by sex.

There were no significant differences in the mean frontal skull HU values according to HT (Table 2). The overall mean frontal skull HU value was 670.4; the mean frontal skull HU value was 833.5 for male and 538.0 for female patients, showing a significant difference (Table 3).

Trend in infarction volume according to HT

We observed a significant difference in the volume of cerebral infarction according to HT. The HT group had a larger infarction volume than that in the none-HT group (Fig. 3A). The area under the ROC curve for the volume of cerebral infarction was 0.784 (p<0.001; cutoff, 28.220 mL) (Fig. 3B). There was no significant difference between the sexes in terms of the volume of cerebral infarction according to HT (Fig. 3C). The areas under the ROC curves for the volume of cerebral infarction in men and women were 0.779 (p<0.001; cutoff,

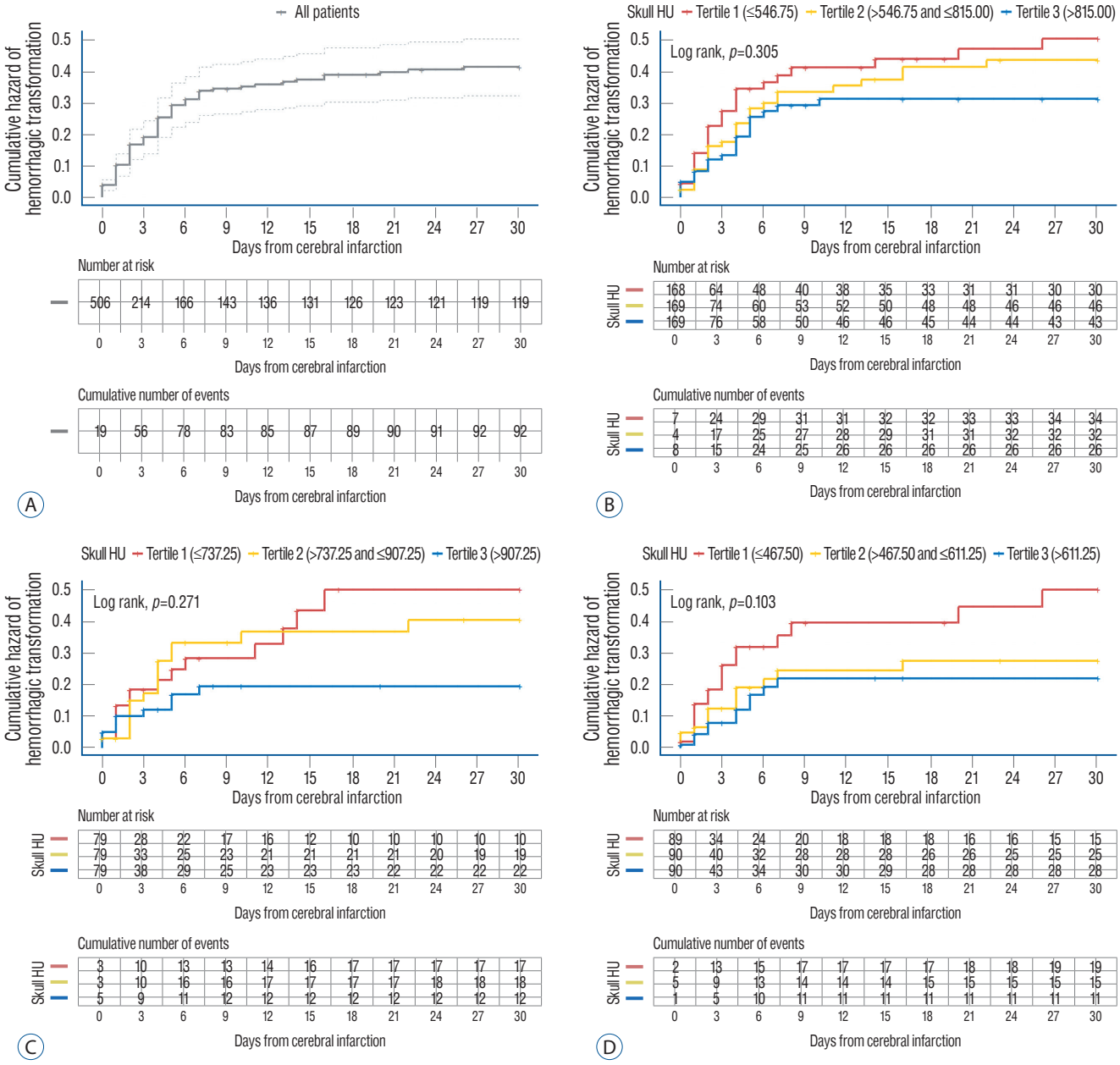

Fig. 4. Kaplan-Meier curves showing the cumulative hazards of hemorrhagic transformation (HT) after acute cardioembolic stroke. A : Cumulative hazard of HT. B : Cumulative hazards of HT according to tertile groups of frontal skull Hounsfield unit (HU) values. C : Cumulative hazards of HT according to tertile groups of frontal skull HU values in men. D : Cumulative hazards of HT according to tertile groups of frontal skull HU values in women.

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32.870 mL) and 0.790 (p<0.001; cutoff, 10.090 mL), respectively (Fig. 3D).

Cumulative hazard of HT after acute cardioembolic stroke according to skull HU tertile groups

Fig. 4A showed cumulative hazard of HT after acute cardioembolic stroke. Although not statistically significant, the first tertile of skull HU values showed greater HT within 1 month

Table 4. Univariate and multivariate Cox regression analyses of hemorrhagic transformation after acute cerebral infarction based on predictive factors

Variable	Univariate		Multivariate	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Sex				
Male	Reference		Reference	
Female	0.82 (0.54–1.23)	0.328	0.76 (0.46–1.26)	0.282
Age, per 1-year increase	0.99 (0.97–1.01)	0.195	0.97 (0.95–1.00)	0.020
BMI, per 1-unit increase	0.98 (0.93–1.04)	0.548	0.96 (0.91–1.01)	0.126
NIHSS at admission, per 1-unit increase	1.05 (1.02–1.07)	<0.001	1.04 (1.01–1.07)	0.024
Infarction volume, per 1 mL increment	1.01 (1.00–1.01)	<0.001	1.00 (1.00–1.01)	<0.001
Use of tPA				
No	Reference		Reference	
Yes	1.55 (0.99–2.45)	0.058	1.15 (0.71–1.85)	0.569
Platelet count				
Normal or high	Reference		Reference	
Low (<150000 per microliter)	1.53 (0.93–2.51)	0.094	1.32 (0.79–2.20)	0.296
Tertile groups of mean frontal skull HU				
Tertile 1 (≤546.8)	1.48 (0.89–2.46)	0.136	2.12 (1.13–3.98)	0.020
Tertile 2 (>546.8 and ≤815.0)	1.20 (0.71–2.01)	0.496	1.65 (0.94–2.91)	0.080
Tertile 3 (>815.0)	Reference		Reference	
Hypertension				
No	Reference		Reference	
Yes	1.33 (0.86–2.08)	0.205	1.66 (1.03–2.69)	0.038
Diabetes				
No	Reference		Reference	
Yes	0.82 (0.51–1.30)	0.392	0.88 (0.54–1.43)	0.607
Current smoking				
No	Reference		Reference	
Yes	1.39 (0.82–2.36)	0.217	1.13 (0.61–2.09)	0.695
Hyperlipidemia				
No	Reference		Reference	
Yes	0.98 (0.52–1.84)	0.945	0.92 (0.48–1.76)	0.806
Antithrombotics				
No	Reference		Reference	
Yes	0.63 (0.33–1.18)	0.147	0.66 (0.35–1.27)	0.210

HR : hazard ratio, CI : confidence interval, BMI : body mass index, NIHSS : National Institutes of Health Stroke Scale, tPA: tissue plasminogen activator, HU : Hounsfield unit

Table 5. Univariate and multivariate Cox regression analyses of hemorrhagic transformation after acute cerebral infarction based on predictive factors in the male group

Variable	Univariate		Multivariate	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age, per 1-year increase	0.98 (0.96–1.01)	0.188	0.97 (0.94–1.01)	0.126
BMI, per 1-unit increase	1.02 (0.95–1.10)	0.581	0.98 (0.91–1.07)	0.669
NIHSS at admission, per 1-unit increase	1.04 (1.00–1.07)	0.031	1.04 (0.99–1.08)	0.137
Infarction volume, per 1 mL increment	1.01 (1.00–1.01)	<0.001	1.00 (1.00–1.01)	0.036
Use of tPA				
No	Reference		Reference	
Yes	1.68 (0.91–3.11)	0.098	1.17 (0.59–2.32)	0.653
Platelet count				
Normal or high	Reference		Reference	
Low (<150000 per microliter)	1.29 (0.67–2.49)	0.445	1.52 (0.76–3.06)	0.238
Tertile groups of mean frontal skull HU				
Tertile 1 (≤737.3)	1.77 (0.84–3.71)	0.132	1.87 (0.87–4.02)	0.111
Tertile 2 (>737.3 and ≤907.3)	1.58 (0.76–3.29)	0.218	1.70 (0.79–3.66)	0.173
Tertile 3 (>907.3)	Reference		Reference	
Hypertension				
No	Reference		Reference	
Yes	1.43 (0.78–2.61)	0.249	1.80 (0.92–3.53)	0.087
Diabetes				
No	Reference		Reference	
Yes	0.88 (0.45–1.74)	0.718	0.96 (0.48–1.95)	0.916
Current smoking				
No	Reference		Reference	
Yes	1.47 (0.81–2.67)	0.205	1.36 (0.68–2.71)	0.382
Hyperlipidemia				
No	Reference		Reference	
Yes	0.95 (0.40–2.25)	0.913	1.01 (0.40–2.59)	0.977
Antithrombotics				
No	Reference		Reference	
Yes	0.71 (0.30–1.67)	0.434	0.73 (0.29–1.80)	0.488

HR : hazard ratio, CI : confidence interval, BMI : body mass index, NIHSS : National Institutes of Health Stroke Scale, tPA: tissue plasminogen activator, HU : Hounsfield unit

after acute cerebral infarction compared to the second and third tertiles (Fig. 4B). Even when sepaearwly analyzed for males and females, the first tertile of skull HU value tended to have a higher risk of HT than the second and third teitiles but had no statistical significe (Fig. 4C and D).

Independent predictive factors for HT in acute cardioembolic stroke

Multivariate Cox regression analysis showed that skull HU within the first tertile was an independent predictor of HT after acute cardioembolic stroke compared to those in the highest tertile group (hazard ratio, 2.12; 95% CI, 1.13–3.98; p=0.020) (Table 4). The other independent predictors of HT were young-

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Table 6. Univariate and multivariate Cox regression analyses of hemorrhagic transformation after acute cerebral infarction based on predictive factors in the female group

Variable	Univariate		Multivariate	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age, per 1-year increase	1.00 (0.97–1.03)	0.960	0.97 (0.93–1.01)	0.093
BMI, per 1-unit increase	0.95 (0.89–1.02)	0.187	0.96 (0.88–1.03)	0.255
NIHSS at admission, per 1-unit increase	1.06 (1.02–1.10)	0.002	1.04 (0.99–1.08)	0.122
Infarction volume, per 1 mL increment	1.01 (1.00–1.01)	<0.001	1.01 (1.00–1.01)	0.001
Use of tPA				
No	Reference		Reference	
Yes	1.38 (0.70–2.73)	0.353	1.32 (0.64–2.73)	0.458
Platelet count				
Normal or high	Reference		Reference	
Low (<150000 per microliter)	1.84 (0.85–3.95)	0.121	1.24 (0.52–2.92)	0.628
Tertile groups of mean frontal skull HU				
Tertile 1 (≤467.5)	2.15 (1.02–4.52)	0.044	2.55 (1.07–6.09)	0.035
Tertile 2 (>467.5 and ≤611.3)	1.42 (0.65–3.10)	0.375	1.29 (0.54–3.10)	0.569
Tertile 3 (>611.3)	Reference		Reference	
Hypertension				
No	Reference		Reference	
Yes	1.29 (0.67–2.50)	0.452	1.51 (0.75–3.04)	0.246
Diabetes				
No	Reference		Reference	
Yes	0.79 (0.42–1.52)	0.485	0.90 (0.45–1.79)	0.769
Current smoking				
No	Reference		Reference	
Yes	0.05 (0.00–346.59)	0.503	0.00 (0.00–0.00)	0.971
Hyperlipidemia				
No	Reference		Reference	
Yes	0.99 (0.39–2.52)	0.989	0.93 (0.35–2.47)	0.878
Antithrombotics				
No	Reference		Reference	
Yes	0.55 (0.22–1.40)	0.210	0.72 (0.27–1.90)	0.500

HR : hazard ratio, CI : confidence interval, BMI : body mass index, NIHSS : National Institutes of Health Stroke Scale, tPA: tissue plasminogen activator, HU : Hounsfield unit

er age, higher NIHSS score, larger infarction volume, and hypertension. In men, a larger infarction volume was the only independent predictor of HT (Table 5). However, among women, the first tertile of skull HU (hazard ratio, 2.55; 95% CI, 1.07–6.09; p=0.035) and larger infarction volume were independent predictors of HT (Table 6).

Interaction analysis between age and skull HU values with respect to HT

Because age is correlated with BMD, we further performed an interaction analysis between age and skull HU with respect to HT in patients with after acute cardioembolic stroke. However, we observed no significant interactions between age and skull HU values. Similarly, the analysis classified by sex also

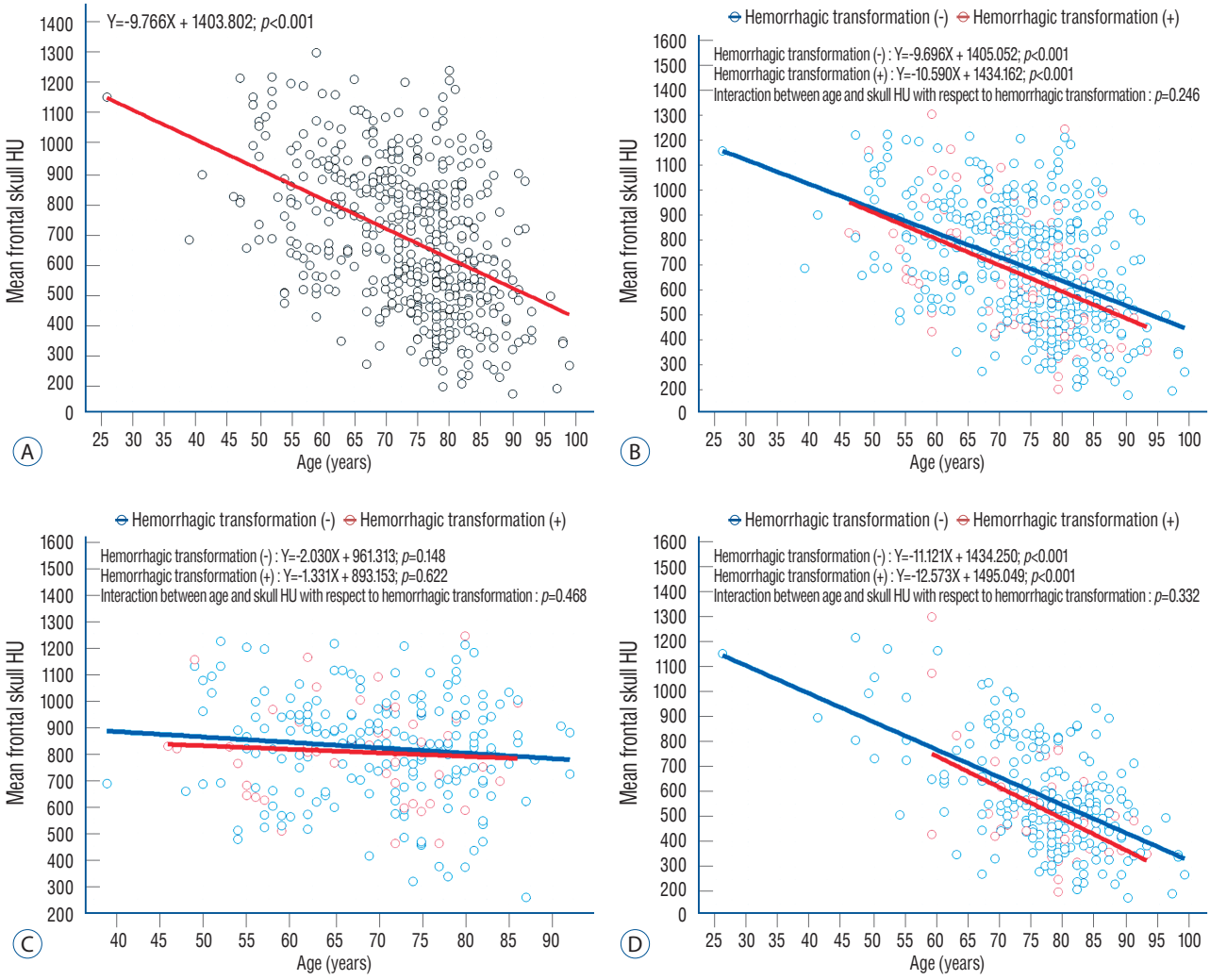

Fig. 5. Interaction plots between age and frontal skull Hounsfield units (HUs) with respect to hemorrhagic transformation (HT) after acute cardioembolic stroke. A : Scatter plots with linear regression lines depicting the associations between age and mean frontal skull HU values. B : Interaction between age and frontal skull HU with respect to HT. C : Interaction between age and frontal skull HU with respect to HT in men. D : Interaction between age and frontal skull HU with respect to HT in women.

showed no significant interactions between age and skull HU values (Fig. 5).

DISCUSSION

The results of our study show that a low frontal skull HU is associated with a higher risk of HT in patients with acute cardioembolic stroke compared to a higher frontal skull HU. Therefore, a low BMD state or osteoporotic condition may be independently associated with HT in the clinical course of acute cardioembolic stroke. In addition, when we classified patients by sex, we observed that only women showed a significant association between low skull HU and HT development in the multivariate analysis.

Osteoporosis is a systemic disease that is strongly associated with the genetic components of type 1 collagen, such as COL1A1 and COL1A2. Cancellous bone structures in the skull may also be affected by osteoporotic conditions. Previous studies have shown that the HU value of the cancellous bone can be useful in predicting the osteoporotic condition because this value in a specific area on CT scans is strongly related to the T score[6,26]. We also reported a strong association between skull HU values and T-scores and that the HU values of the frontal skull cancellous bone predicted osteoporotic status[13,31].

Type 1 collagen is a major component of bone. Genetic muta-

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tions in type 1 collagen can lead to osteoporosis or low BMD. Among the many components that make up blood vessels, smooth muscle is also composed of type 1 collagen[24]. Smooth muscles control artery contraction and relaxation; thus, lack or degeneration of smooth muscles can lead to secondary vascular changes, including fibrinoid necrosis and aneurysm-like vasodilatation that can cause vessel fragility and rupture[10,29]. Osteogenesis imperfecta (OI) caused by mutations in type 1 collagen genes is also associated with hemorrhagic diathesis, and is also hypothesized to be associated with vascular fragility[12,21]. In addition, abnormalities in the cerebral arterial system have been reported in OI[2]. Some patients with OI show distal internal cerebral artery stenosis, middle cerebral artery occlusion, and moyamoya-like collateral arising from the lenticulostriate arteries. These findings were interpreted as vasculopathic changes secondary to vascular fragility caused by collagen abnormalities in OI. Therefore, our results can be explained by the following hypothetical mechanism. Reperfusion occurs after acute cerebral infarction; moreover, the higher the fragility of blood vessels due to the weakened integrity of smooth muscle, the lower the ability to withstand reperfusion, thus increasing the possibility of HT. Among the women in this study, those with a low frontal skull HU value showed an approximately 2.6-fold higher risk of HT after cardiac embolism infarction compared to those with a higher frontal skull HU value after adjusting for other predictive factors, including age. In men, however, the difference between the frontal skull HU values and HT was not significant. Women aged 50 and over are reported to have four times higher rates of osteoporosis than men[3]. We also found that women had a higher rate of possible osteoporosis than men. The mean frontal skull HU value of men was significantly higher than that of women (833.5 vs. 538.0), and this result is likely not to have been analyzed as a risk factor for HT because men are more likely to have less osteoporosis than women.

However, in a recent study with the parenchymal type HT as the only dependent variable, contrary to our findings, only men showed a significant association between hypothetical osteoporosis and parenchymal type HT development in the multivariate Cox analysis[30]. Although, more research is needed in the future, we believe that men with osteoporosis may be more vulnerable to severe HT development after cardioembolic stroke than women. Males with ICH was more associated with risk of hematoma expansion and mortality rate compared to females[20]. In addition, males showed more osteoporosis-related complications and a higher mortality rate than females in osteoporotic fractures[3,5]. Furthermore, estrogen is known to have an important role in maintaining adequate cerebral perfusion and this may cause sex differences in hemorrhage expansion and mortality[25].

Our findings suggest that, additional possible predictive factors for HT after acute cerebral infarction include younger age, higher NIHSS score at admission, hypertension and larger infarction volume. These variables are predictive factors of HT after acute cerebral infarction, as reported previously[7,8,14,15,17,18,23,27].

Our study has some limitations. First, the time between subsequent CT images was irregular due to the retrospective nature of the study. In particular, in the case of asymptomatic HT, there may be an error in time between the occurrence of HT and the CT scan. Second, true T scores were not available in patients with acute cerebral infarction because the assessment of BMD status is generally not required. Moreover, while the cancellous bone HU values of the frontal skull are strongly correlated with the actual BMD, they may not directly reflect the exact T score. Third, measurement errors may have occurred. However, we enlarged all brain CT images for HU measurement to exclude cortical bones; moreover, patients without measurable frontal bone cancellous bones were excluded from the study. Fourth, it is well known that BBB disruption is crucial for HT development[4]. Therefore, our findings, which show the association between weakened vascular smooth muscle integrity and HT, should be validated by future study. Finally, we analyzed only Korean patients, which may limit the generalizability of the results owing to genetic differences between regions and races that affect BMD. Therefore, further research is required to verify these results.

CONCLUSION

In conclusion, the results of our study suggest an association between osteoporotic conditions and HT development after acute cerebral infarction with cardiac embolism. This association was more prominent in women than in men. Our findings may be useful for predicting HT in patients with acute cerebral infarction using a convenient method to measure the HU value of the cancellous bone of the frontal skull using brain CT imaging. However, confirming these initial results

require further studies, including different types of acute cerebral infarction. Our findings may help improve our understanding of the underlying mechanisms of the relationship between HT and BMD in acute cerebral infarction.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

INFORMED CONSENT

This type of study does not require informed consent.

AUTHOR CONTRIBUTIONS

Conceptualization : MHH, YDW
Data curation : YDW
Formal analysis : MHH
Funding acquisition : MHH
Methodology : MHH, YDW
Project administration : JHC
Visualization : MHH
Writing - original draft : YDW, MHH
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