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). Multivariate 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\(^ {11} \).
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 undergo 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.

**MATERIALS 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.
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-

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**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.

**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    |
| 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     |
| 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
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, 26.908 mL) (Fig. 3D).

**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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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           | 0.058                | Reference           | 0.569                |
| Yes                              | 1.55 (0.99–2.45)    |                      | 1.15 (0.71–1.85)    |                      |
| Platelet count                   |                     |                      |                     |                      |
| Normal or high                   | Reference           | 0.094                | Reference           | 0.296                |
| Low (<150000 per microliter)     | 1.53 (0.93–2.51)    |                      | 1.32 (0.79–2.20)    |                      |
| 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           | 0.205                | Reference           | 0.038                |
| Yes                              | 1.33 (0.86–2.08)    |                      | 1.66 (1.03–2.69)    |                      |
| Diabetes                         |                     |                      |                     |                      |
| No                               | Reference           | 0.392                | Reference           | 0.607                |
| Yes                              | 0.82 (0.51–1.30)    |                      | 0.88 (0.54–1.43)    |                      |
| Current smoking                  |                     |                      |                     |                      |
| No                               | Reference           | 0.217                | Reference           | 0.695                |
| Yes                              | 1.39 (0.82–2.36)    |                      | 1.13 (0.61–2.09)    |                      |
| Hyperlipidemia                   |                     |                      |                     |                      |
| No                               | Reference           | 0.945                | Reference           | 0.806                |
| Yes                              | 0.98 (0.52–1.84)    |                      | 0.92 (0.48–1.76)    |                      |
| Antithrombotics                  |                     |                      |                     |                      |
| No                               | Reference           | 0.147                | Reference           | 0.210                |
| Yes                              | 0.63 (0.33–1.18)    |                      | 0.66 (0.35–1.27)    |                      |

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 separately 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 tertiles but had no statistical significance (Fig. 4C and D).

### 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            | 0.249                | 1.80 (0.92–3.53)     | 0.087                |
| Yes                                                | 1.43 (0.78–2.61)     |                      |                      |                      |
| Diabetes                                           |                      |                      |                      |
| No                                                 | Reference            | 0.718                | 0.96 (0.48–1.95)     | 0.916                |
| Yes                                                | 0.88 (0.45–1.74)     |                      |                      |                      |
| Current smoking                                    |                      |                      |                      |
| No                                                 | Reference            | 0.205                | 1.36 (0.68–2.71)     | 0.382                |
| Yes                                                | 1.47 (0.81–2.67)     |                      |                      |                      |
| Hyperlipidemia                                     |                      |                      |                      |
| No                                                 | Reference            | 0.913                | 1.01 (0.40–2.59)     | 0.977                |
| Yes                                                | 0.95 (0.40–2.25)     |                      |                      |                      |
| Antithrombotics                                    |                      |                      |                      |
| No                                                 | 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

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-
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).

### 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 (<150 000 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         | 0.452            | Reference         | 0.246            |
| Yes                             | 1.29 (0.67–2.50)  |                  | 1.51 (0.75–3.04)  |                  |
| Diabetes                        |                   |                  |                  |
| No                              | Reference         | 0.485            | Reference         | 0.769            |
| Yes                             | 0.79 (0.42–1.52)  |                  | 0.90 (0.45–1.79)  |                  |
| Current smoking                 |                   |                  |                  |
| No                              | Reference         | 0.503            | Reference         | 0.971            |
| Yes                             | 0.05 (0.00–346.59)|                  | 0.00 (0.00–0.00)  |                  |
| Hyperlipidemia                  |                   |                  |                  |
| No                              | Reference         | 0.989            | Reference         | 0.878            |
| Yes                             | 0.99 (0.39–2.52)  |                  | 0.93 (0.35–2.47)  |                  |
| Antithrombotics                 |                   |                  |                  |
| No                              | Reference         | 0.210            | Reference         | 0.500            |
| Yes                             | 0.55 (0.22–1.40)  |                  | 0.72 (0.27–1.90)  |                  |

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

### 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...
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-
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 vaso-dilatation that can cause vessel fragility and rupture\(^ {10,20}\). 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\(^ {22,21}\). In addition, abnormalities in the cerebral arterial system have been reported in OI\(^3\). 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 abnormali-ties 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 osteopo-rosis and parenchymal type HT development in the multivari-ate Cox analysis\(^ {25}\). 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\(^ {4,30}\). 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\(^ {23}\).

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 previous-ly\(^ {7,8,14,15,17,18,23,27}\).

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 ex-cluded from the study. Fourth, it is well known that BBB disrup-tion is crucial for HT development\(^6\). Therefore, our find-ings, which show the association between weakened vascular smooth muscle integrity and HT, should be validated by fu-ture 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. There-fore, 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
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