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Comparison of bone age between both limbs in patients with congenital hemihyperplasia or hemihypoplasia: A retrospective study

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Abstract

Purpose: Side-to-side differences in bone age may exist due to somatic mosaicism in congenital hemihyperplasia or hemihypoplasia. We aimed to assess bone age differences between limbs in these conditions.

Methods: We retrospectively identified 118 children who underwent molecular testing for congenital hemihyperplasia or hemihypoplasia. Diagnoses included Beckwith-Wiedemann syndrome (BWS) ($n = 34$), Silver-Russell syndrome ($n = 14$), PIK3CA-related overgrowth spectrum (n = 14), and idiopathic isolated hemihyperplasia or hemihypoplasia ($n = 56$). Hand and knee bone ages were compared between the right and left limbs and between the longer and shorter limbs.

Results: In the overall cohort or each disease group, there was no difference in hand or knee bone age between the right and left limbs. However, the hand bone age of the longer limb was 1.2 ± 2.6 months older than that of the shorter limb ($p = 0.005$). In subgroup analysis, patients with BWS showed older knee (7.1 ± 9.9 months, $p = 0.031$) and hand (3.2 ± 2.5 months, $p = 0.026$) bone ages in the longer limb compared to the shorter limb. No significant differences were observed in the other disease groups.

Conclusions: Pediatric patients with congenital hemihyperplasia or hemihypoplasia generally show minimal bone age differences between limbs. However, in BWS, the longer limb may have a bone age several months older than the shorter limb.

Significance of study: Surgeons need to consider potential side-to-side differences in bone age when estimating remaining growth and determining the timing for epiphysiodesis in these patients.

Level of Evidence: III—Study of nonconsecutive patients

Keywords: hemihyperplasia, hemihypoplasia, Beckwith-Wiedemann syndrome, bone age, limb length discrepancy

Introduction

Congenital hemihyperplasia or hemihypoplasia is a condition characterized by lateralized overgrowth or undergrowth of body segments.[1,2] These conditions can occur as part of various syndromes and diseases, most of which are linked to genetic or epigenetic abnormalities. For example, Beckwith-Wiedemann syndrome (BWS)—primarily caused by gain or loss of methylation at imprinting center 1 or 2 on chromosome 11p15, respectively, or paternal uniparental disomy (pUPD) 11p15—results in lateralized overgrowth.[3–8] By contrast, Silver-Russell syndrome (SRS), often caused by loss or gain of methylation at imprinting center 1 or 2, respectively, or maternal uniparental disomy on the same

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11p15 region, leads to growth restriction on one side of the body.[5,9–12] The PIK3CA-related overgrowth spectrum (PROS), resulting from mutations in the PIK3CA gene and abnormal activation of the PI3K/AKT/mTOR signaling pathway, induces asymmetric tissue overgrowth.[13–15] In some patients, hemihyperplasia or hemihypoplasia can occur as an isolated form, without other signs or symptoms, and idiopathically without alterations on chromosome 11p15 or in the *PIK3CA* gene.[2,9]

Hemihyperplasia and hemihypoplasia involving the lower limbs cause limb length discrepancy (LLD), which can lead to spinal scoliosis,[16] limping,[17] and degenerative changes of the hip, knee, and spine.[18–20] If the LLD exceeds 2 cm, surgery is often required.[21] Epiphysiodesis is the preferred treatment for patients with open physis and mild to moderate LLD, reserving limb lengthening surgery for severe LLD.[21] Epiphysiodesis is usually recommended for patients with hemihyperplasia or hemihypoplasia, as the associated LLD is mostly mild to moderate.[22–24]

Bone age estimation is crucial for determining the optimal timing for epiphysiodesis because the remaining growth of the limbs is determined by skeletal maturity rather than chronological age.[25] Previous studies have noted differences between bone age and chronological age in certain conditions causing hemihyperplasia[2,7,26] or hemihypoplasia.[9,12] In clinical practice, some patients with hemihyperplasia or hemihypoplasia present not only with a discrepancy between bone age and chronological age but also with a bone age difference between the two limbs (Figure 1). Given that somatic mosaicism is considered the genetic basis of these conditions, side-to-side differences in bone age may exist. Therefore, we aimed to assess bone age differences between the two limbs in several conditions that cause hemihyperplasia or hemihypoplasia.

Methods

Patients

We reviewed the medical records of 865 pediatric patients diagnosed with congenital hemihyperplasia or hemihypoplasia at a single tertiary care pediatric center between January 2000 and September 2023. We excluded 540 patients without bilateral posteroanterior (PA) hand radiographs taken on the same day and 190 patients without diagnostic molecular test results. In addition, we excluded 12 patients whose clinical manifestations were suggestive of Klippel-Trenaunay-Weber syndrome but did not show any mutations on molecular testing. Three patients diagnosed with neurofibromatosis type 1, one with Smith-Kingsmore syndrome, and one with Jaffe-Campanacci syndrome were also excluded due to their small numbers. Eventually, 118 pediatric patients were included as study participants (Figure 2).

The study participants were categorized into four groups based on their molecular testing results: BWS ($n=34$), SRS ($n=14$), PROS ($n=14$), and idiopathic isolated hemihyperplasia or hemihypoplasia (IH) ($n=56$). The IH group consisted of patients presenting with hemihyperplasia or hemihypoplasia without additional syndromic features and with no detectable genetic or epigenetic abnormalities on molecular testing.

Molecular testing

In the BWS group, 33 patients (33/34, 97%) were diagnosed using methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) on chromosome 11p15[23]: 30 (30/34, 88%) with blood samples, two (2/34, 6%) with fat tissue obtained from the lower limb during epiphysiodesis, and one (1/34, 3%) with a buccal sample. The remaining patient (1/34, 3%) was diagnosed using bisulfite pyrosequencing with a blood sample.[8] Eighteen patients (18/34, 53%) had loss of methylation at imprinting center 2 (IC2-LoM), while 16 patients (16/34, 47%) had pUPD 11p15.

In the SRS group, 11 patients (11/14, 79%) were diagnosed using MS-MLPA on chromosome 11p15 with blood samples, and one (1/14, 7%) with fat tissue from the lower limb. Two patients (2/14, 14%) were diagnosed using bisulfite pyrosequencing with blood samples.[11] All patients had loss of methylation at the imprinting center 1 (IC1-LoM).

All 14 patients in the PROS group were diagnosed using high-depth next-generation sequencing (NGS) techniques.[13] Eleven patients (11/14, 79%) were diagnosed using skin samples, two (2/14, 14%) with buccal samples, and one (1/14, 7%) with a blood sample. Twelve patients (12/14, 86%) had a missense mutation in the *PIK3CA* gene, while two (2/14, 14%) had an in-frame deletion mutation in the same gene.

The molecular tests performed in the IH group were MS-MLPA on chromosome 11p15 in 51 patients (51/56, 91%) and high-depth NGS in the remaining 5 patients (5/56, 9%). The type of molecular test performed in the IH group was determined at the clinician's discretion to rule out specific syndromes when subtle phenotypic findings raised clinical suspicion. For the MS-MLPA, blood samples were used in 43 patients, and blood samples along with skin, fat, and muscle tissue from the lower leg were used in 8 patients. For the high-depth NGS, blood samples were used in four patients, and blood, skin, fat, and muscle samples obtained during surgery for macrodactyly were used in one patient.

Bone age estimation

Hand bone age was estimated radiographically using the Korean standard (KS) bone age chart,[27] which is derived from left-hand posteroanterior (PA) radiographs of 3407

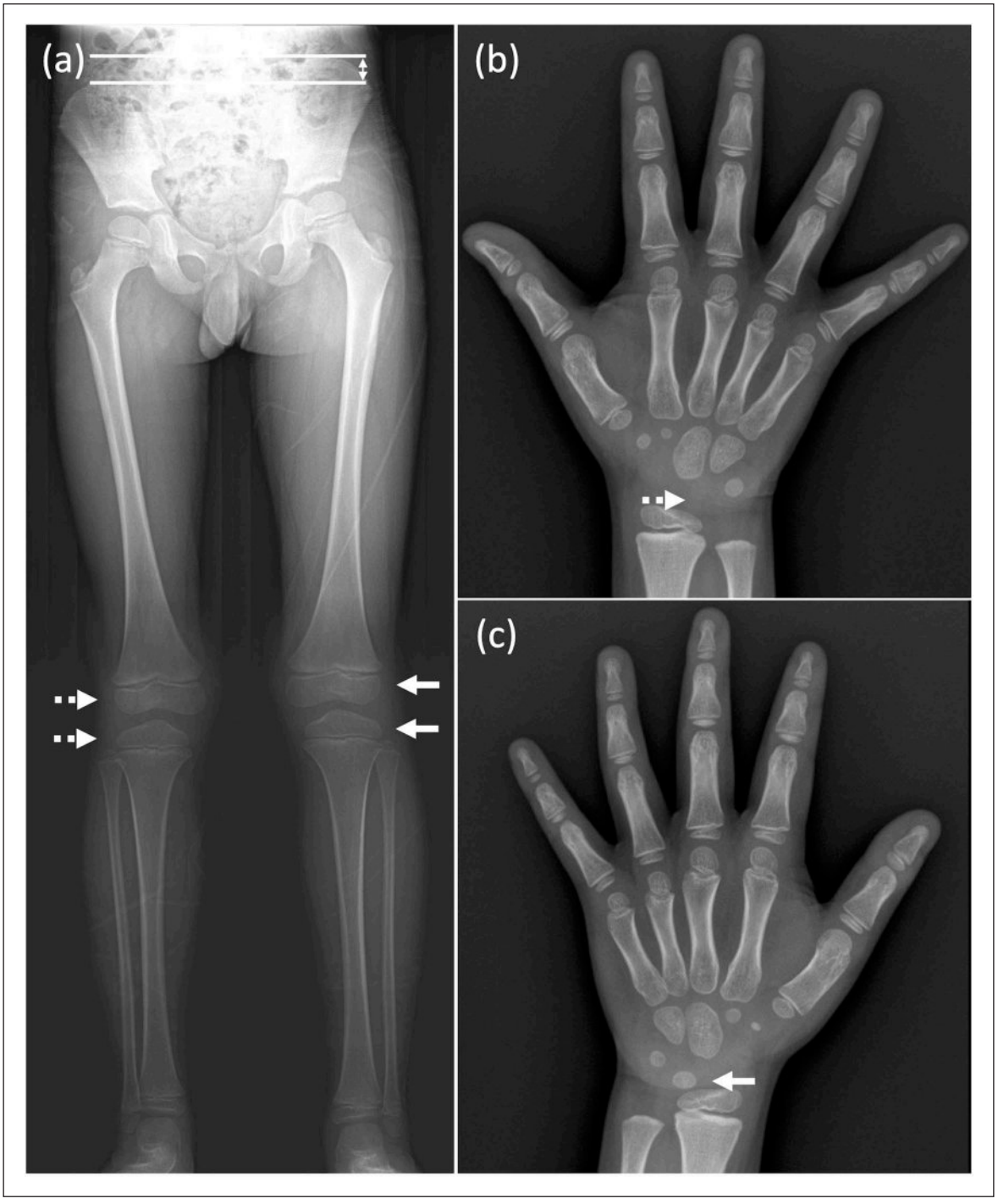

Figure 1. A 5.5-year-old boy with Beckwith-Wiedemann syndrome showing asymmetric skeletal maturation.
(a) A whole-leg radiograph shows leg length discrepancy, with the left lower limb longer than the right. The epiphyses of the distal femur and proximal tibia are larger on the left side (solid arrows) than on the right (dashed arrows). (b and c) Bilateral hand radiographs demonstrate discordant bone age. The right hand (b) shows no ossification of the lunate (dashed arrow), consistent with chronological age (5.5 years). By contrast, the left hand (c) shows ossification of the lunate (solid arrow), indicating advanced bone age (6.1 years).

South Korean children and is analogous to the Greulich and Pyle bone age atlas.[28] Previous studies reported an excellent correlation between bone age estimates from the KS bone age chart, the Greulich and Pyle bone age atlas, and the Tanner-Whitehouse 3 method.[29,30] When multiple radiographs were available for a single patient, the most recent radiograph taken before skeletal maturity or epiphysiodesis was used for bone age assessment.

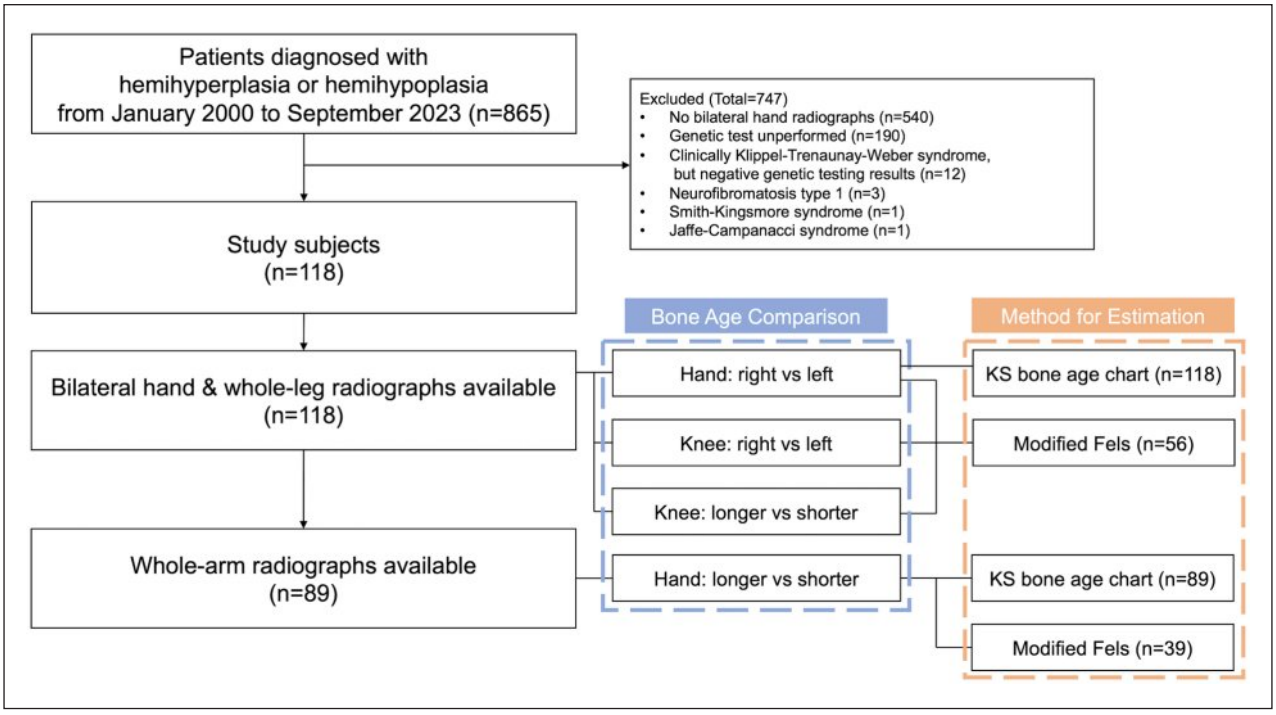

Figure 2. Flowchart of the study population.

In a subset of boys aged 9–15 years ($n=21$) and girls aged 7–13 years ($n=35$), hand and knee bone ages were also evaluated using a modified Fels system.[31,32] The term "modified" refers to the adaptations of the original Fels system[33] by isolating key parameters from the original system. We did not alter the scoring system, parameters, or prediction algorithms in the present study. Because the modified Fels system was validated only within these age ranges (boys 9–15 years; girls 7–13 years), we applied it exclusively to patients within the validated age range to avoid extrapolation beyond the validated population. This system estimates the bone age of preadolescents and adolescents based on their chronological age, sex, and multiple radiographical parameters. Since this system utilizes quantitative parameters, the modified Fels system provides finer measurement resolution and can therefore detect subtler differences in bone age than conventional atlas-based methods, which assign skeletal maturity to broader categorical intervals. Knee bone age was estimated using whole-leg anteroposterior (AP) radiographs.[34]

The radiographs of the right and left hands and knees were first separated and anonymized by one of the authors (S.Y.Y.) to avoid bias in bone age estimation from knowledge of the contralateral side's bone age. Then, another author (W.L.), blinded to the clinical information, limb laterality, and limb length, independently estimated the bone ages.

Three reviewers independently estimated the bone age of 30 randomly selected patients to facilitate the assessment of interobserver reliability. Reviewer 1 (W.L.) was a pediatric orthopedic fellowship-trained surgeon, Reviewer 2 (K.I.S.) was a board-certified orthopedic surgeon, and Reviewer 3 (S.Y.Y.) was a research coordinator without a medical degree. The reviewers received brief instructions for estimating bone age. They were blinded to the patients' chronological age but were given the patients' sex to select the appropriate atlas from the KS bone age chart or the modified Fels system. Reviewer 1 reassessed the bone age 4 weeks after the initial bone age estimation to evaluate intraobserver reliability.

Limb length measurement

We measured the lengths of the lower and upper limbs on whole-leg and whole-arm AP radiographs, respectively, to compare bone age between the longer and shorter limbs. Whole-leg radiographs were available for all patients ($n=118$), while whole-arm radiographs were available for 89 patients (89/118, 75%) (Figure 2). These imaging studies were performed based on clinical suspicion of LLD.

The lengths of the arms and legs were calculated by summing the lengths of the humerus and radius on whole-arm radiographs and by summing the lengths of the femur and tibia on whole-leg radiographs, respectively (Figure 3). The lengths of the humerus, radius, femur, and tibia were defined as the length from the top of the humeral head to the distal end of the capitellum, the length from the top of the radial head to the distal tip of the radial styloid process, the length from the top of the femoral head to the distal end of the medial femoral condyle, and the length from the

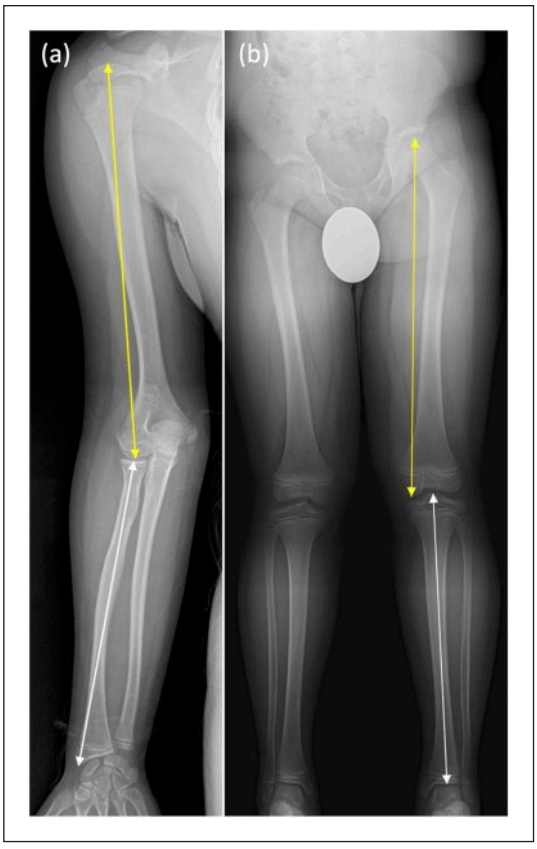

Figure 3. Measurements of the limb length.
(a) The length of the arms was calculated by summing the lengths of the humerus and radius. The lengths of the humerus and radius were defined as the length from the top of the humeral head to the distal end of the capitellum (yellow line) and the length from the top of the radial head to the distal tip of the radial styloid process (white line), respectively. (b) The length of the legs was calculated by summing the lengths of the femur and tibia. The lengths of the femur and tibia were defined as the length from the top of the femoral head to the distal end of the medial femoral condyle (yellow line) and the length from the center of the medial and lateral tibial spines to the center of the distal end of the tibial epiphysis (white line), respectively.

center of the medial and lateral tibial spines to the center of the distal end of the tibial epiphysis, respectively. Limb lengths were measured by Reviewer 3 (S.Y.Y.), who was blinded to the patient's age and clinical information. Reviewer 3 reassessed the limb length of 30 randomly selected patients 4 weeks after the first measurements to evaluate intraobserver reliability. Reviewer 2 (K.I.S.) independently assessed the limb length to evaluate interobserver reliability.

Statistical analysis

The intraclass correlation coefficient for absolute agreement was calculated using a two-way random-effects model with single measurement to examine the intra- and interobserver reliability of bone age estimation and limb length measurements, in which values less than 0.4 indicated poor, 0.4–0.59 fair, 0.6–0.75 good, and greater than 0.75 excellent.[35,36]

Bone age and limb length were compared between the right and left limbs and between the longer and shorter limbs using a paired t-test or Wilcoxon signed-rank test after performing the Shapiro–Wilk test for normality. Statistical significance was set at $p < 0.05$.

A power analysis was conducted using G*Power (version 3.1.9.6; Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) to determine the statistical power for detecting an effect size of 0.72 with the Wilcoxon signed-rank test.[37] This effect size was derived from a reported 0.18-year difference and 0.25-year standard deviation in hand bone age between the right and left sides in a healthy population.[38] Based on the sample size, the power of the current study was determined to be 100% in the overall group, 98% in the BWS group, 69% in the SRS group, 69% in the PROS group, and 99% in the IH group.

Results

Demographics

Among all patients, the mean chronological age at the time of both hand and whole leg radiographs was 7.9 ± 3.6 years (ranges, 0.9–15.3 years) (Table 1). The right leg was 17.9 ± 12.7 mm (range, 0–73 mm) longer than the left leg in 69 patients (69/118, 58%) ($p < 0.001$), while the left leg was 14.5 ± 8.1 mm (range, 0–32 mm) longer than the right leg in 49 patients (49/118, 42%) ($p < 0.001$). In 89 patients with whole-arm radiographs, the right arm was 6.7 ± 6.7 mm (range, 0–36 mm) longer than the left arm in 56 patients (56/89, 63%) ($p = 0.002$), while the left arm was 7.3 ± 8.9 mm (range, 0–30 mm) longer than the right arm in 33 patients (33/89, 37%) ($p < 0.001$). Their demographic characteristics are shown in Supplemental Table 1.

The demographic characteristics of boys aged 9–15 years and girls aged 7–13 years, whose bone age was additionally assessed using the modified Fels system, are presented in Supplemental Table 2.

Reliability of bone age estimation and limb length measurement

Intra- and interobserver reliability were excellent for all bone age estimation methods (Table 2). Intra- and interobserver reliability for upper or lower limb lengths measurements were also excellent (Table 3).

Comparison of the bone ages between the right and left limbs

There was no significant difference in bone age between the right and left hands in the overall cohort or each disease group when assessed using the KS bone age chart (Table 4).

Table 1. Demographic characteristics of overall patients, grouped by the underlying conditions causing hemihyperplasia or hemihypoplasia.

Group	Sex[a] (M:F)	Longer leg[a] (R:L)	CA at hand radiographs[b] (year)	CA at whole-leg radiographs[b] (year)
Overall ($n=118$)	50:68 (42%:58%)	69:49 (58%:42%)	7.9 ± 3.6 (0.9 to 15.3)	7.9 ± 3.6 (0.4 to 15.3)
BWS ($n=34$)	16:18 (47%:53%)	21:13 (62%:38%)	7.1 ± 2.8 (2.5 to 11.7)	7.1 ± 2.8 (1.8 to 13.0)
SRS ($n=14$)	6:8 (42%:58%)	9:5 (64%:36%)	7.8 ± 4.5 (2.0 to 14.3)	8.0 ± 4.4 (0.4 to 13.9)
PROS ($n=14$)	7:7 (50%:50%)	7:7 (50%:50%)	8.6 ± 4.0 (2.2 to 15.3)	8.6 ± 4.0 (0.7 to 14.0)
IH ($n=56$)	21:35 (38%:62%)	32:24 (57%:43%)	8.3 ± 3.8 (0.9 to 14.2)	8.2 ± 3.8 (0.9 to 15.3)

CA: chronological age; BWS: Beckwith-Wiedemann syndrome; SRS: Silver-Russell syndrome; PROS: PIK3CA-related overgrowth spectrum; IH: idiopathic isolated hemihyperplasia/hemihypoplasia.
[a]These values are given as the number of patients, with the percentage in parentheses.
[b]These values are given as the mean and the standard deviation, with the range in parentheses.

Table 2. Intra- and interobserver reliability of bone age estimation using the KS bone age chart and the modified Fels system.

Reliability	ICC (95% CI)
Intraobserver ($n=30$)	
KS bone age chart	0.937 (0.872–0.969)
Modified Fels wrist system	0.995 (0.990–0.998)
Modified Fels knee system	0.982 (0.962–0.991)
Interobserver ($n=30$)	
KS bone age chart	0.905 (0.835–0.950)
Modified Fels wrist system	0.988 (0.978–0.994)
Modified Fels knee system	0.864 (0.767–0.928)

ICC: intraclass correlation coefficient; CI: confidence interval.

Table 3. Intra- and interobserver reliability of limb length measurements.

Reliability	ICC (95% CI)
Intraobserver ($n=30$)	
Upper limb	0.988 (0.970–0.995)
Lower limb	0.982 (0.964–0.992)
Interobserver ($n=30$)	
Upper limb	0.967 (0.904–0.988)
Lower limb	0.979 (0.958–0.990)

ICC: intraclass correlation coefficient; CI: confidence interval.

In a subset of patients—boys aged 9–15 years and girls aged 7–13 years—hand and knee bone ages estimated using the modified Fels system also showed no difference between the right and left upper limbs in the overall cohort or within each disease group (Tables 5 and 6).

Comparison of the bone ages between the longer and shorter limbs

In 89 patients with whole-arm radiographs, hand bone age estimated using the KS bone age chart showed no difference between the longer and shorter upper limbs in the overall cohort and within each disease group (Table 7).

However, in a subset of patients—boys aged 9–15 years and girls aged 7–13 years—when using the modified Fels system, the BWS group showed 7.1 ± 9.9 months ($p=0.031$) and 3.2 ± 2.5 months ($p=0.026$) older knee and hand bone ages in the longer limb, respectively, compared to the shorter limb (Tables 8 and 9). In the other disease groups, knee or hand bone age estimated using the modified Fels system did not differ between the longer and shorter limbs.

Subgroup analysis by epigenotypes causing BWS

In the subgroup analysis by epigenotypes causing BWS, no differences in hand and knee bone age were found between the right and left limbs, in patients with either IC2-LoM or pUPD 11p15 (Table 10, Supplemental Tables 3 and 4). No differences in hand and knee bone age were also found between the longer and shorter limbs in patients with either IC2-LoM or pUPD 11p15 (Supplemental Tables 5–7). When comparing the degree of bone age difference between the longer and shorter limbs assessed by the modified Fels method, the pUPD group showed greater differences than the IC2-LoM group: hand bone age difference was 3.7 months in the pUPD group versus 3.1 ± 2.8 months in the IC2-LoM group, and knee bone age difference was 12.6 ± 14.4 months versus 5.3 ± 8.3 months, respectively (Supplemental Tables 6–7). The difference in knee bone age was not statistically significant ($p=0.291$), and statistical testing was not feasible for hand bone age due to the small sample size.

Discussion

This study is the first to evaluate bone age differences between both limbs in conditions causing congenital hemihyperplasia or hemihypoplasia. Our findings reveal that while most conditions associated with hemihyperplasia or hemihypoplasia do not show significant side-to-side bone age differences, BWS presents a notable exception. When assessed using the modified Fels system, patients with

Table 4. Comparison of hand bone ages estimated by the KS bone age chart between the right and left upper limbs.[a]

Group	Right-hand BA (year)	Left-hand BA (year)	Mean BA difference between the right and left upper limbs[b] (month)	*p* Value
Overall (*n* = 118)	7.9 ± 4.0 (0.8–15.0)	7.9 ± 3.9 (0.8 to 15.0)	0.2 ± 1.8 (−7.0 to 13.0)	0.279
BWS (*n* = 34)	7.3 ± 3.1 (2.5 to 13.1)	7.3 ± 3.1 (2.5 to 13.1)	0.0 ± 4.7 (−7.0 to 0.0)	1.000
SRS (*n* = 14)	8.0 ± 5.0 (1.8 to 15.0)	8.0 ± 5.0 (1.8 to 15.0)	0.0 ± 0.0 (0.0 to 0.0)	1.000
PROS (*n* = 14)	8.1 ± 4.1 (1.0 to 14.1)	8.1 ± 4.1 (1.0 to 14.1)	−0.3 ± 4.8 (−3.5 to 0.0)	0.336
IH (*n* = 56)	8.2 ± 4.2 (0.8 to 15.0)	8.2 ± 4.2 (0.8 to 15.0)	0.4 ± 2.2 (0.0 to 13.0)	0.180

BA: bone age; BWS: Beckwith-Wiedemann syndrome; SRS: Silver-Russell syndrome; PROS: PIK3CA-related overgrowth spectrum; IH: idiopathic isolated hemihyperplasia/hemihypoplasia.
[a]Bone ages and mean differences are presented as the mean and the standard deviation, with the range in parentheses.
[b]Positive values indicate that the right-hand bone age is older than the left-hand bone age, while negative values indicate the opposite.

Table 5. Comparison of hand bone ages estimated by the modified Fels wrist system between the right and left upper limbs in boys aged 9–15 years and girls aged 7–13 years.[a]

Group	Right-hand BA (year)	Left-hand BA (year)	Mean BA difference between the right and left upper limbs[b] (month)	*p* Value
Overall (*n* = 56)	11.3 ± 1.8 (7.8 to 15.2)	11.3 ± 1.8 (7.7 to 15.1)	0.1 ± 2.6 (−6.4 to 6.0)	0.722
BWS (*n* = 12)	10.7 ± 1.7 (7.8 to 12.4)	10.7 ± 1.7 (7.7 to 12.1)	0.1 ± 3.5 (−6.4 to 6.0)	0.814
SRS (*n* = 6)	12.5 ± 1.6 (10.5 to 15.2)	12.6 ± 1.6 (10.3 to 15.1)	−1.0 ± 2.6 (−5.1 to 2.3)	0.397
PROS (*n* = 8)	10.9 ± 1.4 (7.8 to 12.1)	10.8 ± 1.4 (7.8 to 12.3)	0.4 ± 1.7 (−2.0 to 3.5)	0.600
IH (*n* = 30)	11.4 ± 1.9 (8.4 to 15.0)	11.4 ± 1.9 (8.4 to 15.1)	0.3 ± 2.5 (−5.1 to 5.9)	0.545

BA: bone age; BWS: Beckwith-Wiedemann syndrome; SRS: Silver-Russell syndrome; PROS: PIK3CA-related overgrowth spectrum; IH: idiopathic isolated hemihyperplasia/hemihypoplasia.
[a]Bone ages and mean differences are presented as the mean and the standard deviation, with the range in parentheses.
[b]Positive values indicate that the right-hand bone age is older than the left-hand bone age, while negative values indicate the opposite.

Table 6. Comparison of knee bone ages estimated by the modified Fels knee system between the right and left lower limbs in boys aged 9–15 years and girls aged 7–13 years.[a]

Group	Right-knee BA (year)	Left-knee BA (year)	Mean BA difference between the right and left lower limbs[b] (month)	*p* Value
Overall (*n* = 56)	11.4 ± 1.7 (6.7 to 14.5)	11.6 ± 1.5 (8.5 to 14.8)	−2.1 ± 14.2 (−33.2 to 28.3)	0.357
BWS (*n* = 12)	10.9 ± 2.0 (6.7 to 12.9)	11.1 ± 1.6 (8.5 to 13.6)	−2.4 ± 12.1 (−24.9 to 15.9)	0.515
SRS (*n* = 6)	12.6 ± 1.9 (9.8 to 14.6)	12.3 ± 1.6 (10.6 to 14.5)	3.1 ± 7.9 (−8.8 to 10.5)	0.385
PROS (*n* = 8)	11.5 ± 1.6 (8.4 to 13.5)	11.8 ± 1.6 (9.1 to 14.1)	−4.0 ± 20.4 (−33.2 to 28.3)	0.601
IH (*n* = 30)	11.4 ± 1.6 (8.4 to 14.4)	11.6 ± 1.5 (9.4 to 14.8)	−2.6 ± 14.4 (−25.0 to 23.3)	0.477

BA: bone age; BWS: Beckwith-Wiedemann syndrome; SRS: Silver-Russell syndrome; PROS: PIK3CA-related overgrowth spectrum; IH: idiopathic isolated hemihyperplasia/hemihypoplasia.
[a]Bone ages and mean differences are presented as the mean and the standard deviation, with the range in parentheses.
[b]Positive values indicate that the right-knee bone age is older than the left-knee bone age, while negative values indicate the opposite.

BWS showed a significantly older knee bone age (7.1 ± 9.9 months) in the longer limb compared with the shorter limb. A smaller but concordant difference was also observed in hand bone age (3.2 ± 2.5 months), supporting the presence of asymmetric skeletal maturation rather than a site-specific phenomenon. Recognizing such asymmetry may contribute to more accurate timing of epiphysiodesis and improved outcomes in limb length equalization.

In the BWS group, comparisons of hand or knee bone age between the left and right limbs revealed no differences, regardless of the bone age assessment method. Similarly, hand bone age assessed using the KS bone age chart showed no significant difference between the longer and shorter limbs. Only the hand and knee bone ages assessed using the modified Fels system were several months older in the longer limb. We were unable to

Table 7. Comparison of hand bone ages estimated by the KS bone age chart between the longer and shorter upper limbs.[a]

Group	Longer-side hand BA (year)	Shorter-side hand BA (year)	Mean BA difference between the longer and shorter upper limbs[b] (month)	*p* Value
Overall (*n* = 89)	7.6 ± 4.1 (0.8 to 15.0)	7.6 ± 4.0 (0.8 to 15.0)	0.4 ± 1.9 (0.0 to 13.0)	0.068
BWS (*n* = 22)	6.9 ± 3.3 (2.5 to 13.1)	6.9 ± 3.3 (2.5 to 13.1)	0.3 ± 1.5 (0.0 to 7.0)	0.329
SRS (*n* = 7)	7.3 ± 5.4 (2.3 to 15.0)	7.3 ± 5.4 (2.3 to 15.0)	0.0 ± 0.0 (0.0 to 0.0)	1.000
PROS (*n* = 8)	6.7 ± 4.0 (1.3 to 12.0)	6.6 ± 4.1 (1.0 to 12.0)	0.4 ± 1.2 (0.0 to 3.5)	0.351
IH (*n* = 52)	8.2 ± 4.2 (0.8 to 15.0)	8.1 ± 4.2 (0.8 to 15.0)	0.4 ± 2.3 (0.0 to 13.0)	0.163

BA: bone age; BWS: Beckwith-Wiedemann syndrome; SRS: Silver-Russell syndrome; PROS: PIK3CA-related overgrowth spectrum; IH: idiopathic isolated hemihyperplasia/hemihypoplasia.
[a]Bone ages and mean differences are presented as the mean and the standard deviation, with the range in parentheses.
[b]Positive values indicate that the longer-side hand bone age is older than the shorter-side hand bone age, while negative values indicate the opposite.

Table 8. Comparison of knee bone ages estimated by the modified Fels knee system between the longer and shorter lower limbs in boys aged 9–15 years and girls aged 7–13 years.[a]

Group	Longer-side knee BA (year)	Shorter-side knee BA (year)	Mean BA difference between the longer and shorter lower limbs[b] (month)	*p* Value[c]
Overall (*n* = 56)	11.6 ± 1.6 (8.4 to 14.6)	11.5 ± 1.7 (6.7 to 14.8)	0.6 ± 14.3 (−33.2 to 24.9)	0.643
BWS (*n* = 12)	11.3 ± 1.7 (8.7 to 13.6)	10.7 ± 1.9 (6.7 to 12.9)	7.1 ± 9.9 (−3.2 to 24.9)	**0.031**
SRS (*n* = 6)	12.5 ± 2.0 (9.8 to 14.6)	12.3 ± 1.5 (10.6 to 14.2)	1.9 ± 8.3 (−8.8 to 10.5)	0.599
PROS (*n* = 8)	11.5 ± 1.8 (8.4 to 14.1)	11.8 ± 1.5 (9.1 to 13.5)	−3.7 ± 20.5 (−33.2 to 23.8)	0.626
IH (*n* = 30)	11.5 ± 1.5 (8.4 to 14.4)	11.5 ± 1.6 (8.9 to 14.8)	−1.2 ± 14.6 (−25.0 to 24.3)	0.844

BA: bone age; BWS: Beckwith-Wiedemann syndrome; SRS: Silver-Russell syndrome; PROS: PIK3CA-related overgrowth spectrum; IH: idiopathic isolated hemihyperplasia/hemihypoplasia.
[a]Bone ages and mean differences are presented as the mean and the standard deviation, with the range in parentheses.
[b]Positive values indicate that the longer-side knee bone age is older than the shorter-side knee bone age, while negative values indicate the opposite.
[c]Bold font indicates statistical significance.

Table 9. Comparison of hand bone ages estimated by the modified Fels wrist system between the longer and shorter upper limbs in boys aged 9–15 years and girls aged 7–13 years with whole-arm radiographs.[a]

Group	Longer-side hand BA (year)	Shorter-side hand BA (year)	Mean BA difference between the longer and shorter upper limbs[b] (month)	*p* Value[c]
Overall (*n* = 39)	11.4 ± 1.8 (7.8 to 15.0)	11.3 ± 1.8 (7.8 to 15.1)	1.2 ± 2.6 (−5.1 to 6.4)	**0.005**
BWS (*n* = 6)	11.6 ± 0.5 (10.9 to 12.2)	11.4 ± 0.5 (10.5 to 12.0)	3.2 ± 2.5 (−1.0 to 6.4)	**0.026**
SRS (*n* = 2)	12.7 ± 1.4 (8.4 to 15.0)	12.5 ± 1.0 (8.4 to 15.1)	1.8 ± 4.7 (−1.6 to 5.1)	N/A
PROS (*n* = 4)	10.3 ± 1.7 (7.8 to 11.8)	10.2 ± 1.7 (7.8 to 11.8)	1.2 ± 1.6 (−0.1 to 3.5)	0.211
IH (*n* = 27)	11.4 ± 2.0 (8.4 to 15.0)	11.3 ± 2.0 (8.4 to 15.1)	0.7 ± 2.5 (−5.1 to 5.9)	0.137

BA: bone age; BWS: Beckwith-Wiedemann syndrome; SRS: Silver-Russell syndrome; PROS: PIK3CA-related overgrowth spectrum; IH: idiopathic isolated hemihyperplasia/hemihypoplasia; N/A, not applicable.
[a]Bone ages and mean differences are presented as the mean and the standard deviation, with the range in parentheses.
[b]Positive values indicate that the longer-side hand bone age is older than the shorter-side hand bone age, while negative values indicate the opposite.
[c]Bold font indicates statistical significance. N/A indicates that statistical analysis was not possible due to an insufficient number of samples.

compare our results with previous studies, as no prior research has investigated side-to-side bone age differences in BWS. The KS bone age chart, an atlas-based method with broader categorical intervals, may lack the resolution needed to detect meaningful asymmetry. By contrast, the modified Fels system provides finer age estimates based on quantitative parameters and was developed for use in preadolescents and adolescents, the age group in which epiphysiodesis is most commonly performed. Therefore, the bone age differences identified by the modified Fels system may carry greater clinical relevance. In addition, laterality based on right versus left sides is distinct from

Table 10. Comparison of hand bone ages estimated by the KS bone age chart between the right and left upper limbs, grouped by BWS epigenotypes.[a]

Group	Right-hand BA (year)	Left-hand BA (year)	Mean BA difference between the right and left hands[b] (month)	*p* Value
IC2-LoM (*n* = 18)	8.5 ± 2.7 (4.0 to 13.1)	8.5 ± 2.7 (4.0 to 13.1)	−0.4 ± 1.6 (−7.0 to 0.0)	0.331
pUPD 11p15 (*n* = 16)	6.0 ± 3.0 (2.5 to 11.0)	6.0 ± 3.0 (2.5 to 11.0)	0.4 ± 1.8 (0.0 to 7.0)	0.333

BA: bone age; BWS: Beckwith-Wiedemann syndrome; IC2-LoM: Loss of methylation in imprinting center 2; pUPD: paternal uniparental disomy.
[a]Bone ages and mean differences are presented as the mean and the standard deviation, with the range in parentheses.
[b]Positive values indicate that the right-hand bone age is older than the left-hand bone age, while negative values indicate the opposite.

that based on affected versus unaffected limbs. Given previous reports of advanced bone age relative to chronological age in BWS and the presence of somatic mosaicism,[3,4,26] it is reasonable that bone age was advanced in the longer (affected) limb rather than related to anatomical laterality.

The bone age asymmetry observed in BWS might be explained by underlying epigenetic and molecular mechanisms. Chromosome 11p15, which is frequently altered in BWS, consists of two imprinting control regions: imprinting center 1 (IC1, telomeric) and imprinting center 2 (IC2, centromeric).[5–7] The centromeric domain includes *CDKN1C*, a maternally expressed growth repressor regulated by IC2, while the telomeric domain includes *IGF2*, a paternally expressed growth factor regulated by IC1. Common molecular alterations in BWS include loss of methylation at IC2 (~50%), gain of methylation at IC1 (5–10%), and pUPD of 11p15 (20%–25%), all of which lead to dysregulated expression of imprinted growth-related genes.[5] Both *CDKN1C* and *IGF2* play roles in regulating chondrocyte proliferation and differentiation within the growth plate.[39–44] Their dysregulation might lead to accelerated ossification, thereby advancing bone age and promoting excessive longitudinal growth in the affected limb. Consequently, the longer limb in patients with BWS may exhibit advanced skeletal maturation, resulting in the bone age asymmetry identified in our study.

A 7.1 ± 9.9 month difference in knee bone age between the longer (11.3 ± 1.7 years) and shorter limbs (10.7 ± 1.9 years) observed in the BWS group (Table 8) may have important clinical implications for predicting future LLD and determining the optimal timing of epiphysiodesis. At this age range, when the growth spurt typically occurs, the annual growth is approximately 8–9.5 cm,[45,46] and about 65% of leg growth[47,48] originates from the distal femur and proximal tibia—sites commonly targeted for epiphysiodesis. Therefore, a 7.1 month difference in bone age may significantly affect the remaining growth potential. In general, for patients with the same degree of LLD, epiphysiodesis needs to be performed earlier in limbs with advanced bone age than in those with normal or delayed bone age. If, in patients with BWS, the longer limb is skeletally more mature and standard prediction models rely on the shorter limb's bone age, LLD at skeletal maturity may be overestimated. Whether LLD naturally decreases over time in such patients remains uncertain, as the longer limb with advanced bone age might have already completed a larger portion of its growth. Shapiro[49] reported that approximately half of the patients with hemihyperplasia experience a proportional increase in LLD with age, while about 21% show stabilization after a certain point. However, that study lacked molecular diagnoses, and growth patterns may differ in patients with confirmed BWS.

While the overall BWS group showed significant bone age asymmetry, subgroup analyses by epigenotype (IC2-LoM vs. pUPD) did not reach statistical significance, likely because of small sample sizes. Nevertheless, the pUPD group tended to show greater bone age differences between the longer and shorter limbs, particularly at the knee (Supplemental Tables 6–7). This trend suggests that the underlying molecular subtype might influence the degree of bone age asymmetry in BWS. pUPD affects both *IGF2* and *CDKN1C*, whereas IC2-LoM affects only *CDKN1C*. This broader disruption of growth regulation in pUPD may explain the observed trend toward greater bone age advancement and is consistent with previous reports of more severe phenotypes—such as larger LLD and higher tumor risk—compared to IC2-LoM.[6,23,50,51]

In the SRS group, no statistically significant bone age differences were observed between the limbs, regardless of the bone age estimation method used. Since SRS is generally considered the phenotypic and genetic opposite of BWS—and given that our study identified bone age asymmetry between the longer and shorter limbs in BWS when assessed using the modified Fels system—one might expect a corresponding inverse pattern in SRS.[5] The most common molecular etiology of SRS is loss of methylation at IC1 on chromosome 11p15, which leads to reduced expression of *IGF2*. Reduced *IGF2* expression may impair chondrocyte proliferation and early differentiation by disrupting growth signaling pathways,[41,42] potentially affecting skeletal maturation in a lateralized manner in the presence of mosaicism. However, no such asymmetry was observed in our SRS cohort. The most likely explanation is the relatively small sample size, which limited statistical power. In addition, the age at which radiographs were taken may have influenced the results. Previous studies

reported that bone maturation in SRS tends to be delayed during early childhood but accelerates around 8–9 years of age, often in association with precocious puberty.[12,52] This biphasic pattern could obscure consistent bone age asymmetry depending on the timing of evaluation.

In the PROS and IH groups, no significant side-to-side bone age differences were observed. Although PROS is associated with segmental overgrowth and asymmetry caused by mosaic activating mutations in *PIK3CA*, current evidence does not support a consistent effect of these mutations on the pace of skeletal maturation.[13–15,53–55] Moreover, in some patients, the affected limb may be shorter due to physeal involvement by vascular or other pathological tissue, which could obscure or counteract detectable bone age asymmetry between the longer and shorter limbs.[54] In the IH group, the absence of significant bone age asymmetry may reflect heterogeneous and often undetected underlying etiologies. Without molecular confirmation, distinguishing between hemihyperplasia and hemihypoplasia can be challenging, particularly in patients without overt clinical features,[23] potentially complicating the comparison of bone age between the longer and shorter limbs. We speculate that even when mosaic mutations affecting growth are present and lead to hemihyperplasia or hemihypoplasia, bone age may not differ between limbs if the affected genes do not regulate skeletal maturation pathways.

Our study has several limitations. First, due to its cross-sectional design, we were unable to assess age-related changes in bone age asymmetry between limbs. Longitudinal data would help estimate future LLD more precisely and guide surgical timing more effectively. Second, we did not include a control group. However, previous studies have reported no significant difference in bone age between the right and left hands in the normal pediatric population,[38,56] suggesting that the observed asymmetry in BWS is probably syndrome-specific. Third, the sample size in some subgroups—particularly SRS and PROS—was relatively small, limiting the statistical power and underscoring the need for further research with larger cohorts. Fourth, our study is subject to selection bias, as we included only patients who underwent molecular testing. Focusing exclusively on patients who underwent molecular testing likely resulted in an overrepresentation of those with more clinically apparent features, while milder or atypical forms may have been underrepresented. Although this limits generalizability, focusing on genetically tested patients allowed for more accurate classification and reduced diagnostic ambiguity. Lastly, the IH group may not truly represent "idiopathic" patients, as molecular testing was limited to either MS-MLPA on chromosome 11p15 or high-depth NGS, primarily using blood samples. Broader testing, including tissue samples, might have revealed undetected syndromic patients. However, comprehensive molecular analysis and tissue collection are not always feasible in clinical settings.

Conclusions

Pediatric patients with congenital hemihyperplasia or hemihypoplasia generally show minimal bone age differences between limbs. However, in BWS, the longer limb may have a bone age several months older than the shorter limb. Surgeons need to consider potential side-to-side differences in bone age when estimating remaining growth and determining the timing of epiphysiodesis in these patients. Further longitudinal studies with larger sample sizes are warranted to validate these findings and clarify age-related changes in bone age asymmetry.

Author notes

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Author contributions

Wonik Lee: Data curation, Formal analysis, Methodology, Validation, Writing– original draft
Jung Min Ko: Methodology, Project administration, Revising the manuscript
Ki Ill Song: Data curation, Revising the manuscript, Validation
Su Yeon Yu: Data curation, Revising the manuscript, Validation
Mi Hyun Song: Writing– review & editing
Tae-Joon Cho: Writing– review & editing
Chang Ho Shin: Conceptualization, Data curation, Investigation, Methodology, Supervision, Validation, Writing– review & editing

Consent to participate

The IRB waived the requirement for informed consent.

Data availability statement

The data supporting this study are not publicly available due to patient privacy and ethical restrictions. De-identified data may be available from the corresponding author upon reasonable request and with appropriate institutional approvals.

Declaration of conflicting interests

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Ethical statement

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki (2013 version) and the International Council for Harmonization Good Clinical Practice

(ICH-GCP) guidelines. The study protocol was reviewed and approved by the Institutional Review Board (IRB) of Seoul National University Hospital (IRB No. 2311-136-1487). This study involved secondary analysis of previously collected clinical data; no additional procedures or interventions were performed. All data were fully anonymized, and no identifiable personal information was used.

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Supplemental material

Supplemental material for this article is available online.

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