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Establishing Normative Values for Entire Spinal Cord Morphometrics in East Asian Young Adults

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Objective: The quantitative assessment of spinal cord volume is still in the early stages of development. Recently, normative morphometric values of the cervical spinal cord have been reported. This study aimed to establish normative values for spinal cord morphometry, extending beyond the cervical region to include the thoracic and lumbar spinal cord, and to examine the influence of sex and ethnicity on these measurements.

Materials and Methods: This prospective study included 28 young, healthy, East Asian volunteers (14 males and 14 females; mean age, 30.14 ± 4.07 years) who underwent spinal cord MRI using a 3T scanner. The cross-sectional areas (CSAs), anteroposterior (AP) and transverse diameters, and compression ratios of the entire spinal cord were calculated. Additionally, the effects of sex and ethnicity on spinal cord volumetry were evaluated, with the influence of ethnicity assessed by comparing the findings with a Caucasian dataset from the PAM50 study.

Results: The CSAs demonstrated two enlargements at the cervical and lumbar levels. The cervical enlargement at C4–5 exhibited an elliptical shape, while the lumbar enlargement at T12 appeared more circular. The CSAs and AP and transverse diameters of the spinal cords in males were significantly larger than that of females ($P < 0.001$). The spinal cord compression ratios in East Asians were significantly lower than those in Caucasians ($P < 0.001$).

Conclusion: This study revealed that the two spinal cord enlargements exhibit different patterns and suggest significant differences in spinal cord morphometric values according to sex and ethnicity.

Keywords: Spinal cord; Morphometry; Measurement; Size; Shape; Cervical enlargement; Lumbar enlargement; Sex; Ethnicity; Asian; Normative; Normal; Reference; Standard

INTRODUCTION

In recent years, volumetric MRI-based quantitative assessment of brain volumes is increasingly used to investigate a broad spectrum of neurodegenerative diseases [1-4]. In this context, the FDA has approved several commercially available software tools for measuring brain volume [5,6]; however, the quantitative assessment of spinal cord volume is still in its early stages of development. The PAM50 study introduced an MRI template of the spinal cord, which established a foundation for standardization and reproducibility [7]. Subsequent studies have identified spinal cord atrophy linked to white matter damage and changes in neuronal function within the spinal cord [8-10]. In addition, previous studies have demonstrated that morphometric measures derived from structural spinal MRI can serve as objective indicators for evaluating spinal cord pathologies, such as multiple sclerosis [11] and amyotrophic lateral sclerosis [12].

A recent large multicenter study provided normative values of spinal cord morphometry in 203 healthy adult volunteers, highlighting cervical enlargement at C4–5. Additionally, the study noted that the cross-sectional areas (CSAs), anteroposterior (AP) diameters, and transverse diameters observed in females were smaller than those observed

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in males [13]. However, the scan range in the study was limited to the cervical spinal cord, with no information on normative values for spinal morphometry below T1. Furthermore, the effect of ethnicity on spinal cord structure remains uninvestigated.

The present study aimed to establish normative values for spinal cord morphometry, covering not only the cervical, but also the thoracic and lumbar spinal cord in young, healthy, East Asian volunteers. Additionally, we compared normative spinal cord morphometry between males and females and between East Asian participants from our cohort and Caucasian individuals from the PAM50 study to explore the influence of sex and ethnicity on spinal cord structure.

MATERIALS AND METHODS

This prospective study was approved by our hospital's Institutional Review Board (IRB No. 3-2023-0285) and was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Study Participants

In this prospective study, 32 healthy participants were consecutively recruited between October 2023 and February 2024. The inclusion criteria were as follows: 1) age between 20 and 40 years, 2) no pain or weakness in either limb, 3) intact activities of daily living, 4) no history of neurological or psychiatric diseases or previous spine surgery, and 5) no contraindication to MRI examination. The exclusion criteria were abnormal findings such as spinal cord compression or severe scoliosis on previous spinal cord MRI. Thirty-two participants were initially screened for this study. One participant withdrew due to a fall injury one day before the MRI scan. Consequently, 31 participants underwent MRI and were analyzed in this study. After conducting MRI, three participants were excluded from the analysis due to unexpected abnormal MR findings, such as a ruptured disc with spinal cord compression, severe scoliosis, and a severe motion artifact, respectively. Minor abnormalities such as mild disc protrusions, spine misalignments, and minimal widening of the central canal of the spinal cord were not considered significant pathologies. Ultimately, 28 participants were included in the final analysis.

MR Acquisition

All participants were scanned with a 3T scanner (MAGNETOM VIDA, Siemens Healthcare, Erlangen, Germany) using the consensus spine generic acquisition protocol [14]. 3D T2-weighted (T2W) volumes were acquired for each subject, covering the entire spinal cord and brainstem. This extensive coverage was achieved by acquiring two fields of view (FOVs) per contrast: one including the head, cervical spine, and upper thoracic spine and the other including the thoracic and lumbar cord. Sequence parameters for the T2W slab-selective fast spin echo (SPACE sequence) were as follows: repetition time (TR) = 1500 ms, echo time (TE) = 120 ms, flip angle = 120°, bandwidth = 625 Hz/voxel, voxel size = 0.8 x 0.8 x 0.8 mm^3, generalized auto-calibrating partial parallel acquisition (GRAPPA) = 3, and time of acquisition = 4 minutes and 6 seconds. Additionally, 3D T1-weighted (T1W) magnetization prepared rapid gradient echo was obtained with scan parameters set to TR = 2000 ms, TE = 3.72 ms, inversion time (TI) = 1000 ms, bandwidth = 150 Hz/voxel, voxel size = 1.0 x 1.0 x 1.0 mm^3, GRAPPA = 2, and time of acquisition = 4 minutes and 44 seconds.

Data Pre-Processing and Normalization

The spinal cord was segmented, and the intervertebral disc was labeled automatically using the Spinal Cord Toolbox version 6.0 [15]. The initial results of the segmentation were visually inspected and, if necessary, manually corrected by one author (B.J.). In cases of ambiguous findings, they were reviewed and confirmed by a more senior neuroradiologist (S.A.). After spinal cord segmentation and labeling, morphometric measures were computed across individual axial slices from the spinal cord segmentation mask in the subject's native space. Computed morphometric measures included the CSAs, AP diameter, transverse diameter, and compression ratio. These measures were then linearly interpolated to the anatomical dimensions of the PAM50 study's unbiased multimodal brainstem and full spinal cord MRI template, based on 50 healthy Caucasian subjects (Fig. 1) [7].

Statistical Analysis

Morphometric measures registered in the PAM50 space were averaged across participants for each slice and compared between females and males using the student's *t*-test. Adjustments for multiple comparisons were performed using the Benjamini–Hochberg false discovery rate (FDR) procedure [16]. Combined adjusted *P*-values were calculated using Fisher's method [17]. To explore the effect of ethnicity on spinal cord structure, normative morphometry data

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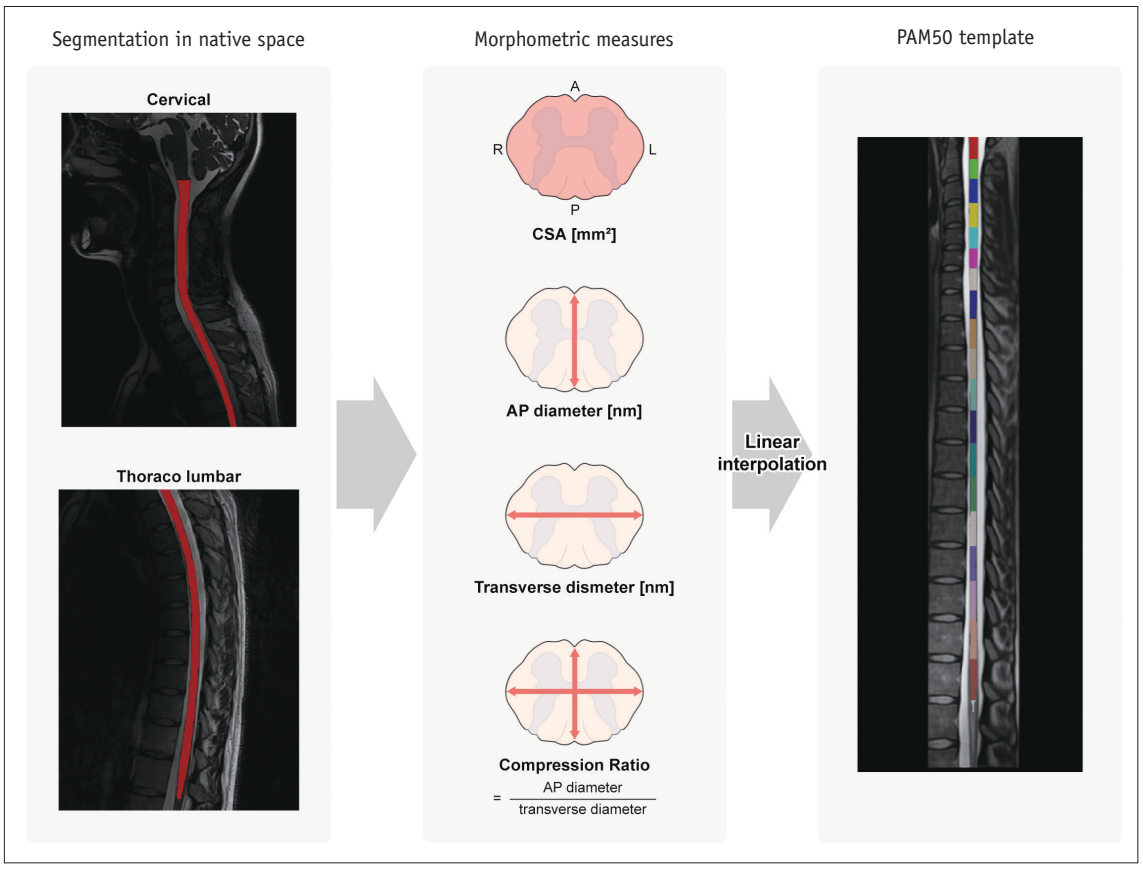

Fig. 1. Schematic representation of imaging processing. CSA = cross-sectional area, AP = anteroposterior

from 50 young, healthy Caucasians, kindly provided by De Leener et al. [7], were used as a comparison group. The morphometric measures of the spinal cord were then compared between East Asians and Caucasians using the student's *t*-test. Adjustments for multiple comparisons were performed using the Benjamini–Hochberg FDR procedure. Combined adjusted *P*-values were calculated using Fisher's method. Statistical significance was set at an alpha level of 0.05. All analyses were performed using the SciPy Python library v1.10. and the Statsmodels library v0.14.1 [18,19].

RESULTS

Participants

A total of 28 subjects (14 males and 14 females) were analyzed. The mean age of participants was 30.14 ± 4.07 years.

CSA Across the Vertebral Levels

The CSA values across standardized slices at vertebral levels (C1–T12) in the PAM50 template along with detailed normative values corresponding to the middle of each vertebral level, are presented in Figure 2 and Table 1. The CSA increased from the vertebral level of C2, peaked at C4, decreased markedly toward the upper thoracic segments, and remained nearly constant through the middle thoracic levels. It increased again at T6, forming a secondary peak at T12. The largest CSA for cervical enlargement was 78.69 ± 8.45 mm^2 at the C4 level, corresponding to axial slice number 856. The largest CSA for thoracolumbar enlargement was 61.08 ± 6.16 mm^2 at the T12 level, corresponding to axial slice number 146.

AP Diameter Across the Vertebral Levels

The AP diameters across standardized slices with vertebral levels (C1–T12) in the PAM50 template, along with detailed normative values corresponding to the middle of each vertebral level, are presented in Figure 2 and Table 1. The AP diameter decreased from C1, reached its lowest value at T5, and then increased until T12. The lowest AP diameter was 5.76 ± 0.42 mm at the T5 level, corresponding to axial slice number 526.

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Transverse Diameter Across the Vertebral Levels

The transverse diameters across standardized slices with vertebral levels (C1–T12) in the PAM50 space, along with detailed normative values corresponding to the middle of each vertebral level, are presented in Figure 2 and Table 1. Mirroring the changes in CSAs, the transverse diameter increased from C1 to its main peak at C4, decreased toward T8, and then increased again, forming a secondary peak at T12. The transverse diameter at the first (C4 level) and second peak (T12 level) was 13.75 ± 0.78 mm and 9.61 ± 0.89 mm, respectively.

Compression Ratio Across the Vertebral Levels

The compression ratio across standardized slices with

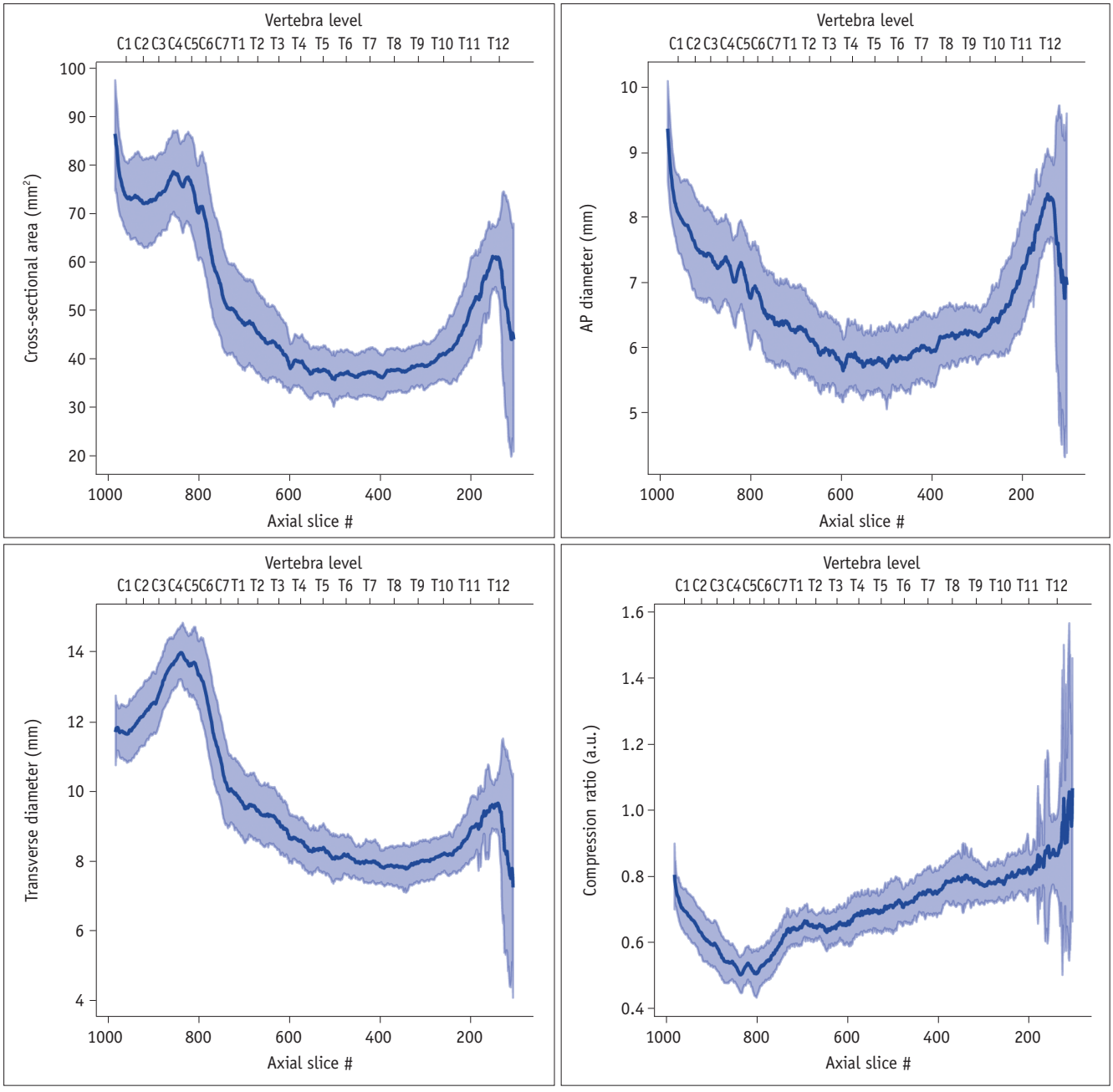

Fig. 2. Comparison of PAM50 slices with those of 28 young Asian adults. Cross-sectional area (top left), AP diameter (top right), transverse diameter (bottom left), and compression ratio (bottom right) plotted across individual slices with vertebral levels (C1–T12). The solid line indicates the mean, and the shaded area represents the standard deviation across the data obtained from 28 young Asian adults for each slice in the PAM50 space. AP = anteroposterior

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Table 1. Normative morphometric measures of the spinal cord (C1–T12) of 28 young Asian adults

Axial slice #	Vertebral level	CSA, mm^2 (n = 28)	AP diameter, mm (n = 28)	Transverse diameter, mm (n = 28)	Compression ratio, a.u. (n = 28)
962	C1	73.85 ± 7.10 (68.07, 80.02)	8.08 ± 0.59 (7.58, 8.45)	11.66 ± 0.77 (11.28, 11.90)	0.70 ± 0.07 (0.64, 0.75)
923	C2	72.21 ± 8.92 (65.33, 77.74)	7.56 ± 0.75 (7.03, 8.19)	12.18 ± 0.86 (11.67, 12.52)	0.62 ± 0.07 (0.57, 0.67)
889	C3	73.88 ± 8.27 (68.09, 80.74)	7.40 ± 0.67 (6.97, 7.81)	12.78 ± 0.90 (11.98, 13.30)	0.58 ± 0.07 (0.53, 0.62)
852	C4	78.40 ± 8.64 (73.42, 84.86)	7.33 ± 0.64 (6.88, 7.74)	13.75 ± 0.78 (13.07, 14.20)	0.53 ± 0.05 (0.49,0.57)
817	C5	76.39 ± 9.56 (69.32, 83.16)	7.20 ± 0.65 (6.80, 7.57)	13.62 ± 0.87 (13.14, 14.28)	0.53 ± 0.05 (0.50, 0.55)
785	C6	68.83 ± 11.67 (61.90, 79.84)	6.84 ± 0.71 (6.27, 7.28)	12.83 ± 1.24 (12.14, 13.63)	0.54 ± 0.06 (0.50, 0.56)
753	C7	55.75 ± 10.77 (49.72, 63.38)	6.45 ± 0.68 (6.05, 6.91)	10.97 ± 1.20 (10.23, 11.63)	0.59 ± 0.06 (0.53, 0.63)
714	T1	48.93 ± 9.56 (44.36, 54.90)	6.28 ± 0.64 (5.85, 6.64)	9.86 ± 0.99 (9.44, 10.48)	0.64 ± 0.04 (0.60,0.66)
670	T2	45.50 ± 8.48 (41.00, 48.12)	6.09 ± 0.61 (5.73, 6.40)	9.48 ± 0.85 (8.92, 9.83)	0.64 ± 0.04 (0.62, 0.65)
624	T3	42.46 ± 6.76 (38.49, 45.73)	5.93 ± 0.53 (5.53, 6.20)	9.10 ± 0.77 (8.70, 9.48)	0.65 ± 0.05 (0.60, 0.69)
576	T4	39.46 ± 5.26 (35.36, 43.31)	5.85 ± 0.50 (5.56, 6.10)	8.60 ± 0.64 (8.23, 9.15)	0.68 ± 0.06 (0.63, 0.72)
526	T5	37.72 ± 4.78 (34.33, 41.13)	5.76 ± 0.42 (5.47, 5.99)	8.36 ± 0.69 (7.79, 8.93)	0.69 ± 0.06 (0.67, 0.73)
475	T6	37.13 ± 4.82 (32.94, 39.99)	5.83 ± 0.49 (5.47, 6.21)	8.16 ± 0.53 (7.86, 8.53)	0.72 ± 0.06 (0.67, 0.75)
423	T7	37.26 ± 4.78 (34.41, 39.94)	5.99 ± 0.50 (5.62, 6.29)	7.97 ± 0.58 (7.52, 8.37)	0.75 ± 0.07 (0.71, 0.79)
370	T8	37.82 ± 4.45 (34.07, 41.22)	6.18 ± 0.46 (5.98, 6.387)	7.86 ± 0.55 (7.66, 8.19)	0.79 ± 0.07 (0.73, 0.82)
316	T9	38.71 ± 4.25 (35.79, 42.43)	6.24 ± 0.38 (5.98, 6.45)	7.95 ± 0.56 (7.59, 8.41)	0.79 ± 0.06 (0.74, 0.83)
261	T10	41.24 ± 5.50 (37.12, 42.76)	6.44 ± 0.54 (6.11, 6.66)	8.20 ± 0.52 (7.75, 8.47)	0.79 ± 0.06 (0.74, 0.81)
200	T11	50.62 ± 10.39 (44.28, 52.14)	7.23 ± 0.84 (6.58, 7.59)	8.94 ± 0.87 (8.41, 9.14)	0.81 ± 0.06 (0.76, 0.84)
137	T12	60.48 ± 8.29 (55.73, 65.55)	8.27 ± 0.65 (7.82, 8.62)	9.61 ± 0.89 (9.30, 10.23)	0.87 ± 0.14 (0.81, 0.90)

The axial slice number indicates the standardized slice number in the PAM50 template. The values are presented as means ± standard deviations. Numbers in parentheses indicate the first and third quartiles. CSA = cross-sectional area, AP = anteroposterior

vertebral levels (C1–T12) in the PAM50 space, along with the detailed normative values corresponding to the middle of each vertebral level, are presented in Figure 2 and Table 1. The compression ratio decreased from C1, reached its lowest at C4 and C5, and then increased again up to T12. The minimum compression ratios were 0.53 ± 0.05 at the C4 and C5 levels.

Influence of Sex on CSA, AP Diameter, Transverse Diameter, and Compression Ratio

The CSA of the spinal cord in males was significantly larger than that of females ($P < 0.001$; Fig. 3). Similarly,

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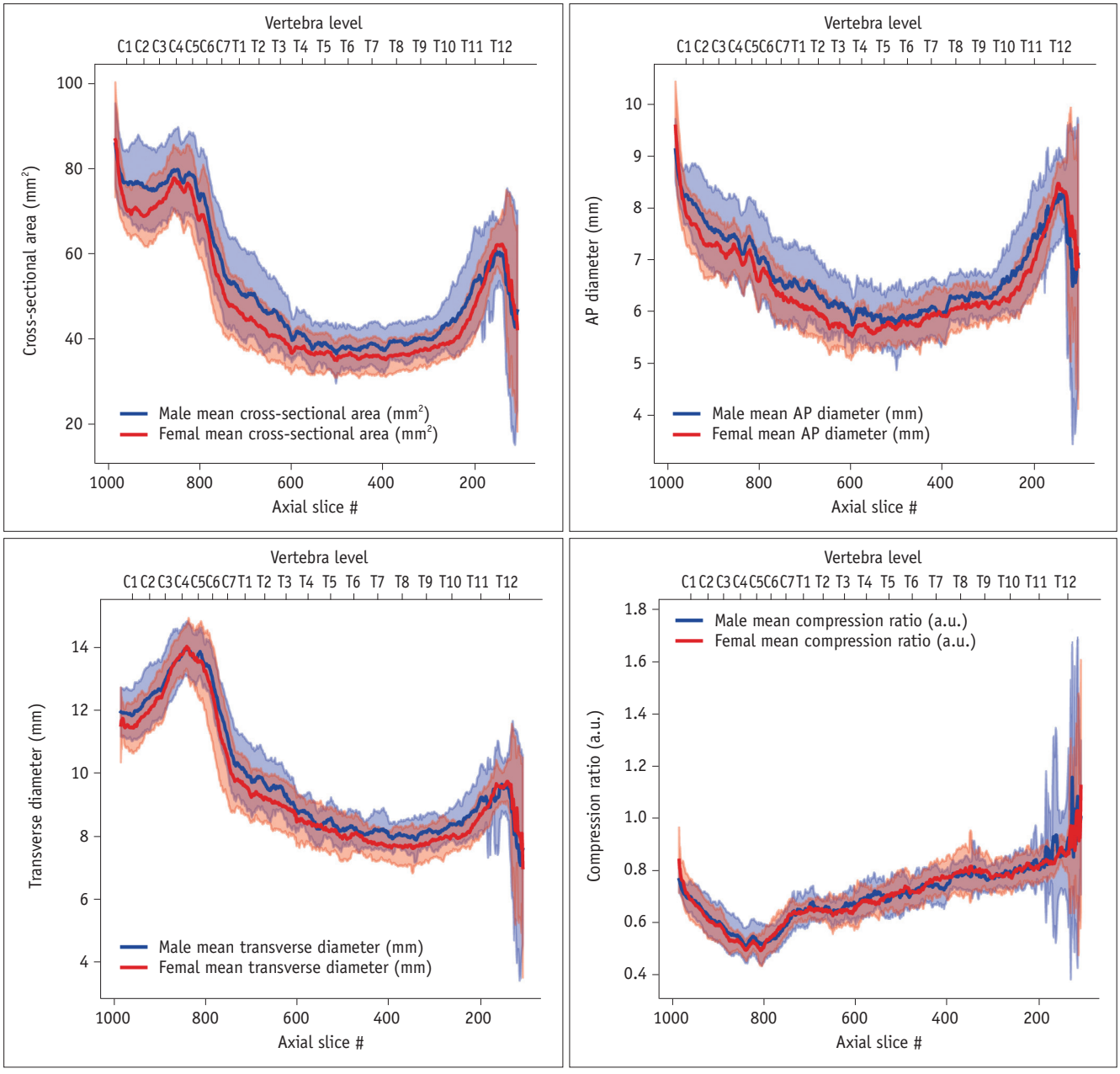

Fig. 3. Comparison of spinal cord measurements between males and females. Comparison of cross-sectional area (top left), AP diameter (top right), transverse diameter (bottom left), and compression ratio (bottom right) of the spinal cord between males (blue) and females (red). The solid line indicates the mean, and the shaded area represents the standard deviation. AP = anteroposterior

the AP and transverse diameters of the spinal cord in males were also significantly greater than those measured in females (both, $P < 0.001$). However, the compression ratio of the spinal cord did not significantly differ between males and females ($P = 1.000$). Comparisons of these morphometric measures between males and females across vertebral levels are shown in Table 2 and Supplementary Table 1.

Influence of Ethnicity on CSA, AP Diameter, Transverse Diameter, and Compression Ratio

The CSA of the spinal cord did not significantly differ between East Asian and Caucasian individuals (Fig. 4). However, the AP diameter of the spinal cord in East Asians was significantly smaller than that in Caucasians ($P < 0.001$). Conversely, the transverse diameter of the spinal cord in East Asians was significantly larger than that in Caucasians ($P < 0.001$). Additionally, the compression ratio of the

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Table 2. Comparison of the CSA of the spinal cord between males and females

Axial slice #	Vertebral level	Male (n = 14), CSA, mm^2	Female (n = 14), CSA, mm^2	*P**
962	C1	76.73 ± 7.31 (74.32, 81.98)	70.98 ± 5.49 (68.00, 76.08)	<0.001
923	C2	75.68 ± 9.60 (73.20, 80.82)	68.74 ± 6.47 (64.60, 72.89)	<0.001
889	C3	75.77 ± 8.89 (72.70, 81.48)	71.98 ± 7.10 (66.61, 76.49)	0.021
852	C4	79.50 ± 9.53 (75.28, 86.19)	77.30 ± 7.48 (70.50, 84.53)	0.195
817	C5	78.47 ± 9.14 (73.50, 83.40)	74.31 ± 9.50 (69.18, 82.78)	0.028
785	C6	71.03 ± 11.48 (62.04, 80.85)	66.64 ± 11.42 (57.48, 74.27)	0.057
753	C7	58.67 ± 11.17 (51.70, 64.26)	52.84 ± 9.47 (45.55, 60.24)	0.007
714	T1	51.40 ± 10.53 (47.19, 55.02)	46.46 ± 7.70 (41.74, 52.26)	0.010
670	T2	48.04 ± 9.69 (44.11, 51.24)	42.96 ± 6.04 (39.40, 46.32)	0.003
624	T3	44.58 ± 7.02 (41.35, 45.86)	40.33 ± 5.72 (36.96, 43.88)	0.002
576	T4	41.01 ± 5.50 (37.93, 44.34)	37.92 ± 4.48 (35.02, 42.04)	0.004
526	T5	38.84 ± 4.71 (36.10, 42.09)	36.60 ± 4.57 (32.60, 39.78)	0.019
475	T6	38.03 ± 5.21 (35.37, 41.31)	36.22 ± 4.21 (32.25, 39.23)	0.058
423	T7	38.75 ± 4.77 (36.28, 41.39)	35.77 ± 4.28 (32.49, 38.55)	0.002
370	T8	39.39 ± 4.42 (37.25, 41.23)	36.25 ± 3.87 (32.50, 38.87)	0.001
316	T9	40.07 ± 4.18 (37.52, 42.74)	37.34 ± 3.84 (34.18, 40.07)	0.002
261	T10	43.66 ± 5.89 (41.22, 46.32)	38.82 ± 3.68 (35.80, 42.22)	<0.001
200	T11	53.53 ± 12.21 (47.08, 54.65)	47.70 ± 7.01 (42.10, 50.39)	0.006
137	T12	59.40 ± 8.20 (54.50, 65.79)	61.56 ± 8.24 (57.73, 65.47)	0.183

The axial slice number indicates the standardized slice number in the PAM50 template. The values are presented as means ± standard deviations. Numbers in parentheses indicate the first and third quartiles.
*Adjustments for multiple comparisons were performed using the Benjamini–Hochberg false discovery rate procedure. CSA = cross-sectional area

spinal cord in East Asians was significantly lower than that in Caucasians ($P < 0.001$). Comparisons of these morphometric measures between East Asians and Caucasians across cervical vertebral levels are shown in Supplementary Table 2.

DISCUSSION

Our results demonstrate that the spinal cord exhibits two enlargements: at the cervical and lumbar levels. The CSA increased from the vertebral level of C2, peaked at C4, and then decreased markedly toward the upper thoracic segments before increasing again and forming a secondary peak at T12. However, the compression ratio, combined with the AP and transverse diameters along the z-axis, revealed a different enlargement pattern with two distinct peaks. The cervical enlargement at C4–5 exhibited an elliptical shape, whereas the lumbar enlargement at T12 was more circular. Additionally, factors such as sex and ethnicity could influence spinal cord morphometry. Our findings provide deeper insights into the anatomy of the spinal cord in healthy individuals, enhancing the interpretation of pathological conditions in the spinal cord by comparison with healthy controls.

The increase in CSA around the vertebral level at C4–5 indicates the location of the cervical enlargement. This finding is consistent with previous studies involving healthy controls [7,20,21]. The enlargements result from the increased amount of neural tissue required for the brachial plexus [22]. The cervical enlargement, which facilitates arm innervation, encompasses spinal segments from C5–T1. The changing trends in the compression ratio suggest a more elliptical shape at cervical enlargement than the more circular shape of the cranial and caudal spinal cord. Consequently, cervical enlargement was influenced more by the transverse diameter than the AP diameter, evidenced by an increase in the transverse diameter and a decrease in the AP diameter at the cervical enlargement.

The lumbar enlargement, associated with the innervation of the lower limbs via the lumbosacral plexus, comprises the spinal segments L2–S3. Our findings indicate that the lumbosacral enlargement occurs at the vertebral level of T12. Several studies that measured the AP and transverse diameters of the thoracolumbar spinal cord using MRI have revealed the largest measurements at the T12 level, consistent with our results [23,24]. Notably, the lumbar enlargement demonstrated a more circular shape than

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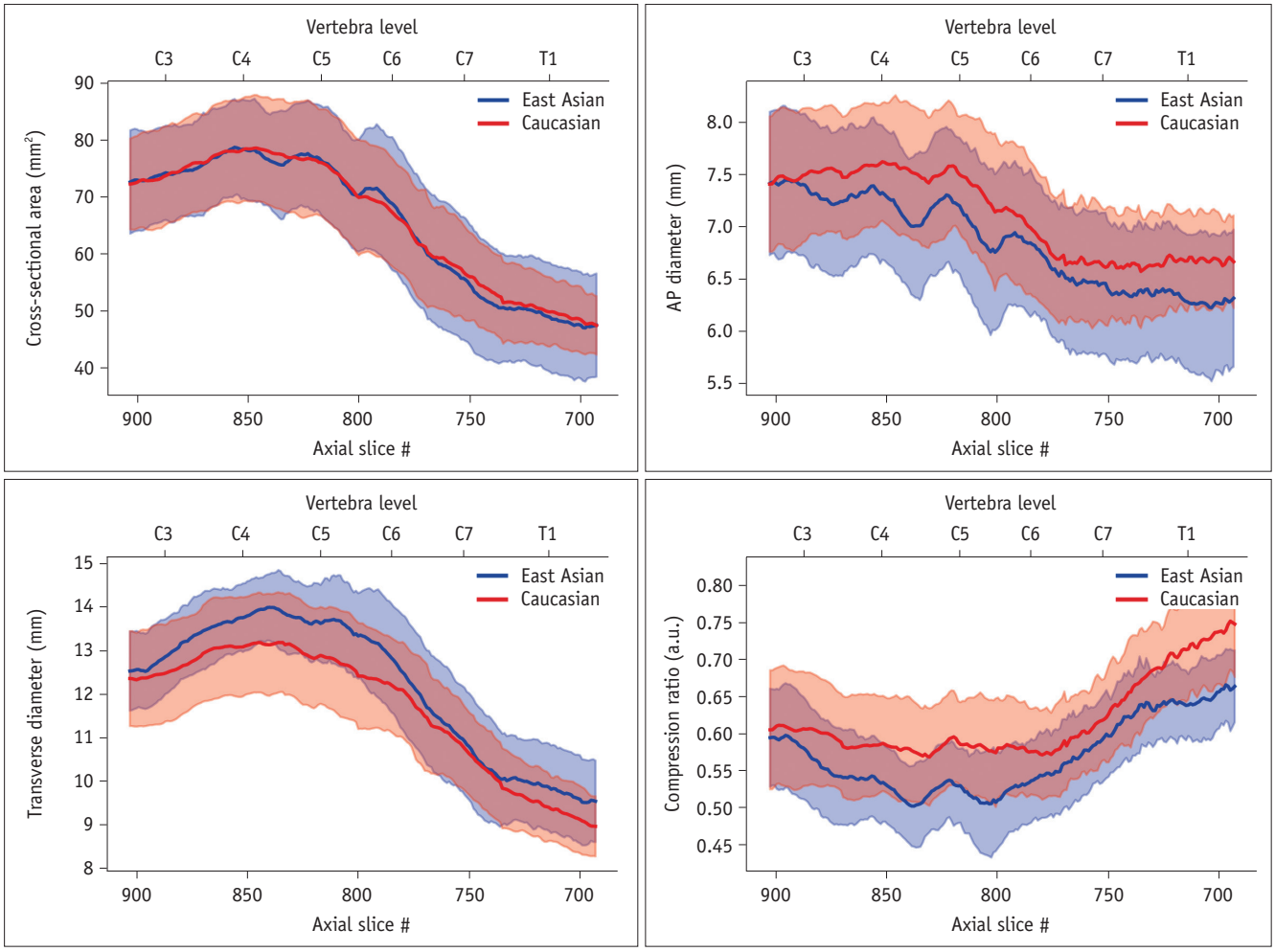

Fig. 4. Comparison of spinal cord measurements between East Asian and Caucasian adults. Comparison of cross-sectional area (top left), AP diameter (top right), transverse diameter (bottom left), and compression ratio (bottom right) of the spinal cord between East Asian (blue) and Caucasian (red) individuals. The solid line indicates the mean, and the shaded area represents the standard deviation. AP = anteroposterior

the more elliptical shape of the cervical enlargement, as indicated by an increase in both AP and transverse diameters. These morphological changes can be partially attributed to the enlargement of the gray matter. Studies involving human cadavers have shown that gray matter volume increases with CSA, peaking at the point of the lumbar enlargement, whereas white matter volume remains constant [25]. Notably, changes in the shape of the ventral horns of the gray matter during lumbar enlargement have been reported in animal studies [26,27].

Previous MRI studies exploring the effects of age and sex on spinal cord metrics in healthy controls have primarily focused on the spinal cord volume at the cervical level [28-30]. Males tend to have a larger spinal cord volume than females. However, the influence of sex on the CSAs at the thoracic and lumbar levels has rarely been studied. Our results concerning the influence of sex on cervical spine align with previous findings. We revealed that males have a significantly larger spinal cord volume than females at the thoracic and lumbar levels. Nonetheless, the CSA, AP diameter, and transverse diameter showed no significant differences in lumbar enlargement (vertebral level T12) between males and females.

Notably, the influence of ethnicity on spinal cord volume has rarely been studied. We assessed this by indirectly comparing our data from East Asian participants with the PAM50 study's dataset, comprising Caucasian participants. Our results demonstrated that the CSA at the cervical spine did not significantly differ between East Asians and Caucasians. However, East Asians tended to have larger transverse and smaller AP diameters than Caucasians. Interestingly, the morphometry of the brain based on Asians also demonstrated a 'rounder' appearance compared to that

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of Caucasians [31]. Further research is required to explain this phenomenon.

This study has several limitations. First, to explore the effect of ethnicity, we utilized the PAM50 dataset, assuming that most participants were Caucasian based on their recruitment locations in Montreal and Marseille. However, the specific ethnicities of the participants have not been documented. Therefore, our findings regarding the effect of ethnicity on spinal cord volumetry should be interpreted with caution and validated in future studies. Second, this study does not provide normative morphometries below the vertebral level of T12 as the segmentation algorithm in Spinal cord toolbox version 6.0 did not perform effectively below this level. Consequently, the transition of spinal cord morphometry from the conus to the cauda equina should be addressed in future studies. Third, our cohort is limited to young adults aged 20 to 40 years. Given that spinal cord volume is expected to decrease with age, our findings may not apply to groups of older adults. Acknowledging this limitation, future studies should include older adults to validate and extend our normative data across a broader age range.

In conclusion, this study revealed that lumbar enlargement of the spinal cord occurs at the vertebral level of T12 and exhibits a more circular shape than the cervical enlargement observed at C4–5. Additionally, spinal cord morphometric values differed significantly based on sex and ethnicity.

Supplement

The Supplement is available with this article at https://doi.org/10.3348/kjr.2024.0907.

Availability of Data and Material

The datasets generated or analyzed during the study are included in this published article and its supplement.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Data curation: Mina Park, Sang Hyun Suh. Funding acquisition: Sung Jun Ahn. Methodology: Bio Joo, Sung Jun Ahn. Project administration: Sung Jun Ahn. Resources: Hyung Jun Park. Software: Bio Joo. Writing—original draft: Bio Joo, Hyung Jun Park, Sung Jun Ahn. Writing—review & editing: Mina Park, Sang Hyun Suh, Sung Jun Ahn.

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