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Standardization and validation of a novel and simple method to assess lumbar dural sac size

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Abstract

AIM—To develop and validate a simple, reproducible method to assess dural sac size using standard imaging technology.

MATERIALS AND METHODS—This study was institutional review board-approved. Two readers, blinded to the diagnoses, measured anterior–posterior (AP) and transverse (TR) dural sac diameter (DSD), and AP vertebral body diameter (VBD) of the lumbar vertebrae using MRI images from 53 control patients with pre-existing MRI examinations, 19 prospectively MRI-imaged healthy controls, and 24 patients with Marfan syndrome with prior MRI or CT lumbar spine imaging. Statistical analysis utilized linear and logistic regression, Pearson correlation, and receiver operating characteristic (ROC) curves.

RESULTS—AP-DSD and TR-DSD measurements were reproducible between two readers (r = 0.91 and 0.87, respectively). DSD (L1–L5) was not different between male and female controls in the AP or TR plane (p = 0.43; p = 0.40, respectively), and did not vary by age (p = 0.62; p = 0.25) or height (p = 0.64; p = 0.32). AP-VBD was greater in males versus females ($p = 1.5 \times 10^{-8}$), resulting in a smaller dural sac ratio (DSR) (DSD/VBD) in males ($p = 5.8 \times 10^{-6}$). Marfan patients had larger AP-DSDs and TR-DSDs than controls ($p = 5.9 \times 10^{-9}$; $p = 6.5 \times 10^{-9}$, respectively). Compared to DSR, AP-DSD and TR-DSD better discriminate Marfan from control subjects based on area under the curve (AUC) values from unadjusted ROCs (AP-DSD $p < 0.01$; TR-DSD p = 0.04).

CONCLUSION—Individual vertebrae and L1–L5 (average) AP-DSD and TR-DSD measurements are simple, reliable, and reproducible for quantitating dural sac size without needing to control for gender, age, or height.

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Introduction

Patients with heritable connective tissues disorders (HCTD), such as Marfan syndrome, Ehlers–Danlos syndrome (EDS), and Loeys–Dietz syndrome (LDS), show diverse manifestations of disorganized connective tissue matrices, particularly in the cardiovascular and skeletal systems. Lung disease in Marfan patients includes apical blebs and spontaneous pneumothorax, and is included in the systemic score of the Ghent criteria for Marfan syndrome.[1] These patients also have an increased frequency of pneumonia and bronchiectasis.[2–8] Although dural ectasia, dilation of the dural sac surrounding the spinal cord, is sensitive for the diagnosis of Marfan syndrome,[9–11] it is not specific and can be seen in LDS and variant EDS.[1,12–14] Data regarding the presence of both dural ectasia and lung abnormalities in HCTD patients is limited. In one study, ~10% of 138 Marfan patients had apical blebs or spontaneous pneumothorax, even though ~50% had dural ectasia; however, it is unclear how many patients had both lung disease and dural ectasia.[15] In another study of 33 patients with Marfan-like features without mutations in *FBN1*, *TGFβR1*, or *TGFβR2*, two patients had spontaneous pneumothorax and dural ectasia.[16]

The present authors have studied dural ectasia in patients with HCTD and idiopathic bronchiectasis because of the physical morphological similarities in idiopathic bronchiectasis and Marfan patients. However, there is currently no preferred method for quantification of dural sac size in the literature,[10] and a method that has been validated in normal and diseased subjects is needed. Published methods of quantitating dural ectasia do not routinely account for the effects of gender, height, or age. The most widely used approaches are those published by Oosterhof,[17] Habermann,[18] Lundby,[19] and Ahn.[20] The Oosterhof, Habermann, and Lundby methods rely on a dural sac “ratio” (DSR), calculated by dividing the lumbar anterior–posterior (AP) dural sac diameter (DSD) by the AP vertebral body diameter (VBD), as determined via MRI or CT imaging. All of these methods also focus on S1 measurements (either DSD or DSR). Conceptually, S1 should demonstrate robust dural ectasia in Marfan syndrome, as it is the most caudal and has the greatest cerebrospinal fluid (CSF) pressures in an upright position. However, the S1 vertebra is structurally different compared with the lumbar vertebrae in several ways, which may confound measurements. The five sacral vertebrae fuse to form the sacrum,[21] and the sacral base is pitched forward, creating the sacrovertebral angle,[22] which progressively increases from 20° at birth to 70° by adulthood. Although the sacrum is larger in men,[23] none of the published assessments of DSR account for potential differences in size of dural sac or vertebral body due to gender, height, age, or race. This is despite recognition that the AP diameters, TR diameters, and volumes of all the lumbar vertebral bodies are smaller in women as compared to men, even when matched for age, height, and weight.[24] Cross-sectional vertebral area is also significantly smaller in women as compared to age-matched men.[25,26]

The aim of the present study was to develop and validate a simple, reproducible, standardized method of quantitating dural sac size, and assess for the effects of gender, height, age, and race by using measurements from a large healthy control population. Measurements were also performed in a smaller group of Marfan syndrome patients for comparison.

Materials and methods

The local institutional review board approved the present study. Informed consent was waived for evaluation of pre-existing MRI images; informed consent and MRI safety screening forms were completed in prospective subjects. All data were recorded in a Health Insurance Portability and Accountability Act (HIPAA)-compliant protected database.

Patients

Normal adult (>18 years of age) control subjects (n = 53) who had normal pre-existing MRI examinations of the lumbo-sacral spine, obtained for clinical purposes, were used in a retrospective fashion. Normality was determined by a consensus of the MRI examination report, and re-review by a radiologist with >10 years of experience. Clinical information from medical records was used to exclude patients with definite or possible HCTD, lung disease, or any spinal disease not recognized on the MRI examination. Measurements were not made on imaging from these excluded individuals. Subsequently, healthy adult controls (n = 19), matched by age and gender to the retrospective control group, were prospectively enrolled for lumbo-sacral MRI examinations (Supplementary Material Fig S1). Exclusion criteria for all subjects included severe thoracic or lumbar scoliosis, thoracic or lumbar spine surgery, spinal stenosis, or spine injury. Exclusion criteria for the prospectively enrolled healthy controls included: presence of lung disease; bone or connective tissue disease (including hypermobility); history of malignancy; endocrine disorder requiring medication; atopy; chronic or recurrent systemic steroids; ≤50 years of age taking prescription medications; and >50 years of age taking prescription medication except for hypertension or hyperlipidaemia. An additional 24 subjects carrying a genetic or clinical diagnosis of Marfan syndrome and had a pre-existing MRI or CT examination of the lumbo-sacral spine available for measurement were included for comparison.

Imaging protocol

Both pre-existing and prospective lumbar MRI examinations were performed using a Siemens (Iselin, NJ, USA) 1.5 T Avanto or 3 T Biograph MRI machine. Pre-existing spine MRI images were generated using a clinical unenhanced protocol; T2-weighted 5 mm axial and sagittal images were viewed on an Agfa (Mortsel, Belgium) PACS workstation using standard Agfa measuring tools and were amenable to 3D manipulation with the Agfa PACS tools. Prospective scans were performed using a single unenhanced 7 min MRI sequence [T2-weighted 3-dimensional (3D) turbo spin echo without fat suppression], which yielded a single 3D-dataset. From this dataset, 1.5 mm images in the axial, sagittal, and coronal planes were reconstructed at the scanner workstation and evaluated on the same Agfa PACS station.

Image analysis

All examinations were reviewed by a board-certified radiologist with >10 years of experience (reader 1) and a second-year medical student (reader 2), both of whom were blinded to diagnosis. Reader 2 was trained on measurement techniques by the radiologist, and completed several practice cases under supervision before measuring study cases. Similar to methods described by Oosterhof[17] and Ahn,[20] mid-sagittal images were used to

measure the AP-VBD and AP-DSD (Fig 1a–b) from L1 to S1. Axial or axial–oblique images were used to measure the orthogonal transverse (TR)-DSD (Fig 1c–d). If needed, images were manipulated with the 3D PACS tool in order to obtain true orthogonal measurements. Vertebral body and dural sac measurements were made at the mid-corpus level of the vertebral body, perpendicular to the long axis of the dural sac. For the final analysis, the S1 vertebral level was excluded because S1 segments are highly variable in morphology (described above), resulting in irregular measures.

Statistical analysis

Beginning with measurements of controls made by reader 1 (radiologist), linear regression was performed to compare the effects of covariates, including height, gender, age, and race on AP-DSD, TR-DSD, and AP-VBD measurements of L1 through L5 and the L1–L5 (average). Scatter plots were also used to assess the relationship between APDSD and TR-DSD by age and height in females and males. To validate the method, separate linear models were employed, which were fit to each control group with height, gender, age, and race as predictor variables, and then whether the coefficients of the covariates in the two models were significantly different using the Bonferroni correction.

Pearson's correlation was used to calculate the adjusted and unadjusted correlation between readers 1 and 2 of the AP-DSD, TR-DSD, and AP-VBD measurements. For the adjusted correlation, pairwise correlation between residuals in the regression model was used.

The combined control group ($n = 72$) measures of L1–L5 (average) AP-DSD, TR-DSD, and DSR by reader 1 were compared to patients with Marfan syndrome using linear regression. For all linear regression analysis, both the unadjusted and adjusted models were examined; significance was not changed based on model type. $p < 0.05$ indicated a statistically significant difference.

AP-DSDs, TR-DSDs, and DSRs were individually included in a logistic regression model as the sole predictor variable and diagnosis of Marfan as the outcome to obtain the receiver operating characteristics (ROC) curves and corresponding area under the curve (AUC). Separate model fits were also performed with the same variables, after adjusting for height, age, race, and gender. The unadjusted logistic regression models were used as these covariates are not adjusted for in the currently employed methods of assessing dural sac size. DeLong's test was used to compare AUC values. All statistical analysis was performed using STATA (StataCorp 2011; Stata Statistical Software: release 12, StataCorp, College Station, TX, USA) and R.[27]

Results

Measurements were initially made in 53 control subjects (26 female and 27 male subjects; age range 18 to 88 years) by reader 1 (demographics in Supplementary Material Table S1a). The AP- and TR-DSD measures for males and females were similar at each level (L1 to L5), and the calculated L1–L5 (average) AP- and TR-DSD were not different between males and females ($p = 0.43$ and 0.40; Supplementary Material Table S2; Table 1). AP-DSD and TR-DSD did not differ between subjects self-identified as white or African-American ($p = 0.85$

and 0.41), respectively. Scatter plots and multiple linear regression, which included gender in the model, demonstrated no variation in AP-DSD and TR-DSD by age ($p = 0.62$ and 0.25) or height ($p = 0.64$ and 0.32), respectively (Supplementary Material Fig S2).

To validate the method, it was applied to 19 prospectively imaged control subjects (nine females and 10 males; demographics in Supplementary Material Table S1b). Again, no difference was found in the AP- and TR-DSD measurements between males and females at each level (L1 to L5) and for the calculated L1–L5 (average) (Supplementary Material Table S3). Bonferroni correction was used to test for a difference between the coefficients of the covariates from each control group's model, which included height, gender, age, and race as predictor variables. L1–L5 (average) AP-DSD ($p = 0.81$) and TR-DSD ($p = 0.37$; Table 2; reader 1) were non-significant, as was AP-VBD ($p = 0.47$; data not shown), confirming that the two groups are similar (Table 2 and Supplementary Material Table S4).

As AP-DSD and TR-DSD at L1 through L5 did not differ by gender, height, age, or control group, all control subjects were combined to plot the L1–L5 (average) AP-DSD and TR-DSD (±95% confidence intervals; Fig 2). As seen in Fig 2, there is a slight increase in variability in TR-DSD at the more caudal vertebral levels, but there was reasonable correlation between AP-DSD and TR-DSD measurements ($r = 0.74$) (Supplementary Material Fig S3).

To substantiate the approach to quantitate AP-DSD, TR-DSD, and AP-VBD, reader 2 performed the same L1 to L5 measurements in the same 72 subjects in a blinded fashion. Reader 2 also showed that TR-DSD was larger than AP-DSD with slightly greater variability at more caudal levels (Supplementary Material Fig S4). As seen in the plot of all 360 measurements of L1 through L5, there was good correlation between the two readers for AP-DSD ($r = 0.91$) and TR-DSD ($r = 0.87$; Fig 3), as well as AP-VBD ($r = 0.91$; data not shown). It is noteworthy that AP-DSD and TR-DSD were not different in the 10 African-American subjects, compared to the 56 white subjects ($p = 0.46$ and 0.67, respectively).

As seen in Supplementary Material Table S4, AP-VBD was substantially greater in males ($p = 1.5 \times 10^{-8}$), which led us to explore the relationship between height and VBD. APVBD is positively correlated to height in both males and females ($p = 3.6 \times 10^{-5}$; $p = 0.001$, respectively). As height increases, AP-VBD increases in both men and women (Supplementary Material Fig S5); thus, males are taller than females ($p = 7.5 \times 10^{-12}$), and AP-VBD is significantly larger in males.

Because previous methods of assessing dural ectasia in Marfan syndrome used the ratio of AP-DSD to AP-VBD, DSRs between control males and females were examined. VBDs (AP) are significantly larger in males, whereas DSDs (AP) show no difference between genders (Supplementary Material Table S4; Table 1); therefore, the ratios are strikingly smaller in males versus females ($p = 5.8 \times 10^{-6}$). This clearly demonstrates that "ratios" distort the assessment of dural sac size in males versus females, and between individuals of different heights; therefore, direct measurements of AP-DSD are most accurate to define the size of the dural sac.

The same methods of measuring dural sac size were applied to 24 subjects with Marfan syndrome (demographics in SupplementaryMaterial Table S5a); again, we noted good reader agreement (AP-DSD $r = 0.85$; TR-DSD $r = 0.90$; AP-VBD $r = 0.87$). As seen in controls, there was no difference in L1–L5 (average) DSD between males and females with Marfan syndrome in both the AP and TR planes ($p = 0.59$ and 0.83, respectively; Supplementary Material Table S5b). The 24 Marfan patients were then compared to the 72 control subjects. Marfan subjects (males and females combined) have significantly larger L1–L5 (average) AP-DSD and TR-DSD measurements, as compared to control subjects ($p = 5.9 \times 10^{-9}$ and 6.5×10^{-9}, respectively; Table 3). Similar to control subjects, Marfan males tend to have larger L1–L5 (average) AP-VBD and DSR measures as compared to Marfan females ($p = 0.03$ and 0.06 respectively; Supplementary Material Table S5b). When the control and Marfan subjects were compared by gender, L1–L5 (average) DSR is significantly larger in Marfan males versus control males ($p = 8.2 \times 10^{-5}$), but there was no significant difference in L1–L5 (average) DSR between Marfan females and control females ($p = 0.07$; Table 3). These results again demonstrate that using “ratios” distort the assessment of dural sac size in males versus females. AP-DSD alone gives a much more robust difference ($p = 5.9 \times 10^{-9}$) than DSR ($p = 0.001$) between controls and Marfan subjects, when gender is not considered. Further evidence demonstrating the superiority of AP-DSD and TR-DSD measures over DSR is seen in the AUC values calculated from the unadjusted logistic regression model ROCs. L1 through L5 and L1–L5 (average) AP-DSD and TR-DSD have significantly higher AUC values as compared to DSR (AP-DSD $p < 0.01$; TR-DSD $p = 0.04$; Table 4; Fig 4).

Discussion

The present authors have studied dural ectasia in patients with HCTD and idiopathic bronchiectasis because of physical morphological similarities in idiopathic bronchiectasis and Marfan patients. Prior published methods to quantitate dural sac size have not been standardized to address comparisons by gender, age, and height.[17–20] Therefore, the present study was undertaken to develop a simple method of assessing dural sac size that could be replicated in a variety of patient types by investigators with varying experience using readily available imaging technology. The present systematic approach involved two independent readers who undertook blinded measurements in two normal (control) groups: those with previously obtained MRI images ($n = 53$) and those prospectively imaged ($n = 19$). The method was validated using measures of APDSD and TR-DSD to assess dural sac size, and established normal reference values. These measures are easily obtained from sagittal images of the lumbar spine, are reproducible by readers of different experience, and are not influenced by age, gender, height, or race.

Prior methods of assessing dural sac size have largely relied upon DSR, which is the AP-DSD divided by the AP-VBD. Age-related declines in vertebral body height correspond to an increase in AP-VBD and TR-VBD size, confounding the use of DSR to assess dural sac size.[28,29] The present study demonstrates that DSR is flawed for comparisons between subjects of different heights, because vertebral body sizes vary by height in both genders, a finding reported previously.[24,30] Females are shorter than males, and have larger DSRs, which can lead to erroneous classification of dural sac size if gender, height, and age are not

considered. The robust discriminatory power of AP-DSD measurements in the lumbar spine as compared to DSR is seen in the magnitude of the *p*-value ($p = 5.9 \times 10^{-9}$ vs 0.001) when comparing all Marfan subjects to all control subjects, the lack of a detectable difference in L1–L5 (average) DSR between Marfan females and control females, and the significantly higher AUC value ($p < 0.01$). DSR clearly distorts the assessment of dural sac size due to gender, height, and age factors; therefore, direct measurements of AP-DSD alone are most accurate.

Published methods about dural sac size in Marfan subjects have focused heavily on the measurements obtained at the S1 level, because in these patients, dural ectasia is most pronounced at and below the S1 vertebral level (Fig 1b). Although this is well-substantiated in the Marfan population, this observation may not apply to non-Marfan subjects. The substantial structural variability of the S1 vertebra between genders and individuals results in highly variable measures, even in normal subjects. Further, DSD is significantly larger at all lumbar vertebral levels in Marfan patients in both the AP and TR plane, as compared to non- Marfan subjects, which obviates the need to assess dural sac size at the highly variable S1 vertebral level.

One limitation of the present study is the smaller number of validation subjects. A volume measurement to further validate the method was not used due to the skill required and lack of universally available software to quantitate volumes. For a small number of Marfan patients without available MRI images, CT images were used, which have a lower soft-tissue contrast resolution and may have a blooming artefact from bone. However, there are studies validating both CT and MRI.[20,31,32] Additionally, pre-existing MRI images used a 5 mm section thickness, whereas prospective scans used a 1.5 mm section thickness. Although the Marfan group had a larger proportion of African-American patients as compared to the control group, this likely did not influence the present findings, as there was no difference in the AP-DSDs or TR-DSDs in the African-Americans studied.

In summary, individual lumbar vertebral AP-DSD measurement is a simple, reliable, and reproducible method of assessing dural sac size without potential confounding variability from gender, height, age, or race.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix A. Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.crad.2014.10.009.

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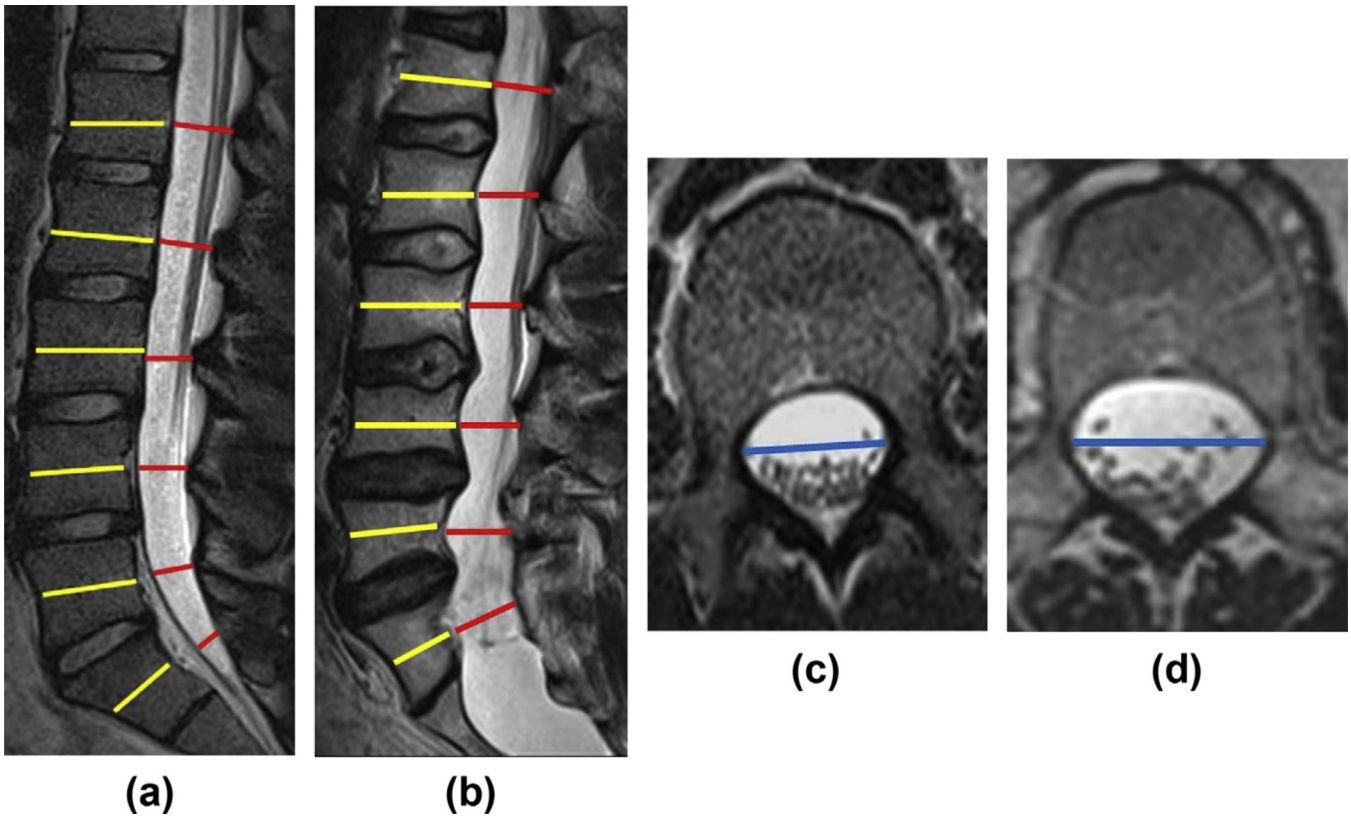

Figure 1.

Sagittal and axial unenhanced T2 weighted 3D-turbo spin echo MRI images of the lumbosacral spine. Measurements of AP-VBD (yellow lines) and AP-DSD (red lines) in a healthy control subject (a) and a patient with Marfan's syndrome (b). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

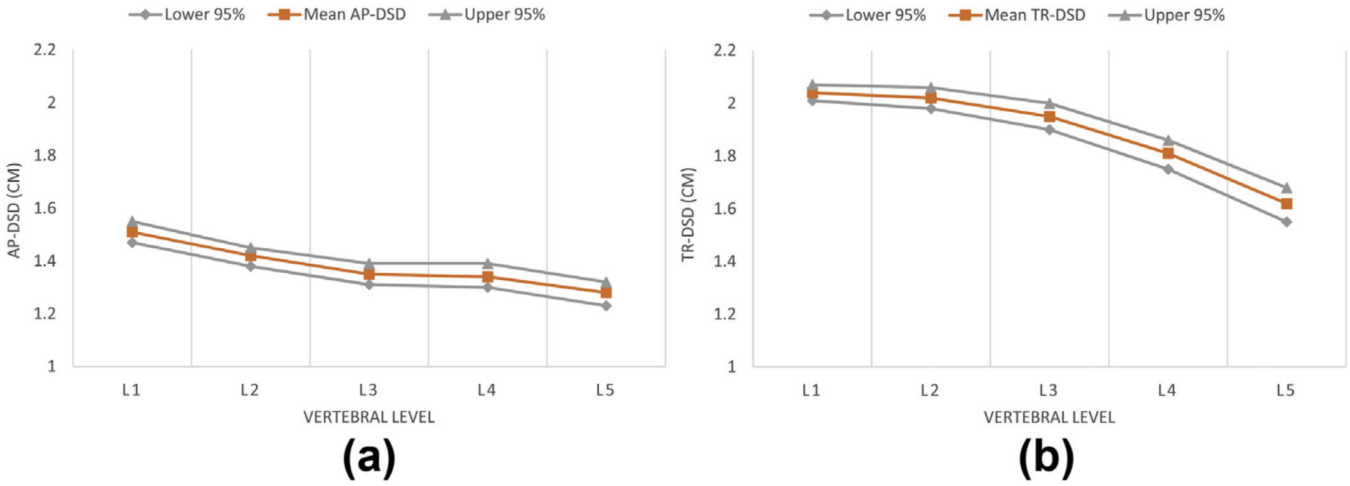

Figure 2.

Mean and 95% confidence intervals of AP-DSD and TR-DSD at L1 through L5 in 72 control subjects (reader 1). (a) Mean AP-DSD diameter decreases in size moving caudally through the lumbar spine. Variability in AP-DSD is small and does not vary by vertebral level. (b) Mean TR-DSD diameter decreases in size moving caudally through the lumbar spine and variability increases slightly increases.

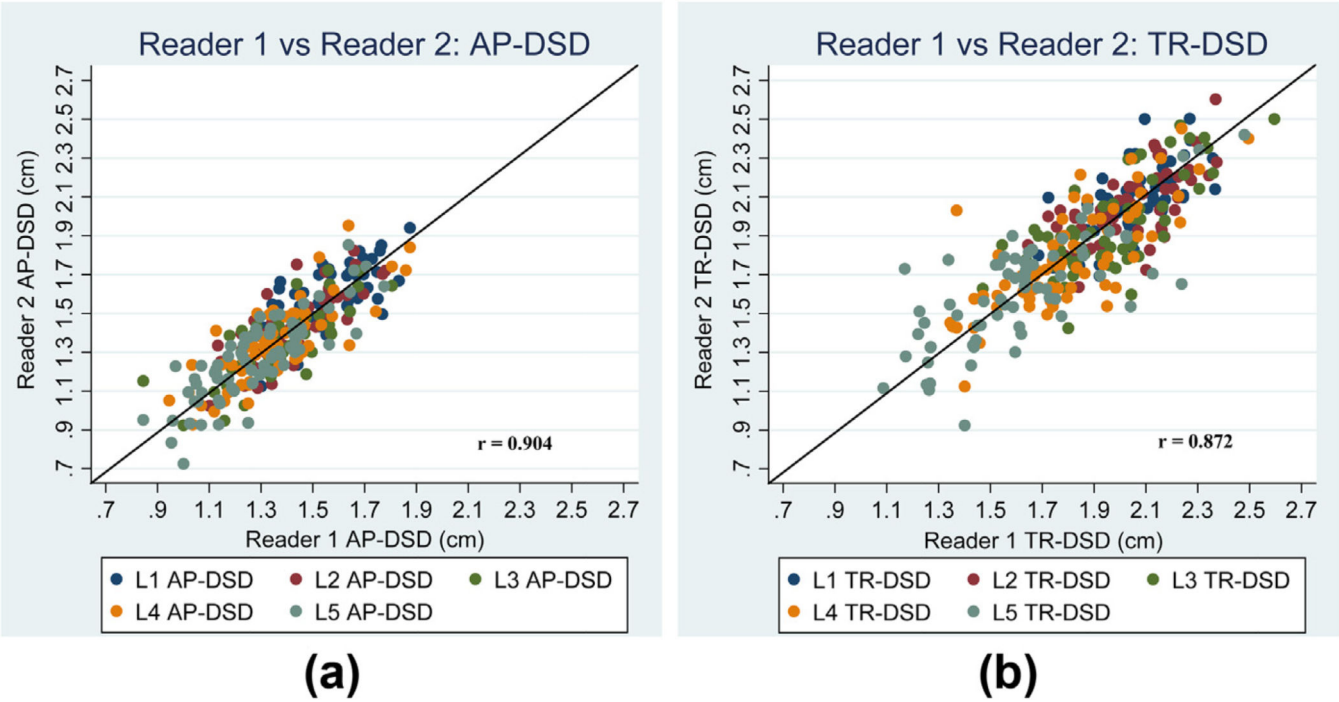

Figure 3.

Correlation of reader 1 and 2 measurements for AP-DSD and TR-DSD of L1 through L5. Graphs show correlation of measurements between reader 1 and reader 2 for all measures from L1 through L5. (a) Pearson correlation coefficient for all measures of AP-DSD = 0.91 ($p < 0.01$). (b) Pearson correlation coefficient for all measures of TR-DSD = 0.87 ($p < 0.01$). Degree of correlation varies by vertebral level.

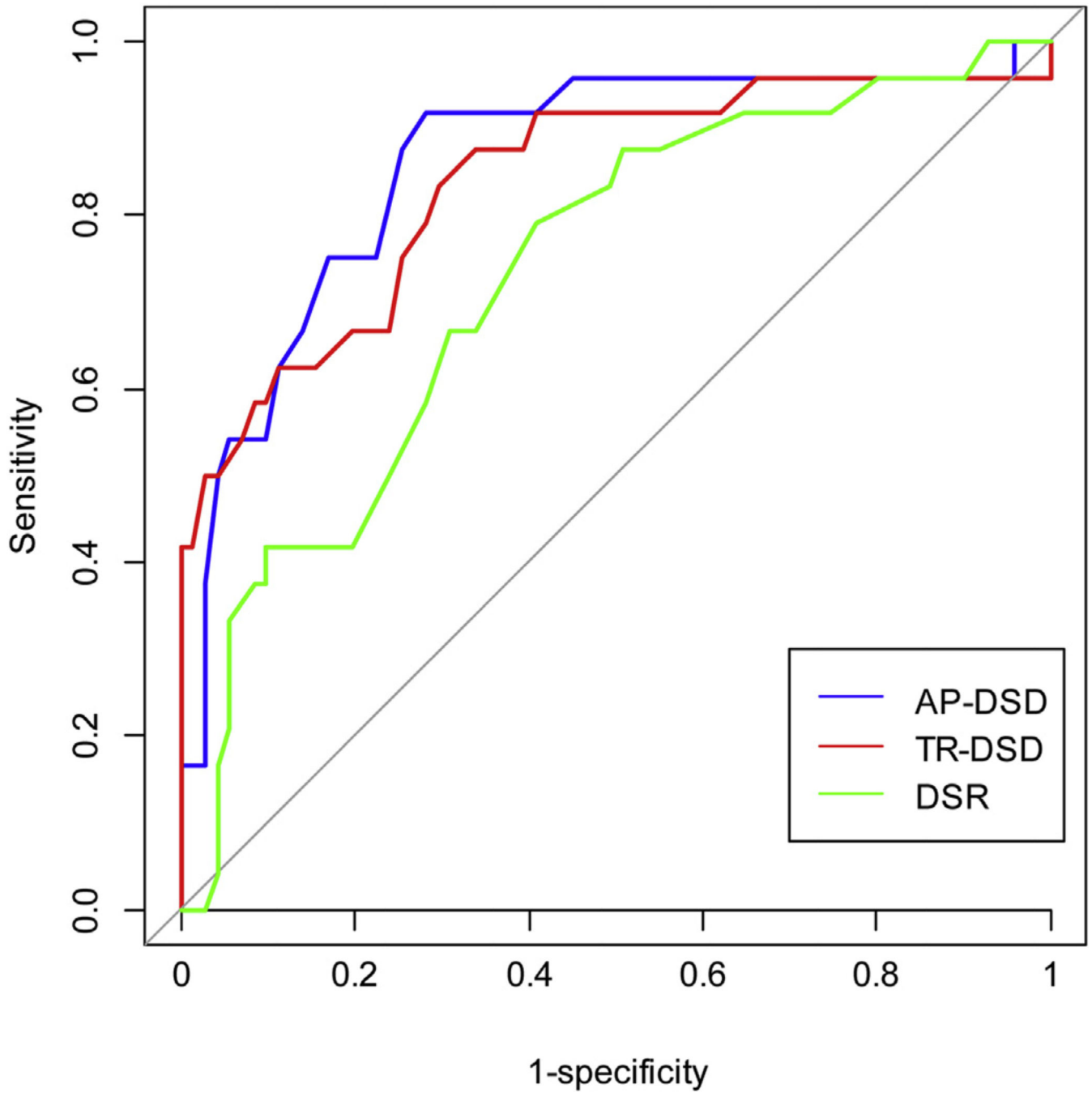

Figure 4.

Unadjusted ROC curves of L1–L5 (average) AP-DSD, TR-DSD, and DSR (reader 1). L1–L5 (average) AP-DSD (blue; $p < 0.01$) and TR-DSD (red; $p = 0.04$) discriminate Marfan from control subjects better than L1–L5 (average) DSR (green). ROC curves are unadjusted for gender, age, height, and race. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1

L1–L5 (average) anterior-posterior (AP) dural sac diameter (DSD) and transverse (TR) DSD by gender for initial controls (reader 1).

	Female (*n* = 26)	Male (*n* = 27)	*p*-Value
L1–L5 AP-DSD (cm)	1.38 + 0.15	1.35 + 0.12	0.43
L1–L5 TR-DSD (cm)	1.86 + 0.20	1.89 + 0.14	0.40

Data are means + standard deviation.

Table 2

L1–L5 (average) anterior-posterior (AP) dural sac diameter (DSD) and transverse (TR) DSD by control subject group (reader 1).

	Initial controls (*n* = 53)	**Validation controls (*n* = 19)**	***p*-Value**	**All controls (*n* = 72)**
L1–L5 AP-DSD (cm)	1.37 + 0.13	1.42 + 0.18	0.81	1.38 + 0.15
L1–L5 TR-DSD (cm)	1.88 + 0.17	1.91 + 0.18	0.37	1.89 + 0.17

Data are means + standard deviation.

Table 3

Measurements of L1–L5 (average) for anterior-posterior (AP) dural sac diameter (DSD) and transverse (TR) DSD, AP-vertebral body diameter (VBD), and calculated dural sac ratio (DSR) in controls and Marfan patients (reader 1).

		Control (*n* = 72) Female = 35 Male = 37	**Marfan (*n* = 24) Female = 10 Male = 14**	***p*-Value**
AP-DSD (cm)	Female & male	1.38 + 0.15	1.61 + 0.17	5.9×10^{-9}
TR-DSD (cm)	Female & male	1.89 + 0.17	2.22 + 0.32	6.5×10^{-9}
AP-VBD (cm)	Female	2.78 + 0.21	2.91 + 0.19	
	Male	3.11 + 0.23	3.14 + 0.25	
DSR (AP-DSD/AP-VBD)	Female	0.51 + 0.08	0.56 + 0.06	0.07
	Male	0.44 + 0.05	0.51 + 0.06	8.2×10^{-5}

Data are means + standard deviation.

Table 4

Unadjusted AUC values of individual vertebral levels and L1–L5 (average) for anterior-posterior (AP) dural sac diameter (DSD) and transverse (TR) DSD, and dural sac ratio (DSR) for determining Marfan diagnosis (reader 1).

	L1	L2	L3	L4	L5	L1–L5 (average)
AP-DSD	0.68	0.8	0.85	0.81	0.86	0.86[a]
TR-DSD	0.71	0.74	0.79	0.82	0.86	0.84[b]
DSR	0.56	0.67	0.74	0.69	0.79	0.73

No significant difference between AUC values of L1–L5 (average) AP-DSD and TR-DSD ($p = 0.51$).

[a] $p < 0.01$ as compared to DSR.

[b] $p = 0.04$ as compared to DSR.