Estimation of normal computed tomography measurements for the upper cervical spine in the pediatric age group

Clinical article

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Object. Upper cervical spine injuries in the pediatric age group have been recognized as extremely unstable from ligamentous disruption and as potentially lethal. Few measurement norms have been published for the pediatric upper cervical spine to help diagnose this pathological state. Instead, adult measurement techniques and results are usually applied inappropriately to children. The authors propose using high-resolution reconstructed CT scans to define a range of normal for a collection of selected upper cervical spine measurements in the pediatric age group.

Methods. Sagittal and coronal reformatted images were obtained from thin axial CT scans obtained in 42 children (< 18 years) in a 2-month period. There were 25 boys and 17 girls. The mean age was 100.9 months (range 1–214 months). Six CT scans were obtained for nontrauma indications, and 36 were obtained as part of a trauma protocol and later cleared for cervical spine injury. Six straightforward and direct linear distances—basion-dental interval (BDI); atlantodental interval (ADI); posterior atlantodental interval (PADI); right and left lateral mass interval (LMI); right and left craniocervical interval (CCI); and prevertebral soft-tissue thickness at C-2—that minimized logistical and technical distortions were measured and recorded. Statistical analysis including interobserver agreement, age stratification, and sex differences was performed for each of the 6 measurements.

Results. The mean ADI was 2.25 ± 0.24 mm (±SD), the mean PADI was 18.3 ± 0.07 mm, the mean BDI was 7.28 ± 0.10 mm, and the mean prevertebral soft tissue width at C-2 was 4.45 ± 0.43 mm. The overall mean CCI was 2.38 ± 0.44 mm, and the overall mean LMI was 2.91 ± 0.49 mm. Linear regression analysis demonstrated statistically significant age effects for PADI (increased 0.02 mm/month), BDI (decreased 0.02 mm/month), and CCI (decreased 0.01 mm/month). Similarly significant effects were found for sex; females demonstrated on average a smaller CCI by 0.26 mm and a smaller PADI by 2.12 mm. Moderate to high interrater reliability was demonstrated across all parameters.

Conclusions. Age-dependent and age-independent normal CT measurements of the upper cervical spine will help to differentiate physiological and pathological states in children. The BDI appears to change significantly with age but not sex; on the other hand, the LMI and ADI appear to be age-independent measures. This preliminary study suggests acceptable levels of interrater reliability, and further expanded study will aim to validate these measurements to produce a profile of normal upper cervical spine measurements in children.

Key Words • pediatric spine • cervical spine • occipitoatlantoaxial spine • computed tomography

The craniocervical junction is susceptible to trauma resulting from exaggerated movement in any of the normal directions of motion: vertical, anteroposterior, and rotation. Imaging of the upper cervical spine after trauma is crucial for injury detection and anatomical description, given the potential for dire neurological consequences of a missed bone or disco-ligamentous injury.14,19,24,38 Because of the rarity of occipitocervical trauma in children, clinicians may not be well versed in the normal spatial relationships between the occiput, atlas, and
axis. Hypermobility from ligamentous laxity, epiphyseal variation, unique vertebral architecture, and incomplete ossification of the pediatric cervical spine may further cloud the diagnosis of a pathological state after trauma.

Adult criteria for instability following upper cervical spine trauma have been inappropriately extrapolated to that of the pediatric age group, possibly because of the familiarity with their radiographic measurement techniques. These measurements, although accurate in defining relationships between anatomical structures, do not take into account the complexity and peculiarity of the pediatric spine, especially in very young children. In recent years, many published reports of new protocols devised to assess the pediatric cervical spine have been vague in their criteria or have used adult parameters. This study aims to develop normal values, in a very preliminary fashion, for selected anatomical relationships in the pediatric upper cervical spine. Using these early numbers as a stepping stone, along with studies of their reliability, we hope to begin the process of establishing truly valid, reliable normal estimates for these measurements in children. The value of such population-specific parameters cannot be understated.

Methods

Patient Group

During a 2-month study period, 42 consecutive patients (25 boys and 17 girls; mean age 100.9 months, range 1–214 months) who had undergone CT scanning of the cervical spine with coronal and sagittal reconstructions at Texas Children’s Hospital were reviewed. Computed tomography scans were read by a group of independent fellowship-trained pediatric neuroradiologists. Only those patients with “normal” CT scans were included; those with a history of trivial trauma were included if clinical follow-up showed no delayed signs or symptoms of upper cervical spine injury, such as neurological deficit, persistent neck pain, or abnormal repeat plain radiographs. This group was chosen given the otherwise healthy nature of these children and the anticipated future use of these data in excluding cervical spine injury.

Technique of CT of the Cervical Spine

All CT examinations were performed using a 64-slice Lightspeed VCT with Halo detector (Model No. 5124069-5, General Electric Medical Systems) and included images of the skull base and C1–2 junction. Helically acquired axial images were reconstructed in 3 dimensions (2 mm thick, 2-mm intervals) in the coronal and sagittal planes. Linear measurements were obtained with the standard measurement palette in our picture archiving and communications system (PACS) (Philips iSite) and were automatically rounded to the nearest 0.1 mm.

On midsagittal images of the skull base, the distance between the basion and the odontoid process of C-2 was defined as the basion-dental interval (BDI) (Fig. 1). The distance between the anterior arch of C-1 and the odontoid process was defined as the atlantodental interval (ADI), and the distance between the odontoid process and the posterior arch of C-1 was defined as the spinal canal width, or posterior ADI (PADI). The width of the prevertebral soft-tissue stripe at the level of C-2 was defined as the narrowest distance between the trachea and C-2 vertebral body.

On coronal images, the widest distance between the lateral masses of C-1 and C-2 was measured in a plane perpendicular to the joint space on the right and left sides, respectively, and defined as the lateral mass interval (LMI) (Fig. 2).

We calculated the CCI by drawing a line perpendicular to the articular surfaces of the occipital condyle and the lateral mass of C-1. This line was drawn at the center of the articulation by correlating the sagittal and coronal images. Measurements of the CCI were performed bilaterally (Fig. 2). Each measurement was taken and recorded by 2 different authors (K.S. and A.J.) according to the aforementioned set protocols for how to measure each of these distances.

Statistical Analysis

Descriptive statistics, including measures of central tendency, were calculated for all measured parameters as well as selected patient demographics. Linear regression analysis was performed to examine the relationship of measured parameters to patient age and sex. The upper tolerance limit (UTL), the maximum value calculated to include 95% of the population with 99% certainty, was derived to represent the upper limit of normal for each parameter. For the PADI the lower tolerance limit was calculated, as measured values smaller than this limit could be deleterious to patients. Intrarater and interrater reliability are represented by the intraclass correlation coef-

Fig. 1. Midsagittal reconstructed CT scan of the pediatric upper cervical spine demonstrating the BDI, ADI, PADI, and prevertebral soft-tissue width at C-2.
Normative CT measurements in children

Fig. 2. Coronal reconstructed CT image defining the LMI and CCI.

Three variables were found to have a statistically significant independent relationship with patient age. The PADI increased by 0.01 mm for every month increase in patient age (p = 0.0002), whereas the BDI decreased by 0.02 mm each month (p < 0.0001) and the CCI decreased by 0.01 mm each month (p < 0.0001). Scatter plots and regression equations outlining the relationships between age and the PADI, BDI, and CCI are demonstrated in Figs. 3, 4, and 5, respectively. Similarly, the PADI and CCI demonstrated statistically significant relationships with patient sex; on average, the PADI was found to be smaller in females by 2.12 mm (p < 0.0004) and the CCI was smaller in females by an average of 0.26 mm (p = 0.05). All other measured parameters were found to be age and sex independent.

Interrater reliability, as suggested by the ICC, was found to be moderate to high for all parameters (Table 3). Of these, the PADI and BDI were found to have the most reliable measurements between observers. The CVME ranged from 0.09 for the BDI to 0.23 for the PADI. For the latter measurement particularly, this suggested some discordance in the reliability estimates. However, this may

### Results

There were 42 patients (25 males) who met the inclusion criteria for the study. The mean age was 100.9 ± 66.5 months (± SD), with a range of 1–214 months. Table 1 lists the reasons for CT acquisition in the study population as listed in the hospital records. Thirty-six of 42 scans were obtained for traumatic indications; however, all scans were read as normal by the reporting pediatric neuroradiologist.

The average, standard deviation, and UTL for each measured parameter in the study are listed in Table 2. The lower tolerance limit for the PADI is listed in Table 2.

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**TABLE 1: Indications for acquisition of cervical spine CT scans as listed in the hospital record**

<table>
<thead>
<tr>
<th>Reason for CT Scan</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV accident</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>bicycle accident</td>
<td>2 (4.8)</td>
</tr>
<tr>
<td>brachial plexus injury</td>
<td>2 (4.8)</td>
</tr>
<tr>
<td>C-2 osteoid osteoma</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>fall</td>
<td>10 (23.8)</td>
</tr>
<tr>
<td>garage door</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>hand numbness</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>MVA</td>
<td>3 (7.1)</td>
</tr>
<tr>
<td>near drowning</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>neck pain</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>posterior fossa tumor</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>television tipover</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>torticollis</td>
<td>2 (4.8)</td>
</tr>
<tr>
<td>trauma</td>
<td>15 (35.7)</td>
</tr>
</tbody>
</table>

* ATV = all-terrain vehicle; MVA = motor vehicle accident.

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**TABLE 2: Mean, standard deviation, and upper tolerance limit for measured cervical spine parameters**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (mm)</th>
<th>SD (mm)</th>
<th>95% UTL (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADI</td>
<td>2.25</td>
<td>0.244</td>
<td>2.76</td>
</tr>
<tr>
<td>PADI†</td>
<td>18.3</td>
<td>0.065</td>
<td>18.16</td>
</tr>
<tr>
<td>BDI</td>
<td>7.28</td>
<td>0.098</td>
<td>7.49</td>
</tr>
<tr>
<td>C-2 prevertebral soft tissue width</td>
<td>4.45</td>
<td>0.429</td>
<td>5.35</td>
</tr>
<tr>
<td>LMI</td>
<td>2.91</td>
<td>0.487</td>
<td>3.86</td>
</tr>
<tr>
<td>CCI</td>
<td>2.38</td>
<td>0.441</td>
<td>3.24</td>
</tr>
</tbody>
</table>

* UTL = upper tolerance limit.
† Lower tolerance limit applies for this measurement.
be explained by the properties of the reliability estimates themselves. The CV was found to be high both within each observer as well as overall between observers, suggesting considerable dispersion of each parameter within the data set. This is not surprising given the heterogeneity of the data set and preliminary nature of the study.

The Bland-Altman limits of agreement for each measured relationship are also listed in the last column of Table 3. These numbers represent the mean difference between the 2 observers and the 95% confidence interval, or limits of agreement as it is known in this context, of this difference. This analysis was entirely exploratory in nature and was conducted without prior hypotheses, which was a requirement of this method. Therefore, no firm conclusions regarding clinical applicability can be drawn from this.

Discussion

Few measurement norms have been established for the pediatric upper cervical spine based on CT scans. Adult injury thresholds and measurement techniques have been applied to children, failing to take into account differences in configuration and biomechanics between the adult and pediatric spines. A recent study examining the blinded assessment of atlantooccipital dissociation blended adult and pediatric patients and used measurement criteria published in the 1950s. In many case se-
ries, it is difficult to discern what proportion of patients may have suffered ligamentous injuries in which the previously mentioned spatial relationships are disrupted, as authors often synonymize fracture with spinal injury while ignoring these other possibilities.7,12 Moreover, some measurements defining the upper range of normal have been based on analysis of pathological studies instead of “normal” imaging.37

CT Imaging

Although many studies describing different methods of clearing the cervical spine in children have been previously published, no standard of care exists.2,4,21,28,34,36,39 Clearing the spine of suspected injury is especially difficult in children because spine injuries are uncommon in this age group, children are often noncommunicative, and many normal variants are found in the pediatric spine, such as pseudosubluxation, synchondroses, and incomplete ossification. Recent studies have expanded the use of clinical decision rules, such as NEXUS and the Canadian C-spine Rule, to the pediatric population. However, these simply aid in the acquisition of imaging and not its subsequent interpretation.11

Establishment of CT-based protocols to clear the pediatric spine of suspected injury has been shown to decrease the time required to accomplish clearance and reduce the number of missed injuries.6,8,9,13,14,21–23,29 Furthermore, present measurement techniques are based on bony landmarks, which may be better visualized on CT scans over plain radiographs and MR images.

**BDI**

The BDI has been used to identify occipitoatlantal dislocation.23,41 Harris et al. measured the BDI on lateral radiographs obtained in 400 normal adults.17 The BDI did not exceed 12 mm in 95% of adults. This range is slightly greater than that observed in a normative patient population based on CT scans.

Gonzalez et al. reported that BDI values greater than 9 mm from sagittal CT reconstructions likely indicate the possibility of traumatic disruption of the craniocervical junction.15 As mentioned previously, CT may represent a more accurate and sensitive measure of BDI than plain radiographs.

Few pediatric patients were included in the aforementioned studies.15,27,23,41 Since the tip of the odontoid does not ossify until the age of 12 years, applying the adult definition of BDI to the immature pediatric cervical spine may result in an overdiagnosis of distraction injuries and a high incidence of false-positive results.

**TABLE 3: Interrater reliability estimates for measured cervical spine parameters**

<table>
<thead>
<tr>
<th>Variable</th>
<th>ICC</th>
<th>CV</th>
<th>CVME</th>
<th>Mean Bias (95% limits of agreement) (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADI</td>
<td>0.457</td>
<td>0.25</td>
<td>0.16</td>
<td>−0.35 (−1.39 to 0.69)</td>
</tr>
<tr>
<td>PADI</td>
<td>0.963</td>
<td>0.12</td>
<td>0.23</td>
<td>−0.22 (−1.39 to 0.95)</td>
</tr>
<tr>
<td>BDI</td>
<td>0.914</td>
<td>0.32</td>
<td>0.09</td>
<td>−0.14 (−2.1 to 1.78)</td>
</tr>
<tr>
<td>C-2 prevertebral soft-tissue width</td>
<td>0.599</td>
<td>0.32</td>
<td>0.19</td>
<td>−0.61 (−2.95 to 1.73)</td>
</tr>
<tr>
<td>LMI</td>
<td>0.423</td>
<td>0.25</td>
<td>0.11</td>
<td>−0.69 (−1.61 to 0.23)</td>
</tr>
<tr>
<td>CCI</td>
<td>0.526</td>
<td>0.34</td>
<td>0.16</td>
<td>−0.62 (−1.69 to 0.44)</td>
</tr>
</tbody>
</table>
In our study, the 95% UTL for BDI was 7.49 mm, with good interrater reliability as measured by both ICC and CV$_{ME}$. A statistically significant age effect was found, with BDI decreasing by 0.02 mm for every month increase in patient age, which is likely explained by age-dependent ossification of the tip of the odontoid. The upper limit of BDI suggested in this study is significantly smaller than the value currently used in clinical practice. This should be interpreted with caution given the small sample size of the study and heterogeneous age group, particularly given the potential for an age-dependent effect. These results do, however, provide an anchor for further study.

**ADI and PADI**

Measurement of the ADI is the most common method for evaluating stability at the atlantoaxial joint and the integrity of the transverse ligament. Reported maximum distances for the so-called normal ADI in children are 3–6 mm on plain radiographs. Any ADI measurement greater than 6 mm in children suggests ligamentous rupture.

The PADI represents the anteroposterior diameter of the spinal canal at this level with a normal value of 14 mm or more. It has been shown to be a useful prognosticator in adult patients with rheumatoid arthritis. However, it has not been validated in the same manner for traumatic pediatric atlantoaxial instability.

The results of our study suggest, at least on a preliminary basis, that the normal ADI value of 3 mm currently used is likely valid as a clinical indicator of instability. The 95% UTL for ADI in our study was 2.76 mm. Interrater reliability for this parameter (ICC = 0.457) was not as high as in the measurement of the BDI. However, this may be explained by the potential for larger measurement error in relation to the true variability of ADI values; a broad range of ADI values is more difficult to obtain given the small and tight range under which it normally exists. The lack of age or sex effect corroborates this invariance, particularly in the setting of such a heterogeneous population. The CV$_{ME}$ of 0.16 supports the potential for larger measurement error when compared with other measured parameters.

The interpretation of PADI is more problematic, largely given its uncommon measurement and application in this setting. The 95% lower tolerance limit for PADI was 18.16 mm, suggesting that clinicians may expect a higher canal diameter than the previously established normal threshold of 14 mm. The derivation of normal values will need to account for the potential age and sex dependence identified in this study, but also may benefit from the calculation of the lower tolerance limit to help clinicians determine a minimum value below which cord compromise could be expected.

**LMI**

The LMI is useful in the diagnosis of vertical C1–2 distraction injuries. Few pediatric patients were included in the CT-based study that established an LMI range between 0.7 mm and 2.6 mm for 95% of healthy individuals. Because of this, the normative data from that study are not necessarily applicable to children. Although the C1–2 interspace narrows with age, the change is relatively small in proportion to the width of the interspace indicating a weak inverse correlation with age.

The upper limit of the normal LMI, according to our study measuring 3.86 mm, may be larger than that suggested by previous literature. Similar to ADI, this was neither age nor sex dependent in keeping with previous reports. The ICC for LMI was the lowest among all of the variables, potentially explained by the relative infrequency by which it is measured by clinicians, leading to increased measurement error. The CV$_{ME}$ was only 0.11, suggesting that the error that contributed to the low ICC likely applied to both observers.

**CCI**

The normal occipital condyle–C1 joint in children 0–18 years is defined by a mean CCI of 1.28 mm in 89 pediatric patients examined. Measurements were taken from reformatted CTs. The CCI and left-right symmetry do not appear to change significantly with age. Taking into account “normal” stresses to the pediatric spine such as nondisruptive distraction, Pang et al. set an arbitrary discriminator of 4 mm between normal and atlantooccipital dislocation.

Our study, in a similar fashion to ADI, suggests that 4 mm may serve as a useful discriminator for atlantooccipital dissociation. The 95% UTL was 3.24 mm; however, there was a significant age-dependent effect with CCI decreasing by 0.01 mm for every month increase in patient age. This contradicts the conclusions of Pang et al., and further study will be necessary to confirm this finding in larger study populations. Interrater reliability for the CCI was moderate, likely for many of the same reasons previously discussed. A valid and reliable value for the CCI will serve as a useful adjunct to BDI in the diagnosis of vertical distraction injuries.

**Prevertebral Soft-Tissue Width**

Soft-tissue swelling is an indirect indicator of significant trauma, especially when the soft-tissue swelling is above the epiglottis. In adults, the distance between the tracheal air column and anterior aspect of the vertebral body should be no greater than 6 mm at C-2 or 22 mm at C-6 on plain radiographs. The same thresholds have been applied to children. However, in pediatric patients, widening of the prevertebral soft tissues may be a normal finding related to expiration.

The prevertebral soft-tissue width at C-2 may be close to the previously accepted value of 6 mm. In our study, the 95% UTL was 5.35 mm, and not surprisingly, this parameter was found to be both age and sex independent. Interrater reliability was moderate, and with measurement error diminished given significant clinician experience with this variable.

**Study Limitations and Analytical Caveats**

There are several limitations to this study related both to pediatric physiology and the exploratory nature of the study. Like the study of Pang et al., our study contains

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only static data. In young children, the ligaments and muscles are known to be elastic and yielding, allowing wide variability in measurements even under “normal” physiological conditions. The use of dynamic imaging, with appropriate adjustment of measured parameters, may help to overcome this limitation.

The exploratory nature of this study introduces some important caveats into the statistical analysis. A convenience sample of patients evaluated over a 2-month period was included, and this resulted in a sample size much too small upon which to derive definitive normal values. Less intuitive is the effect of small sample size on the variability and measurement error. With large enough sample sizes, the sample mean can be assumed to approach the population mean with concomitant decreases in the variation, or standard deviation, of the data set. As such, the calculated tolerance limit can more credibly be thought to reflect a value that represents the prespecified portion of the population with its accompanying certainty.

Estimates of interrater reliability may also be diminished by inflation of the measurement error in relation to true values. The ICC can be thought of as the ratio of the true variability in the data set to the sum of the true variability and measurement error. The last of these is an immeasurable value and is expected to decrease with observer practice resulting from increasing sample size. Measurements with small absolute variation in their values, such as the ADI, CCI, and LMI, may be particularly susceptible, and larger sample sizes are therefore necessary to minimize the influence of measurement error and maximize interrater reliability. The CV_ME was used in this study as a surrogate of interrater reliability; however, its initial reported use was in the measurement of test-retest reliability. In measurements where the CV_ME and ICC are discordant, it may reflect an unmeasured difference in the observers that is not accounted for by the calculation of the former coefficient. As such, the interrater reliability may be underestimated. Finally, the Bland-Altman limits of agreement method was used to examine the agreement between 2 measurement methods or 2 observers. The resulting mean bias, or the mean difference between methods, and their corresponding 95% limits of agreement, can be used to establish the robustness of a measurement method. Use of this information in the clinical context requires, however, an a priori decision about how large of a difference one accepts to consider the methods equal. Given the exploratory nature of this study, we had not made such a decision and we present the Bland-Altman limits of agreement as the basis for further study.

We also cannot overlook the effects of population heterogeneity. The CV, defined earlier, revealed significant dispersion of the data particularly for the BDI and CCI. Both of these parameters showed significant age effects, and the increased CV reflects that given its calculation does not adjust for the influence of covariates. As such, although we report the CV as part of this study, we appreciate that it does not provide a reliable estimate of measurement precision. Additionally, while it may be feasible to use the provided linear regression equations in Fig. 3 to determine clinically relevant age-appropriate means for the BDI, CCI, and PADI, we advise caution in such application due to our small sample size and population heterogeneity. A study with a larger sample size, in which the population could potentially be divided into more homogeneous age subgroups, would allow appropriate assessment of our ability to precisely collect these measurements.

Finally, measurements for this study were performed by 2 neurorsurgeons, and this could be optimized by recruiting more neuroradiologists to examine scans and collect data. In routine practice, it is these individuals who provide definitive interpretation of cervical spine imaging and enrolling them in a study like this one will undoubtedly improve its external validity.

Future Directions

Further stepwise study will be necessary to definitively establish norms for these upper cervical spine measurements. A small convenience sample from a single institution makes it difficult to broadly apply these data, but it provides a starting point for further study. A multicenter study of consecutive pediatric patients with normal CT scans should be conducted. Standardized patient positioning, image acquisition, and measurement techniques will be integral. Recruitment should also be stratified by age to ensure that sufficient patients are included within each age group. Establishing such normal values will consequently permit the comparison of these values against measurements in patients with known cervical spine injury through a known groups validation process. That validation step would represent the final stage of establishing normal values for parameters in the upper cervical spine in children. As the routine use of MRI increases for this patient population, measured parameters established using CT scanning could possibly be validated using MRI.

Conclusions

Defining normal CT measurements of the pediatric upper cervical spine is important for the recognition and diagnosis of potentially unstable and neurologically devastating injuries in this region. We present preliminary estimates of upper normal values for several anatomical relationships between components of the pediatric upper cervical spine. There is significant change in the PADI, BDI, and CCI with age between birth and 18 years, whereas other parameters appear to be age independent. The PADI and CCI appear to be significantly smaller in females compared with males of similar age. Measurement of the PADI and BDI seems to be the most reliable among independent observers. Further study must include the validation of these derived values in a larger and geographically diverse patient cohort. Additionally, the ability of these measurements to discriminate between injured and normal spines will need systematic study.

Nonetheless, clinicians must remember that there is no single radiologically diagnostic criterion or radiological protocol that is failure-proof for the identification of pediatric upper cervical spine injury. These CT measure-
ments serve only as an aid to the clinician. Diagnosis must remain an integration of clinical data with various supporting radiographic measurements.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Jea. Acquisition of data: Jea. Analysis and interpretation of data: Jea, Vachhrajani, Sen. Drafting the article: Jea, Vachhrajani. Critically revising the article: Jea, Vachhrajani, Sen, Satyan, Kulkarni. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Jea. Statistical analysis: Sen.

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