Advanced Vertebral Fracture Among Newly Diagnosed Children With Acute Lymphoblastic Leukemia: Results of the Canadian Steroid-Associated Osteoporosis in the Pediatric Population (STOPP) Research Program

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ABSTRACT: Vertebral compression is a serious complication of childhood acute lymphoblastic leukemia (ALL). The prevalence and pattern of vertebral fractures, as well as their relationship to BMD and other clinical indices, have not been systematically studied. We evaluated spine health in 186 newly diagnosed children (median age, 5.3 yr; 108 boys) with ALL (precursor B cell: N = 167; T cell: N = 19) who were enrolled in a national bone health research program. Patients were assessed within 30 days of diagnosis by lateral thoraco-lumbar spine radiograph, bone age (also used for metacarpal morphometry), and BMD. Vertebral morphometry was carried out by the Genant semiquantitative method. Twenty-nine patients (16%) had a total of 75 grade 1 or higher prevalent vertebral compression fractures (53 thoracic, 71%; 22 lumbar). Grade 1 fractures as the worst grade were present in 14 children (48%), 9 patients (31%) had grade 2 fractures, and 6 children (21%) had grade 3 fractures. The distribution of spine fracture was bimodal, with most occurring in the midthoracic and thoraco-lumbar regions. Children with grade 1 or higher vertebral compression had reduced lumbar spine (LS) areal BMD Z-scores compared with those without (mean ± SD, 2.1 ± 1.5 versus 1.1 ± 1.2; p < 0.001). LS BMD Z-score, second metacarpal percent cortical area Z-score, and back pain were associated with increased odds for fracture. For every 1 SD reduction in LS BMD Z-score, the odds for fracture increased by 80% (95% CI: 10–193%); the presence of back pain had an OR of 4.7 (95% CI: 1.5–14.5). These results show that vertebral compression is an under-recognized complication of newly diagnosed ALL. Whether the fractures will resolve through bone growth during or after leukemia chemotherapy remains to be determined.

Bone morbidity in childhood ALL has long been studied through retrospective review of radiographs and found to be associated with the leukemic process. Bone lesions have been apparent at the time of diagnosis and are purportedly more frequent in the appendicular than in the axial skeleton. At appendicular sites, transverse metaphyseal radiolucencies, lytic and osteosclerotic lesions, and periosteal lifting have been observed in numerous reports. Vertebral fractures have also been reported to occur in children with newly diagnosed ALL and have typically been considered a rare manifestation of the disease. A large series of almost 1500 children who were evaluated for vertebral compression on routine chest radiographs at the

INTRODUCTION

A CUTE LYMPHOBLASTIC LEUKEMIA (ALL), a malignant disorder of lymphoid progenitor cells, is the most common form of childhood cancer. Fortunately, continued progress in the development of effective treatment regimes for ALL has led to a cure rate of >80%. As cure rates improve, the sequelae attributed to the disease or its treatment are increasingly recognized, with skeletal health having emerged as an important short- and long-term concern for childhood ALL survivors.
time of ALL diagnosis found a vertebral fracture prevalence of <2%.(11) However, the specific methodology directing the vertebral fracture assessment, the pattern of vertebral fractures in the lumbar and thoracic spine, and the relationship between vertebral fractures and other skeletal parameters such as BMD were not reported.

Therefore, the purpose of this report was to carry out a prospective evaluation of the prevalence, location, severity, and morphology of thoracic and lumbar vertebral fractures in a large, multicenter cohort of children with newly diagnosed ALL. We further sought to determine the relationship between vertebral fractures and relevant clinical parameters such as the characteristics of the ALL, frequency of back pain, spine BMD, and cortical thickness.

**MATERIALS AND METHODS**

**Patients and study design**

Children and adolescents enrolled in the study were recruited through the Canadian Steroid-Associated Osteoporosis in the Pediatric Population (STOPP) research initiative, a national pediatric bone health research program funded by the Canadian Institutes of Health Research to study bone health and determinants of bone morbidity in children with chronic illnesses. Patients from 1 mo to 17 yr of age were enrolled in the study (N = 186) between January 1, 2005 and December 31, 2007 in 10 participating tertiary care children’s hospitals across Canada. Patients were studied within 30 days of chemotherapy initiation for the treatment of ALL. Children with newly diagnosed ALL were excluded if the study procedures could not be carried out within 30 days of chemotherapy initiation, if they had received prior therapy with medication to treat osteoporosis, if they had received prior treatment with calcium and/or vitamin D supplementation that exceeded the Dietary Reference Intake for age,(12) or if they were pregnant or menstruating and unwilling to use a medically approved method of contraception during the course of the study. Patients were also excluded from the study if they had received, in the 12 mo preceding enrollment, intravenous or oral glucocorticoids for >14 consecutive days before initiation of chemotherapy for the treatment of the leukemia. The study was approved by the Research Ethics Boards in each of the participating institutions, and informed consent and/or assent, as appropriate, was obtained before study enrollment.

**Clinical data**

Standard demographic data including age, ethnicity, and ALL subdiagnosis (precursor B or T cell) were recorded. All patients were treated according to the Children’s Oncology Group protocols (nine sites) or the Dana Farber Cancer Institute protocols (one site). The children were assigned to a leukemia risk category for relapse (high or standard risk) as per the National Cancer Institute risk criteria. Height was measured using a regularly calibrated stadiometer by a pediatric nurse or research associate. Measurements were taken three times, and the average was recorded. Infants and children unable to stand were measured in the supine position; others were measured standing. Weight was determined using either a digital or mechanical scale. Height and weight raw values were transformed into age- and sex-matched Z-scores according to the U.S. CDC National Center for Health Statistics normative database.(13) Pubertal staging was carried out according to the methods of Marshall and Tanner.(14,15) The presence or absence of back pain at the time of diagnosis was recorded.

**Bone densitometry**

BMD was measured in the anterior-posterior direction at the lumbar spine (L₁–L₄) using either Hologic machines (QDR 4500, three centers; Discovery, two centers; Delphi, one center) or Lunar Prodigy (four centers). Machines were cross-calibrated using a spine phantom that was circulated before the study, and measurements were converted to Hologic units. LS BMD results were transformed to age- and sex-specific Z-scores using the Hologic 12.4 normative database. In vivo precision was available in 9 of 10 centers and ranged from 0.003 to 0.0173 g/cm².

**Bone age assessment**

Radiographs of the left hand and wrist for bone age were assessed independently by two pediatric radiologists (N.S., M.M.) according to Greulich and Pyle.(16) If results for the two examiners were within 12 mo of each other, the average of the two readings was used. For results that differed by >12 mo (n = 3), a third reader (L.M.W.), blinded to the results of the first two readings, adjudicated the discrepant reports. The intraclass correlation coefficient, which assessed interobserver reliability, was 0.992 (95% CI: 0.989–0.994) between the two initial examiners. The radiographs were also evaluated for the possibility of rickets.

**Hand morphometry**

From the hand radiographs used for bone age determination, a single observer measured second metacarpal length, midshaft periosteal diameter, and inner diameter.(17) From these measurements, the following indices were derived: combined cortical thickness, cortical area, percent cortical area, and inner diameter area. Measured and derived indices were converted into age- and sex-matched Z-scores as previously described.(18) The intra-observer reliability scores assessed by intraclass correlation coefficient for hand morphometry measurements were as follows: 1.0 (95% CI: 0.999–1.0), 0.99 (95% CI: 0.986–0.997), and 0.89 (95% CI: 0.777–0.945) for metacarpal length, outer diameter, and inner diameter, respectively.

**Vertebral morphometry**

Lateral spine radiographs were taken on one or two cassettes, according to the size of the child. Vertebral fracture assessment was carried out independently by two radiologists (N.S., M.M.) from T₄ to L₄ according to the Genant semiquantitative(19) method. Discrepancies in specific vertebral body readings between the first two radiologists were resolved by a third expert radiologist (B.L.), who was blinded to the results of the other two. The
interobserver reliability for the first two readers, as assessed by Cohen’s \( \kappa \), was 0.44 (95% CI: 0.28, 0.59) for fracture defined as grades 1, 2, or 3 and 0.66 (95% CI: 0.46, 0.87) for fracture defined as grades 2 or 3.

Genant semiquantitative analyses: The Genant semiquantitative method for vertebral morphometry, the primary spine film assessment method for this study, was performed in the following manner: vertebral bodies were first assigned a severity score: grade 0 (normal), grade 1 (mild), grade 2 (moderate), and grade 3 (severe). The morphometric grading corresponded to the extent of the reduction in height ratios when the anterior vertebral height was compared with the posterior height (defined as a wedge fracture), the middle height to the posterior height (biconcave fracture), and the posterior height to the posterior height of the adjacent vertebral bodies (crush fracture). The scores corresponded to the following reduction in height ratios: grade 0, 20% or less; grade 1, >20–25%; grade 2, >25–40%; Grade 3, >40%. Grade 0 was considered to be normal, whereas grade 1, 2, or 3 was considered to be a fracture. Figures 1A–1C show examples of mild, moderate, and severe fractures that were representative of the types of fractures assigned the three severity scores in this study. Minimal physiological rounding of vertebral bodies in the midthoracic region of the spine, as can be seen in normal children,\(^{20}\) was assigned a grade 0 score.

Algorithm-based qualitative analyses: As a subanalysis, lateral spine radiographs were also assessed for radiological signs of fracture according to the algorithm-based qualitative (ABQ) method recently described,\(^{21}\) including loss of endplate parallelism, endplate depression, and anterior cortical buckling. The ABQ analysis was carried out by a single radiology expert (B.L.). Figures 1D–1F provide examples of typical radiological signs of fractures observed in this cohort. (D) Five-year-old girl with loss of endplate parallelism on the T9 inferior endplate. (E) Five-year-old boy with anterior cortical buckling at L2. (F) Eight-year-old boy with endplate interruption at L2.

Physical activity assessment: the habitual activity estimation scale: The habitual activity estimation scale (HAES) was used to determine the amount of time spent in physical activity. The HAES is a self/proxy report that provides an estimation of the intensity and duration of physical activity and has been validated in the pediatric setting.\(^{22,23}\) Activity was reported for both a typical school day and weekend day as an average representation of the activity level in the previous 3 mo as follows: inactive (e.g., lying down), somewhat inactive (e.g., sitting), somewhat active (e.g., walking), and active (e.g., running). The two inactive categories reflected largely non–weight-bearing, sedentary activities, whereas the two active categories were largely weight-bearing and required whole body movements. Reporting the percentage of time spent in each category over four time segments defined by wakeup, meals, and bedtime allowed the duration spent in each intensity level to be determined. Total inactive and total active times were determined by summing the two inactive and the two active categories for each of the weekend and weekday reports.

Statistical analyses: Analyses were conducted using SPSS 16.0 (SPSS, Chicago, IL, USA) and CIA 2.0.0. Presented \( p \) values were two-sided and were deemed significant at or below a 5% level. Descriptive statistics such as mean (SD) and frequency were used to summarize demographic and clinical characteristics for all participants. Variables that were not found to be normally distributed were expressed in terms of median and 25th and 75th percentile interquartile range (IQR). Participants were clustered into two different groups given their vertebral fracture
status at baseline: fracture (grades 1–3) versus no fracture (grade 0) as assessed by the Genant score. Differences between these two groups in clinical parameters measured on a continuous scale were assessed using Student’s t-test. A nonparametric approach (Wilcoxon Mann-Whitney test) was used when required by the shape of the parameter’s distribution. Sex, leukemia diagnosis, and leukemia risk category, as well as pubertal stage and presence of back pain, were compared using \( \chi^2 \) test or Fisher’s exact test, as appropriate.

A logistic regression was performed to identify whether LS BMD Z-score, percent cortical area Z-score, and presence of back pain were statistically related to vertebral fracture in the study sample. These variables were chosen a priori based on the parameters that were anticipated to be relevant clinically. ORs along with their 95% CIs were presented. Differences in LS BMD Z-score between fracture severity grades were assessed using a one-way ANOVA and the Scheffe posthoc analysis.

**RESULTS**

**Clinical characteristics**

Clinical characteristics of the 186 children with newly diagnosed ALL are provided in Table 1. Most of the children were white (75%), precursor B-cell ALL was the most common immunophenotype (90%), and the majority of subjects were assessed as standard risk ALL (63%). Bone age (median, 5.0 yr) and chronological age (median, 5.3 yr) were similar among this largely prepubertal (Tanner stage 1, 78%) cohort. Weight and stature were above average. The LS BMD Z-score was reduced for the entire cohort when determined based on chronological age, with similar results when the BMD Z-score was determined using bone age instead of chronological age. There were no signs of rickets on any of the hand and wrist radiographs.

Children were studied for spine BMD at a median of 12.5 days (IQR: 4, 22) from chemotherapy initiation and underwent lateral thoraco-lumbar spine radiograph at a median of 18 days (IQR: 7, 25) from first chemotherapy. Among the children with fractures, 10/29 (35%) underwent spine radiographs the day of or before chemotherapy initiation.

**Vertebral fracture status**

*Genant semiquantitative analyses:* Twenty-nine patients had prevalent vertebral fractures (16%). Fifteen patients (52%) had one prevalent vertebral fracture, eight patients manifested 2–5 fractures (27%) and six patients had between 6 and 10 fractures (21%). Grade 1 fractures were present in 14 patients (48%), 9 patients (31%) had a
grade 2 fracture as the worst grade, and 6 patients (21\%) had grade 3 fractures. The anatomical distribution of vertebral fractures, fracture morphology, and severity are presented in Figs. 2A and 2B. A total of 75 fracture events occurred in 29 patients (53 thoracic and 22 lumbar). The distribution of fractures was bimodal, with most occurring in the midthoracic (18/75, 24\% at T6/T7) and thoracolumbar (23/75, 31\% at T12–L2) regions. Forty-three percent (32/75) of all fracture events were moderate or severe; of the 32 moderate and severe fractures, 16 (50\%) occurred in the T5–T9 region. Eighty-five percent (64/75) of fractures had anterior wedging, of which 60\% were mild. Fewer fractures were noted with crush (8/75, 11\%) and biconcave (3/75, 4\%) morphology. Thirty-eight percent of the crush fractures were mild compared with 67\% of the biconcave deformities. Endplate (crush and biconcave) fractures were more frequent in the lumbar spine compared with the thoracic region (RR, 2.7; 95\% CI: 0.7–11.2).

**ABQ analyses:** According to the ABQ method for fracture assessment, a total of 58 radiological signs of fractures were observed in 24 of the 29 patients who had Genant grade 1, 2, or 3 fractures. Loss of endplate parallelism was the most frequently observed radiological sign of fracture (57\%, 33/58 fractures), followed by endplate interruption (14\%), anterior cortical buckling (12\%), a combination of loss of endplate parallelism/endplate interruption (14\%), and loss of endplate parallelism/endplate interruption/anterior cortical buckling combined (3\%).

**Differences in clinical parameters for patients with vertebral fracture compared with those without**

The differences in clinical characteristics of patients with vertebral fractures compared with those without fractures are provided in Table 2. There was no significant difference between those with fractures and those without for the following clinical parameters: age, sex, leukemia subdiagnosis, white blood count, leukemia risk category, height Z-score, weight Z-score, pubertal stage, bone age, or family history of osteoporosis.

Differences were observed between the two groups for LS BMD Z-score, second metacarpal morphometry, and the presence of back pain (Table 2). Whereas metacarpal length and outer diameter were the same between the two groups of children, combined cortical thickness, cortical area, and percent cortical area were reduced in those with vertebral fracture, with a trend toward increased metacarpal inner diameter and inner diameter area in the fracture group. The mean LS BMD Z-score was significantly reduced in children with vertebral fractures, with a 1.0 Z-score difference between the two groups (mean Z-score, −2.1 ± 1.5 in the fracture group compared with −1.1 ± 1.2 in the children without vertebral fractures; \( p < 0.001 \)). Back pain was more frequent in children with fractures (55\%) compared with those without (20\%). Thirty-six percent (5/14) with mild fractures reported back pain, whereas 11/15 (73\%) with moderate or severe fracture were symptomatic.

Lumbar spine BMD Z-score, second metacarpal percent cortical area Z-score, and back pain were associated with increased odds for fracture on logistic regression (Table 3). For every 1 SD reduction in LS BMD Z-score, the odds for fracture increased by 80\% (95\% CI: 10–193\%), for every 1 SD reduction in second metacarpal percent cortical area Z-score, there was a doubling of the odds for fracture (95\% CI: 1.0–3.2), and the presence of back pain had an OR of 4.7 (95\% CI: 1.5–14.5). In addition, there was a progressive decline in mean LS BMD Z-score as the severity in fracture grade increased (Fig. 3).
TABLE 2. Clinical Parameters in Children With Vertebral Compression Compared With Those Without

<table>
<thead>
<tr>
<th>Clinical parameters</th>
<th>Compression (N = 29)</th>
<th>No compression (N = 157)</th>
<th>Difference (95% CI)</th>
<th>p</th>
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<tbody>
<tr>
<td>Demographic data</td>
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<tr>
<td>Male [n (%)]</td>
<td>17 (59)</td>
<td>91 (58)</td>
<td>1 (−19, 18)</td>
<td>1.0*</td>
</tr>
<tr>
<td>Age (yr) [median (IQR)]</td>
<td>6.1 (3.8, 9.9)</td>
<td>5.1 (3.3, 9.6)</td>
<td>−0.7 (−2.2, 0.5)</td>
<td>0.29†</td>
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<tr>
<td>Diagnosis</td>
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</tr>
<tr>
<td>Pre-B-cell acute lymphoblastic leukemia [n (%)]</td>
<td>27 (93)</td>
<td>140 (89)</td>
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<tr>
<td>T-cell acute lymphoblastic leukemia [n (%)]</td>
<td>2 (7)</td>
<td>17 (11)</td>
<td>4 (−12, 12)</td>
<td>0.74*</td>
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<tr>
<td>Leukemia characteristics</td>
<td></td>
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<tr>
<td>White blood count at diagnosis</td>
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<tr>
<td>White blood count [median (IQR)]</td>
<td>5.8 (2.5, 18.1)</td>
<td>7.1 (3.8, 30.2)</td>
<td>1.6 (−1.0, 4.0)</td>
<td>0.20†</td>
</tr>
<tr>
<td>≥50 [n (%)]</td>
<td>4 (14)</td>
<td>23 (15)</td>
<td>−1 (−12, 16)</td>
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<tr>
<td>&lt;50–20 [n (%)]</td>
<td>2 (7)</td>
<td>18 (12)</td>
<td>−5 (−13, 11)</td>
<td>0.54*</td>
</tr>
<tr>
<td>&lt;20–5 [n (%)]</td>
<td>9 (31)</td>
<td>59 (38)</td>
<td>−8 (−23, 12)</td>
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<tr>
<td>&lt;5 [n (%)]</td>
<td>14 (48)</td>
<td>53 (35)</td>
<td>14 (−5, 32)</td>
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<tr>
<td>Leukemia risk assignment</td>
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<tr>
<td>Standard risk [n (%)]</td>
<td>19 (66)</td>
<td>98 (62)</td>
<td>3 (−17, 19)</td>
<td>0.84*</td>
</tr>
<tr>
<td>High risk [n (%)]</td>
<td>10 (34)</td>
<td>58 (37)</td>
<td>0 (−15, 53)</td>
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<tr>
<td>Anthropometry</td>
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<tr>
<td>Height Z-score [mean (SD)]</td>
<td>0.2 (1.2)</td>
<td>0.3 (1.2)</td>
<td>−0.1 (−0.6, 0.3)</td>
<td>0.59†</td>
</tr>
<tr>
<td>Pubertal stage (stage 1) [n (%)]</td>
<td>21 (72)</td>
<td>124 (81)</td>
<td>−8 (−27, 7)</td>
<td>0.33*</td>
</tr>
<tr>
<td>Pubertal stage (stages 2–5) [n (%)]</td>
<td>8 (28)</td>
<td>30 (19)</td>
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<tr>
<td>Second metacarpal morphology</td>
<td></td>
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<tr>
<td>Metacarpal length Z-score [mean (SD)]</td>
<td>0.6 (0.9)</td>
<td>0.4 (0.9)</td>
<td>0.2 (−0.2, 0.7)</td>
<td>0.19†</td>
</tr>
<tr>
<td>Inner diameter Z-score [mean (SD)]</td>
<td>0.2 (0.9)</td>
<td>−0.2 (0.8)</td>
<td>0.3 (−0.1, 0.7)</td>
<td>0.13†</td>
</tr>
<tr>
<td>Outer diameter Z-score [mean (SD)]</td>
<td>0.1 (0.7)</td>
<td>0.2 (0.9)</td>
<td>−0.2 (−0.6, 0.3)</td>
<td>0.44†</td>
</tr>
<tr>
<td>Combined cortical thickness Z-score [mean (SD)]</td>
<td>−0.1 (1.0)</td>
<td>0.5 (0.9)</td>
<td>−0.6 (−1, −0.1)</td>
<td>0.01†</td>
</tr>
<tr>
<td>Inner diameter area Z-score [mean (SD)]</td>
<td>0.1 (0.9)</td>
<td>−0.2 (0.8)</td>
<td>0.3 (−0.1, 0.7)</td>
<td>0.12†</td>
</tr>
<tr>
<td>Total area Z-score [mean (SD)]</td>
<td>0.1 (0.8)</td>
<td>0.2 (0.9)</td>
<td>−0.2 (−0.6, 0.3)</td>
<td>0.42†</td>
</tr>
<tr>
<td>Cortical area Z-score [mean (SD)]</td>
<td>−0.01 (0.8)</td>
<td>0.5 (1.0)</td>
<td>−0.5 (−1.0, −0.1)</td>
<td>0.03†</td>
</tr>
<tr>
<td>Percent cortical area Z-score [mean (SD)]</td>
<td>−0.2 (0.9)</td>
<td>0.3 (0.8)</td>
<td>−0.5 (−0.9, −0.1)</td>
<td>0.02†</td>
</tr>
<tr>
<td>Spine areal BMD</td>
<td></td>
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</tr>
<tr>
<td>Lumbar spine areal BMD Z-score [mean (SD)]</td>
<td>−2.1 (1.5)</td>
<td>−1.1 (1.2)</td>
<td>−1.1 (−1.6, −0.6)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Lumbar spine areal BMD Z-score for bone age [mean (SD)]</td>
<td>−2.2 (1.5)</td>
<td>−1.04 (1.2)</td>
<td>−1.1 (−1.6, −0.6)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Back pain</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Yes [n (%)]</td>
<td>16 (55)</td>
<td>31 (20)</td>
<td>35 (17, 53)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>HAES activity levels</td>
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<tr>
<td>Overall relative activity (% to waking hours) [median (IQR)]</td>
<td>19 (8, 42)</td>
<td>26 (7, 49)</td>
<td>−2 (−13, 7)</td>
<td>0.60†</td>
</tr>
</tbody>
</table>

* Statistical significance determined by χ² test or Fisher’s exact test.
† Statistical significance determined by nonparametric test (Mann-Whitney U—two independent samples).
‡ Statistical significance determined by independent sample t-tests.

TABLE 3. Clinical Parameters Associated With Increased Odds for Fracture

<table>
<thead>
<tr>
<th>Parameters</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spine BMD Z-score</td>
<td>1.8 (1.10, 2.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Back pain</td>
<td>4.7 (1.5, 14.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Second metacarpal percent</td>
<td>2.0 (1.0, 3.2)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Dependent variable: spine fracture (yes or no).

DISCUSSION

This study highlighted the prevalence (16%) and severity of vertebral fractures as a complication of newly diagnosed childhood ALL. Whereas back pain occurred in 55% of children with vertebral fractures and was highly associated with vertebral compression, a significant proportion of children nevertheless did not manifest overt symptoms of their spinal involvement. Children with ALL can also present with vertebral fractures well after diagnosis (during chemotherapy) and may rebuild spine fractures through bone growth after leukemia treatment. At the same time, ALL treatment involves glucocorticoid and other potentially osteotoxic therapy that may cause further deterioration in spine health or inhibit the restoration process. Our data underscore the importance of identification of vertebral fractures at the time of ALL diagnosis, which will allow children with compromised skeletal health, whether symptomatic or not, to be monitored for further deterioration from the outset of their illness.

Our results, based on prospective radiographic screening of a large cohort of patients, suggest that vertebral fractures around the time of ALL diagnosis are more common than previously thought. Most of the related literature in this area stems from case report documentation of painful vertebral fractures as an initial presenting symptom of...
We found a bimodal distribution of fractures, with a predilection for fractures in the midthoracic region and the thoraco-lumbar junction. This distribution of fractures is similar to what has been consistently reported in adult men and women and is proposed to result from the mechanical stresses on vertebrae induced by the shape of the spine. The thoracic kyphosis is most pronounced at the midthoracic region so that loading in flexion is accentuated. The thoraco-lumbar junction is the site at which the spine transitions from being more rigidly fixed by ribs to freely mobile, maximizing compression stresses. This bimodal fracture distribution suggests that fractures were appropriately identified in our cohort of ALL children. Furthermore, the association between fractures and clinically relevant parameters such as lower LS BMD Z-score, reduced second metacarpal percent cortical area Z-score, and back pain lend further support to the fracture assignment. We also found that endplate fractures were more common in the lumbar spine compared with the thoracic region, a phenomenon that has also been reported in adults and is attributed to a more posterior center of gravity in this region. The fact that wedge deformity was the most common morphological finding is further in keeping with observations in large populations of adults with vertebral fractures. Another interesting finding was that many of the children with vertebral fractures (45%) were asymptomatic. This is consistent with data from women with postmenopausal osteoporosis in whom vertebral compression frequently occurs in the absence of symptoms.

The relationship between clinical parameters and vertebral fractures in childhood ALL has been an important topic of discussion in the pediatric ALL literature. In this study, we showed that LS BMD, a technique that has been used in childhood chronic illness for many years despite a paucity of available information on its relationship to bone fragility, is a clinically useful tool. Reductions in LS BMD Z-score were clearly associated with increased odds for fracture, with second metacarpal percent cortical area Z-score also emerging as a relevant clinical correlate (although to a lesser extent). Although the relationship between spine BMD and vertebral compression in ALL has not been studied previously, the link between the characteristics of the leukemia and vertebral compression has been addressed in a number of prior reports, with conflicting results. Ribeiro et al. found that children with vertebral compression were more likely to manifest favorable leukemia prognostic features, including a leukocyte count <25 × 10^9/liter. Other reports have noted that lower or normal leukocyte counts tend to be associated with back pain or vertebral compression. Alternatively, Clausen et al. found no relationship between skeletal scintigraphy or radiographic changes and leukemia features. In our study, we did not find a relationship between vertebral fractures and leukocyte counts, leukemia risk category, or leukemia subdiagnosis. The discrepancy among findings remains unclear, but conclusions may be clouded by a lack of systematic definition of fractures in previous reports.

The mechanism of the advanced bone morbidity observed in childhood ALL around the time of diagnosis has not been fully elucidated to date. We observed that spine

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**FIG. 3.** Median LS BMD Z-score for children with ALL at diagnosis in relation to fracture severity grade (25th and 75th percentiles). Patients with multiple compression fractures were classified according to the highest severity score. A Significant difference in LS BMD Z-score between children with grade 3 vs. grade 0 compression (p = 0.05). B Significant difference in LS BMD Z-score between children with grade 2 vs. grade 0 compression (p = 0.001).
BMD is affected in all children with newly diagnosed ALL regardless of their vertebral fracture status, as evidenced by the fact that the entire cohort showed reductions in spine BMD (mean Z-score, −1.2) despite above-average height. Whereas the purpose of our investigation was to study the clinical factors associated with spine fracture, and not to unveil mechanisms per se, the second metacarpal morphometry measurements do provide insight into the pathophysiological events surrounding the effect of ALL on bone. The normal second metacarpal length and diameter in children with vertebral compression but reduced percent cortical area suggest cortical thinning caused by increased endosteal resorption (as opposed to reduced periosteal apposition). One of the prevailing theories around the cause of ALL-induced bone morbidity is the liberation of osteoclast-activating factors by the leukemic cells. Our study supports the suggestion that increased skeletal resorption is a contributing pathological event.

In conclusion, these results highlight the potential for advanced spine fractures among children with newly diagnosed ALL. The potential for rebuilding of the spine through bone growth versus further deterioration in the face of bone health threats such as compromised mobility and medication osteotoxicity remains to be determined through longitudinal study.

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REFERENCES


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