JPPT | Single Center Retrospective Study

# Dose-Related Effect of Chemotherapy on Bone Mineral Density Among Pediatric Acute Lymphoblastic Leukemia Survivors

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**OBJECTIVES** Reduced bone mineral density (BMD) can negatively affect lifelong skeletal health by increasing the risk for developing osteopenia and osteoporosis. This study evaluated the relationship between BMD and cumulative doses of intravenous (IV) methotrexate (MTX) and glucocorticoids in pediatric acute lymphoblastic leukemia (ALL) survivors. The association between BMD and vitamin D concentrations measured at the time of entry into the long-term follow-up program was also assessed.

**METHODS** This retrospective study included pediatric ALL survivors who had received a dual-energy X-ray absorptiometry (DXA) scan after the end of therapy (EOT) or within the 6 months prior to the EOT. Low/intermediate and high cumulative IV MTX doses were defined as doses less than 20,000 mg/m$^2$ and greater than or equal to 20,000 mg/m$^2$, respectively. Descriptive statistics, Student *t* test, and linear regression were used to analyze the data.

**RESULTS** A total of 62 patients, with 34 patients in the low/intermediate and 28 patients in the high cumulative IV MTX dose groups, were analyzed. The median time from EOT to DXA scan was 2.3 years. The mean DXA lumbar spine *z* score was significantly lower in the high cumulative IV MTX dose group compared with the low/intermediate dose group (−0.86 vs −0.14; p = 0.008). Cumulative glucocorticoid doses and vitamin D concentrations were not associated with BMD.

**CONCLUSIONS** Pediatric patients who had received cumulative IV MTX doses of greater than or equal to 20,000 mg/m$^2$ during their ALL treatment had lower BMD than those who had received lower cumulative doses.

**ABBREVIATIONS** ALL, acute lymphoblastic leukemia; BMD, bone mineral density; COG, Children's Oncology Group; DXA, dual-energy X-ray absorptiometry; EMR, electronic medical record; EOT, end of therapy; IT, intrathecal; IV, intravenous; MTX, methotrexate

**KEYWORDS** acute lymphoblastic leukemia; bone density; glucocorticoids; methotrexate; pediatrics; survivors

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## Introduction

Pediatric cancer survival rates have significantly improved with the optimization of and advancements in treatment.[1] Specifically, the 5-year overall survival rate for patients younger than 14 years with acute lymphoblastic leukemia (ALL), the most commonly diagnosed childhood cancer, has exceeded 90% with risk-stratified treatment.[2–4] With this increased survival rate in the pediatric patient population, it has become essential to monitor for late effects of chemotherapy.[5] The Children's Oncology Group (COG) provides recommendations for late-effect screening and follow-up according to the type and intensity of therapeutic exposure.[6] A bone mineral density (BMD) evaluation using a dual-energy X-ray absorptiometry (DXA) scan is recommended at the time of entry into a long-term follow-up program for pediatric cancer survivors who had received corticosteroids, methotrexate (MTX), or hematopoietic stem cell transplant. Bone mineral density results are reported as *z* scores, which are calculated by comparing the BMD to that of healthy children of the same age and sex.[7] The International Society for Clinical Densitometry recommends DXA scans of the posterior-anterior spine and total body, less the head, to measure BMD in pediatric patients.[8] A diagnosis of osteoporosis in pediatric patients requires either a finding of a vertebral compression fracture or a clinically significant fracture history along with a BMD *z* score of less than or equal to −2.

The attainment of peak bone mass during puberty impacts lifelong skeletal health.[1,7] Unfortunately, pediatric patients treated for cancer may not achieve peak

bone mass and are thus predisposed to reduced BMD. Reduced BMD, which is defined by the COG as a *z* score of less than −2, can negatively affect lifelong skeletal health by increasing the risk for developing osteopenia and osteoporosis.[6,9]

Several factors can contribute to reduced BMD in pediatric cancer survivors, including chemotherapy, gonadal impairment secondary to radiation, leukemic process, nutritional deficiency, and decreased physical activity.[1,7,10–12] In particular, higher cumulative doses of MTX and glucocorticoids may increase the risk of BMD deficits. However, there have been conflicting data, with some studies reporting that low BMD was not significantly associated with MTX or glucocorticoid exposure.[13,14] The purpose of this study was to evaluate the effects of cumulative intravenous (IV) MTX and glucocorticoid doses on BMD and the predictive value of vitamin D concentrations on BMD among pediatric ALL survivors.

## Materials and Methods

This single-center, retrospective study was conducted to evaluate the risk factors of total IV MTX exposure, glucocorticoid exposure, and vitamin D concentrations for reduced BMD in the pediatric ALL survivor population. Patients were identified using electronic medical record (EMR) reports of patients with a history of cancer who had received care from the institution's long-term follow-up care clinic and of DXA scan results during the study period of January 2012 to August 2020. Childhood, adolescent, and young adult ALL survivors who were 25 years or younger at the time of cancer diagnosis and who had a DXA scan after the end of therapy (EOT) or within the 6 months prior to the EOT were included in this study. Patients with a history of growth hormone deficiency or chronic steroid use for indications other than for treatment of ALL were excluded. Inadequate documentation in the EMR, such as that due to transfer of care from another institution, was another exclusion criteria.

The primary aim of this study was to assess the relationship between BMD and cumulative doses of IV MTX and glucocorticoids. Mean DXA lumbar spine *z* scores were compared between low/intermediate and high cumulative doses of IV MTX. Cumulative IV MTX doses were defined in this study as low/intermediate for doses less than 20,000 mg/m$^2$ and high for doses greater than or equal to 20,000 mg/m$^2$. The threshold of 20,000 mg/m$^2$ was chosen to categorize ALL patients who had received high-dose MTX of 5000 mg/m$^2$ every other week for 4 doses in interim maintenance per the COG protocols. The secondary aim was to evaluate the extent of association between BMD and vitamin D concentrations measured at the time of entry into the long-term follow-up program by comparing mean DXA lumbar spine *z* scores between low and normal vitamin D concentrations, which were defined as plasma or serum 25-hydroxyvitamin D measurements of less than 30 ng/mL and greater than or equal to 30 ng/mL, respectively.

Data were collected by retrospective chart review of the EMR. The following information was collected: sex, age, height, weight, diagnosis, protocol, history of radiation, history of hematopoietic stem cell transplantation, history of disease relapse, history of fracture, history of bisphosphonate use, DXA scan results, time from EOT to DXA scan, cumulative IV MTX dose, cumulative glucocorticoid dose, and vitamin D concentration. For patients with multiple DXA scan results, the results from the first scan after the EOT were recorded and analyzed. Cumulative IV MTX doses were calculated after confirmation of dose administration from the patients' treatment plans. Cumulative glucocorticoid doses were calculated as prednisone equivalent doses in mg/m$^2$ (1 mg of prednisone = 0.15 mg of dexamethasone). For each patient, the vitamin D concentration that was within 6 months of and closest to the date of the DXA scan was included in the analysis.

Patients were classified as having received low/intermediate or high cumulative IV MTX doses based on the sum of doses that had been administered throughout their treatment. To highlight the variability of MTX exposure among the different COG ALL protocols, a reference table was created.[15–20] This was achieved by reviewing the doses for each of the protocol arms and estimating the IV, intrathecal (IT), and oral MTX exposure; estimated exposure was then reported as either multiple doses or ranges to include all of the arms of the protocol. The possible cumulative doses of IV and oral MTX were calculated in mg/m$^2$. For the protocols that included Capizzi escalating MTX, it was assumed that there were 50 mg/m$^2$ dose escalations every 10 days. The oral MTX cumulative doses were estimated on the assumption of no dose escalations, holds, or de-escalations during maintenance. The IT MTX exposure was an estimation of the maximum possible number of doses that could have been administered to patients with CNS1 status (no blasts in the cerebrospinal fluid).

Patient characteristics were reported using descriptive statistics. Student *t* test was performed to assess differences in the mean DXA lumbar spine *z* scores between both the cumulative IV MTX dose groups and the vitamin D concentration groups. Linear regression was used to identify the relationship between DXA lumbar spine *z* scores and cumulative prednisone equivalent doses. Statistical significance was defined as a p value of less than 0.05.

## Results

A total of 62 patients, with 34 patients in the low/intermediate and 28 patients in the high cumulative IV MTX dose groups, were analyzed in this study (Table 1). The median age of patients at the time of diagnosis was 5.2 years, with a range from 0.9 to 17.2 years, and the

**Table 1.** Patient Characteristics

| Variable | Cumulative IV MTX Dose Group* | | Overall |
|---|---|---|---|
| | Low/Intermediate | High | |
| Patients, n (%) | 34 (54.8) | 28 (45.2) | 62 (100) |
| Male, n (%) | 11 (32.4) | 12 (42.9) | 23 (37.1) |
| Age, median (range), yr | | | |
| Diagnosis | 4.9 (0.9–13.1) | 6.1 (1.7–17.2) | 5.2 (0.9–17.2) |
| DXA scan | 9.8 (5–20.4) | 11.5 (5.2–21) | 10.4 (5–21) |
| Time from EOT to DXA scan, median (range), yr | 2.5 (0–6) | 2.1 (−0.5 to 3.9) | 2.3 (−0.5 to 6) |
| BMI weight status, n (%)†‡ | | | |
| Underweight | 0 (0) | 0 (0) | 0 (0) |
| Normal | 17 (50) | 17 (60.7) | 34 (54.8) |
| Overweight | 7 (20.6) | 4 (14.3) | 11 (17.7) |
| Obese | 10 (29.4) | 7 (25) | 17 (27.4) |
| BSA, median (range), $m^2$† | 1.1 (0.7–2.1) | 1.4 (0.7–2.1) | 1.2 (0.7–2.1) |
| Diagnosis, n (%) | | | |
| Infant ALL | 1 (2.9) | 0 (0) | 1 (1.6) |
| B-cell ALL | 32 (94.1) | 25 (89.3) | 57 (91.9) |
| T-cell ALL | 1 (2.9) | 3 (10.7) | 4 (6.5) |
| COG protocol, n (%) | | | |
| AALL0232 | 0 (0) | 1 (3.6) | 1 (1.6) |
| AALL0434 | 1 (2.9) | 2 (7.1) | 3 (4.8) |
| AALL0631 | 1 (2.9) | 0 (0) | 1 (1.6) |
| AALL0932 | 31 (91.2) | 0 (0) | 31 (50) |
| AALL1131 | 1 (2.9) | 16 (57.1) | 17 (27.4) |
| AALL1231 | 0 (0) | 1 (3.6) | 1 (1.6) |
| Multiple protocols | 0 (0) | 8 (28.6) | 8 (12.9) |
| Treatment, n (%) | | | |
| IV MTX and glucocorticoids | 34 (100) | 28 (100) | 62 (100) |
| Radiation | 1 (2.9) | 3 (10.7) | 4 (6.5) |
| HSCT | 0 (0) | 0 (0) | 0 (0) |
| History of disease relapse, n (%) | 0 (0) | 0 (0) | 0 (0) |
| History of fracture, n (%) | 3 (8.8) | 3 (10.7) | 6 (9.7) |
| History of bisphosphonate use, n (%) | 1 (2.9) | 1 (3.6) | 2 (3.2) |
| DXA *z* score, n (%) | | | |
| ≥ −2 | 33 (97.1) | 24 (85.7) | 57 (91.9) |
| < −2 | 1 (2.9) | 4 (14.3) | 5 (8.1) |
| Vitamin D concentration, n (%)† | | | |
| < 30 ng/mL | 14 (41.2) | 10 (35.7) | 24 (38.7) |
| ≥ 30 ng/mL | 19 (55.9) | 18 (64.3) | 37 (59.7) |
| No data | 1 (2.9) | 0 (0) | 1 (1.6) |

*ALL, acute lymphoblastic leukemia; BMI, body mass index; BSA, body surface area; COG, Children's Oncology Group; DXA, dual-energy X-ray absorptiometry; EOT, end of therapy; HSCT, hematopoietic stem cell transplant; IV, intravenous; MTX, methotrexate*

* Cumulative IV MTX doses were defined as low/intermediate for doses less than 20,000 mg/$m^2$ and high for doses greater than or equal to 20,000 mg/$m^2$.

† At the time of DXA scan.

‡ BMI percentile was used to determine the weight status for patients younger than 20 years.

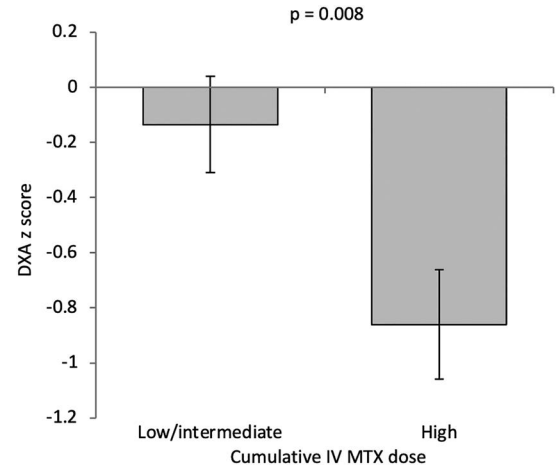
median age at the time of the DXA scan was 10.4 years, with a range from 5 to 21 years. The median time from EOT to DXA scan was 2.3 years. Most patients had a diagnosis of B-cell ALL, and thus most patients received treatment per COG protocols AALL0932 and AALL1131. All patients had received IV MTX and glucocorticoids as part of their standard regimen for ALL treatment. None of the patients had a history of disease relapse. A total

of 6 patients (9.7%), 3 from the low/intermediate and 3 from the high cumulative IV MTX dose groups, had a history of fracture. There were 2 patients who had received bisphosphonates during ALL treatment; both patients continued taking bisphosphonates after EOT until the BMD normalized. A total of 5 patients had DXA lumbar spine *z* scores of less than −2. The median cumulative IV MTX doses were 2425 and 20,000 mg/m$^2$ for the low/intermediate and high cumulative IV MTX dose groups, respectively. The median cumulative prednisone equivalent doses were 5953 mg/m$^2$ for the low/intermediate and 6413 mg/m$^2$ for the high cumulative IV MTX dose groups. More than a third (38.7%) of the study population had low vitamin D concentrations (i.e., < 30 ng/mL) at the time of their DXA scan. Of those patients, the median vitamin D concentration was 25 ng/mL, with a range from 14 to 29 ng/mL.

The differences in MTX exposure among the various COG ALL protocols were highlighted in a reference table (Table 2). Patients on protocol AALL1131 were estimated to have received a greater number of IT MTX doses and a higher cumulative dose of IV MTX compared with those on protocol AALL0932. When treated on the same arm of a protocol, male patients typically had greater IT and oral MTX exposure than female patients because male patients usually received an extra year of maintenance therapy compared with female patients for most protocols during this study period; however, the cumulative dose of IV MTX was estimated to be the same regardless of sex.

The mean DXA lumbar spine *z* score was significantly lower in the high cumulative IV MTX dose group compared with the low/intermediate cumulative IV MTX dose group (−0.86 vs −0.14; p = 0.008; Figure 1).

**Figure 1.** Bar chart with error bars comparing mean DXA *z* score between low/intermediate and high cumulative IV MTX dose groups. Cumulative IV MTX doses were defined as low/intermediate for doses less than 20,000 mg/m$^2$ and high for doses greater than or equal to 20,000 mg/m$^2$.




*DXA, dual-energy X-ray absorptiometry; IV, intravenous; MTX, methotrexate*

There was no association between DXA lumbar spine *z* scores and cumulative prednisone equivalent doses ($R^2$ = 0.05; p = 0.08; Figure 2). Furthermore, there was no association between DXA lumbar spine *z* scores and cumulative prednisone equivalent doses when patients were stratified into low/intermediate and high cumulative IV MTX dose groups. There were no significant differences in the mean DXA lumbar spine *z* scores

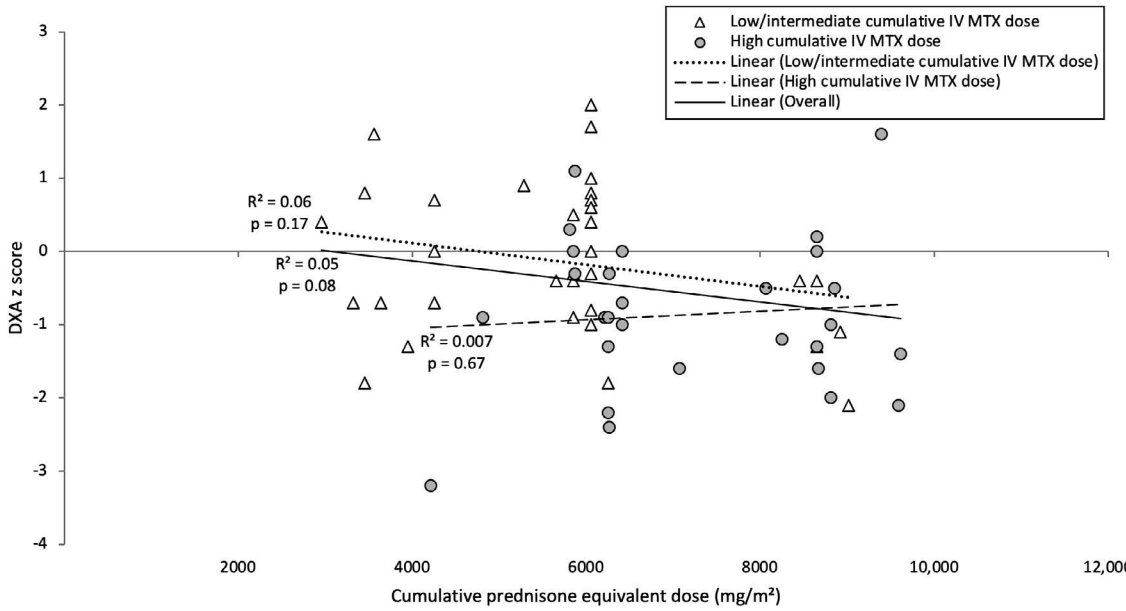
**Table 2.** Reference of Estimated Methotrexate (MTX) Exposure by Children's Oncology Group Protocol[15–20]

| Protocol | IV MTX Dose Exposure, mg/m$^2$* | Number of IT MTX Doses† | | PO MTX Dose Exposure, mg/m$^2$‡ | |
|---|---|---|---|---|---|
| | | Male | Female | Male | Female |
| AALL0232§ | 21,000 or 21,750 | 26–27 | 22–23 | 2240–2460 | 1300–1500 |
| AALL0434 | 1000 or 20,000 | 23–27 | 19–23 | 1500–2540 | 1500–1580 |
| AALL0631¶ | 16,240 or 16,260 | 17 | | 820–940 | |
| AALL0932¶ | 2500 or 6000 | 16–21 | 16–17 | 1460–2420 | 1460–1960 |
| AALL1131# | 8000; 20,000; or 21,000 | 23–27 | 22–23 | 1500–2460 | 1400–1500 |
| AALL1231 | 1000; 11,000; or 21,000 | 21–27 | 21–23 | 1400–2460 | 1400–1500 |

*IT, intrathecal; IV, intravenous; PO, oral*

* Assumption of 50 mg/m$^2$ dose escalations every 10 days with Capizzi escalating MTX.
† Assumption of CNS1 status (no blasts in the cerebrospinal fluid).
‡ Assumption of no dose escalations, holds, or de-escalations during maintenance.
§ Estimations after changes with Amendment 8A.
¶ Estimations after changes with Amendment 5.
# Estimations after changes with Amendment 7A.

**Figure 2.** Linear regressions of DXA *z* score and cumulative prednisone equivalent dose stratified by cumulative IV MTX dose groups. Cumulative IV MTX doses were defined as low/intermediate for doses less than 20,000 mg/m$^2$ and high for doses greater than or equal to 20,000 mg/m$^2$.




*DXA, dual-energy X-ray absorptiometry; IV, intravenous; MTX, methotrexate*

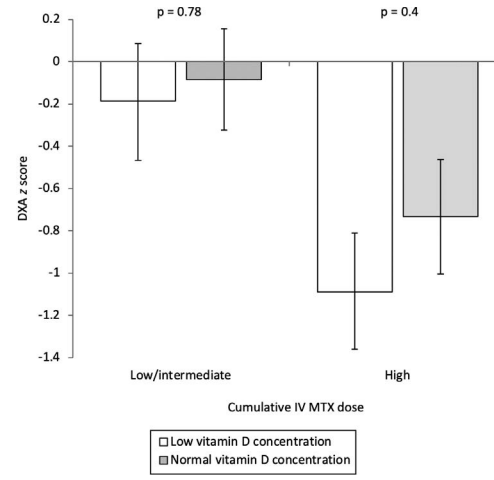
between the low and normal vitamin D concentration groups for both the low/intermediate and high cumulative IV MTX dose groups (Figure 3). One patient was not included in the secondary outcome analysis since a vitamin D concentration was not obtained.

## Discussion

In this study, pediatric ALL survivors who had received higher cumulative IV MTX doses had significantly lower DXA lumbar spine *z* scores. This finding suggests that IV MTX may have a negative dose-related effect on BMD among pediatric ALL survivors at the beginning of their long-term follow-up care. By contrast, there was no association between cumulative glucocorticoid doses and BMD.

Methotrexate and glucocorticoids are 2 chemotherapy agents used in ALL treatment that have been shown to affect BMD.[1] Methotrexate increases bone resorption while inhibiting bone formation.[21] Glucocorticoids also increase bone resorption, decrease bone mass, and inhibit osteoblast synthesis and proliferation, leading to reduced bone formation.[22] However, the effect of chemotherapy on BMD in pediatric patients who had been treated for ALL is still debated in the literature. Many of these studies include different patient populations, ALL treatment protocols, DXA scan timing from EOT, and methods of BMD measurement, all of which may contribute to the lack of clear, consistent findings regarding the effect of MTX and glucocorticoids on BMD.[13,23–28]

**Figure 3.** Bar chart with error bars comparing mean DXA *z* score between low and normal vitamin D concentrations stratified by cumulative IV MTX dose groups. Vitamin D concentrations were drawn as plasma or serum 25-hydroxyvitamin D and defined as low for measurements less than 30 ng/mL and normal for those greater than or equal to 30 ng/mL. Cumulative IV MTX doses were defined as low/intermediate for doses less than 20,000 mg/m$^2$ and high for doses greater than or equal to 20,000 mg/m$^2$.




*DXA, dual-energy X-ray absorptiometry; IV, intravenous; MTX, methotrexate*

Studies have reported a relationship between low BMD and treatment courses with high doses of MTX and glucocorticoids among survivors of pediatric ALL.[23,24,29] Mandel and colleagues[24] found that patients with low BMD of the femoral neck were more likely to have received either cumulative MTX doses greater than 50,000 mg/m$^2$ or prednisone equivalent doses greater than 9000 mg/m$^2$. Although our study had a similar finding of lower BMD in patients who had received higher cumulative IV MTX doses, it is important to recognize that the study by Mandel and colleagues had a different patient population and skeletal site for measuring BMD. None of the patients in our study had received cumulative IV MTX doses greater than 50,000 mg/m$^2$ because very large doses of MTX were not incorporated in the COG protocols that were used to treat patients, and only 4 patients had received prednisone equivalent doses greater than 9000 mg/m$^2$. Interestingly, Mandel et al[24] noted that there was no relationship between decreased BMD of the lumbar spine and larger cumulative MTX or glucocorticoid doses, whereas the population in our study had lower DXA lumbar spine *z* scores with higher IV MTX doses. Other studies have found that higher cumulative MTX or prednisone equivalent doses were not associated with increased risk for low BMD.[13,25,26]

Of the patients who had evaluable vitamin D concentrations, there were no significant differences in the mean DXA lumbar spine *z* scores between the low and normal vitamin D concentration groups for both the low/intermediate and the high cumulative IV MTX dose groups. In a study of pediatric patients receiving chemotherapy for ALL, a significant positive correlation was found between DXA femoral neck scan results 6 months after treatment completion and vitamin D concentrations.[30] Jain et al[26] also found that among pediatric ALL survivors, those with vitamin D concentrations less than or equal to 10 ng/mL had a significantly lower mean height-adjusted whole body *z* score than those with vitamin D concentrations greater than 10 ng/mL. Of note, the difference in mean height-adjusted lumbar spine *z* scores between these 2 vitamin D concentration groups was not significant. Similarly, our study did not find a significant difference in DXA lumbar spine *z* scores between the vitamin D concentration groups. However, the threshold of vitamin D concentration that was used to stratify our patients was different, and none of our patients had a vitamin D concentration less than or equal to 10 ng/mL.

Limitations to this study include the small sample size, variable timing of and patient age at the time of the DXA scans, and the skeletal site of the DXA scan that was chosen for the analyses. Because the DXA scans were not all uniformly obtained at the same time after EOT, this variability could have affected our results. Previous studies suggest that BMD improves with increased time from EOT.[25,31] Additionally, the extent of change in BMD that could be attributed to IV MTX and glucocorticoids was not captured for individual patients because DXA scans were not regularly obtained prior to starting treatment. DXA lumbar spine *z* scores were analyzed in this study because it is the preferred skeletal site for measuring BMD in pediatric patients.[8,32] However, the spine is primarily composed of trabecular bone, which may make it more susceptible to the effects of chemotherapy because of the higher bone turnover rate that occurs compared with cortical bone.[33] Another limitation of using the DXA lumbar spine *z* score is that it may not accurately reflect BMD in certain patients, such as those with nonremovable hardware or abnormal skeletal morphometry.[8,32]

Factors contributing to bone health, such as nutrition and physical activity, were not controlled for in our study, but they could have affected the results. Studies have reported a positive correlation between calcium intake and BMD among pediatric ALL survivors.[26,31,34] However, the intake of cholecalciferol and calcium supplements during treatment was not analyzed in our study. Patients who had received DXA scans during treatment and had DXA *z* scores of less than −1 were either newly prescribed or, if already receiving therapy, given optimized doses of cholecalciferol and/or calcium supplements. In addition to receiving supplements, those with DXA *z* scores of less than −2 had DXA scans repeated in 1 to 2 years and/or were referred to endocrinology for consideration of treatment with bisphosphonates. Two of our patients had started taking bisphosphonates during ALL treatment because of their history of fracture and DXA *z* score of less than −2. The use of bisphosphonates could have impacted the BMD and thus affected the EOT DXA scan results. Also, a positive correlation has been described between physical activity and BMD in this population.[23,31] Tillmann and colleagues[23] had observed that pediatric ALL survivors had lower measurements of physical activity compared with their healthy controls, and low levels of physical activity were associated with low BMD in the ALL group.

## Conclusion

Pediatric patients who had received higher cumulative IV MTX doses during their ALL treatment course had lower BMD toward the beginning of their long-term follow-up care. However, cumulative glucocorticoid doses and vitamin D concentrations measured near the time of the DXA scans were not associated with BMD. Currently, the COG long-term follow-up guidelines recommend that pediatric cancer survivors with a history of MTX exposure receive a DXA scan to evaluate BMD at baseline and then repeat it as clinically indicated.[6] The results from our study suggest that close monitoring for possible BMD deficits could be most beneficial for pediatric ALL patients who received cumulative IV MTX doses of greater than or equal to 20,000 mg/m$^2$ because this population had significantly lower BMD at the beginning of their long-term follow-up care. Other

studies, however, have reported no significant association between MTX exposure and BMD among pediatric cancer survivors.[14,35,36] Thus, further investigation with a larger study population exploring the dose-related risk factor of IV MTX on BMD is warranted to better understand the population that would benefit most from BMD screening and close monitoring.

## Article Information

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**Ethical Approval and Informed Consent.** This study was approved by the University of California, San Diego Institutional Review Board and was granted a waiver of informed consent.

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