

Original Article



Prevalence and Associated Factors of Vertebral Fractures in Children with Chronic Liver Disease with and without Liver Transplantation

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ABSTRACT



Purpose: To evaluate the prevalence of vertebral fracture (VF) in children with chronic liver disease (CLD) with and without liver transplantation (LT) and to determine the associated factors.

Methods: A cross-sectional study was conducted. Patients aged 3–21 years with CLD both before and after LT were enrolled in the study. Lateral thoracolumbar spine radiographs were obtained and assessed for VF using Mäkitie's method. Clinical and biochemical data were collected.

Results: We enrolled 147 patients (80 females; median age 8.8 years [interquartile range 6.0–11.8]; 110 [74.8%] in the LT group and 37 [25.2%] in the non-LT group). VF was identified in 21 patients (14.3%): 17/110 (15.5%) in the LT group and 4/37 (10.8%) in the non-LT group ($p=0.54$). Back pain was noted in only three patients with VF. In the univariate analysis, a height z-score below -2.0 ($p=0.010$), pre-LT hepatopulmonary syndrome ($p=0.014$), elevated serum direct and total bilirubin levels ($p=0.037$ and $p=0.049$, respectively), and vitamin D deficiency at 1-year post-LT ($p=0.048$) were associated with VF in the LT group. In multivariate analysis, height z-score below -2.0 was the only significant associated factor (odds ratio, 5.94; 95% confidence interval, 1.49–23.76; $p=0.012$) for VF. All VFs in the non-LT group were reported in males.

Conclusion: In children with CLD, VF is common before and after LT. Most patients with VF are asymptomatic. Screening for VF should be considered in patients with a height z-score below -2.0 after LT.

Keywords: Chronic liver disease; Fibrosis; Hepatic osteodystrophy; Vertebral fracture; Vitamin D deficiency; Liver transplantation

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Conflict of Interest

The authors have no financial conflicts of interest.

INTRODUCTION

Chronic liver disease (CLD) is defined as an ongoing injury in the liver persisting for at least 6 months with the potential to progress to cirrhosis [1]. With advancements in medical care and liver transplantation (LT), the long-term survival rates of children with CLD have improved. However, these patients experience short- and long-term complications, including bone fractures [2,3].

Vertebral fracture (VF) is a sequela of a spine's low bone mineral density (BMD). Patients with CLD have an increased risk of VF in both the pre- and post-LT periods [2-6]. Hepatic osteodystrophy, a metabolic bone disease associated with CLD, is the primary cause of VF during the pre-LT period [2]. The pathogenesis of hepatic osteodystrophy is multifactorial and includes abnormal vitamin D metabolism, malnutrition, hypogonadism, vitamin K deficiency, insulin-like growth factor 1 deficiency, and inflammation [2,6]. The prevalence of low BMD has been reported to be as high as 100% in children with end-stage liver disease before LT [7]. After LT, patients remain at risk of VF due to slow recovery from pre-existing hepatic osteodystrophy, immobilization after transplant surgery, and the effects of long-term use of immunosuppressive medications [2,8,9]. A large pediatric study demonstrated that children who underwent solid organ transplants had a 160-fold higher incidence of VF than that observed in the normal population [9]. VF in adults with CLD is well described, with the prevalence as high as 36% and 29% in the pre-LT and post-LT periods, respectively [10,11]. However, data on the prevalence of VF in children with CLD are limited [8,12]. This study aimed to evaluate the prevalence of VF in children with CLD in both the pre- and post-LT periods and to determine the factors associated with VF.

MATERIALS AND METHODS

Study design

This cross-sectional study was conducted at the Faculty of Medicine Ramathibodi Hospital, Mahidol University between April 2021 and February 2022.

Patient population

Patients aged 3–21 years diagnosed with CLD who underwent regular follow-up visits to our institute were enrolled. Lateral thoracolumbar spine radiographs were obtained from enrolled patients and assessed for VFs. Clinical and biochemical data were collected at the time of enrollment.

CLD was diagnosed when fibrosis or cholestasis was observed in histopathological examination of liver biopsy specimens, along with the presence of clinical features of CLD such as cholestatic jaundice, ascites, variceal bleeding, enlarged left lobe of the liver, splenomegaly, prolonged international normalized ratio, and hypoalbuminemia. Patients were classified into LT and non-LT groups. However, patients with pre-existing primary bone disease or chronic kidney disease were excluded.

This study was conducted with the approval of the Ramathibodi Hospital Human Research Ethics Committee (RF_64088) and in accordance with the ethical standards of the National Guidelines and Helsinki Declaration. Informed consents were obtained from patients aged 18 years and older. For patients below 18 years of age, informed consents were obtained from their caregivers, and additional assents were obtained from patients over 6 years old.

Clinical data

Clinical data, including patient characteristics and symptoms associated with back pain, were collected at the time of enrollment. Patient characteristics included weight, height, underlying liver disease, history of bone fractures, and complications of CLD. The weight and height z-scores of patients were calculated using the standard references according to the age group; World Health Organization AnthroPlus version 1.0.4 for patients aged 3–6 years, the national growth reference for Thai children aged 19 years for patients aged 19–21 years.

The pediatric end-stage liver disease (PELD) or model for end-stage liver disease (MELD) scores at enrollment were collected from non-LT patients. Moreover, the PELD/MELD score with a negative value was converted to zero.

In the LT group, additional data were gathered including the PELD and MELD scores at the time of LT, age at LT, duration of follow-up, cumulative corticosteroid exposure after LT, and the mean serum tacrolimus level. At our center, tacrolimus and corticosteroids were the main immunosuppressive agents in LT patients. The corticosteroids were typically tapered off over 4–6 months. Cumulative corticosteroid exposure was calculated by multiplying the daily dosage by the number of days and then dividing it by the patient's body weight in mg/kg of prednisolone. If the patients received corticosteroids at the same dosage continuously for more than 3 months, the body weight every 3 months was used for the calculation.

The serum tacrolimus levels were monitored in all LT recipients at each visit. The mean serum tacrolimus level was calculated as the sum of the serum tacrolimus levels at each visit multiplied by the number of days at each level and divided by the total duration. Serum tacrolimus levels in the first month after LT were excluded due to wide fluctuations observed during this period.

Biochemical data

Liver chemistry, serum albumin levels, and prothrombin time were measured at enrollment. We collected 25-hydroxyvitamin D levels within the past year, selecting the lowest value when multiple blood test results were available. We also retrospectively reviewed 25-hydroxyvitamin D levels post-LT and vitamin D deficiency at 1-year post-LT. Vitamin D deficiency was defined as a 25-hydroxyvitamin D level <20 ng/mL.

Serum magnesium levels were routinely monitored in the LT recipients. The mean serum magnesium level was calculated using a similar method to that of the mean serum tacrolimus level.

Assessment of VF

The lateral thoracolumbar spine radiographs were assessed according to the Mäkitie classification [13]. Vertebral changes were classified as follows:

- Grade 0 or grade 1: normal.
- Grade 2a: mild anterior wedge deformity, 20–49% anterior height reduction compared to posterior height.
- Grade 2b: severe anterior wedge deformity, $\geq 50\%$ anterior height reduction compared to posterior height.
- Grade 3a: mild compression deformity, 5–29% middle height reduction compared to a normal adjacent vertebra.

- Grade 3b: severe compression deformity, $\geq 30\%$ middle height reduction compared to a normal adjacent vertebra.

VF was diagnosed when the radiograph displayed grade 2a or more.

Radiographs of the first 30 patients were evaluated independently by two experienced musculoskeletal radiologists (PT and NC) blinded to the patient's clinical characteristics. The results of the VF assessments, which eight VFs were detected in 30 patients, were analyzed for inter-observer agreement. A kappa value of 1 was noted, indicating that the two researchers diagnosed VF similarly. Consequently, each of the subsequently recruited patient radiographs was evaluated separately by a single reader.

Statistical analysis

Descriptive data are reported as median and interquartile range (IQR). Chi-square and unpaired *t*-tests were used to compare parameters between patients with and without VF. Factors associated with VFs were analyzed using logistic regression. Statistical significance was considered at a *p*-value of <0.05 . Statistical analyses were performed using the Stata software version 17 (StataCorp).

RESULTS

Patient characteristics and previous history of bone fractures

A total of 147 patients including 80 females, with a median age (IQR) of 8.8 (6.0–11.8) years, were enrolled. In most patients (87.1%), biliary atresia (BA) was identified as the primary cause of CLD. One hundred ten patients (74.8%) were in the LT group and 25.2% were in the non-LT group. In the non-LT group, 29 patients (78%) had PELD/MELD scores <10 . The patient characteristics are displayed in **Table 1**. The height z-score, serum direct and total bilirubin (TB) levels, and serum albumin levels were significantly different between the two groups (**Table 1**).

Table 1. Patient characteristics

Characteristics	Overall (n=147)	LT group (n=110)	Non-LT group (n=37)	<i>p</i> -value
Male	67 (45.6)	48 (43.6)	18 (48.6)	0.596
Age (yr)	8.8 (6.0–11.8)	8.9 (5.8–11.8)	8.6 (6.9–11.2)	0.994
Weight z-score	-0.76 (-1.35 to -0.11)	-0.78 (-1.35 to -0.02)	-0.71 (-1.21 to -0.23)	0.755
Height z-score	-1.13 (-1.74 to -0.09)	-1.32 (-2.03 to -0.21)	-0.74 (-1.28 to 0.21)	$<0.001^*$
Underlying liver disease				
Biliary atresia	128 (87.1)	95 (86.4)	33 (89.2)	0.783
Alagille syndrome	5 (3.4)	3 (2.7)	2 (5.4)	0.600
Other causes	5 (3.4)	4 (3.6)	1 (2.7)	1.000
Cryptogenic cirrhosis	9 (6.1)	8 (7.3)	1 (2.7)	0.450
Previous bone fractures	19 (12.9)	16 (14.5)	3 (8.1)	0.404
Vertebral fracture	5 (3.4)	5 (4.5)	0 (0)	0.331
Back pain	10 (6.8)	9 (8.2)	1 (2.7)	0.452
Serum 25-hydroxy vitamin D (ng/mL)	24.9 (18.8–32.6)	23.5 (18.6–28.0)	25.6 (19.0–33.4)	0.090
Serum total bilirubin (mg/dL)	0.6 (0.4–1.0)	0.5 (0.4–0.8)	1.3 (0.8–3.2)	$<0.001^*$
Serum direct bilirubin (mg/dL)	0.3 (0.2–0.5)	0.2 (0.2–0.3)	0.6 (0.3–2.2)	$<0.001^*$
Serum albumin (g/L)	41.2 (38.7–43.3)	41.9 (39.9–43.5)	38.7 (32.1–42.7)	$<0.001^*$

Values are presented as number (%) or median (interquartile range) unless otherwise specified.

LT: liver transplantation.

* $p < 0.05$ (comparison between the LT and non-LT groups).

Nineteen patients (12.9%) had a history of fractures, with five of them having VF. The VFs were incidentally identified on imaging studies performed for other purposes without prior injury.

Prevalence of VFs

VF was identified in 21 patients with an overall prevalence of 14.3%. The prevalence of VF in the LT and non-LT groups was 15.5% (17/110) and 10.8% (4/37), respectively ($p=0.54$). The grades and sites of the VF are demonstrated in **Fig. 1**. Of the 21 patients with VF, only three reported a history of nonspecific back pain, while the remaining patients, including two cases of severe compression deformity (grade 3b), were asymptomatic. None of the patients had a history of back injury. The prevalence of VF according to age group was 9.1% (3–5 years), 16.9% (>5–10 years), 9.8% (>10–15 years), and 21.1% (15–21 years).

At the time of enrollment, of the five patients with a history of previous VF, three cases displayed no evidence of VF in the radiographs, suggesting a reshaping of the previous VF, and were thus classified into the non-VF group. Conversely, the other two cases demonstrated VF at the same sites as the previous VF. These five patients were LT group.

Factors associated with VFs based on the LT status

In the LT group, patients with VF had a significantly factor associated with VF was male sex ($p=0.046$), whereas other parameters did not differ between those with and without VF (**Table 2**). In the LT group, patients with VF had a significantly low height z-score, high prevalence of height z-score below -2.0 , low 25-hydroxyvitamin D levels, frequent pre-LT hepatopulmonary syndrome, frequent vitamin D deficiency after 1-year post-LT, and elevated serum TB and direct bilirubin (DB) levels at enrollment, when compared to those without VF (**Table 3**). Univariate analysis demonstrated that height score below -2.0 , pre-LT hepatopulmonary syndrome, elevated serum TB and DB levels, and vitamin D deficiency at 1 year post-LT were associated with VF in the LT group. Multivariate analysis established that height z-score below -2.0 was the only significant associated factor for VF (odds ratio, 5.94; 95% confidence interval, 1.49–23.76; $p=0.012$) (**Table 4**).

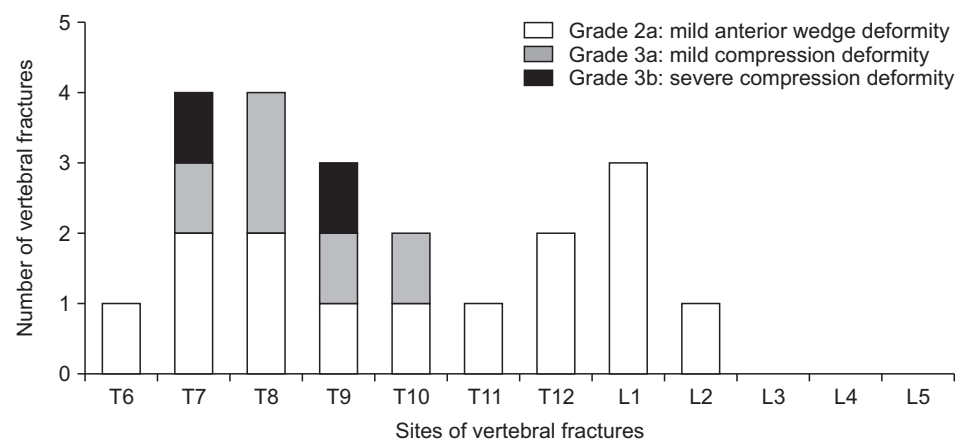


Fig. 1. Number, grading, and sites of vertebral fractures among the patients.

Table 2. Characteristics of patients with and without vertebral fracture in the non-LT group

Characteristics	VF (n=4)	No VF (n=33)	p-value
Male	4 (100)	14 (42.4)	0.046*
Age (yr)	9.0 (6.8–13.6)	8.5 (6.6–12.0)	0.696
Weight z-score	-0.96 (-1.33 to -0.47)	-0.69 (-1.21 to -0.14)	0.625
Height z-score	-0.48 (-1.34 to 0.62)	-0.74 (-1.28 to 0.07)	0.864
Height z-score below -2.0	0 (0)	3 (9.1)	-
Underlying liver disease			
BA	4 (100)	29 (87.9)	1.000
Non-BA	0 (0)	4 (12.1)	1.000
History of complications			
Ascites	1 (25.0)	4 (12.1)	0.456
Variceal bleeding	2 (50.0)	11 (33.3)	0.602
Hepatopulmonary syndrome	1 (25.0)	0 (0)	0.108
PELD/MELD score at enrollment	4 (0–16)	0 (0–8)	0.545
Serum 25-hydroxy vitamin D (ng/mL)	22.9 (19.8–26.5)	23.5 (17.6–29.7)	0.942
Serum total bilirubin (mg/dL)	1.2 (0.6–18.6)	1.3 (0.8–3.5)	0.883
Serum direct bilirubin (mg/dL)	0.6 (0.3–13.1)	0.6 (0.3–2.3)	1.000
Serum albumin (g/L)	34.4 (21.2–41.5)	40.0 (32.0–42.8)	0.493
International normalized ratio	1.2 (1.0–1.4)	1.1 (1.1–1.2)	0.493

Values are presented as number (%) or median (interquartile range) unless otherwise specified.

VF: vertebral fracture, LT: liver transplantation, PELD: pediatric end-stage liver disease, MELD: model for end-stage liver disease, -: not available.

* $p < 0.05$.

Table 3. Characteristics of patients with and without vertebral fracture in the LT group

Characteristics	VF (n=17)	No VF (n=93)	p-value
Male	7 (41.2)	41 (44.1)	0.824
Age (yr)	9.1 (6.3–13.4)	8.8 (5.5–11.8)	0.744
Weight z-score	-0.79 (-1.43 to 0)	-0.77 (-1.35 to -0.04)	0.744
Height z-score	-2.12 (-2.66 to -0.89)	-1.19 (-1.74 to -0.13)	0.016*
Height z-score below -2.0	9 (52.9)	20 (21.5)	0.010*
Underlying liver disease			
BA	14 (82.4)	81 (87.1)	0.700
Non-BA	3 (17.6)	12 (12.9)	0.700
History of pre-LT complications [†]			
Ascites	10/15 (66.7)	64/88 (72.7)	0.757
Variceal bleeding	9/15 (60.0)	39/88 (44.3)	0.260
Hepatopulmonary syndrome	3/15 (20.0)	2/88 (2.3)	0.021*
PELD/MELD score at LT	20 (17–23)	18 (15–22)	0.414
Age at LT (yr)	1.8 (1.3–5.0)	1.6 (1.1–2.2)	0.203
Duration of follow-up following LT (yr)	4.7 (2.5–10.2)	6.6 (3.9–9.6)	0.454
Vitamin D deficiency after 1-year post-LT	10 (62.5) [§]	33 (35.5)	0.041*
Cumulative prednisolone dose (mg/kg)	278.5 (146.5–559.0)	209.7 (131.3–365.6)	0.166
Serum tacrolimus level (ng/mL)	5.5 (4.4–6.0)	4.8 (4.1–5.4)	0.073
Serum magnesium level (mg/dL)	1.7 (1.6–1.8)	1.7 (1.6–1.8)	0.979
Serum 25-hydroxy vitamin D (ng/mL)	19.8 (16.0–28.3)	26.7 (20.6–34.1)	0.038*
Serum total bilirubin (mg/dL)	0.6 (0.5–1.5)	0.5 (0.4–0.7)	0.030*
Serum direct bilirubin (mg/dL)	0.3 (0.2–0.6)	0.2 (0.2–0.3)	0.014*
Serum albumin (g/L)	41.1 (38.6–42.8)	42.2 (40.0–43.6)	0.218

Values are presented as number (%) or median (interquartile range) unless otherwise specified.

LT: liver transplantation, VF: vertebral fracture, BA: biliary atresia, PELD: pediatric end-stage liver disease, MELD: model for end-stage liver disease.

* $p < 0.05$.

[†]Data of seven patients were missing.

[§]Data of one patient was missing.

Table 4. Univariate and multivariate analyses of factors associated with vertebral fracture in the LT group

Characteristics	Univariate analysis		Multivariate analysis	
	Odds ratios (95% CI)	<i>p</i> -value	Odds ratios (95% CI)	<i>p</i> -value
Height z-score below -2.0	4.11 (1.40–12.01)	0.010	5.94 (1.49–23.76)	0.012
Pre-LT hepatopulmonary syndrome	10.75 (1.63–71.04)	0.014	7.70 (0.75–78.74)	0.085
Vitamin D deficiency after 1-year post-LT	3.03 (1.01–9.08)	0.048	2.03 (0.53–7.82)	0.304
Serum total bilirubin	3.80 (1.00–14.43)	0.049	5.50 (0.20–191.00)	0.347
Serum direct bilirubin	18.70 (1.20–291.85)	0.037	0.37 (0.00–367.3)	0.777

LT: liver transplantation; CI: confidence interval.

DISCUSSION

In the present study, the overall prevalence of VF in children with CLD was 14.3%, with a slightly higher prevalence in the LT group than in the non-LT group (15.5% and 10.8% in the LT and non-LT groups, respectively). These results indicate that VF is common in children with CLD and can manifest across all age groups, both before and after LT. This study highlights that early detection of VF in children with CLD is essential, regardless of back pain symptoms, to avoid long-term spine deformities.

VF is common in adults with CLD before LT, with a reported prevalence of 8–36% [4,5,10]. However, data on pediatric patients before and after LT are limited. In a retrospective study involving 29 children with BA, with and without LT, VFs were assessed using dual-energy X-ray absorptiometry (DXA) taken at a median age of 7.9 years. The study identified no evidence of VF in these patients [12]. The prevalence of VF in our LT recipients was consistent with that reported by Valta et al. [8]. The authors reported a VF prevalence of 18% in 40 adolescent LT recipients (median age, 14.0 years) at 7 years post-LT, as assessed by DXA and spinal radiographs. In contrast, Ee et al. [14] evaluated BMD using DXA in 42 LT recipients and reported no fractures occurring after LT for more than 5 years. Another study utilizing plain spinal radiographs of 40 young adults following solid organ transplantation in childhood with a mean follow-up of 11 years revealed a VF prevalence of 35% [15]. This discrepancy in the prevalence of VF may be attributed to differences in the study population, sample size, and methods used for VF documentation. The assessment of VFs using DXA is generally less accurate and less sensitive than that with plain radiography [16,17]. Therefore, VFs can either be missed or underdiagnosed when using DXA. In this study, we employed plain radiography due to its lower cost and higher accuracy than those of DXA in assessing VF.

Most patients with VF were asymptomatic, including the two patients with severe compression deformities. Back pain was observed in only three patients with VF, while seven of the 10 patients who reported a history of back pain had no VF. Therefore, back pain is neither sensitive nor specific for VFs. This finding is consistent with those of the previous studies demonstrating that VFs in children are frequently asymptomatic and remain undetected without active surveillance [8,9]. Young children may not express back pain symptoms. However, most VFs in our study were diagnosed in children older than 5 years, with only two patients below 5 years of age.

Five patients in the LT group had previously documented VF. Three of these patients (aged 16.4, 12.8, and 12.1 years) had no VF at enrollment, suggesting a reshaping of previous VFs, documented at the ages of 1.3, 2.5, and 11.1 years, with LT performed at 2.9, 1.3 and 1.0 years of age, respectively. The remaining two patients (aged 15.7 years both) had a history of VF at the ages of 4 and 5.5 years and these fractures were still present at enrollment at the

same sites. The lack of VF reshaping may be explained by the fact that these patients were older at LT (13.7 and 5 years), and long-standing chronic cholestatic liver disease could have contributed to poor bone health.

The present study demonstrated that the male sex was the only factor associated with VF in the non-LT group. This may be attributed to the fact that male patients engaged in more physical activity compared to female patients. However, this observation may be coincidental due to the small number of patients in the non-LT group. The prevalence and risk factors for VF in children with CLD without LT require further research with a large sample size.

In the LT group, univariate analysis demonstrated that a height z-score below -2.0 , pre-LT hepatopulmonary syndrome, vitamin D deficiency after 1-year post-LT, and high serum total and DB were associated with VFs. However, height z-score below -2.0 remained the only factor statistically significant in multivariate analysis. These findings differ from those of a previous study on post-LT adolescents that confirmed that the essential factors associated with VF included older age at LT, recent LT, high body mass index, and low BMD z-scores [8]. Another study involving children who underwent solid organ transplantation demonstrated that LT recipients had a higher risk of VF than those receiving other solid organ transplants. Furthermore, other risk factors for VF included older age at transplantation and fractures before transplantation [9]. The variations in risk factors could be due to differences in the study population and VF assessment methods. However, we did not identify differences in the cumulative dosages of corticosteroids and tacrolimus between patients with and without fractures. These findings were similar to those of a previous study [9].

In LT recipients, cholestatic jaundice arising from various etiologies, mainly bile duct stenosis, contributed to the malabsorption of fat-soluble vitamins and vitamin D deficiency. The association between pre-LT hepatopulmonary syndrome and VF has not yet been reported. Hepatopulmonary syndrome, a complication of long-standing cirrhosis and portal hypertension [18], is associated with systemic inflammation and hepatic osteodystrophy rather than being a direct causal factor of VF. However, this study included only a small number of patients with cholestasis after LT and pre-LT hepatopulmonary syndrome. Therefore, these associations warrant further research.

The vitamin D status in children with CLD usually improves after LT [19]. However, vitamin D deficiency can still be detected in post-LT children during long-term follow-up [8,20]. Vitamin D deficiency can result in low bone mass, leading to fractures. Therefore, vitamin D levels after LT should be monitored and treatment should be offered when vitamin D deficiency is detected.

Patients with VF in the LT group had a significantly lower height z-score than the score of those without VF. The median height z-scores of these patients were -2.12 and -1.19 at the median duration of follow-up after LT of 4.7 years and 6.6 years, respectively. Children catch up with linear growth, with their height z-scores gradually improving after LT [21-24]. Reported mean height z-scores at 5 years after pediatric LT vary from -1.2 to -0.1 [21-24]. In this study, the height z-scores of the patients with VF after LT were significantly lower than those reported in previous studies. Multiple factors are associated with linear growth impairment after LT, including growth retardation at the time of LT, graft dysfunction, high cumulative steroid doses, and prolonged steroid exposure [21-25]. Additionally, VF not only reduces the vertebral height but also causes the bending of the spine. Therefore, VF could

partly contribute to reducing height z-scores in the aforementioned patients. Given that a height z-score below -2.0 was the only significantly associated factor for VF in children after LT, these findings imply the importance of establishing this threshold for screening VF in these patients.

This study had several limitations. Our data were based on a single-center study, with the determination of risk factors relying on the retrospective review of clinical data, some of which were incomplete. The frequency of vitamin D level monitoring was not uniform among the post-LT patients. Moreover, a single spine radiograph performed in a cross-sectional study could not determine the onset of VF, whether it transpired before or after LT, because reshaping of the VF in young children has been reported [26,27]. Additionally, we included a small number of patients in the non-LT group, most of whom had mild liver disease. Our study included only children older than 3 years due to unproven accuracy in the radiographic interpretation of VF in young children [13]. Therefore, the prevalence of VF in children below 3 years of age was not accounted for in the study. Finally, we did not collect patient nutritional data, calcium intake data, or pubertal status.

Conclusion

VF in children with CLD is common before and after LT, with an overall prevalence of 14.3%. Most patients with VFs remain asymptomatic. Screening for VF should be considered in those with a height z-score below -2.0 after LT. The prevalence and risk factors of VF in children with CLD without LT require further research with a large sample size.

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