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Association between pre-operative concurrent fibular pseudoarthrosis and risk of ankle valgus after surgery of congenital pseudarthrosis of the tibia

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Declarations

Ethical approval

This study was approved by Institutional Review Board of the Hunan Children's Hospital permission and informed consent from all included patients, and all informed consents were obtained from all included patients' parents or legal guardian.

Data availability statement

Data will be made available on request.

Declaration of interests statement

No financial or non-financial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

Author contribution statement

Ge Yang: Conceived and designed the study; Analysed and interpreted the data; wrote the paper.

Hui Yu: Conceived and designed the study; Review and record data; Analysed and interpreted the data; wrote the paper.

Zhuoyang Li: Conceived and designed the study; Analysed and interpreted the data; Wrote the paper.

Haibo Mei: Analysed and interpreted the data; Review and record data.

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Qian Tan: Conceived and designed the study; Analysed and interpreted the data; Wrote the paper.

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Abstract

Background: This study evaluated whether the pre-operative concurrent fibular pseudoarthrosis related to risk of ankle valgus deformity in congenital pseudarthrosis of the tibia (CPT) patients with successful surgery treatment after adjusting for other covariates.

Method: Children with CPT who were treated at our institution from January 1, 2013, and December 31, 2020 were retrospectively reviewed. The independent variable was the pre-operative concurrent fibular pseudoarthrosis and the dependent variable was ankle valgus. A multivariable logistic regression analysis was performed adjusting for variables that might affect the ankle valgus. Then, a subgroup analysis with stratified multivariate logistic regression models was used to access this association.

Results: Of all included 319 children with successful surgery treatment, 140 (43.89%) developed an ankle valgus deformity. Among them, 104 (50.24%) of 207 patients with pre-operative concurrent fibular pseudoarthrosis developed an ankle valgus deformity, compared with 36 (32.14%) of 112 patients without pre-operative concurrent fibular pseudoarthrosis (p = 0.002). After adjusting for gender; body mass index (BMI); fracture age; surgery age; surgery method; type 1 neurofibromatosis (NF-1); limb-length discrepancy (LLD); CPT location and fibula cystic degeneration, patients who with concurrent fibular pseudoarthrosis had a higher risk of ankle valgus compared with those without concurrent fibular pseudoarthrosis (odds ratio [OR]: 2.326, 95%

confidence interval [CI]: 1.345-4.022). This risk further increased in CPT location with lower 3rd (OR: 2.195, 95% CI: 1.154-4.175), surgery age less than 3-years (OR: 2.485, 95% CI: 1.188-5.200), LLD less than 2cm (OR: 2.478, 95% CI: 1.225-5.015), and patients with NF-1 positive (OR: 2.836, 95% CI: 1.517- 5.303).

Conclusion: Our results indicated that patients CPT patients with pre-operative concurrent fibular pseudoarthrosis is associated with a significantly increased risk of ankle valgus when compared with those without pre-operative concurrent fibular pseudoarthrosis, especially in patients with CPT location at distal third, surgery age less than 3-years, LLD less than 2cm, and NF-1 positive.

Key words: Congenital pseudarthrosis of the tibia, fibular pseudoarthrosis, ankle valgus, NF-1

Introduction

Congenital pseudarthrosis of the tibia (CPT) is one of the most challenging conditions in paediatric orthopaedics. Its incidence varies between 1 in 140,000 and 1 in 250,000[1]. Over 50% of these cases are associated with type 1 neurofibromatosis (NF-1) and 15% with fibrous dysplasia[2, 3]. Almost half of the fractures occurred before the patient was 2 years old. Most cases were unilateral, occurring between the middle and lower third of the tibia. Notably, more than half of the cases involve the fibula at the same time[4].

A variety of prognostic factors have been considered to be associated with the disease[5, 6]. Neurofibromatosis has an uncertain impact on the course of the disease[7, 8]. In addition, the earlier the fracture occurs, the more adverse consequences are expected[6, 9]. In fact, the more distal the fracture and closer to the ankle, the more difficult it is to fix the distal end and the more complications there will be[6]. Severe atrophy and extensive sclerosis of the bone fragments at the pseudarthrosis, narrowing of the tibia and the co-existence of a peroneal pseudarthrosis are also considered to be poor prognostic factors for the treatment of pseudarthrosis[6]. Although the current stage of surgical treatment has been partially successful, some patients with initially good results have experienced serious functional complications such as ankle valgus that have led to deterioration in function as the follow-up period has increased[6, 10].

Though the etiology of ankle valgus in children with CPT is poorly understood [11], fibular lesions are thought to be a closely related common pathophysiology [12]. Despite some authors believe that the presence or absence of fibular pseudarthrosis does

not affect the refracture of the tibia, whereas the concurrent presence of fibular involvement appears to cause ankle valgus deformity [13-15]. Their conclusions are unconvincing due to the small sample size. Accordingly, the aim of the current study was to evaluate authors' results of the correlation between the presence or absence of fibular pseudarthrosis and risk of ankle valgus in successful healing CPT patients with a large sample size, and to search for the special population who would more likely to have postoperative ankle valgus with fibular pseudarthrosis.

Materials and Methods

Study Design

After obtaining Institutional Review Board of the XXX Children's Hospital permission and informed consent from their parents, we retrospectively reviewed all 528 children with CPT who were treated at our institution from January 1, 2013, and December 31, 2020.

The inclusion criteria were as follows: (1) more than 18 months of follow-up data available; (2) diagnosed with CPT and receive surgical treatment; (3) CPT is located on a unilateral tibia; (3) operations were performed in The XXX Children's Hospital; (4) a complete dataset existed for each patient. The exclusion criteria were as follows: (1) received surgical treatment at another hospital; (2) concomitant other diseases requiring surgical treatment such as tumors; (3) had any known bone disease, other chronic diseases (eg, celiac disease, thyroid disorder, systemic glu-cocorticoids).

According to the inclusion and exclusion criteria, 201 cases were excluded for no surgical treatment. To avoid statistical duplication of baseline data, 6 cases with bilateral CPT were excluded. In order to obtain more precise statistical results, 2 cases with non-healing were excluded. Finally, 319 cases were included. The flow chart of sample selection was shown in Figure 1. We finally included 319 pediatric patients with Crawford type IV CPT who underwent surgical treatment[16], and 3 orthopedic surgeons retrospectively reviewed all clinical and imaging examination data. Medical records were reviewed for demographic information, age of fracture, surgery age, concurrent fibular pseudoarthrosis, CPT location, fibula cystic degeneration, surgical

method, and complication of ankle valgus. Follow-up was defined as one year after final bone union.

Surgical Methods

We divided the 319 cases into 2 groups according to surgical methods: simple intramedullary rod fixation group and cross-union group. The "cross-union" procedure was based on previous literature [17, 18], which means both the tibia and fibula were united through autogenous iliac wrapped bone transplantation. Moreover, depending on how the fibula ends were treated, the cross-union group was categorized into 2 subgroups: 3-in-1 and 4-in-1 groups [19, 20]. No matter in which group, the intramedullary rod fixation was used through ankle. All cases included in this study were performed by the same surgical group.

Covariates

In the present study, the independent variable was whether the fibula have a concurrent fibular pseudoarthrosis. The dependent variable was postoperative ankle valgus. The degree of ankle valgus was assessed by the tibiotalar angle measured at the intersection of the midline of the tibial tuberosity and the inferior line of the flat cartilage of the talar dome. Patients with more than 4° of ankle valgus were defined as having an ankle valgus deformity. The covariates were as follows: gender, body mass index (BMI), fracture age, surgery age, NF-1, surgery method, limb-length discrepancy (LLD), CPT location, and fibula cystic degeneration. We defined 2 cm as a turn point of LDD for this is an indication for treatment in patients with a leg length discrepancy of ≥2 cm [21].

Statistical Analysis

The significant differences between different groups were tested by Chi-squared tests and one-way analysis of variance or Kruskal–Wallis's H test. The risk of ankle valgus between patients with concurrent fibular pseudoarthrosis and those without concurrent fibular pseudoarthrosis were estimated by using multivariate logistic regression models. Then, a stratified multivariate logistic regression was used to perform the subgroup analysis. $P < 0.05$ mean statistically significant. All calculations were performed using R version 3.4.3 (http://www.R-project.org, The R Foundation) and Empower software (www.empowerstats.com; X&Y solutions, Inc., Boston MA).

Results

The demographic and all clinical data of the studied patients are summarized in Table 1. Of all 319 patients undergoing surgery treatment, 141 (44.20%) were treated with 4-in-1, and 178 (55.80%) were treated with 3-in-1. 140 (43.89%) developed an ankle valgus deformity, among them 104 (50.24%) of 207 patients with concurrent fibular pseudoarthrosis developed an ankle valgus deformity, compared with 36 (32.14%) of 112 patients without concurrent fibular pseudoarthrosis ($p = 0.002$).

Table 2 showed the results of univariate analysis. Concurrent fibular pseudoarthrosis, fibula cystic degeneration, surgery age, and LLD were risk factors of ankle valgus ($p < 0.05$). We also conducted multivariable logistic regression analyses for the independent effects of NF-1, CPT location, fibula cystic degeneration, surgery age, and LLD on the risk of ankle valgus, respectively (Supplementary Table S1). The results showed that only NF-1 was significantly independent risks for ankle valgus after adjusting for other covariates.

Table 3 showed the relationships between concurrent fibular pseudoarthrosis and ankle valgus in different models. The results from unadjusted, minimally adjusted, and fully adjusted analyses were shown simultaneously according to the recommendation of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement[22]. In the fully adjusted model, OR for developing an ankle valgus deformity in patients with concurrent fibular pseudoarthrosis was 2.326 (95% CI: 1.345-4.022) compared with those without concurrent fibular pseudoarthrosis.

Table 4 showed the results of subgroup analyses stratified by NF-1, CPT location,

surgery age, and LLD. In CPT location with lower 3rd (OR: 2.195, 95% CI: 1.154-4.175), surgery age less than 3-years (OR: 2.485, 95% CI: 1.188-5.200), LLD less than 2cm (OR: 2.478, 95% CI: 1.225-5.015), and patients with NF-1 positive (OR: 2.836, 95% CI: 1.517- 5.303) the risk of ankle valgus further increased with a concurrent fibular pseudoarthrosis.

Discussion

Considering that CPT is a rare disease[1], this study here comprehensively investigate that whether concurrent fibular pseudoarthrosis affects the risk of postoperative ankle valgus deformity with a large sample size. Our study demonstrated that after adjusting for potential risk factors for developing an ankle valgus deformity, CPT patients with preoperative concurrent fibular pseudoarthrosis had a significantly higher risk of postoperative ankle valgus compared with those without concurrent fibular pseudoarthrosis. Especially, this risk further increased in CPT location at distal third, surgery age less than 3-years, LLD less than 2cm, and patients with NF-1 positive.

There are several treatments available for CPT to achieve a long-term union[10, 23, 24]. However, little research attention has been paid to the ankle valgus deformity that occurs in its postoperative period. Whereas, this is considered by many researchers as a possible important cause of postoperative re-fracture [6, 13-15]. Therefore, it is necessary to identify high-risk patients and correct modifiable risk factors to minimize the risk of ankle valgus. In this research, we found that concurrent fibular pseudoarthrosis, and NF-1 were significantly independent risks for developing ankle valgus after bone union, which is consistent with the results of previous researches [6, 14, 25-27]. However, none of them discussed the association between concurrent fibular pseudoarthrosis and the risk of ankle valgus.

Previous studies have reported that concurrent fibular pseudarthrosis is present in more than half of the cases [28, 29]. Our study showed a consistent result. Studies of normal growth have documented the distal migration of the fibula relative to the tibia

that the total percentage contribution to longitudinal growth from the proximal fibular epiphysis is greater than that from the distal fibular epiphysis (61% versus 39%) [30-32]. Whereas, histologic studies indicate the presence of fibrous hamartoma tissue and an increase in the thickness of the abnormal periosteum at the site of pseudarthrosis [33, 34]. We surmised that the concurrent presence of fibular pseudarthrosis paly a poor prognostic factors in the growth of the tibiofibula after bone union and lead to ankle valgus. The effect on the subsequent growth of the fibula is particularly pronounced in the distal third. Our subgroup analyses further supported this hypothesis that CPT location with distal 3rd had a higher risk of ankle valgus with a concurrent fibular pseudoarthrosis.

The choice of surgery age for CPT patients is still controversial. Various studies have shown that youth is an unfavourable prognostic factor for CPT treatment and that these patients have a higher rate of bone nonunion [13, 14, 35, 36]. However, our previous study shows that there is no need to defer surgery time until the child is older than 3 years of age [37]. Other studies have similarly supported the safety and effectiveness of surgical intervention in young patients aged 1 to 3 years [6, 38]. Our study here further discovers that surgery age less than 3 years has no significantly affect for ankle valgus. This result suggests there is no need to delay surgery to the age of 3 to 10. Notably, however, our subgroup analysis suggested a higher risk of postoperative ankle valgus in children under 3 years of age with concurrent fibular pseudoarthrosis. We therefore recommend that the surgery age for the patients with concurrent fibular pseudoarthrosis could be deferred to the age of 3 to 10.

The site of the pseudoarthrosis also plays a crucial role. Distal fractures closer to the ankle are more difficult to fix and associate with more complications [10]. In addition, CPT located in the distal third undoubtedly has a more pronounced negative effect on the specific growth pattern of the tibiofibular[32]. It may cause the tibia to grow faster than the fibula, leading to ankle valgus deformity. The results of our subgroup analysis further validate this conclusion, suggesting a higher risk of postoperative ankle valgus in CPT patients with concurrent fibular pseudoarthrosis located in the distal third. LLD should also be noted as an independent factor influencing ankle valgus in CPT patients with concurrent fibular pseudoarthrosis. This may be related to the fact that patients with an LLD less than 2 cm bear more weight on the affected limb after healing, which also suggests that we should avoid premature weight-bearing walking on the affected limb after surgery. Neurofibromatosis may have a detrimental effect on the prognosis of pseudarthrosis. Our results also indicate that NF-1 is a negative independent factor of ankle valgus. Furthermore, in the results of our subgroup analysis, the incidence of ankle valgus was significantly higher in NF-1 positive CPT patients with concurrent fibular pseudoarthrosis than in those without concurrent fibular pseudoarthrosis. However, many studies have shown that the role of NF-1 in the prognosis of CPT is uncertain, as is its impact on the development of complications[2, 39, 40]. Our results suggest a different conclusion. Post-operative ankle protection for these patients needs to be more careful to avoid ankle valgus deformity.

Our study also has some limitations. First, the observational design of the cross-sectional study does not allow us to determine the time correlation of the fibular pseudarthrosis on postoperative ankle valgus. Second, the biases caused by other potential confounding factors are not excluded. For example, as the data of preoperative course is missing because many parents cannot record it accurately, we did not adjust this potential confounding factor in the present study. Third, it is mandatory to do the evaluation at skeletal maturity due to growth abnormalities of the distal tibia and fibula, while this cross-sectional study is lack of long-term follow-up results. Our another ongoing RCTs may be able to address these shortcomings.

Conclusion

Our results lead to the following conclusions that CPT patients with concurrent fibular pseudoarthrosis is associated with an increased risk of ankle valgus when compared with those without concurrent fibular pseudoarthrosis. This risk further increased in CPT location at distal third, surgery age less than 3-years, LLD less than 2cm, and patients with NF-1 positive.

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Table 1 Description of 319 patients included in the present study.

Fibular pseudoarthrosis	**All (319)**	**Yes (207)**	**No (112)**	***P*-value**
BMI (kg/m^2)	16.76 ± 3.19	16.74 ± 3.09	16.80 ± 3.38	0.862
Gender (%)				
Male	202 (63.32%)	139 (67.15%)	63 (56.25%)	0.054
Female	117 (36.68%)	68 (32.85%)	49 (43.75%)	
Fracture age (years)	1.68 ± 2.01	1.57 ± 2.11	1.45 ± 1.59	0.596
Surgery age (years)	3.84 ± 3.31	3.71 ± 3.34	3.15 ± 3.40	0.156
LLD (cm)	2.58 ± 2.91	2.72 ± 3.14	1.52 ± 2.16	<0.001
Surgery method				
4-in-1	141 (44.2%)	79 (44.1%)	62 (44.3%)	0.164
3-in-1	178 (55.8%)	100 (55.9%)	78 (55.7%)	
CPT location				
Proximal 2/3	85 (26.65%))	44 (39.29%)	41 (19.81%)	<0.001
Distal 1/3	234 (73.35%)	166 (80.19%)	68 (60.71%)	
NF-1				
Yes	231 (72.41%)	147 (71.01%)	84 (75.00%)	0.447
No	88 (27.59%)	60 (28.99%)	28 (25.00%)	
Fibula cystic degeneration				
Yes	23 (7.21%)	4 (1.93%)	19 (16.96%)	<0.001
No	296 (92.79%)	203 (98.07%)	93 (83.04%)	
Ankle valgus				
Yes	140 (43.89%)	104 (50.24%)	36 (32.14%)	0.002
No	179 (56.11%)	103 (49.76%)	76 (67.86%)	

Mean ± SD for continuous variables: *P* value was calculated by one-way ANOVA (normal distribution) and Kruskal-Wallis H (skewed distribution) test % for categorical variables: *P* value was calculated by chi-square test. Abbreviations: BMI, body mass index; LLD, limb-length discrepancy; CPT, congenital pseudarthrosis of the tibia; NF-1, type 1 neurofibromatosis.

Table 2. Univariate analysis of the risk factors of ankle valgus.

Ankle valgus	Statistics, n (%)	OR (95% CI)	*P*-Value
Gender			
Female	117 (36.677%)	Reference	
Male	202 (63.323%)	0.914 (0.578, 1.445)	0.699
Fracture age (years)			
<1	163 (51.097%)	Reference	
≥1	156 (48.903%)	1.326 (0.851, 2.066)	0.212
Surgery age (years)			
<3	190 (59.561%)	Reference	
≥3	129 (40.439%)	2.266 (1.435, 3.579)	0.001
Surgery method			
4-in-1	141 (44.2%)	Reference	
3-in-1	178 (55.8%)	1.0 (0.6, 1.6)	0.978
NF-1			
No	88 (27.586%)	Reference	
Yse	231 (72.414%)	1.537 (0.927, 2.547)	0.096
CPT location			
Proximal 2/3	85 (26.646%)	Reference	
Distal 1/3	234 (73.354%)	1.626 (0.973, 2.718)	0.063
Fibula cystic degeneration			
No	296 (92.790%)	Reference	
Yes	23 (7.210%)	0.331 (0.120, 0.916)	0.033
LLD (cm)			
<2	204 (63.950%)	Reference	
≥2	115 (36.050%)	2.114 (1.328, 3.364)	0.002
BMI (kg/m^2)			
<20	296 (92.790%)	Reference	
≥20	23 (7.210%)	1.432 (0.612, 3.349)	0.408
Concurrent fibular pseudoarthrosis			
No	112 (35.110%)	Reference	
Yes	207 (64.890%)	2.132 (1.318, 3.449)	0.002

Abbreviations: BMI, body mass index; LLD, limb-length discrepancy; CPT, congenital pseudarthrosis of the tibia; NF-1, type 1 neurofibromatosis; CI, confidence interval; OR, odds ratio.

Table 3 Relationship between the concurrent fibular pseudoarthrosis and ankle valgus in different models.

Concurrent fibular pseudoarthrosis	Unadjusted model β (95% CI)	Minimally adjusted model β (95% CI)	Fully adjusted model β (95% CI)
No	Reference	Reference	Reference
Yes	2.132 (1.318, 3.449)	2.270 (1.370, 3.759)	2.326 (1.345, 4.022)
P value	0.00205	0.00145	0.00252

Unadjusted model adjust for: None.

Minimally adjusted model adjust for: Gender; BMI; Fracture age; Surgery age.

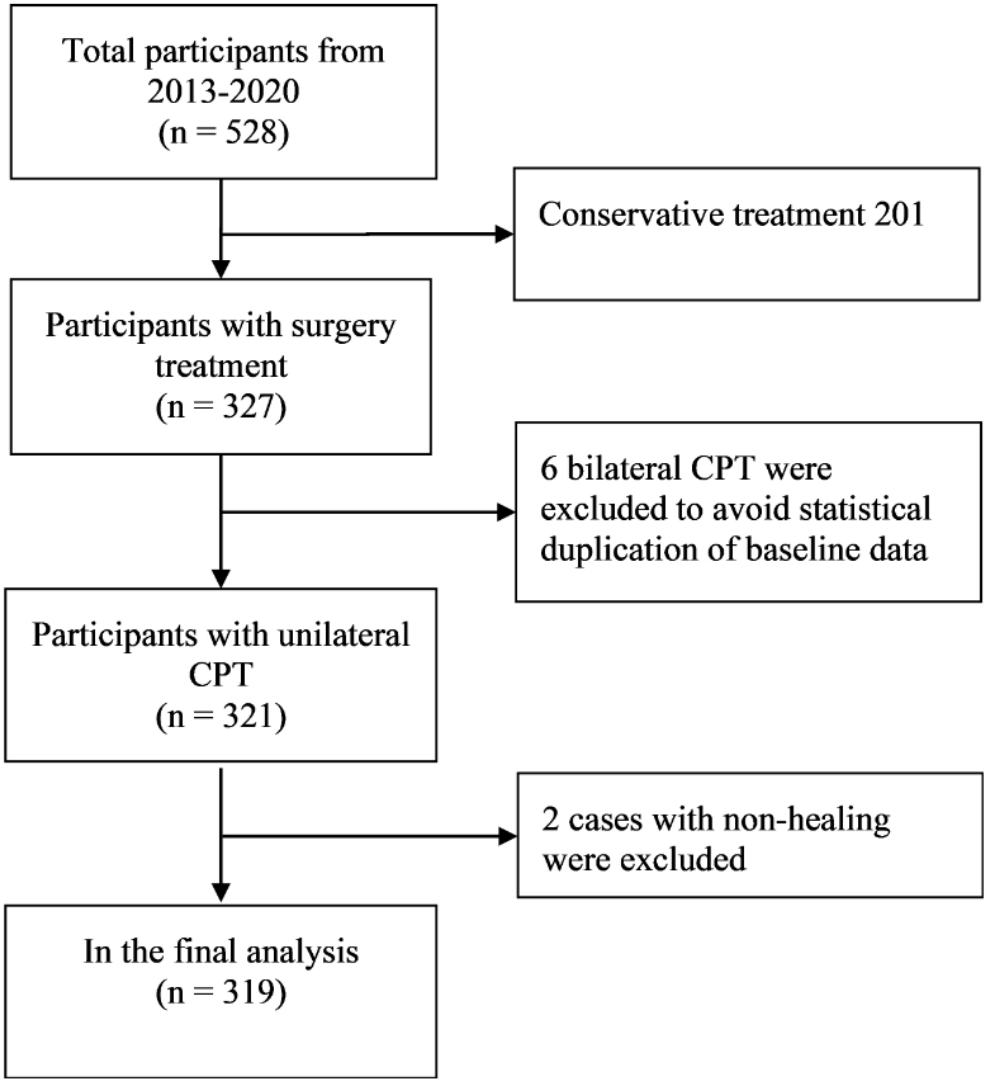
Fully adjusted model adjust for: Gender; BMI; Fracture age; Surgery age; Surgery method; NF-1; LLD; CPT location; Fibula cystic degeneration.

Abbreviations: BMI, body mass index; LLD, limb-length discrepancy; CPT, congenital pseudarthrosis of the tibia; NF-1, type 1 neurofibromatosis; CI, confidence interval; OR, odds ratio.

Table 4 Effect modification of patients with concurrent fibular pseudoarthrosis on risk of ankle valgus compared with those without concurrent fibular pseudoarthrosis, stratified by NF-1, CPT location, surgery age, and LLD.

	OR (95% CI)	***P*-Value**
CPT location		
Proximal 2/3	1.580 (0.563, 4.431)	0.3850
Distal 1/3	2.195 (1.154, 4.175)	0.0166
Surgery age (years)		
<3	2.485 (1.188, 5.200)	0.0157
≥3	1.392 (0.604, 3.208)	0.4370
LLD (cm)		
<2	2.478 (1.225, 5.015)	0.0116
≥2	1.035 (0.394, 2.723)	0.9441
NF-1		
No	0.981 (0.335, 2.871)	0.9725
Yes	2.836 (1.517, 5.303)	0.0011

Above models adjusted for: gender; BMI; Gender; BMI; Fracture age; Surgery age; Surgery method; NF-1; LLD; CPT location; Fibula cystic degeneration. In each case, the model is not adjusted for the stratification variable itself.



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Supplementary Table S1 Relationships between NF-1, CPT location, Fibula cystic degeneration, and LLD and ankle valgus in different models.

	Unadjusted model	**Minimally adjusted model**	**Fully adjusted model**
	OR (95% CI), *p*-value	**OR (95% CI), *p*-value**	**OR (95% CI), *p*-value**
NF-1			
No	Reference	Reference	Reference
Yse	1.5 (0.9, 2.5) 0.096	1.5 (0.9, 2.5) 0.114	1.9 (1.1, 3.3) 0.021
CPT location			
Proximal 2/3	Reference	Reference	Reference
Distal 1/3	1.6 (1.0, 2.7) 0.063	1.7 (1.0, 2.8) 0.054	1.4 (0.8, 2.5) 0.214
Fibula cystic degeneration			
No	Reference	Reference	Reference
Yes	0.3 (0.1, 0.9) 0.033	0.3 (0.1, 0.9) 0.036	0.6 (0.2, 1.8) 0.349
LLD (cm)			
<2	Reference	Reference	Reference
≥2	2.1 (1.3, 3.4) 0.002	2.1 (1.3, 3.4) 0.001	1.6 (1.0, 2.8) 0.060

Unadjusted model adjust for: None.

Minimally adjusted model adjust for: Gender; BMI; Fracture age; Surgery age.

Fully adjusted model adjust for: Gender; BMI; Fracture age; Surgery age; Surgery method; NF-1; LLD; CPT location; Fibula cystic degeneration; Concurrent fibular pseudoarthrosis.

In each case, the model is not adjusted for the variable itself.

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Association between preoperative concurrent fibular pseudoarthrosis and risk of postoperative ankle valgus in patients with congenital pseudarthrosis of the tibia

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Association between preoperative concurrent fibular pseudoarthrosis and risk of postoperative ankle valgus in patients with congenital pseudarthrosis of the tibia

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Association between preoperative concurrent fibular pseudoarthrosis and risk of postoperative ankle valgus in patients with congenital pseudarthrosis of the tibia

Abstract

Background: This study evaluated the correlation of preoperative concurrent fibular pseudoarthrosis with the risk of ankle valgus deformity in patients with congenital pseudarthrosis of the tibia (CPT) who underwent successful surgical treatment.

Method: The children with CPT who were treated at our institution between January 1, 2013 and December 31, 2020 were retrospectively reviewed. The independent variable was preoperative concurrent fibular pseudoarthrosis, and the dependent variable was postoperative ankle valgus. Multivariable logistic regression analysis was performed after adjusting for variables that might affect the risk of ankle valgus. Subgroup analyses with stratified multivariable logistic regression models was used to assess this association.

Results: Of the 319 children who underwent successful surgical treatment, 140 (43.89%) developed ankle valgus deformity. Moreover, 104 (50.24%) of 207 patients with preoperative concurrent fibular pseudoarthrosis developed an ankle valgus deformity compared with 36 (32.14%) of 112 patients without preoperative concurrent fibular pseudoarthrosis (p = 0.002). After adjusting for sex, body mass index (BMI), fracture age, age of patient undergoing surgery, surgery method, type 1 neurofibromatosis (NF-1), limb-length discrepancy (LLD), CPT location, and fibular cystic change, patients with concurrent fibular pseudoarthrosis presented a higher risk of ankle valgus than those without concurrent fibular pseudoarthrosis (odds ratio

[OR]: 2.326, 95% confidence interval [CI]: 1.345–4.022). This risk further increased with CPT location at the distal one third of the tibia (OR: 2.195, 95% CI: 1.154–4.175), age <3 years of patient undergoing surgery (OR: 2.485, 95% CI: 1.188–5.200), LLD <2 cm (OR: 2.478, 95% CI: 1.225–5.015), and occurrence of NF-1 disorder (OR: 2.836, 95% CI: 1.517–5.303).

Conclusion: Our results indicate that patients with CPT and preoperative concurrent fibular pseudoarthrosis have a significantly increased risk of ankle valgus compared with those without preoperative concurrent fibular pseudoarthrosis, particularly in those with CPT location at the distal third, age less than 3 years at surgery, LLD less than 2 cm, and NF-1 disorder.

Key words: congenital pseudarthrosis of the tibia, fibular pseudoarthrosis, ankle valgus, type 1 neurofibromatosis

Introduction

Congenital pseudarthrosis of the tibia (CPT) is one of the most challenging conditions in pediatric orthopedics. Its incidence varies between 1 in 140,000 and 1 in 250,000[1]. Our latest study revealed that 68.9% of these cases were associated with type 1 neurofibromatosis (NF-1) and 53.7% with fibrous dysplasia in China[2, 3]. Almost half of the fractures occur before the age of two years, with most patients presenting unilateral signs, particularly occurring between the middle and distal one third of the tibia. Notably, more than half of the cases simultaneously involve fibula[4].

Various prognostic factors are considered to be associated with this disease[5, 6]. Neurofibromatosis has an uncertain impact on the course of the disease[7, 8]. In addition, the earlier a fracture occurs, the worse adverse consequences are expected[6, 9]. Moreover, the more distal but closer to the ankle, the more complicated to fix the distal end of the fractured bone[6]. Severe atrophy and extensive sclerosis of bone fragments in pseudarthrosis, shortened tibia, and the co-existence of fibular pseudarthrosis are also considered to be poor prognostic factors affecting CPT treatment[6]. The main goal of the current surgical treatment of CPT is to obtain long-term bone union, prevent limb-length discrepancy (LLD), and avoid mechanical axis deviation, soft tissue lesions, nearby joint stiffness, and pathological fracture[10]. Although the current surgical treatment has been partially successful, some patients showing good results initially have experienced serious functional complications such as ankle valgus, leading to deterioration of ankle function along with the extension of

follow-up time[6, 11].

Although the etiology of ankle valgus in children with CPT is poorly understood[12], fibular lesions are considered as a closely-related common pathophysiology[13]. Some authors believe that the presence or absence of fibular pseudarthrosis does not cause refracture of the tibia, whereas the concurrent fibular involvement is likely to cause ankle valgus deformity[14-16]. Deng *et al.* demonstrated that shortening or pseudarthrosis of the fibula was associated with ankle valgus and proximal tibial valgus deformities[17]. However, their conclusions need to be further confirmed through a study with larger sample size. Accordingly, the current study was aimed to evaluate the study findings of the correlation between the presence or absence of fibular pseudarthrosis and the risk of ankle valgus in patients with CPT showing successful healing; the current study has a large sample size to identify a distinct population more likely to have postoperative ankle valgus with fibular pseudarthrosis.

Materials and Methods

Patient and Public Involvement

Study Design

The study was approved by the Institutional Review Board of the Hunan Children's Hospital, and informed consent was obtained from parents of patients with CPT. We retrospectively reviewed all 528 children with CPT who were treated at our institution from January 1, 2013 to December 31, 2020.

The inclusion criteria were as follows: (1) availability of follow-up data of more than 18 months, (2) diagnosed with CPT and received combined surgical treatment [18], (3) CPT being unilateral, (4) operations being performed in the Hunan Children's Hospital, and (5) a complete dataset existed for each patient. The exclusion criteria were as follows: (1) received surgical treatment at another hospital, (2) comorbidities such as tumors requiring surgical treatment, and (3) had any known bone disease or other chronic diseases (for example, celiac disease, thyroid disorder, systemic toxicity of glucocorticoids).

According to the inclusion and exclusion criteria, 201 patients were excluded because of either the absence of surgical treatment or treatment without combined surgical method. To avoid statistical duplication of the baseline data, six cases with bilateral CPT were excluded. To obtain more precise statistical results, two non-healing cases were excluded. Finally, 319 patients were included in this study. The flow chart of sample selection is shown in **Figure 1**. We finally included 319 pediatric patients with Crawford type IV CPT who underwent surgical treatment[19].

Three orthopedic surgeons retrospectively reviewed all clinical and imaging examination data of these patients. Medical records were reviewed for demographic information, age at fracture, age of patients undergoing surgery, concurrent fibular pseudoarthrosis, CPT location, cystic changes in the fibula, surgical method, and complication of ankle valgus. Follow-up was defined as one year after the last bone union.

Surgical Methods

We divided the 319 cases into two groups based on the surgical method used: cross-union group and non-cross-union group. The "cross-union" procedure was performed as described in previous literature[16, 20], which involves union of the tibia and fibula through autogenous iliac wrapped bone transplantation. Moreover, depending on the fibular condition (intact or not), the cross-union group was treated with either of the two surgical techniques, 3-in-1 and 4-in-1[18, 21]. Currently, there are no guidelines for the treatment of fibula pseudarthrosis[22]. The type of surgical treatment used for CPT was based on the presence or absence of concurrent fibular pseudarthrosis; if the fibula was intact, then 3-in-1 technique was performed, and if the fibula was incomplete, then 4-in-1 was performed. Regardless of the group, intramedullary rod fixation was performed through the ankle. All cases included in this study were treated by the same surgical group.

Covariates

In the present study, independent variable was the presence of concurrent fibular pseudoarthrosis, and dependent variable was the occurrence of postoperative ankle

valgus. The degree of ankle valgus was assessed using the tibiotalar angle measured at the intersection of the midline of the tibial tuberosity and inferior line of the flat cartilage of the talar dome. Patients with >4° ankle valgus were defined as having ankle valgus deformity. The covariates were as follows: sex, body mass index (BMI), fracture age, age of patients undergoing surgery, NF-1, surgery method, LLD, CPT location, and cystic change in the fibula. We considered 2-cm LLD as a turning point and an indication for treatment of patients with a leg length discrepancy of ≥2 cm[23].

Statistical Analysis

Significant differences between different groups were assessed using the chi-squared test and one-way analysis of variance or Kruskal–Wallis's H test. The association between the risk of ankle valgus in patients and the presence of concurrent fibular pseudoarthrosis was estimated using multivariable logistic regression models. Stratified multivariable logistic regression was then used to perform subgroup analyses. Statistical significance was set at p <0.05. All calculations were performed using the R software, version 3.4.3 (http://www.R-project.org; The R Foundation) and Empower software (www.empowerstats.com; X&Y Solutions, Inc., Boston, MA).

Results

Demographic and clinical data of the patients are summarized in Table 1. Of the 319 patients undergoing surgery, 141 (44.20%) were treated with 4-in-1, and 178 (55.80%) were treated with 3-in-1 technique. A total of 140 (43.89%) developed ankle valgus deformity, and 104 (50.24%) of 207 patients with concurrent fibular pseudoarthrosis developed ankle valgus deformity compared with 36 (32.14%) of 112 patients without concurrent fibular pseudoarthrosis ($p = 0.002$).

Table 2 shows the results of bivariate analysis. Concurrent fibular pseudoarthrosis, cystic change in the fibula, age of patient undergoing surgery, and LLD were identified as risk factors for ankle valgus ($p < 0.05$). We also conducted multivariable logistic regression analyses for independent correlation of NF-1, CPT location, fibular cystic change, age of patient undergoing surgery, and LLD with the risk of ankle valgus (Supplementary Table S1). The results showed that only NF-1 was a significant independent risk factor for ankle valgus after adjusting for other covariates.

Table 3 shows the relationship between concurrent fibular pseudoarthrosis and ankle valgus in different models. The results from unadjusted, minimally adjusted, and fully adjusted analyses are shown simultaneously according to the recommendation of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement[24]. In the fully adjusted model, odds ratio (OR) for developing ankle valgus deformity in patients with concurrent fibular pseudoarthrosis was 2.326 (95% confidence interval [CI]: 1.345–4.022) compared

with those without concurrent fibular pseudoarthrosis.

Table 4 shows the results of subgroup analyses stratified by NF-1, CPT location, age of patient undergoing surgery, and LLD. In patients with CPT location of distal 1/3 (OR: 2.195, 95% CI: 1.154–4.175), age <3 years of patient undergoing surgery (OR: 2.485, 95% CI: 1.188–5.200), LLD <2 cm (OR: 2.478, 95% CI: 1.225–5.015), and NF-1 positive (OR: 2.836, 95% CI: 1.517–5.303), the risk of ankle valgus further increased with the presence of concurrent fibular pseudoarthrosis.

Discussion

Considering that CPT is a rare disease[1], this study used a large sample size to comprehensively investigate whether concurrent fibular pseudoarthrosis affects the risk of postoperative ankle valgus deformity. Our study demonstrated that after adjusting for potential risk factors of developing ankle valgus deformity, patients with CPT having preoperative concurrent fibular pseudoarthrosis had a significantly higher risk of postoperative ankle valgus than those without concurrent fibular pseudoarthrosis. In particular, this risk further increased with CPT location at the distal one third of the tibia, age <3 years of patient undergoing surgery, LLD <2 cm, and occurrence of NF-1.

There are several treatments available for CPT to achieve a long-term bone union[11, 20, 25]. However, little attention has been paid to ankle valgus deformity that occurs during the postoperative period. Further, this is considered by many researchers as a possible cause of postoperative refracture[6, 14-16]. Therefore, it is necessary to identify high-risk patients and correct modifiable risk factors to minimize the risk of ankle valgus. In this study, we observed that concurrent fibular pseudoarthrosis and NF-1 were significant independent risk factors for developing ankle valgus after bone union, which is consistent with the results of previous studies[6, 15, 26-28]. However, none of these studies discussed the association between concurrent fibular pseudoarthrosis and risk of ankle valgus.

Previous studies have reported the presence of concurrent fibular pseudarthrosis in more than half of total cases[29, 30]. Our study yielded consistent results. Studies

of normal growth have reported distal migration of the fibula relative to the tibia and that the contribution to longitudinal growth from the proximal fibular epiphysis is greater than that from the distal fibular epiphysis (61% versus 39%)[31-33]. However, histological studies indicated the presence of fibrous hamartoma tissue and an increase in the thickness of abnormal periosteum at the site of pseudarthrosis[34, 35]. We speculated that concurrent fibular pseudarthrosis is a poor prognostic factor for the growth of the tibia and fibula after bone union and leads to ankle valgus. The effect on the subsequent growth of the fibula was particularly pronounced in the distal third of the tibia. Our subgroup analyses further supported the hypothesis that CPT located in the distal third tibia had a higher risk of ankle valgus in patients with concurrent fibular pseudoarthrosis.

The choice of age at the index surgery for patients with CPT is still controversial. Various studies have shown that age <3 years is an unfavorable prognostic factor for CPT treatment and that these patients have a higher rate of bone nonunion[14, 15, 36, 37]. However, our previous study showed that there was no need to defer surgery time until the child was older than three years[38]. Other studies have similarly supported the safety and effectiveness of surgical intervention in young patients aged 1–3 years[6, 39]. Our study further showed that age <3 years at the index surgery had no significant effect on the risk of developing ankle valgus. This result suggests that there is no need to delay surgery to the age of 3–10 years. Notably, our subgroup analysis suggested a higher risk of postoperative ankle valgus in children under three years of age with concurrent fibular pseudoarthrosis. Therefore, we recommend that

age at the index surgery for patients with concurrent fibular pseudoarthrosis should be deferred to 3–10 years.

The site of the pseudoarthrosis also plays a crucial role. Distal fractures closer to the ankle are more difficult to fix and associated with greater complications[11]. In addition, CPT located in the distal third undoubtedly has a more pronounced negative effect on the specific growth pattern of the tibia and fibula[33]. This may cause faster growth in the tibia than the fibula, leading to ankle valgus deformity. The results of our subgroup analysis further validated this conclusion, suggesting a higher risk of postoperative ankle valgus in patients with CPT and concurrent fibular pseudoarthrosis located in the distal third. LLD is considered an independent factor influencing ankle valgus in patients with CPT and concurrent fibular pseudoarthrosis. Based on previous evidence that LLD resulted in more work of the ankle joint, inadequate distribution of mechanical loads, and gait kinematics asymmetries[40, 41], we speculated that strong association between LLD and ankle valgus may be related to the altered mechanical distribution and gait patterns at the ankle. Neurofibromatosis may have a detrimental effect on pseudarthrosis prognosis. Our results also indicate that NF-1 is a negative independent factor for ankle valgus. Furthermore, in our subgroup analysis, the incidence of ankle valgus was significantly higher in NF-1-positive patients with concurrent fibular pseudoarthrosis than in those without concurrent fibular pseudoarthrosis. However, many studies have shown that the role of NF-1 in the prognosis of CPT is uncertain, similar to its impact on the development of complications [42-44]. However, our results suggest a different conclusion;

postoperative ankle protection in these patients needs to be performed more carefully to avoid the risk of ankle valgus deformity.

Our study has some limitations. The observational design of the cross-sectional study did not allow us to determine the time correlation of fibular pseudarthrosis with the risk of postoperative ankle valgus. Therefore, a longitudinal study is warranted. Moreover, we did not find any difference in the risk of ankle valgus with respect to the location of fibula pseudarthrosis. The sample size at the proximal region was too small for statistical analysis. Additionally, biases caused by other potential confounding factors were not excluded. For example, the data of the preoperative course were missing because many parents could not record it accurately; however, we did not adjust for this potential confounding factor in the present study. Some patients experienced a refracture during the healing process; whether this has an effect on the ankle joint is yet to be determined. It is mandatory to perform an evaluation at skeletal maturity due to growth abnormalities of the distal tibia and fibula; however, this cross-sectional study lacks long-term follow-up results. Our another ongoing randomized controlled trial may be able to address these limitations.

Conclusion

Conclusively, patients with CPT and concurrent fibular pseudoarthrosis have an increased risk of ankle valgus compared with those without concurrent fibular pseudoarthrosis. This risk further increased with CPT location at the distal third, age <3 years of patient undergoing surgery, LLD <2 cm, and occurrence of NF-1 disorder.

Declarations

Ethical approval

This study was approved by Institutional Review Board of the Hunan Children's Hospital permission and informed consent from all included patients, and all informed consents were obtained from all included patients' parents or legal guardian.

Data availability statement

Data will be made available on request.

Declaration of interests statement

No financial or non-financial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

Author contribution statement

Ge Yang: Conceived and designed the study; Analysed and interpreted the data; wrote the paper.

Hui Yu: Conceived and designed the study; Review and record data; Analysed and interpreted the data; wrote the paper.

Zhuoyang Li: Conceived and designed the study; Analysed and interpreted the data; Wrote the paper.

Haibo Mei: Analysed and interpreted the data; Review and record data.

Kun Liu: Analysed and interpreted the data; Review and record data.

Guanghui Zhu: Analysed and interpreted the data; Review and record data.

Qian Tan: Conceived and designed the study; Analysed and interpreted the data;

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Availability of data and materials

Data are available by request.

Declarations

This study had been approved by the Ethics Committee of Hunan Children's Hospital.

Consent for publication

The patients participated in this study had obtained the informed consent of their parents.

Competing interests

The authors declare that they have no competing interests.

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Table 1 Demographic and clinical data of patients included in the study.

Fibular pseudoarthrosis	**Total (319)**	**Present (207)**	**Absent (112)**	***P*-value**
BMI (kg/m^2), mean ± SD	16.76 ± 3.19	16.74 ± 3.09	16.80 ± 3.38	0.862
Sex, n (%)				
Male	202 (63.32)	139 (67.15)	63 (56.25)	0.054
Female	117 (36.68)	68 (32.85)	49 (43.75)	
Fracture age (years), mean ± SD	1.68 ± 2.01	1.57 ± 2.11	1.45 ± 1.59	0.596
Age of patient undergoing surgery (years), mean ± SD	3.84 ± 3.31	3.71 ± 3.34	3.15 ± 3.40	0.156
LLD (cm), mean ± SD	2.58 ± 2.91	2.72 ± 3.14	1.52 ± 2.16	<0.001
Surgery method, n (%)				
Non-cross union	141 (44.20)	79 (44.10)	62 (44.30)	0.164
Cross union	178 (55.80)	100 (55.90)	78 (55.70)	
CPT location, n (%)				
Proximal 2/3	85 (26.65)	44 (39.29)	41 (19.81)	<0.001
Distal 1/3	234 (73.35)	166 (80.19)	68 (60.71)	
NF-1, n (%)				
Yes	231 (72.41)	147 (71.01)	84 (75.00)	0.447
No	88 (27.59)	60 (28.99)	28 (25.00)	
Fibular cystic change, n (%)				
Yes	23 (7.21)	4 (1.93)	19 (16.96)	<0.001
No	296 (92.79)	203 (98.07)	93 (83.04)	
Ankle valgus, n (%)				
Yes	140 (43.89)	104 (50.24)	36 (32.14)	0.002
No	179 (56.11)	103 (49.76)	76 (67.86)	

Mean ± SD for continuous variables: *P*-value was calculated using one-way ANOVA (normal distribution) and Kruskal–Wallis H test (skewed distribution). n (%) for categorical variables: *P*-value was calculated using chi-square test. Abbreviations: BMI, body mass index; LLD, limb-length discrepancy; CPT, congenital pseudarthrosis of the tibia; NF-1, type 1 neurofibromatosis.

Table 2. Bivariate analysis of the risk factors of ankle valgus.

Ankle valgus	Statistics, n (%)	OR (95% CI)	*P*-value
Sex			
Female	117 (36.677)	Reference	
Male	202 (63.323)	0.914 (0.578, 1.445)	0.699
Fracture age (years)			
<1	163 (51.097)	Reference	
≥1	156 (48.903)	1.326 (0.851, 2.066)	0.212
Age of patient undergoing surgery (years)			
<3	190 (59.561)	Reference	
≥3	129 (40.439)	2.266 (1.435, 3.579)	0.001
Surgery method			
Non-cross union	141 (44.2)	Reference	
Cross union	178 (55.8)	1.0 (0.6, 1.6)	0.978
NF-1			
No	88 (27.586)	Reference	
Yes	231 (72.414)	1.537 (0.927, 2.547)	0.096
CPT location			
Proximal 2/3	85 (26.646)	Reference	
Distal 1/3	234 (73.354)	1.626 (0.973, 2.718)	0.063
Fibular cystic change			
No	296 (92.790)	Reference	
Yes	23 (7.210)	0.331 (0.120, 0.916)	0.033
LLD (cm)			
<2	204 (63.950)	Reference	
≥2	115 (36.050)	2.114 (1.328, 3.364)	0.002
BMI (kg/m^2)			
<20	296 (92.790)	Reference	
≥20	23 (7.210)	1.432 (0.612, 3.349)	0.408
Concurrent fibular pseudoarthrosis			
No	112 (35.110)	Reference	
Yes	207 (64.890)	2.132 (1.318, 3.449)	0.002

Abbreviations: BMI, body mass index; LLD, limb-length discrepancy; CPT, congenital pseudarthrosis of the tibia; NF-1, type 1 neurofibromatosis; CI, confidence interval; OR, odds ratio.

Table 3 Relationship between concurrent fibular pseudoarthrosis and ankle valgus in different models.

Concurrent fibular pseudoarthrosis	Unadjusted model β, OR (95% CI)	Minimally adjusted model β, OR (95% CI)	Fully adjusted model β, OR (95% CI)
No	Reference	Reference	Reference
Yes	2.132 (1.318, 3.449)	2.270 (1.370, 3.759)	2.326 (1.345, 4.022)
P-value	0.00205	0.00145	0.00252

Unadjusted model: adjusted for none.

Minimally adjusted model: adjusted for sex, BMI, fracture age, and age of patient undergoing surgery.

Fully adjusted model: adjusted for sex, BMI, fracture age, age of patient undergoing surgery, surgery method, NF-1, LLD, CPT location, and fibular cystic change.

Abbreviations: BMI, body mass index; LLD, limb-length discrepancy; CPT, congenital pseudarthrosis of the tibia; NF-1, type 1 neurofibromatosis; CI, confidence interval; OR, odds ratio.

Table 4 Effect modification of patients with concurrent fibular pseudoarthrosis on the risk of ankle valgus compared with those without concurrent fibular pseudoarthrosis, stratified by NF-1, CPT location, age of patient undergoing surgery, and LLD.

	OR (95% CI)	***P*-value**
CPT location		
Proximal 2/3	1.580 (0.563, 4.431)	0.3850
Distal 1/3	2.195 (1.154, 4.175)	0.0166
Age of patient undergoing surgery (years)		
<3	2.485 (1.188, 5.200)	0.0157
≥3	1.392 (0.604, 3.208)	0.4370
LLD (cm)		
<2	2.478 (1.225, 5.015)	0.0116
≥2	1.035 (0.394, 2.723)	0.9441
NF-1		
No	0.981 (0.335, 2.871)	0.9725
Yes	2.836 (1.517, 5.303)	0.0011

Above models adjusted for: sex, BMI, fracture age, age of patient undergoing surgery, surgery method, NF-1, LLD, CPT location, and fibular cystic change. In each case, the model was not adjusted for stratification variable itself.

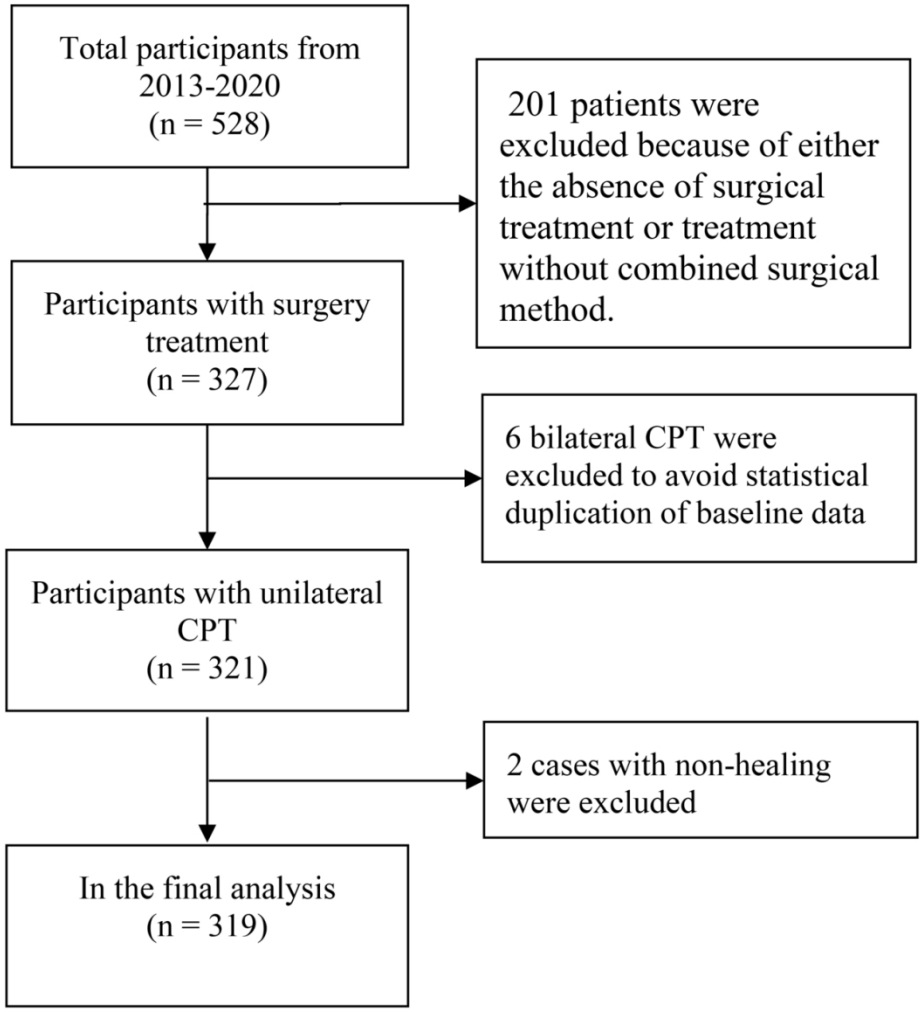

Fig 1

118x142mm (300 x 300 DPI)

Supplementary Table S1 Relationships between NF-1, CPT location, Fibula cystic change, and LLD and ankle valgus in different models.

	Unadjusted model	**Minimally adjusted model**	**Fully adjusted model**
	OR (95% CI), *p*-value	**OR (95% CI), *p*-value**	**OR (95% CI), *p*-value**
NF-1			
No	Reference	Reference	Reference
Yes	1.5 (0.9, 2.5) 0.096	1.5 (0.9, 2.5) 0.114	1.9 (1.1, 3.3) 0.021
CPT location			
Proximal 2/3	Reference	Reference	Reference
Distal 1/3	1.6 (1.0, 2.7) 0.063	1.7 (1.0, 2.8) 0.054	1.4 (0.8, 2.5) 0.214
Fibula cystic change			
No	Reference	Reference	Reference
Yes	0.3 (0.1, 0.9) 0.033	0.3 (0.1, 0.9) 0.036	0.6 (0.2, 1.8) 0.349
LLD (cm)			
<2	Reference	Reference	Reference
≥2	2.1 (1.3, 3.4) 0.002	2.1 (1.3, 3.4) 0.001	1.6 (1.0, 2.8) 0.060

Unadjusted model adjust for: None.

Minimally adjusted model adjust for: Gender; BMI; Fracture age; Surgery age.

Fully adjusted model adjust for: Gender; BMI; Fracture age; Age of patients undergoing surgery; Surgery method; NF-1; LLD; CPT location; Fibula cystic change; Concurrent fibular pseudoarthrosis.

In each case, the model is not adjusted for the variable itself.

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Association between preoperative concurrent fibular pseudoarthrosis and risk of postoperative ankle valgus in patients with congenital pseudarthrosis of the tibia

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Association between preoperative concurrent fibular pseudoarthrosis and risk of postoperative ankle valgus in patients with congenital pseudarthrosis of the tibia

Abstract

Background: This study evaluated the correlation of preoperative concurrent fibular pseudoarthrosis with the risk of ankle valgus deformity in patients with congenital pseudarthrosis of the tibia (CPT) who underwent successful surgical treatment.

Method: The children with CPT who were treated at our institution between January 1, 2013 and December 31, 2020 were retrospectively reviewed. The independent variable was preoperative concurrent fibular pseudoarthrosis, and the dependent variable was postoperative ankle valgus. Multivariable logistic regression analysis was performed after adjusting for variables that might affect the risk of ankle valgus. Subgroup analyses with stratified multivariable logistic regression models was used to assess this association.

Results: Of the 319 children who underwent successful surgical treatment, 140 (43.89%) developed ankle valgus deformity. Moreover, 104 (50.24%) of 207 patients with preoperative concurrent fibular pseudoarthrosis developed an ankle valgus deformity compared with 36 (32.14%) of 112 patients without preoperative concurrent fibular pseudoarthrosis (p = 0.002). After adjusting for sex, body mass index (BMI), fracture age, age of patient undergoing surgery, surgery method, type 1 neurofibromatosis (NF-1), limb-length discrepancy (LLD), CPT location, and fibular cystic change, patients with concurrent fibular pseudoarthrosis presented a higher risk of ankle valgus than those without concurrent fibular pseudoarthrosis (odds ratio

[OR]: 2.326, 95% confidence interval [CI]: 1.345–4.022). This risk further increased with CPT location at the distal one third of the tibia (OR: 2.195, 95% CI: 1.154–4.175), age <3 years of patient undergoing surgery (OR: 2.485, 95% CI: 1.188–5.200), LLD <2 cm (OR: 2.478, 95% CI: 1.225–5.015), and occurrence of NF-1 disorder (OR: 2.836, 95% CI: 1.517–5.303).

Conclusion: Our results indicate that patients with CPT and preoperative concurrent fibular pseudoarthrosis have a significantly increased risk of ankle valgus compared with those without preoperative concurrent fibular pseudoarthrosis, particularly in those with CPT location at the distal third, age less than 3 years at surgery, LLD less than 2 cm, and NF-1 disorder.

Key words: congenital pseudarthrosis of the tibia, fibular pseudoarthrosis, ankle valgus, type 1 neurofibromatosis

What is already known on this topic

Fibrotic lesions of fibular are thought to be a common pathophysiology that causes closely related ankle valgus in children with CPT. Earlier research has demonstrated that shortening or pseudarthrosis of the fibula was associated with ankle valgus and proximal tibial valgus deformities. However, their conclusions need to be further confirmed through a study with larger sample size.

What this study adds

Patients with CPT having preoperative concurrent fibular pseudoarthrosis had a significantly higher risk of postoperative ankle valgus than those without concurrent

fibular pseudoarthrosis. This risk further increased with CPT location at the distal one third of the tibia, age <3 years of patient undergoing surgery, LLD <2 cm, and occurrence of NF-1.

How this study might affect research, practice or policy

Our study alerted paediatricians to the impact of fibular lesions on ankle valgus after CPT surgery. And further provides some clinical advice as fellows: age at the index surgery for patients with concurrent fibular pseudoarthrosis should be deferred to 3–10 years; postoperative ankle protection in these patients with CPT location at the distal one third of the tibia, age <3 years of patient undergoing surgery, LLD <2 cm, and occurrence of NF-1 need to be performed more carefully to avoid the risk of ankle valgus deformity.

Introduction

Congenital pseudarthrosis of the tibia (CPT) is one of the most challenging conditions in pediatric orthopedics. Its incidence varies between 1 in 140,000 and 1 in 250,000[1]. Our latest study revealed that 68.9% of these cases were associated with type 1 neurofibromatosis (NF-1) and 53.7% with fibrous dysplasia in China[2, 3]. Almost half of the fractures occur before the age of two years, with most patients presenting unilateral signs, particularly occurring between the middle and distal one third of the tibia. Notably, more than half of the cases simultaneously involve fibula[4].

Various prognostic factors are considered to be associated with this disease[5, 6]. Neurofibromatosis has an uncertain impact on the course of the disease[7, 8]. In addition, the earlier a fracture occurs, the worse adverse consequences are expected[6, 9]. Moreover, the more distal but closer to the ankle, the more complicated to fix the distal end of the fractured bone[6]. Severe atrophy and extensive sclerosis of bone fragments in pseudarthrosis, shortened tibia, and the co-existence of fibular pseudarthrosis are also considered to be poor prognostic factors affecting CPT treatment[6]. The main goal of the current surgical treatment of CPT is to obtain long-term bone union, prevent limb-length discrepancy (LLD), and avoid mechanical axis deviation, soft tissue lesions, nearby joint stiffness, and pathological fracture[10]. Although the current surgical treatment has been partially successful, some patients showing good results initially have experienced serious functional complications such as ankle valgus, leading to deterioration of ankle function along with the extension of

follow-up time[6, 11].

Although the etiology of ankle valgus in children with CPT is poorly understood[12], fibular lesions are considered as a closely-related common pathophysiology[13]. Some authors believe that the presence or absence of fibular pseudarthrosis does not cause refracture of the tibia, whereas the concurrent fibular involvement is likely to cause ankle valgus deformity[14-16]. Deng *et al.* demonstrated that shortening or pseudarthrosis of the fibula was associated with ankle valgus and proximal tibial valgus deformities[17]. However, their conclusions need to be further confirmed through a study with larger sample size. Accordingly, the current study was aimed to evaluate the study findings of the correlation between the presence or absence of fibular pseudarthrosis and the risk of ankle valgus in patients with CPT showing successful healing; the current study has a large sample size to identify a distinct population more likely to have postoperative ankle valgus with fibular pseudarthrosis.

Materials and Methods

Patient and Public Involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Study Design

When patients are admitted to the hospital, they or their parents usually sign an informed consent form, which includes a clause that their child's medical history and clinical data will be used for retrospective or prospective clinical studies while ensuring that their privacy is not disclosed.We retrospectively reviewed all 528 children with CPT who were treated at our institution from January 1, 2013 to December 31, 2020. The study was approved by the Institutional Review Board of the Hunan Children's Hospital

The inclusion criteria were as follows: (1) availability of follow-up data of more than 18 months, (2) diagnosed with CPT and received combined surgical treatment [18], (3) CPT being unilateral, (4) operations being performed in the Hunan Children's Hospital, and (5) a complete dataset existed for each patient. The exclusion criteria were as follows: (1) received surgical treatment at another hospital, (2) comorbidities such as tumors requiring surgical treatment, and (3) had any known bone disease or other chronic diseases (for example, celiac disease, thyroid disorder, systemic toxicity of glucocorticoids).

According to the inclusion and exclusion criteria, 201 patients were excluded because of either the absence of surgical treatment or treatment without combined

surgical method. To avoid statistical duplication of the baseline data, six cases with bilateral CPT were excluded. To obtain more precise statistical results, two non-healing cases were excluded. Finally, 319 patients were included in this study. The flow chart of sample selection is shown in **Figure 1**. We finally included 319 pediatric patients with Crawford type IV CPT who underwent surgical treatment[19]. Three orthopedic surgeons retrospectively reviewed all clinical and imaging examination data of these patients. Medical records were reviewed for demographic information, age at fracture, age of patients undergoing surgery, concurrent fibular pseudoarthrosis, CPT location, cystic changes in the fibula, surgical method, and complication of ankle valgus. Follow-up was defined as one year after the last bone union.

Surgical Methods

We divided the 319 cases into two groups based on the surgical method used: cross-union group and non-cross-union group. The "cross-union" procedure was performed as described in previous literature[16, 20], which involves union of the tibia and fibula through autogenous iliac wrapped bone transplantation. Moreover, depending on the fibular condition (intact or not), the cross-union group was treated with either of the two surgical techniques, 3-in-1 and 4-in-1[18, 21]. Currently, there are no guidelines for the treatment of fibula pseudarthrosis[22]. The type of surgical treatment used for CPT was based on the presence or absence of concurrent fibular pseudarthrosis; if the fibula was intact, then 3-in-1 technique was performed, and if the fibula was incomplete, then 4-in-1 was performed. Regardless of the group,

intramedullary rod fixation was performed through the ankle. All cases included in this study were treated by the same surgical group.

Covariates

In the present study, independent variable was the presence of concurrent fibular pseudoarthrosis, and dependent variable was the occurrence of postoperative ankle valgus. The degree of ankle valgus was assessed using the tibiotalar angle measured at the intersection of the midline of the tibial tuberosity and inferior line of the flat cartilage of the talar dome. Patients with >4° ankle valgus were defined as having ankle valgus deformity. The covariates were as follows: sex, body mass index (BMI), fracture age, age of patients undergoing surgery, NF-1, surgery method, LLD, CPT location, and cystic change in the fibula. We considered 2-cm LLD as a turning point and an indication for treatment of patients with a leg length discrepancy of ≥2 cm[23].

Statistical Analysis

Significant differences between different groups were assessed using the chi-squared test and one-way analysis of variance or Kruskal–Wallis's H test. The association between the risk of ankle valgus in patients and the presence of concurrent fibular pseudoarthrosis was estimated using multivariable logistic regression models. Stratified multivariable logistic regression was then used to perform subgroup analyses. Statistical significance was set at p <0.05. All calculations were performed using the R software, version 3.4.3 (http://www.R-project.org; The R Foundation) and Empower software (www.empowerstats.com; X&Y Solutions, Inc., Boston, MA).

Results

Demographic and clinical data of the patients are summarized in Table 1. Of the 319 patients undergoing surgery, 141 (44.20%) were treated with 4-in-1, and 178 (55.80%) were treated with 3-in-1 technique. A total of 140 (43.89%) developed ankle valgus deformity, and 104 (50.24%) of 207 patients with concurrent fibular pseudoarthrosis developed ankle valgus deformity compared with 36 (32.14%) of 112 patients without concurrent fibular pseudoarthrosis ($p = 0.002$).

Table 2 shows the results of bivariate analysis. Concurrent fibular pseudoarthrosis, cystic change in the fibula, age of patient undergoing surgery, and LLD were identified as risk factors for ankle valgus ($p < 0.05$). We also conducted multivariable logistic regression analyses for independent correlation of NF-1, CPT location, fibular cystic change, age of patient undergoing surgery, and LLD with the risk of ankle valgus (Supplementary Table S1). The results showed that only NF-1 was a significant independent risk factor for ankle valgus after adjusting for other covariates.

Table 3 shows the relationship between concurrent fibular pseudoarthrosis and ankle valgus in different models. The results from unadjusted, minimally adjusted, and fully adjusted analyses are shown simultaneously according to the recommendation of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement[24]. In the fully adjusted model, odds ratio (OR) for developing ankle valgus deformity in patients with concurrent fibular pseudoarthrosis was 2.326 (95% confidence interval [CI]: 1.345–4.022) compared

with those without concurrent fibular pseudoarthrosis.

Table 4 shows the results of subgroup analyses stratified by NF-1, CPT location, age of patient undergoing surgery, and LLD. In patients with CPT location of distal 1/3 (OR: 2.195, 95% CI: 1.154–4.175), age <3 years of patient undergoing surgery (OR: 2.485, 95% CI: 1.188–5.200), LLD <2 cm (OR: 2.478, 95% CI: 1.225–5.015), and NF-1 positive (OR: 2.836, 95% CI: 1.517–5.303), the risk of ankle valgus further increased with the presence of concurrent fibular pseudoarthrosis.

Discussion

Considering that CPT is a rare disease[1], this study used a large sample size to comprehensively investigate whether concurrent fibular pseudoarthrosis affects the risk of postoperative ankle valgus deformity. Our study demonstrated that after adjusting for potential risk factors of developing ankle valgus deformity, patients with CPT having preoperative concurrent fibular pseudoarthrosis had a significantly higher risk of postoperative ankle valgus than those without concurrent fibular pseudoarthrosis. In particular, this risk further increased with CPT location at the distal one third of the tibia, age <3 years of patient undergoing surgery, LLD <2 cm, and occurrence of NF-1.

There are several treatments available for CPT to achieve a long-term bone union[11, 20, 25]. However, little attention has been paid to ankle valgus deformity that occurs during the postoperative period. Further, this is considered by many researchers as a possible cause of postoperative refracture[6, 14-16]. Therefore, it is necessary to identify high-risk patients and correct modifiable risk factors to minimize the risk of ankle valgus. In this study, we observed that concurrent fibular pseudoarthrosis and NF-1 were significant independent risk factors for developing ankle valgus after bone union, which is consistent with the results of previous studies[6, 15, 26-28]. However, none of these studies discussed the association between concurrent fibular pseudoarthrosis and risk of ankle valgus.

Previous studies have reported the presence of concurrent fibular pseudarthrosis in more than half of total cases[29, 30]. Our study yielded consistent results. Studies

of normal growth have reported distal migration of the fibula relative to the tibia and that the contribution to longitudinal growth from the proximal fibular epiphysis is greater than that from the distal fibular epiphysis (61% versus 39%)[31-33]. However, histological studies indicated the presence of fibrous hamartoma tissue and an increase in the thickness of abnormal periosteum at the site of pseudarthrosis[34, 35]. We speculated that concurrent fibular pseudarthrosis is a poor prognostic factor for the growth of the tibia and fibula after bone union and leads to ankle valgus. The effect on the subsequent growth of the fibula was particularly pronounced in the distal third of the tibia. Our subgroup analyses further supported the hypothesis that CPT located in the distal third tibia had a higher risk of ankle valgus in patients with concurrent fibular pseudoarthrosis.

The choice of age at the index surgery for patients with CPT is still controversial. Various studies have shown that age <3 years is an unfavorable prognostic factor for CPT treatment and that these patients have a higher rate of bone nonunion[14, 15, 36, 37]. However, our previous study showed that there was no need to defer surgery time until the child was older than three years[38]. Other studies have similarly supported the safety and effectiveness of surgical intervention in young patients aged 1–3 years[6, 39]. Our study further showed that age <3 years at the index surgery had no significant effect on the risk of developing ankle valgus. This result suggests that there is no need to delay surgery to the age of 3–10 years. Notably, our subgroup analysis suggested a higher risk of postoperative ankle valgus in children under three years of age with concurrent fibular pseudoarthrosis. Therefore, we recommend that

age at the index surgery for patients with concurrent fibular pseudoarthrosis should be deferred to 3–10 years.

The site of the pseudoarthrosis also plays a crucial role. Distal fractures closer to the ankle are more difficult to fix and associated with greater complications[11]. In addition, CPT located in the distal third undoubtedly has a more pronounced negative effect on the specific growth pattern of the tibia and fibula[33]. This may cause faster growth in the tibia than the fibula, leading to ankle valgus deformity. The results of our subgroup analysis further validated this conclusion, suggesting a higher risk of postoperative ankle valgus in patients with CPT and concurrent fibular pseudoarthrosis located in the distal third. LLD is considered an independent factor influencing ankle valgus in patients with CPT and concurrent fibular pseudoarthrosis. Based on previous evidence that LLD resulted in more work of the ankle joint, inadequate distribution of mechanical loads, and gait kinematics asymmetries[40, 41], we speculated that strong association between LLD and ankle valgus may be related to the altered mechanical distribution and gait patterns at the ankle. Neurofibromatosis may have a detrimental effect on pseudarthrosis prognosis. Our results also indicate that NF-1 is a negative independent factor for ankle valgus. Furthermore, in our subgroup analysis, the incidence of ankle valgus was significantly higher in NF-1-positive patients with concurrent fibular pseudoarthrosis than in those without concurrent fibular pseudoarthrosis. However, many studies have shown that the role of NF-1 in the prognosis of CPT is uncertain, similar to its impact on the development of complications [42-44]. However, our results suggest a different conclusion;

postoperative ankle protection in these patients needs to be performed more carefully to avoid the risk of ankle valgus deformity.

Our study has some limitations. The observational design of the cross-sectional study did not allow us to determine the time correlation of fibular pseudarthrosis with the risk of postoperative ankle valgus. Therefore, a longitudinal study is warranted. Moreover, we did not find any difference in the risk of ankle valgus with respect to the location of fibula pseudarthrosis. The sample size at the proximal region was too small for statistical analysis. Additionally, biases caused by other potential confounding factors were not excluded. For example, the data of the preoperative course were missing because many parents could not record it accurately; however, we did not adjust for this potential confounding factor in the present study. Some patients experienced a refracture during the healing process; whether this has an effect on the ankle joint is yet to be determined. It is mandatory to perform an evaluation at skeletal maturity due to growth abnormalities of the distal tibia and fibula; however, this cross-sectional study lacks long-term follow-up results. Our another ongoing randomized controlled trial may be able to address these limitations.

Conclusion

Conclusively, patients with CPT and concurrent fibular pseudoarthrosis have an increased risk of ankle valgus compared with those without concurrent fibular pseudoarthrosis. This risk further increased with CPT location at the distal third, age <3 years of patient undergoing surgery, LLD <2 cm, and occurrence of NF-1 disorder.

Declarations

Ethical approval

This study was approved by Institutional Review Board of the Hunan Children's Hospital permission and informed consent from all included patients, and all informed consents were obtained from all included patients' parents or legal guardian.

Data availability statement

Data will be made available on request.

Declaration of interests statement

No financial or non-financial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

Author contribution statement

Ge Yang: Conceived and designed the study; Analysed and interpreted the data; wrote the paper.

Hui Yu: Conceived and designed the study; Review and record data; Analysed and interpreted the data; wrote the paper.

Zhuoyang Li: Conceived and designed the study; Analysed and interpreted the data; Wrote the paper.

Haibo Mei: Analysed and interpreted the data; Review and record data.

Kun Liu: Analysed and interpreted the data; Review and record data.

Guanghui Zhu: Analysed and interpreted the data; Review and record data.

Qian Tan: Conceived and designed the study; Analysed and interpreted the data;

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Availability of data and materials

Data are available by request.

Declarations

This study had been approved by the Ethics Committee of Hunan Children's Hospital.

Consent for publication

The patients participated in this study had obtained the informed consent of their parents.

Competing interests

The authors declare that they have no competing interests.

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Table 1 Demographic and clinical data of patients included in the study.

Fibular pseudoarthrosis	**Total (319)**	**Present (207)**	**Absent (112)**	***P*-value**
BMI (kg/m^2), mean ± SD	16.76 ± 3.19	16.74 ± 3.09	16.80 ± 3.38	0.862
Sex, n (%)				
Male	202 (63.32)	139 (67.15)	63 (56.25)	0.054
Female	117 (36.68)	68 (32.85)	49 (43.75)	
Fracture age (years), mean ± SD	1.68 ± 2.01	1.57 ± 2.11	1.45 ± 1.59	0.596
Age of patient undergoing surgery (years), mean ± SD	3.84 ± 3.31	3.71 ± 3.34	3.15 ± 3.40	0.156
LLD (cm), mean ± SD	2.58 ± 2.91	2.72 ± 3.14	1.52 ± 2.16	<0.001
Surgery method, n (%)				
Non-cross union	141 (44.20)	79 (44.10)	62 (44.30)	0.164
Cross union	178 (55.80)	100 (55.90)	78 (55.70)	
CPT location, n (%)				
Proximal 2/3	85 (26.65)	44 (39.29)	41 (19.81)	<0.001
Distal 1/3	234 (73.35)	166 (80.19)	68 (60.71)	
NF-1, n (%)				
Yes	231 (72.41)	147 (71.01)	84 (75.00)	0.447
No	88 (27.59)	60 (28.99)	28 (25.00)	
Fibular cystic change, n (%)				
Yes	23 (7.21)	4 (1.93)	19 (16.96)	<0.001
No	296 (92.79)	203 (98.07)	93 (83.04)	
Ankle valgus, n (%)				
Yes	140 (43.89)	104 (50.24)	36 (32.14)	0.002
No	179 (56.11)	103 (49.76)	76 (67.86)	

Mean ± SD for continuous variables: *P*-value was calculated using one-way ANOVA (normal distribution) and Kruskal–Wallis H test (skewed distribution). n (%) for categorical variables: *P*-value was calculated using chi-square test. Abbreviations: BMI, body mass index; LLD, limb-length discrepancy; CPT, congenital pseudarthrosis of the tibia; NF-1, type 1 neurofibromatosis.

Table 2. Bivariate analysis of the risk factors of ankle valgus.

Ankle valgus	Statistics, n (%)	OR (95% CI)	*P*-value
Sex			
Female	117 (36.677)	Reference	
Male	202 (63.323)	0.914 (0.578, 1.445)	0.699
Fracture age (years)			
<1	163 (51.097)	Reference	
≥1	156 (48.903)	1.326 (0.851, 2.066)	0.212
Age of patient undergoing surgery (years)			
<3	190 (59.561)	Reference	
≥3	129 (40.439)	2.266 (1.435, 3.579)	0.001
Surgery method			
Non-cross union	141 (44.2)	Reference	
Cross union	178 (55.8)	1.0 (0.6, 1.6)	0.978
NF-1			
No	88 (27.586)	Reference	
Yes	231 (72.414)	1.537 (0.927, 2.547)	0.096
CPT location			
Proximal 2/3	85 (26.646)	Reference	
Distal 1/3	234 (73.354)	1.626 (0.973, 2.718)	0.063
Fibular cystic change			
No	296 (92.790)	Reference	
Yes	23 (7.210)	0.331 (0.120, 0.916)	0.033
LLD (cm)			
<2	204 (63.950)	Reference	
≥2	115 (36.050)	2.114 (1.328, 3.364)	0.002
BMI (kg/m^2)			
<20	296 (92.790)	Reference	
≥20	23 (7.210)	1.432 (0.612, 3.349)	0.408
Concurrent fibular pseudoarthrosis			
No	112 (35.110)	Reference	
Yes	207 (64.890)	2.132 (1.318, 3.449)	0.002

Abbreviations: BMI, body mass index; LLD, limb-length discrepancy; CPT, congenital pseudarthrosis of the tibia; NF-1, type 1 neurofibromatosis; CI, confidence interval; OR, odds ratio.

Table 3 Relationship between concurrent fibular pseudoarthrosis and ankle valgus in different models.

Concurrent fibular pseudoarthrosis	Unadjusted model β, OR (95% CI)	Minimally adjusted model β, OR (95% CI)	Fully adjusted model β, OR (95% CI)
No	Reference	Reference	Reference
Yes	2.132 (1.318, 3.449)	2.270 (1.370, 3.759)	2.326 (1.345, 4.022)
P-value	0.00205	0.00145	0.00252

Unadjusted model: adjusted for none.

Minimally adjusted model: adjusted for sex, BMI, fracture age, and age of patient undergoing surgery.

Fully adjusted model: adjusted for sex, BMI, fracture age, age of patient undergoing surgery, surgery method, NF-1, LLD, CPT location, and fibular cystic change.

Abbreviations: BMI, body mass index; LLD, limb-length discrepancy; CPT, congenital pseudarthrosis of the tibia; NF-1, type 1 neurofibromatosis; CI, confidence interval; OR, odds ratio.

Table 4 Effect modification of patients with concurrent fibular pseudoarthrosis on the risk of ankle valgus compared with those without concurrent fibular pseudoarthrosis, stratified by NF-1, CPT location, age of patient undergoing surgery, and LLD.

	OR (95% CI)	***P*-value**
CPT location		
Proximal 2/3	1.580 (0.563, 4.431)	0.3850
Distal 1/3	2.195 (1.154, 4.175)	0.0166
Age of patient undergoing surgery (years)		
<3	2.485 (1.188, 5.200)	0.0157
≥3	1.392 (0.604, 3.208)	0.4370
LLD (cm)		
<2	2.478 (1.225, 5.015)	0.0116
≥2	1.035 (0.394, 2.723)	0.9441
NF-1		
No	0.981 (0.335, 2.871)	0.9725
Yes	2.836 (1.517, 5.303)	0.0011

Above models adjusted for: sex, BMI, fracture age, age of patient undergoing surgery, surgery method, NF-1, LLD, CPT location, and fibular cystic change. In each case, the model was not adjusted for stratification variable itself.

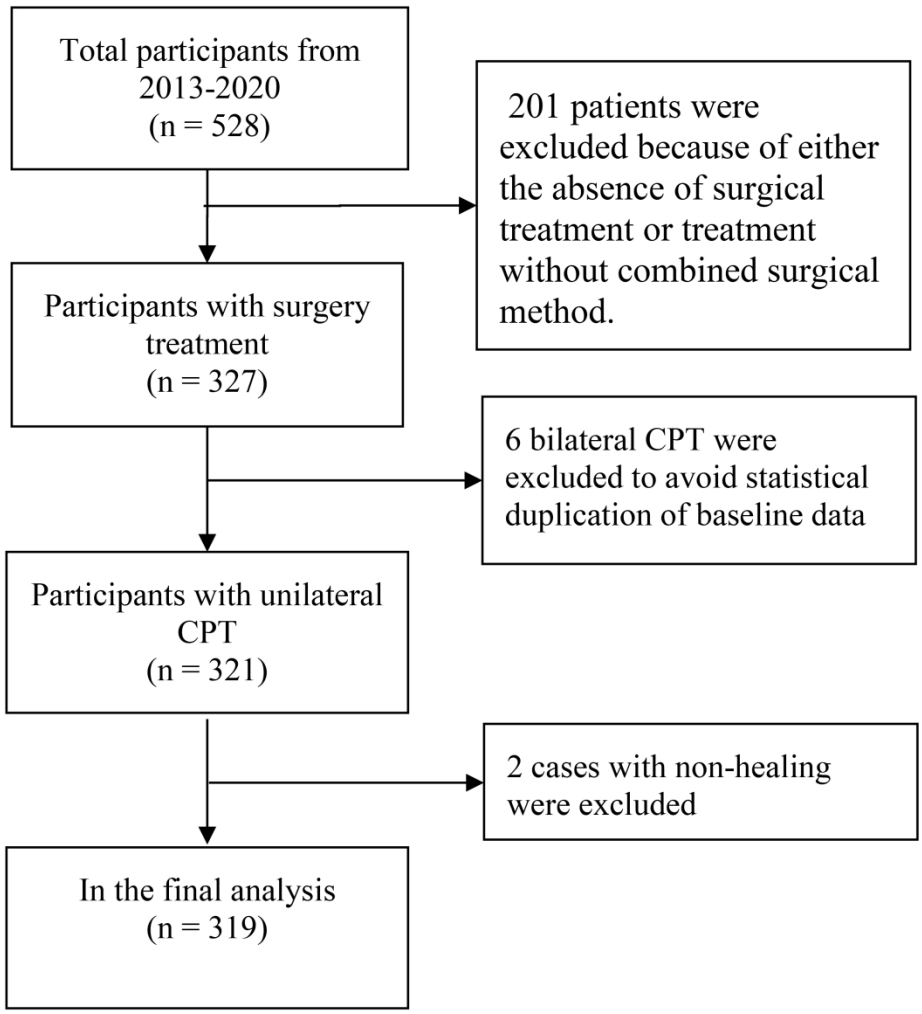

Fig 1

118x142mm (600 x 600 DPI)

Supplementary Table S1 Relationships between NF-1, CPT location, Fibula cystic change, and LLD and ankle valgus in different models.

	Unadjusted model	**Minimally adjusted model**	**Fully adjusted model**
	OR (95% CI), *p*-value	**OR (95% CI), *p*-value**	**OR (95% CI), *p*-value**
NF-1			
No	Reference	Reference	Reference
Yes	1.5 (0.9, 2.5) 0.096	1.5 (0.9, 2.5) 0.114	1.9 (1.1, 3.3) 0.021
CPT location			
Proximal 2/3	Reference	Reference	Reference
Distal 1/3	1.6 (1.0, 2.7) 0.063	1.7 (1.0, 2.8) 0.054	1.4 (0.8, 2.5) 0.214
Fibula cystic change			
No	Reference	Reference	Reference
Yes	0.3 (0.1, 0.9) 0.033	0.3 (0.1, 0.9) 0.036	0.6 (0.2, 1.8) 0.349
LLD (cm)			
<2	Reference	Reference	Reference
≥2	2.1 (1.3, 3.4) 0.002	2.1 (1.3, 3.4) 0.001	1.6 (1.0, 2.8) 0.060

Unadjusted model adjust for: None.

Minimally adjusted model adjust for: Gender; BMI; Fracture age; Surgery age.

Fully adjusted model adjust for: Gender; BMI; Fracture age; Age of patients undergoing surgery; Surgery method; NF-1; LLD; CPT location; Fibula cystic change; Concurrent fibular pseudoarthrosis.

In each case, the model is not adjusted for the variable itself.