



# OPEN Legg-Calve'-Perthes disease - diagnostic value of acetabular-femoral head match index

Dun Zhao<sup>1✉</sup>, Yinuo Fan<sup>1</sup>, Wenru Guan<sup>2</sup>, Hao Xiong<sup>3,4</sup>, Bin Fang<sup>3,4</sup> & Yue Li<sup>3,4✉</sup>

Early treatment of Legg-Calve'-Perthes disease (LCPD) can improve hip joint activity and life management in adulthood. However, the current classification of LCPD is based on imaging findings in the fragmented stage of the disease, which is prone to delay treatment. Therefore the aim of this study is to evaluate the potential risk factors associated with poor radiological outcomes of LCPD, and to develop a new index for hip consistency evaluation, which can be used to speculate radiographic outcomes at the time of the first visit. The acetabular-femoral head match index (AFMI) of each enrolled subject was measured in standard anterior-posterior radiograph images. In the study of patients presenting during necrosis and fragmentation stage, a significant correlation was established between AFMI and modified Stulberg classification ( $P < 0.05$ ). The results of binary logistic regression analyses showed that Herring classification of fragmentation stage and AFMI were the main risk factors for flat hips. Thus, we provide evidence suggesting that AFMI has a potential role in predicting patients who do not respond well to conservative treatment. Although prospective multicenter studies are needed, these results provide useful clinical clues for the early treatment of LCPD.

**Keywords** Legg-Calve'-Perthes disease, Acetabular-femoral head match, Herring classification, Modified Stulberg classification

## Abbreviations

LCPD	Legg-Calve'-Perthes disease
AFMI	Acetabular-femoral head match index
PIEB	Plaster immobilization of the external booth
PNF	Patients in the necrotic stage at the first visit
PFF	Patients in the fragmentation stage at the first visit
PRF	Patients in the repair stage at the first visit

Legg-Calve'-Perthes disease (LCPD) is a self-limiting disease, characterized by osteochondral necrosis of the femoral head, spherical appearance changes and upward movement of the greater trochanter<sup>1-3</sup>. LCPD has a multifactorial etiology where environmental, metabolic and genetic agents could be involved<sup>4</sup>. The detailed pathogenesis of LCPD has not yet been clearly elucidated<sup>5,6</sup>, which, along with the relatively small number of patients and the lack of cohort studies, has led to the current absence of recognized effective treatment guidelines. As a result, many patients cannot receive effective treatment<sup>7-9</sup>.

The patient's age and radiographic stage are the two most important factors affecting the choice of treatment. A number of X-ray-based radiographic staging methods exist for LCPD prognosis evaluation<sup>7,10</sup>. For example, Catterall and Herring classifications categorize the disease in the necrosis stage and fragment stage of the natural history of LCPD, respectively, to infer prognosis<sup>11</sup>. However, these staging methods are effective only at specific stages of the disease.

The treatment options in the published studies are still largely based on the age of the patients<sup>12-14</sup>. Since the inclusion criteria, disease classification, and patient treatment vary considerably in most publications, it is difficult to draw definite conclusions. The key to LCPD treatment is to maintain the sphericity of the femoral head and hip congruency<sup>15,16</sup>. Previous studies have confirmed that poor hip congruency can lead to early onset of hip arthritis<sup>1,13</sup>. Another drawback of Catterall and Herring classifications is that only the epiphysis of the femoral head is considered, whereas the hip congruency is neglected. This disadvantage prompts us to raise the

<sup>1</sup>Guangzhou University of Chinese Medicine, Guangzhou, China. <sup>2</sup>People's hospital of YangDong district YangJiang city, YangJiang, China. <sup>3</sup>Department of Orthopedic, The First Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China. <sup>4</sup>Guangdong Academy of Traditional Chinese Medicine, Guangzhou, China. ✉email: 980819115@qq.com; doctor\_liyue@vip.126.com

question whether it is possible that the hip congruency of the patient has already started to exert an impact at the first visit. Therefore, quantifying the degree of acetabular-femoral head match index (AFMI) in the hip joint of patients with LCPD at the first visit is a potentially meaningful research direction.

The maximum transverse diameter of the femoral head increases significantly during the late fragmentation stage and early repair stage<sup>17</sup>. In our research, the patients were divided into the following groups according to the patient's first visit radiographic stage (based on Waldenström's classification)<sup>18</sup>: Necrosis group, fragmentation group and repair group. The ratio of the maximum transverse diameter of the femoral head to the acetabular radius was measured, referred to as AFMI.

In this study, we describe the cases of a group of LCPD patients who were treated conservatively with plaster immobilization of the external booth (PIEB) regardless of their gender, age of onset, unilateral and bilateral onset, and disease severity. The institution of our research group regularly performs anteroposterior and frog position hip joint X-ray examinations of the hip joints for patients with LCPD to assess the evolution and development of the disease. If the prognosis of the patient can be judged according to the X-ray examinations of the patient at the first visit, then the subsequent treatment will be more targeted. It will be beneficial to save cost, shorten the course of disease and reduce the pain of patients.

## Materials and methods

### Patients

This study included 99 LCPD patients admitted to our hospital from January 2010 to December 2020. This research has obtained the approval of the Ethics Committee of Guangzhou University of Chinese Medicine. To ensure the reliability of the research results, we set up the following inclusion criteria: (1) No other treatment was received before diagnosis; (2) Age under 14 years; (3) Without deformity of both lower limbs; (4) The follow-up records from the first onset to the final healing were complete, especially the imaging records. The exclusion criteria applied were as follows: (1) LCPD is in the healing stage at the time of initial presentation; (2) Children with avascular necrosis of the femoral head caused by trauma and hip dislocation; (3) Receiving surgical treatment before or after conservative treatment; (4) Concomitant severe circulatory system disease or hematopoietic system disease; (5) Patients with hip crisis. Ultimately, we conducted a retrospective observational study on 104 hips.

The following treatment is implemented. Initially, we place a stick between two plaster tubes and extend the lower limbs at 40°–45° and rotate them 5°–10° inward. Every three to six months, hip x-ray images were reexamined without cast removal. If necessary, we replace the cast and encourage the patient to move the knee and ankle during the replacement interval. The interval between the next PIEB is about 1 week. PIEB is usually used for two-three courses before being switched to bracing adjuvant therapy. The whole course usually lasted one to two years (Fig. 1). None of the patients underwent surgery, and to our knowledge, no patients were referred to other hospitals.

### Imaging protocols

The patient maintained a supine position with 15° internal rotation of the lower limbs, centered on the line connecting the midpoint of the anterior superior iliac spine and the pubic symphysis. The film focal length was 100 cm; the X-ray beam was directed at the midpoint of the symphysis pubis to acquire AP images.



**Fig. 1.** Plaster immobilization of the external booth (Six years old, female. Molecular casts were used for both lower limbs. We place a stick between two plaster tubes. The lower limbs were maintained at 40–45 degrees of abduction and 5–10 degrees of internal rotation).

## Measurement and observation of predictive indicators

### *Measurement of predictive indicators*

The AFMI was applied as a predictor. AFMI (maximum transverse diameter of the femoral head/ acetabular radius) was implemented to the AP view (Fig. 2). To establish reliability, the AFMI measurement were performed by two highly qualified physician of pediatric orthopedics, and then take the average. AutoCAD 2020 was used for drawing and calculation.

Shah<sup>19</sup> found that the shape of the femoral head and the conformity of the hip joint hardly changed between healing and skeletal maturation. Therefore, when the disease develops to the healing stage, the treatment results based on these two variables can be evaluated. For this reason, we used the modified Stulberg classification to assess the condition of each patient when the disease progressed to the healing stage.

### *Observation of predictive indicators*

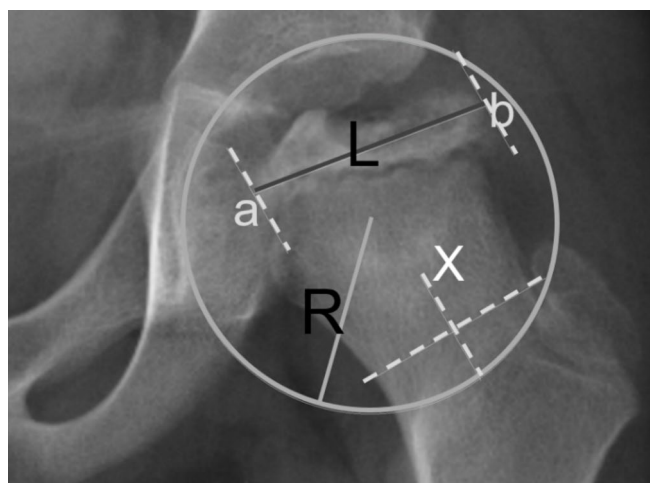
All patients were divided into two groups, group A (PNF and PFF. PNF, patients in the necrotic stage at the first visit; PFF, patients in the fragment stage at the first visit) and group B (PRF. patients in the repair stage at the first visit), based on the different stage of LCPD at the first visit. After identifying AFMI as a risk factor for flat femoral head, ROC-subject curve analysis was performed for these patients. Progression to flattened femoral head is an outcome measure in this study. If at least one-third of the contour of the femoral head resembled a straight line (1-mm deviation was allowed) in one projection, the femoral head was defined as flat<sup>20</sup>. Observations of above predictors were performed blinded by two observers for reliability.

## Statistical analyses

First, we counted the AFMI values at the first visit of each group according to different first visit stages (necrosis stage, fragmentation stage, and repair stage), and performed one-way ANOVA. Patients who were in the healing period at the first visit were excluded. Because we believe that the imaging results of these patients have been basically stable, the effect of conservative treatment was not significant. According to the statistical results, PNF and PFF were represented as group A, and PRF as group B. Subsequently, we included all group A patients, and performed binary logistic regression analysis on their first visit stage, age, gender, unilateral and bilateral onset, Herring classification in the fragmentation stage, and AFMI value. Group B was also subjected to binary logistic regression analysis. The results of our study showed that AFMI was closely related to the occurrence of flat hip in patients in group A, but not significantly related to patients in group B. Receiver operating characteristic (ROC) curve analysis of risk factors was then performed for group A to determine the sensitivity, specificity, and cutoff value of AFMI. Youden's ROC analysis index ranged from 0 to 1 (no diagnostic validity to full diagnostic validity). It was used to evaluate the performance of these diagnostic thresholds. Interobserver agreement was tested using the intraclass correlation coefficient. AFMI in the fragmentation stage was compared between the PNF group and the PFF group using an independent sample t-test. One-way ANOVA was used to compare AFMI during the repair stage among the PNF, PFF, and PRF groups.  $P < 0.05$  was considered to indicate statistically significant differences. All data were statistically analyzed using SPSS software version 23.0 (IBM SPSS, Armonk, New York, USA).

## Results

Of the 99 patients, 93 had unilateral disease. Six patients had bilateral disease, In one patient, the left hip was already healing at the time of presentation, so this hip was excluded. (Patients in the healing stage were



**Fig. 2.** The measurement of AFMI (AutoCAD 2020 was used for drawing and calculation. Make the best fitting circle of acetabulum and confirm its radius R. The axis of the femoral neck is denoted by X, two vertical lines parallel to the femoral neck axis were made, intersecting the medial and lateral necrotic epiphysis at a and b points respectively. The connecting line of a and b is the longest transverse diameter of the necrotic epiphysis.  $AFMI = \text{Length (AB)} / \text{Length R} \times 100\%$ ).

	ICC	95%CI (L)	95% CI (U)	P
	Observer 1			
Observer 2	0.744	0.642	0.820	<0.001

**Table 1.** Intraclass correlation coefficient values for observer 1 and observer 2.

Group	AFMI in the fragmentation stage	AFMI in the repair stage	P
PNF group	1.244 ± 0.125 (n = 31)	1.371 ± 0.137* (n = 41)	0.022
PFF group	1.223 ± 0.135 (n = 43)	1.374 ± 0.136* (n = 43)	0.026
PRF group		1.460 ± 0.117 (n = 17)	

**Table 2.** Comparison of AFMI values between PNF, PFF and PRF groups during fragmentation and repair stage ( $\bar{x} \pm s$ ). \*Compared with PRF group, the difference is statistically significant,  $P < 0.05$ . (In the PNF group, there were 10 patients who did not have obvious manifestations of the fragmentation stage during the follow-up, or the fragmentation period was too short to capture the corresponding X-ray image. In the PRF group, there were 3 patients whose X-ray findings were between the late fragmentation stage and the early repair stage at their first visit, so they were not included in the statistics to avoid interference).

Number of patients: 99		Stulberg A	Stulberg B	Stulberg C	
Age <sup>Δ</sup> (yr): 6.89(3–13)	<6yr: 20 (29.3%)	9 (47%)	7 (37%)	3 (16%)	χ <sup>2</sup> = 3.098 P>0.05
	≥ 6yr: 79 (70.7%)	17 (26%)	34 (52%)	14 (22%)	
Sex	Males (no. [%]): 17 (17.2%)				
	Females (no. [%]): 82 (82.8%)				
Unilateral/bilateral disease	Unilateral: 93 (93.9%)				
	Bilateral: 6 (6.1%)				
Number of hip joints: 104		AFMI			P
Stage at first diagnosis	Necrosis : 41 (39.4%)	1.15 ± 0.11*	Group A 1.19 ± 0.01		<0.001
	Fragment : 43 (41.3%)	1.22 ± 0.13*			
	Repair : 20 (19.2%)	1.41 ± 0.04	Group B 1.41 ± 0.04		
Stulberg classification (Healing stage)	Round and ovoid: 80 (76.9%)	Group A round and ovoid 67 (76.9%) Flat 17 (20.2%)			0.235
	Flat: 24 (23.1%)	Group B round and ovoid 13 (65.0%) Flat 7 (35.0%)			

**Table 3.** The characteristics of 99 patients and 104 hips. <sup>Δ</sup>The values are given as the mean and the range in parentheses. \*Compared with PRF group, the difference is statistically significant,  $P < 0.001$ .

excluded because their femoral head appearance was almost constant. Conversely, patients in the repair stage are undergoing the process of remodeling of the femoral head.) Eighty-two patients were male and 17 were female. The age of the patients ranged from three to 13 years, with a mean age of 6.89 years for all patients. The mean follow-up was  $118 \pm 34$  months.

According to Waldenström classification, at the first visit, of the 104 hips included in the study, 41 were in the necrotic stage, 43 in the fragmentation stage, and 20 in the repair stage. Based on the modified Stulberg classification proposed by Huhnstock et al.<sup>21</sup>, on reaching the healing stage by all hip joints, 80 of them were round or oval, whereas 24 were flat.

The AFMI values measured by the two observers were compared, the agreement between the two observers was 0.744 (Table 1). In the PRF group, the shape of the femoral head tended to be flat, and the transverse diameter of the femoral head increased, resulting in an increase in AFMI value ( $1.41 \pm 0.04$ ). It was significantly higher than that in PNF group ( $1.15 \pm 0.11$ ) and PFF group ( $1.22 \pm 0.13$ ). The mean value of AFMI was higher in the PFF group than in the PNF group, but there was no significant difference between the two groups. We compared the AFMI values of the PNF group and the PFF group during the fragmentation stage (Table 2), and the results were not statistically significant ( $P > 0.05$ ). At the same time, we compared the AFMI values of PNF, PFF, and PRF groups during the repair stage, and the results showed that the AFMI value of the PRF group was significantly higher than that of the first two groups ( $P < 0.05$ ). There was no significant difference in AFMI between the PNF group and the PFF group during the repair stage ( $P > 0.05$ ).

For this reason, all PNF and PFF patients were assigned to group A, and all PRF patients were assigned to group B. We compared the AFMI values of group A and group B, and the two groups were significantly different. At the same time, there was no significant difference in the proportion of flat hips in the healing period between the two groups (Table 3).

	Round and ovoid, Group ( <i>n</i> = 67 hips)	Flat group ( <i>n</i> = 17 hips)	Univariate <i>P</i> value	Multivariate <i>P</i> value <sup>†</sup>	OR (95% CI)	
Age* (yr)	6.6 (3–13)	7.0 (3–9)	0.309			
Sex			0.207			
Male	54	16				
Female	13	1				
Unilateral/bilateral			0.836			
Unilateral	61	15				
Bilateral	6	2				
Stage at first visit			0.538			
Necrosis	35	6				
Fragmentation	32	11				
Herring			0.034	0.998 0.009 0.051 (0.005–0.484)		
A	25	0				
B	24	1				
C	18	16				
AFMI*	1.16 (0.89–1.43)	1.29 (1.03–1.48)	0.013	26,934 (8.27–8.77*10 <sup>7</sup> )		
AFMI		Cutoff value (%)	AUC (%)	Specificity/sensitivity		Youden's index
Group A (necrosis and fragment)		1.275	75.6%	87%/59%		0.454

**Table 4.** Binary logistic regression analysis of Group A. \*The values were given as the mean and the range in parentheses. <sup>†</sup>The statistical results of OR of Herring stage were compared with type C which was a dummy variable.

	Round and ovoid group (n = 13 hips)	Flat group (n = 7 hips)	Univariate P value
Age* (yr)	7.1(5–12)	8.1(4–13)	0.283
Sex			
Male	12	5	0.962
Female	1	2	
Unilateral/bilateral			
Unilateral	12	7	1
Bilateral	1	0	
AFMI*	1.34 (1.05–1.48)	1.55 (1.44–1.71)	0.132

**Table 5.** Binary logistic regression analysis of Group B. \*The values were given as the mean and the range in parentheses.

In group A, binary logistic regression analysis found that the patients with modified Stulberg classification of round and oval had significantly different AFMI values from the patients with flat hips (OR 26934; 95%CI 8.27–8.77\*10<sup>7</sup>;  $P=0.013$ ) (Table 4). There was also a significant difference in the Herring classification of the fragmentation stage between the patients with modified Stulberg classification of round and oval and the patients with flat hips. The multivariate analysis revealed the Herring B classification, OR 0.051; 95% CI 0.005–0.484;  $p=0.009$  (Table 4). There was no flat hip in patients with Herring A, only one flat hip in patients with Herring B, and the number of flat hips increased significantly in patients with Herring C.

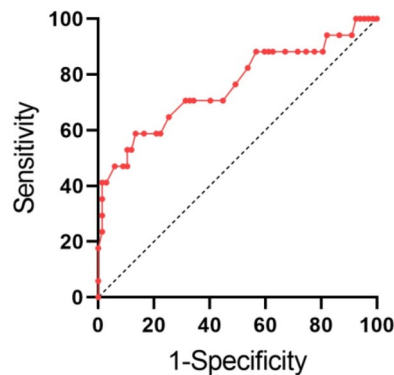
In group B, binary logistic regression analysis found that the patients with modified Stulberg classification of round and oval had no significantly different AFMI values at first visit from patients with flat hips (Table 5). However, the mean AFMI was larger in the flat group (1.55 (1.44–1.71)) than in the round and oval groups (1.34 (1.05–1.48)).

The ROC analysis (Fig. 3) showed that the cutoff points for group A was 1.275 (sensitivity=59%, specificity=87%, AUC=75.6%) The results showed that, for PNF and PFF, an AFMI value greater than 1.275 was significantly associated with flat deformity of the femoral head. There was no significant difference (Table 1) in the fisher exact test of the modified Stulberg classification between patients younger than 6 years and those older than or equal to 6 years ( $P>0.05$ ). Although in terms of the proportion of Stulberg types, patients younger than 6 years old were mainly type A and B (type A 47%, type B 37%), and patients older than or equal to 6 years old were mainly type B and C (type B 52%, type C 22%).

## Discussion

The key to the treatment of LCPD is to prevent the collapse of the femoral head, and studies have shown that hip arthritis with sequelae of LCPD has worse function than primary hip arthritis<sup>22</sup>. The earlier treatment is started, the more likely it is to avoid the risk of future hip arthritis. The purpose of the present investigation is to develop

## ROC curve analysis of AFMI in group A



**Fig. 3.** ROC curve analysis of AFMI in group A (sensitivity = 59%, specificity = 87%, AUC = 75.6%).

a prognostic evaluation method that can be implemented at the first visit of patients. Additionally, we aim to evaluate the risk factors for the poor imaging results in a group of LCPD patients with unified conservative treatment.

To determine the changes in the femoral head and the acetabulum morphology, bone resorption, and bone repair, a series of X-ray observations are to be performed in all patients<sup>17,23</sup>. Joseph et al.<sup>17</sup> refined and further developed the Waldenström's classification and divided each original stage into two substages. The results showed that the transverse diameter of the femoral head would increase significantly in the late stage of fragmentation. In our study, the AFMI value of patients in the PRF group was significantly higher than that in the other two groups. The reason may be that the maximum transverse diameter of the femoral head as the numerator increases significantly, while the radius of the acetabulum as the denominator does not change as much.

The modified Stulberg classification system proposed by Huhnstock<sup>21</sup>, which has been shown to be highly correlated with outcomes at skeletal maturity and to be characterized by simplicity, reliability, and good inter- and intra-observer agreement, as well as many other advantages. The emergence of the modified Stulberg classification has shortened the time for prognosis prediction. The study of Shah et al.<sup>19</sup> also established that the Stulberg classification of patients during the healing period and skeletal maturation hardly changed. Therefore, we used the modified Stulberg classification as an outcome measure in the healing stage of LCPD.

The results of binary logistic regression analysis of group A showed that AFMI and Herring classification in the fragmentation stage were risk factors for poor radiographic prognosis of LCPD. Herring type A and B patients rarely have flat deformity of the femoral head, while Herring type C patients are prone to have flat hips. The cut-off value of AFMI for flat femoral head deformity was 1.275. In clinical work, we can comprehensively analyze the patients by combining the Herring classification and the specific value of AFMI, pay more attention to Herring C type patients or patients with high AFMI, and choose a more reasonable treatment plan. If the patient does not develop to the stage of fragmentation, clinicians can only use AFMI value to make a preliminary prognosis judgment. For patients with a measurement value greater than 1.275, surgical intervention can be used to improve the acetabular inclusion of the femoral head. Among them, our most commonly used surgical procedure is the femoral varus rotation osteotomy. If femoral varus rotation osteotomy alone cannot restore acetabular inclusion of the femoral head, it can be combined with pelvic triple osteotomy or Chiari pelvic osteotomy. It has been suggested that Salter osteotomy can be used in patients under 5 years of age who have a large space for acetabular development<sup>24</sup>. However, in our clinical cases, there are few patients in this age range who need surgery. In the risk factor analysis of group B, AFMI was not significantly associated with the occurrence of flat hips, which may be due to insufficient sample size. Therefore, it is not recommended to use this measuring method in these patients.

Andrej<sup>25</sup> included both surgical and conservative treated patients in one study. He believes that the treatment of LCPD is not related to the choice of treatment method, but to the age of patients, and the treatment effect of children under 6 years old in his study was better than that of children over 6 years old. The findings of Joseph and Stulberg showed that more than seven years of age was a risk factor for poor prognosis of LCPD<sup>12,13</sup>. In addition, Nguyen considered that the effect of surgical treatment was better than that of conservative treatment in patients over six years of age, whereas no significant difference was observed in the treatment efficacy in patients under six years of age<sup>14</sup>. Since the inclusion criteria, disease classification, and patient treatment vary greatly among the studies included in the literature, it was difficult for us to draw firm conclusions on the prognostic factors and the natural course of the disease. In our statistical analysis, patient age was not significantly associated with the occurrence of flat hips, however, the proportion of oval hips was larger in patients older than 6 years than in those younger than 6 years (Table 1). We believe that differences in joint function should be found if the hip function of patients of different age groups is followed up for a long time.

Previous studies have shown the severity of initial disease is a main factor affecting the prognosis of patients with LCPD<sup>26</sup>. The lateral pillar classification usually predicts the severity of the radiographic outcome<sup>25,27–29</sup>. In our study, there was a wide difference in imaging results between Herring B and Herring C. Therefore, patients with LCPD should avoid weight-bearing during the fragmentation stage to avoid becoming Herring C.

Armando<sup>30</sup> reviewed the etiology of LCPD, arguing that although the etiology of LCPD is unknown, the available information indicates that LCPD has a multifactorial etiology, which may involve multiple environmental, metabolic and genetic factors. Elisa B<sup>31</sup> also suggested that the deficiency of innate growth hormone may be related to the occurrence of LCPD. We hypothesize that patients with bilateral LCPD are more likely to be affected by metabolic factors, but our investigation of the metabolic history of the children with bilateral disease found that none of the children had a documented metabolic disease, not even obese children. The study by Singh<sup>32</sup> showed that patients with bilateral onset of LCPD had an earlier age of onset and a relatively longer course of disease than those with unilateral onset, but the prognosis was similar between the two groups. Our findings similarly suggest that bilateral involvement is not an independent risk factor for flat hips in LCPD.

There are still some shortcomings in this article. The study included 99 patients from January 2010 to December 2020, a large time span, so the imaging data collected by the study may be taken by different imaging workers, and the final X-ray results may be slightly different. In addition, the number of patients included in the study was still insufficient, especially in the PRF group. Finally, we did not conduct a study of patients' symptoms because the follow-up was not long enough. We hope to conduct prospective cross-sectional studies with multiple centers in the future to increase the number of cases. Longer-term follow-up will be conducted to observe hip symptoms in midlife of patients.

The results of this study show that the measurement of AFMI can be applied to the interpretation of plain films of LCPD patients at the first visit, which is helpful for judging the prognosis of the disease in advance and selecting a reasonable treatment method. For patients whose disease is in the necrotic or fragmentation stage at the first visit, an AFMI value greater than 1.275 is a sign of poor conservative treatment. For patients in the repair stage at the first visit, there were no positive statistical results because the number of cases was not enough.

Receiving PIEB before the repair stage can improve AFMI values during the repair stage, which means better matching status of acetabulum and femoral head and lower incidence of hip arthritis in the future. Although there was no statistically significant difference in AFMI values between the PNF and PFF groups during the fragmentation and repair stage, we still recommend early treatment because some patients treated during the necrosis stage may skip the fragmentation stage.

# Conclusion

Early treatment of LCPD can improve the patient's acetabular and femoral head matching, and may reduce the incidence of hip arthritis in the future. AFMI is a risk factor for LCPD with flat hip, and it is an effective assessment model for hip congruence. The effectiveness of conservative treatment can be inferred by measuring the AFMI values of patients in the necrotic stage and the fragmentation stage at the first visit, which can guide the direction of future treatment. The cut-off value of AFMI for effective conservative treatment was 1.275.

# Data availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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## Author contributions

Literature search: Dun Zhao, Wenru Guan, Yinuo Fan, Yue Li. Data-extraction and quality assessment: Dun Zhao. Measurement: Dun Zhao, Hao Xiong. Formal analysis: Dun Zhao, Yinuo Fan, Bin Fang. Writing: Dun Zhao, Yue Li. All authors read and approved the final manuscript.

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## Declarations

## Competing interests

The authors declare no competing interests.

## Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the institutional review board of the First Affiliated Hospital of Guangzhou University of Chinese Medicine. The ethics approval number is K-2024-182.

## Informed consent

Approval from the ethics committee of Guangzhou University of Chinese Medicine was obtained and in keeping with the policies for a retrospective review, informed consent was waived by the above mentioned Ethics committee.

## Additional information

**Correspondence** and requests for materials should be addressed to D.Z. or Y.L.

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