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Original article

Diffusion-weighted MRI for outcome prediction in early Legg-Calvé-Perthes disease: Medium-term radiographic correlations

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ABSTRACT

Background: Outcome prediction at the early sclerotic stage of Legg-Calvé-Perthes disease (LCPD) is valuable to select patients likely to benefit from early surgery. The metaphyseal apparent diffusion coefficient (ADC) ratio correlated significantly with Herring's classification of LCPD in a preliminary study of 49 MRIs, in which values greater than 1.63 were associated with poor outcomes. The objective of this study was to determine whether the femoral neck ADC ratio, with the 1.63 cut-off, determined at the initial stage of LCPD correlated with medium-term radiographic outcomes.
Hypothesis: The metaphyseal ADC ratio correlates significantly with medium-term radiographic outcomes of LCPD.
Materials and methods: A prospective study was performed in 27 children (mean age, 13 years; range, 9.5–16 years) who underwent 49 MRIs at the sclerosis or fragmentation stage of unilateral LCPD. ADCs measured bilaterally at the femoral head and neck were used to compute the corresponding ADC ratios between the affected and unaffected sides. The patients received regular follow-up for at least 5 years. The correlation between the ADC ratios and Stulberg grade at last follow-up was assessed.
Results: After a mean follow-up of 6.8 years (range, 5.2–8.4 years) from the date of the first MRI, 13 hips were Stulberg 1 or 2, 13 were Stulberg 3 or 4, and 1 was Stulberg 5. The metaphyseal ADC ratio increased significantly with the Stulberg grade ($p < 0.01$). When only MRIs obtained at the early stage of sclerosis were considered, the correlation remained significant ($p = 0.03$). It was also significant in the subgroup of surgically treated patients ($p < 0.0001$) but was not significant in the subgroup without surgery ($p = 0.51$). A metaphyseal ADC ratio greater than 1.63 was associated with a worse Stulberg grade ($p = 0.02$).
Discussion/conclusion: Diffusion-weighted MRI is a non-irradiating and non-invasive investigation that contributes to the management of LCPD when used in combination with morphological MRI sequences. Elevation of the femoral neck ADC is a finding of adverse prognostic significance that correlates with Herring's grade at the fragmentation stage and with Stulberg's grade at the healed stage. Early ADC elevation in the affected femoral neck can serve to select those patients most likely to benefit from early surgery before the fragmentation stage, i.e., before Herring's classification can be applied.
Level of evidence: III, prospective uncontrolled study 3.

1. Introduction

Legg-Calvé-Perthes disease (LCPD) is a childhood form of idiopathic avascular necrosis of the femoral epiphysis that can result in femoral head deformity with joint incongruity responsible for early osteoarthritis [1,2]. Today, the challenge no longer resides in establishing the diagnosis but consists instead in identifying early outcome predictors. Indeed, when applied early, treatments designed to reduce loads at the initial phase of blood supply disruption are key to the prevention of permanent joint abnormalities [3,4]. The radiographic appearance of the lateral pillar used in Herring's classification can be assessed only relatively late in the disease course, after fragmentation has developed [5,6].

As a complement to radiography, magnetic resonance imaging (MRI) has been proven valuable for establishing the diagnosis and predicting the outcome of LCPD. Diffusion-weighted MRI (DW-MRI) to assess ischaemia-related tissue damage was first validated in patients with stroke [7] then investigated in animal models of

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bone ischaemia [8–10]. DW-MRI to image bone lesions has many applications [11–14], notably in paediatrics [15,16]. Among the few published studies of DW-MRI in LCPD, two have established that an early increase in the metaphyseal apparent diffusion coefficient (ADC) was associated with greater severity as assessed by Catterall's [17] and Herring's [6] classifications. Findings from DW-MRI and gadolinium-enhanced MRI have been compared in two smaller studies. In one of them, ADC measurement was as sensitive as gadolinium enhancement of the lateral pillar for the diagnosis of LCPD, but the ADC seemed more sensitive to changes induced by metabolic variations [18]. The other study was a preliminary prospective investigation of 31 children with unilateral LCPD [19]. Bilateral ADC measurements at the head and femoral neck were used to compute the ratio of ADC values between the affected and unaffected sides. The metaphyseal ADC ratio (mADCr) showed a significant positive correlation with Herring's classification, with values above 1.63 being significantly associated with Herring's B-C and C groups. Inter-observer reproducibility was excellent, with an intra-class coefficient of 0.87. The epiphyseal ADC ratio (eADCr) was not significantly associated with Herring's grade.

The objective of this study was to determine whether the mADCr, with the 1.63 cut-off, determined at the initial stage of LCPD, correlated with medium-term radiographic outcomes. The working hypothesis was that the mADCr correlated significantly with medium-term radiographic outcomes of LCPD.

2. Material and method

The present study was performed on the same 31 patients with unilateral LCPD included prospectively in the previous work between November 2008 and November 2011 [19]. There were 25 boys and 6 girls (male-to-female ratio, 4:1). Of the 31 affected hips, 16 were Herring A or B, 3 were Herring B-C, and 12 were Herring C. Of the 49 MRI scans available for these 31 hips, 16 were obtained within the first 6 months of disease onset, during the sclerotic phase, and 33 were obtained 4 to 12 months after disease onset, during the fragmentation stage.

Triple pelvic osteotomy (TPO) was performed in 15 (48%) patients, at a mean time since diagnosis of 11.5 months. The remaining 16 (52%) patients were managed non-operatively. Decisions to perform TPO were guided by well-established outcome predictors (age at symptom onset, Catterall's grade and Herring's group, head-at-risk signs, and eccentric head position) and by the preferences of the surgeon in charge of the patient.

The last evaluation was performed at least 5 years after study inclusion. Radiographs obtained at last follow-up were used to classify the hips according to Stulberg et al. [1] (Fig. 1). Data at last follow-up were available for 27 (87%) patients, 23 boys and 4 girls; the remaining 4 patients were lost to follow-up. Mean age was 5.2 years range, 2.5–10.5 years) at symptom onset and 13 years (range, 10.5–16.0) at last follow-up. Mean time from the first MRI scan to last follow-up was 6.8 years (range, 5.2–8.4 years).

2.1. Statistical analysis

The patient features were described as number (%) for qualitative variables and mean ± SD for normally distributed quantitative variables. The Kruskal-Wallis test was chosen to assess associations linking mADCr values to Stulberg's class and surgical treatment. Values of $p < 0.05$ were considered to indicate significant differences. The statistical analyses were run on STATA software, release 11.0 (STATA Corporation, College Station, TX, USA).

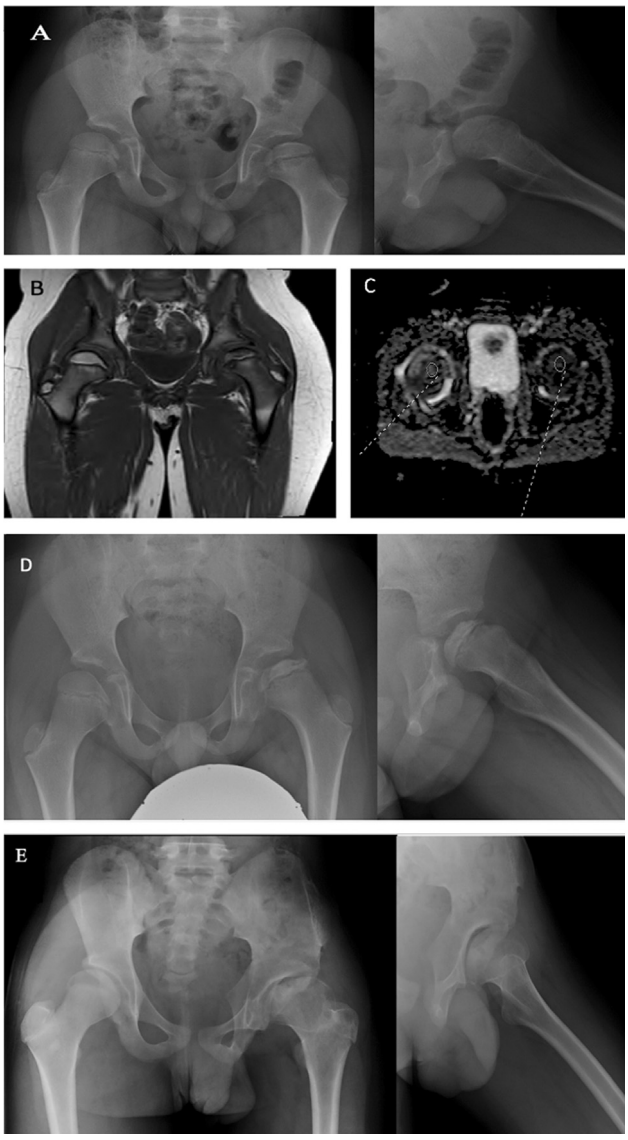

Fig. 1. Legg-Calvé-Perthes disease of the left hip in an 8-year-old. A. Antero-posterior and lateral radiographs at presentation at the stage of sclerosis. B. MRI, T1-weighted sequence at the stage of sclerosis: low-intensity signal from the femoral epiphysis. C. Diffusion-weighted MRI with ADC map, axial slice through the metaphysis: high signal on the affected side (ADC ratio, 3.44). D. Antero-posterior radiographs at the fragmentation stage 8 months after the MRI: Herring group B. E. Radiographs 6 years after the MRI and after triple pelvic osteotomy: Stulberg class 3.

3. Results

Of the 27 hips evaluated after at least 5 years, 6 were Stulberg 1, 7 were Stulberg 2, 7 were Stulberg 3, 6 were Stulberg 4, and 1 was Stulberg 5. The mADCr increased significantly as the Stulberg class increased ($p < 0.01$) (Fig. 2). This positive correlation was replicated in the subgroup of 16 patients whose MRI scan was performed at the initial stage of sclerosis ($p = 0.03$). The mADCr cut-off of 1.63 determined in the preliminary study [19] proved also valid for predicting medium-term radiographic outcomes: thus, the Stulberg classes were significantly higher in the subgroup of patients with values above 1.63 ($p = 0.002$) (Fig. 3). In the 15 (55%) patients managed by TPO, the mean mADCr was 2.15 (range, 1.36–3.44) and correlated significantly with the Stulberg class ($p < 0.0001$) (Fig. 4). The subgroup of 12 (45%) patients managed non-operatively had a significantly lower mean mADCr

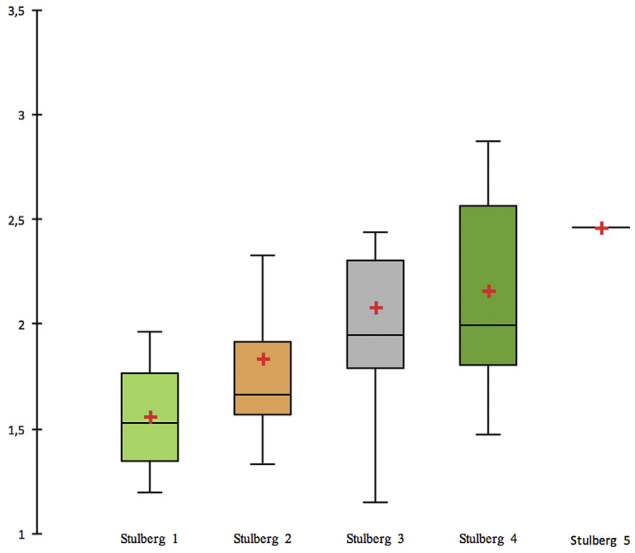

Fig. 2. Correlation between the metaphyseal ADC ratio and Stulberg's class.

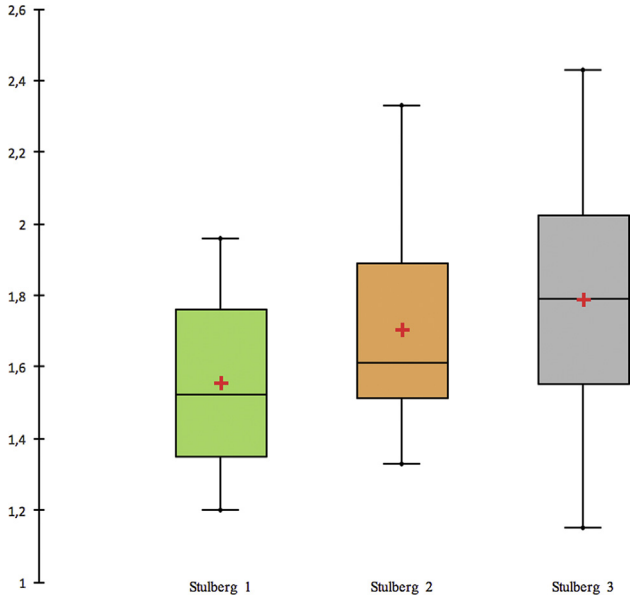

Fig. 3. Distribution of Stulberg classes according to the metaphyseal ADC ratio.

of 1.66 (range, 1.15–2.43) ($p = 0.0008$), which had no significant positive correlation with the Stulberg class ($p = 0.51$) (Fig. 5). An mADCr above 1.63 was significantly associated with surgical treatment ($p < 0.0001$) and predicted surgery with 92% sensitivity and 56% specificity.

4. Discussion

The findings from this study confirm the usefulness of DW-MRI for predicting the medium-term radiographic outcome of early LCPD. Thus, our working hypothesis is confirmed. Similar to the previously reported significant correlation between the mADCr and Herring's group at the fragmentation stage, this study demonstrated a significant correlation of the mADCr with the Stulberg class at last follow-up. An mADCr above 1.63 was significantly associated with a high Stulberg class in the medium term.

Yoo et al. reported correlations linking the metaphyseal ADC to patterns of blood supply to the femoral head [20]. In a more recent study of 46 hips, an increase in metaphyseal diffusion ($p = 0.003$)

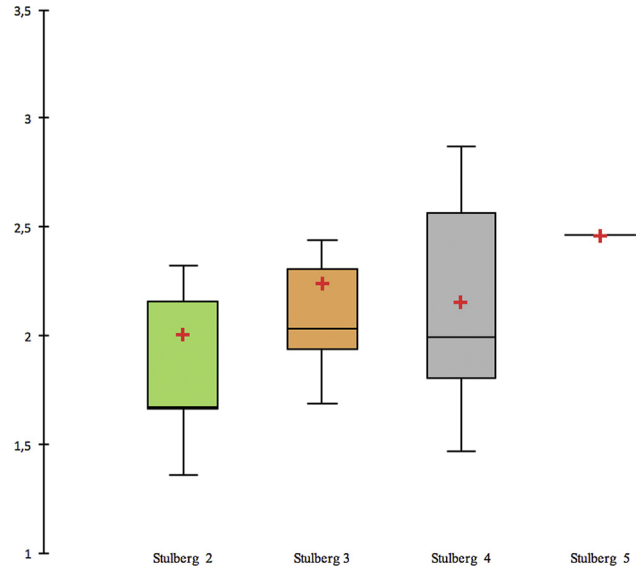

Fig. 4. Correlation between the metaphyseal ADC ratio and Stulberg's class in the subgroup of 16 patients managed non-operatively.

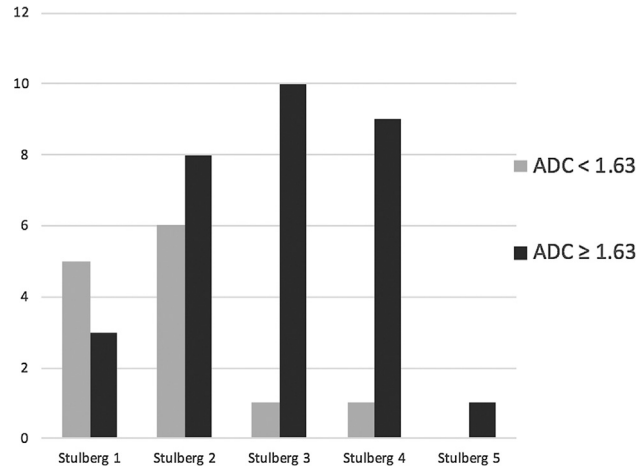

Fig. 5. Correlation between the metaphyseal ADC ratio and Stulberg's class in the subgroup of 15 patients managed by triple pelvic osteotomy.

significantly predicted femoral head deformity 2 years after symptom onset [21].

ADC values at the femoral neck reflect two different phenomena, namely, diffusion related to extension of the necrosis from the ossification centre to the growth plate and pseudo-diffusion related to revascularisation. High femoral-neck ADC values were significantly associated with surgical treatment in our population ($p < 0.0001$). Thus, elevation of the femoral neck ADC seems to reflect transphyseal revascularisation by newly developed vessels, which indicates a poorer prognosis, as shown by scintigraphy studies [22,23]. Yoo et al. suggested that a metaphyseal ADC increase greater than 50% of the normal side may indicate transphyseal revascularisation and, therefore, a poorer prognosis [20].

As the mADCr depends on multiple factors, a cut-off is challenging to determine. Technical factors include the type of antenna, the sequence chosen, and the method used to apply the diffusion gradient [24,25]. Resolution may be affected by the proximity of structures exhibiting different magnetic properties at the proximal femur. Furthermore, the ADC decreases with age due to the conversion of hematopoietic red bone marrow to fatty bone marrow [20,26]. The absolute mean ADC value at the affected femoral

necks in our study (0.776) differed from those reported by Merlini et al. [18] (1.042) and Yoo et al. [20] (0.58). In contrast, the median ratios were similar in the three studies (1.8, 1.7, and 1.63, respectively). Thus, using a ratio instead of the absolute value eliminates the effects of measurement variability.

Herring's classification cannot be applied until the fragmentation stage, which occurred at a mean of 8.5 months after symptom onset in our patients. Mean time to MRI was 6.5 months after symptom onset. Thus, outcome prediction was possible 2 months earlier overall and 4.5 months earlier in the subgroup of 16 patients who underwent MRI at the sclerotic stage. It has been reported that the ADC increase at the femoral neck occurs early, during the first few months. The increase remained stable in patients who had several MRI scans. Thus, early metaphyseal ADC measurement provides outcome prediction before the fragmentation stage, i.e., before Herring's classification can be applied, thereby allowing early patient selection to surgery with the goal of preventing femoral head deformities.

The existence of a statistically significant association between the mADCr and Caterall's grade [26], Herring's group [19], and Stulberg's class supports the use of the mADCr as an outcome prediction tool in everyday clinical practice. Furthermore, the 1.63 cut-off was validated as predicting a higher Stulberg class in the medium term ($p = 0.002$).

The limitations of our study include the variability in patient age at symptom onset. Also, the mADCr cannot be determined if both hips are affected. Management consisted either in surgery ($n = 16$, 52%) or in non-operative methods ($n = 15$, 48%), which differentially affect the natural history of LCPD. The TPO procedures performed in 15 of our patients contributed to influence the shape of the femoral head at skeletal maturity and, therefore, the Stulberg class at last follow-up. Nonetheless, the mADCr correlated significantly with the Stulberg class in this patient subgroup ($p < 0.0001$). The absence of a significant correlation in the subgroup managed non-operatively ($p = 0.51$) is probably ascribable to insufficient statistical power due to the small sample size, although the mean mADCr was significantly lower in this subgroup ($p = 0.0008$).

5. Conclusion

DW-MRI is contributes to the management of LCPD. When used in combination with morphological sequences, this non-irradiating and non-invasive investigation has been proven sensitive for the diagnosis of LCPD and helpful for predicting the outcome at an early stage. However, the mADCr cannot be used in patients with bilateral LCPD. In those with unilateral disease, early ADC elevation in the affected femoral neck, at the stage of sclerosis, may help to select patients to surgery before the occurrence of fragmentation, which must be present for Herring's classification to be applied. The mADCr is a quantitative and reproducible parameter whose potential contribution to the management of LCPD deserves investigation in larger, multicentre cohorts.

Disclosure of interest

The authors declare that they have no competing interest.

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None.

Contribution of each author

G.G.: data collection, drafting of the manuscript.
C.B.: imaging studies.
F.A.: patient follow-up, surgery.
J.S.D.G.: patient follow-up, surgery.

References

[1] Stulberg SD, Cooperman DR, Wallensten R. The natural history of Legg-Calvé-Perthes disease. J Bone Joint Surg Am 1981;63:1095–108.
[2] Wiig O, Terjesen T, Svenningsen S. Prognostic factors and outcome of treatment in Perthes' disease: a prospective study of 368 patients with five-year follow-up. J Bone Joint Surg Br 2008;90:1364–71.
[3] Joseph B, Nair NS, Rao KLN, Mulpuri K, Varghese G. Optimal timing for containment surgery for Perthes disease. J Pediatr Orthop 2003;23:601–6.
[4] Joseph B, Rao N, Mulpuri K, Varghese G, Nair S. How does a femoral varus osteotomy alter the natural evolution of Perthes' disease? J Pediatr Orthop B 2005;14:10–5.
[5] Herring JA, Neustadt JB, Williams JJ, Early JS, Browne RH. The lateral pillar classification of Legg-Calvé-Perthes disease. J Pediatr Orthop 1992;12:143–50.
[6] Herring JA, Kim HT, Browne R. Legg-Calve-Perthes disease. Part I: Classification of radiographs with use of the modified lateral pillar and Stulberg classifications. J Bone Joint Surg Am 2004;86-A:2103–20.
[7] Lee LJ, Kidwell CS, Alger J, Starkman S, Saver JL. Impact on stroke subtype diagnosis of early diffusion-weighted magnetic resonance imaging and magnetic resonance angiography. Stroke 2000;31:1081–9.
[8] Menezes NM, Connolly SA, Shapiro F, Olear EA, Jimenez RM, Zurakowski D, et al. Early ischemia in growing piglet skeleton: MR diffusion and perfusion imaging. Radiology 2007;242:129–36.
[9] Li X, Qi J, Xia L, Li H, Hu J, Yu C, et al., Diffusion MRI. in ischemic epiphysis of the femoral head: an experimental study. J Magn Reson Imaging 2008;28:471–7.
[10] Jaramillo D, Connolly SA, Vajapeyam S, Robertson RL, Dunning PS, Mulkern RV, et al. Normal and ischemic epiphysis of the femur: diffusion MR imaging—Study in piglets. Radiology 2003;227:825–32.
[11] Yao K, Troupis JM. Diffusion-weighted imaging and the skeletal system: a literature review. Clin Radiol 2016;71:1071–82.
[12] Hong N, Du X, Nie Z, Li S. Diffusion-weighted MR study of femoral head avascular necrosis in severe acute respiratory syndrome patients. J Magn Reson Imaging 2005;22:661–4.
[13] Öner AY, Aggunlu L, Akpek S, Celik A, Le Roux P, Tali T, et al. Staging of hip avascular necrosis: is there a need for DWI? Acta Radiol 2011;52:111–4.
[14] Ozel BD, Ozel D, Ozkan F, Halefoglu AM. Diffusion-weighted magnetic resonance imaging of femoral head osteonecrosis in two groups of patients: Legg–Perthes–Calve and avascular necrosis. Radiol Med 2016;121:206–13.
[15] MacKenzie JD, Gonzalez L, Hernandez A, Ruppert K, Jaramillo D. Diffusion-weighted and diffusion tensor imaging for pediatric musculoskeletal disorders. Pediatr Radiol 2007;37:781–8.
[16] Jaramillo D. Whole-body MR imaging, bone diffusion imaging: how and why? Pediatr Radiol 2010;40:978–84.
[17] Catterall A. The natural history of Perthes' disease. J Bone Joint Surg Br 1971;53:37–53.
[18] Merlini L, Combescure C, De Rosa V, Anooshiravani M, Hanquinet S. Diffusion-weighted imaging findings in Perthes disease with dynamic gadolinium-enhanced subtracted (DGS) MR correlation: a preliminary study. Pediatr Radiol 2010;40:318–25.
[19] Baunin C, Sanmartin-Viron D, Accadbled F, Sans N, Vial J, Labarre D, et al. Prognosis value of early diffusion MRI in Legg Perthes Calvé disease. Orthop Traumatol Surg Res 2014;100:317–21.
[20] Yoo WJ, Kim Y-J, Menezes NM, Cheon J-E, Jaramillo D. Diffusion-weighted MRI reveals epiphyseal and metaphyseal abnormalities in Legg-Calvé-Perthes disease: a pilot study. Clin Orthop Relat Res 2011;469:2881–8.
[21] Yoo WJ, Choi IH, Cho T-J, Jang W, Chung CY, Park MS, et al. Risk factors for femoral head deformity in the early stage of Legg-Calvé-Perthes disease: MR contrast enhancement and diffusion indexes. Radiology 2016;279:562–70.
[22] Conway JJ. A scintigraphic classification of Legg-Calvé-Perthes disease. Semin Nucl Med 1993;23:274–95.
[23] Tsao AK, Dias LS, Conway JJ, Straka P. The prognostic value and significance of serial bone scintigraphy in Legg-Calvé-Perthes disease. J Pediatr Orthop 1997;17:230–9.
[24] Sasaki M, Yamada K, Watanabe Y, Matsui M, Ida M, Fujiwara S, et al. Variability in absolute apparent diffusion coefficient values across different platforms may be substantial: a multivendor, multi-institutional comparison study. Radiology 2008;249:624–30.
[25] Ogura A, Hayakawa K, Miyati T, Maeda F. Imaging parameter effects in apparent diffusion coefficient determination of magnetic resonance imaging. Eur J Radiol 2011;77:185–8.
[26] Boutault JR, Baunin C, Bérard E, Vial J, Labarre D, Domenech C, et al. Diffusion MRI of the neck of the femur in Legg-Calve-Perthes disease: a preliminary study. Diagn Interv Imaging 2013;94:78–83.