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CLINICAL ARTICLE

Implication of Changes in the Imaging Measurements after Mechanically Aligned Total Knee Arthroplasty

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Objective: Imaging measurements allow assessment of the mechanical alignment before and after total knee arthroplasty (TKA). The changes in radiographic parameters in each period of time within 1 year after TKA has been poorly understood. The purpose of this study was to examine the timing and causes of imaging changes in lower extremity force lines after total knee arthroplasty with mechanical alignment.

Methods: A total of 93 mechanically-aligned TKA were radiographically examined before, 3 days, 3 months, and 1 year after surgery. Radiographic parameters included hip-knee angle (HKA), lateral distal femoral angle (LDFA), medial proximal tibial angle (MPTA), knee joint line orientation (KJLO), ankle joint line orientation (AJLO), the knee joint line relative to ankle joint line angle (KJLTA) and midpoints of the ankle distance (MAD). Paired *t*-test were used to analyze the changes of these imaging parameters, By establishing a simple tibial model, the time points of changes in the imaging parameters.

Results: Statistically significant differences were found between the preoperative data and the data measured 3 days after surgery in HKA, LDFA, MPTA, MAD, KJLTA, AJLO (P < 0.05) while KJLO exhibited no significant difference (P = 0.089). There existed significant differences between the data measured 3 days and the measurements taken 3 months after operation in HKA, MPTA, KJLTA, KJLO, AJLO (P < 0.05), whereas LDFA and MAD showed no significant differences were revealed between the data measured 3 months and those collected 1 year after surgery in LDFA, MPTA, AJLO, KJLTA (P < 0.05) but HKA, KJLO, AJLO showed no significant differences (P > 0.05). The tibial model was made to look into the changes in postoperative imaging parameters. Δ MAD and postoperative AJLO were calculated to verify the model and hypothesis.

Conclusions: Postoperative changes in radiographic parameters and tibial models showed that the lower extremities were in an unnatural state within 1 year after TKA. The changes in the lower extremities force line were the results of the gradual adaptation of the lower extremities to TKA and the lateral swing of the extremities (3°) after surgery. Imaging data 1 year after surgery should be taken into account in the explanation of post-TKA changes in lower limb force lines.

Key words: Lower extremities force line; Mechanical alignment; Radiographic parameters; Tibial model; Total knee arthroplasty

Introduction

Total knee arthroplasty (TKA) is the only effective treatment for end-stage knee osteoarthritis. While many surgeons follow Install and Ranawat's mechanical alignment principle (IRMP)¹ to achieve a durable and successful TKA^{2,3}, 20% of patients are not satisfied with their results.^{4,5}

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The IRMP refers to two lines on the coronal plane of the lower limb: the vertical force line (referring to making osteotomies of the distal femur and proximal tibia) and the joint line (a line at the keen joint level perpendicular to the vertical force line obtained after the prosthesis has been implanted).⁶ Multiple studies showed that a significantly improved service life of prostheses could be accomplished if the joint line is perpendicular to the vertical force line because the shear stress load on the joint surface and stress concentration are reduced.^{7,8} However, in a biomechanical study, Beek et al.⁹ found that there was an angle between the gravity line and the body's barycenter line during natural standing. As a result, the knee joint line is not perpendicular to the body's barycenter line (that is, the knee joint line is not completely parallel to the ground), which affects the ankle joint line orientation.^{10,11} Currently, it is believed that the change in lower limb force line may be culpable for patients' postoperative dissatisfaction and the limited service life of the prosthesis. Therefore, understanding of the change in lower limb force line after TKA is crucial for improving patients' satisfaction and the service life of the prosthesis. Recently, Zahn et al. examined the mechanical axis of the lower limb and limb loads 10 days and 3 months after TKA.¹² Matsumoto et al. studied the single-leg and doubleleg standing long legs 1 year after TKA.¹³ However, the changes in radiographic parameters in each period of time within 1 year after TKA remain poorly understood. Zahn et al. recognized this gap and conducted a radiographic study on standing long-leg to determine the mechanical axis of the lower limb at 7 days, 3 months, and 12 months after TKA.¹⁴ But the study involved only a few imaging parameters. The changes in radiographic parameters in each period of time within 1 year after TKA is not really explained in these studies.

This study aimed to: (i) evaluate the changes in imaging parameters at different time points after TKA by using standardized full-length lower extremity radiographs and to make recommendations for a reasonable study time; (ii) to study the correlation among various radiological parameters; and (iii) to understand the changes in these post-TKA imaging parameters by establishing a simple tibial model.

Materials and Methods

Patients

From January 2020 to January 2021, 156 patients who had undergone TKA were selected from the joint registry database of our department. The inclusion criteria were patients undergoing TKA due to primary osteoarthritis of the knee. The exclusion criteria included: (i) patients diagnosed with non-primary osteoarthritis such as rheumatoid arthritis, traumatic arthritis, and ankylosing spondylitis; (ii) genu valgus deformity; (iii) incomplete clinical or imaging records; (iv) an early fracture of either lower limb; (v) a previous TKA on either lower limb; and (vi) condylar restricted prosthesis or hinged prosthesis used. Finally, 93 patients were enrolled and analyzed before, 3 days, 3 months, and 1 year after surgery. Among them, 21 were male and 72 were female with a mean age at surgery of 65 years (range, 53–83 years). The mean body mass index (BMI) was 27.1 kg/m². Against the Ranawat classification, 75 patients with varus knee deformities were rated grade I, 43 grade II and three radii. Smith & Nephew (London, England) cruciate-retaining and posterior-stabilized prostheses were employed in all patients. The same senior orthopedic surgeon (DRN) performed all the operations, including 65 unilateral TKAs and 28 bilateral TKAs. The study protocol was approved by the ethics committee of Chinese PLA General Hospital (No. S2021-094-01) and informed consents were obtained from all patients.

Surgery

The operation was performed under general anesthesia and with tourniquet control. We took a standard medial Para patellar approach. The guide was aligned with the anatomical tibial axis (the line from the center of the proximal tibia to the center of talus). The proximal tibial osteotomy was done on the sagittal plane (a 3° posterior inclination for a posterior-stabilized prosthesis and a 5° – 7° of posterior inclination for a cruciate-retaining prosthesis). The thickness of the cut was 8 or 10 mm from the lateral condyle, depending on the wear of the medial condyle. The valgus angle was a preoperatively measured by using a template.

We performed a rotational osteotomy of the femur using the hybrid navigation technique with reference to the posterior



Fig 1 (A) Hip-knee-ankle angle (HKA), (B) Lateral distal femoral angle (LDFA), (C) Medial proximal tibial angle (MPTA), (D) Knee joint line orientation (KJLO), (E) the knee joint line relative to ankle joint line angle (KJLTA)

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condyle line, epicondylar line, and Whiteside line. Adequate soft tissue balance was attained by subperiosteal release and the pie-crust technique.¹⁵ The tibial and femoral components were cemented. On the first postoperative day, the patient was allowed to walk with the aid of a walker. The patients started rehabilitation under the supervision of a physical therapist.

Radiographic Analysis

Preoperative and postoperative X-ray films were taken by using the same machine in our hospital. Radiographs were used to examine the full length of the lower limb from the



Fig 2 (A) Ankle joint line orientation (AJLO), (B) Midpoints of the ankle distance (MAD)

hip joint to the ankle while ensuring that the patella faces forward. The imaging images were digitized and uploaded to the PACS system (EBM Technologies, Taipei, Taiwan), allowing calibration of radiographic measurements with an accuracy of 1×10^{-2} mm and $1 \times 10^{-2\circ}$.

All patients received standard full-length lower limb radiography (from the hip joint to the ankle with the patella facing forward¹⁶) preoperatively and on the third postoperative day. The radio graphical parameters were assessed using Hagstedts' method.¹⁷ The hip-knee-ankle angle (HKA)was measured between the mechanical axis of the femur and mechanical axis of the tibia. The lateral distal femoral angle (LDFA) was measured between the mechanical axis of the femur and the tangent line of the distal lateral condyle of the femur. The medial proximal tibial angle (MPTA) was defined as the angle between the tangent line of tibial plateau and tibial mechanical axis. Knee joint line orientation (KJLO) was the angle between the knee joint line and the horizontal line. The knee joint line relative to ankle joint line angle (KJLTA) was taken as the angle between the knee joint line and ankle joint line (Fig. 1). Ankle joint line orientation (AJLO) was the angle between the ankle joint line and the horizontal line. The midpoints of the ankle distance (MAD) was measured as the spacing between midpoints of ankle joints of both lower $limbs^{9,18}$ (Fig. 2). All parameters were measured twice at a 2-week interval by two orthopedic surgeons who were blind to the study. The interclass correlation of each imaging parameter calculated by product difference method was good (≥ 0.875), and the intraclass correlation of each observer was also good (>0.9).

Statistical Analysis

All analyses were conducted using SPSS 22.0 software package (SPSS, Chicago, IL, USA). Statistical significance was set



Fig. 3 Changes of imaging parameters (HKA, LDFA, MPTA, KJLO, KJLTA, AJLO, MAD) before, 3 days after, 3 months after and 1 year after surgery

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Fig. 4 (A) Changes of HKA before, 3 days after, 3 months after and 1 year after surgery. (B) Changes of LDFA before, 3 days after, 3 months after and 1 year after surgery. (C) Changes of MPTA before, 3 days after, 3 months after and 1 year after surgery. (D) Changes of KJLO before, 3 days after, 3 months after and 1 year after surgery. (E) Changes of KJLTA before, 3 days after, 3 months after and 1 year after surgery. (F) Changes of AJLO before, 3 days after, 3 months after and 1 year after surgery. (G) Changes of MAD before, 3 days after, 3 months after and 1 year after surgery

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as P < 0.05. Imaging parameters (HKA, KJLO, MPTA, LDFA, KJLTA, AJLO and MAD) were presented as mean and standard deviation and significance of differences between preoperative and postoperative imaging parameters was assessed by using the paired *t*-test (for normally distributed parameters) or Wilcoxon signed rank test (for non-normally distributed parameter).

Results

Postoperative Changes in Imaging Parameters

The change trends of imaging parameters after surgery were analyzed (Fig. 3). The varus of HKA gradually decreased from $9.17^{\circ} \pm 5.12^{\circ}$ before operation to $2.36^{\circ} \pm 1.60^{\circ}$ 3 months after operation, and there was no significant difference between the changes in HKA 3 months after surgery and those 1 year after surgery (P = 0.157), showing that HKA did not experience any change 3 months after surgery (Fig. 4).

LDFA changed from preoperative varus $(0.64^{\circ} \pm 2.96^{\circ})$ to postoperative valgus $(-2.18^{\circ} \pm 1.53^{\circ})$, and no significant difference was found in LDFA changes between 3 days after surgery and 3 months after surgery (P = 0.457). Therefore, LDFA changed from preoperative time to the day 3 day after surgery, and from postoperative 3 months to postoperative 1 year (Fig. 4B).

MPTA changed from varus ($4.68^{\circ} \pm 3.77^{\circ}$) before surgery to valgus ($-0.45^{\circ} \pm 1.45^{\circ}$) after surgery, and there were significant differences in MPTA within 1 year after surgery (P < 0.05), showing that MPTA underwent change during the first postoperative year (Fig. 4C).

No significant difference was revealed in the changes of KJLO from pre-operative time to day 3 after surgery (P = 0.089) and preoperative 3 months postoperative 1 year (P = 0.957). The valgus angle increased from 3 days ($-3.50^{\circ} \pm 1.93^{\circ}$) to 3 months after surgery ($-4.59^{\circ} \pm 1.54^{\circ}$), suggesting that KJLO did not go through any change 3 months after surgery (Fig. 4D).

KJLTA changed from varus before surgery $(2.36^{\circ} \pm 5.19^{\circ})$ to valgus 1 year after surgery $(-0.24^{\circ} \pm 3.77^{\circ})$, and gradually approached 0°. There was no significant difference in KJLTA changes between 3 months after surgery and 1 year after surgery (P = 0.076), suggesting that KJLTA did not undergo substantial change 3 months after surgery (Fig. 4E).

The angle of AJLO decreased gradually after surgery $(-5.38^{\circ}\pm 6.35^{\circ} \text{ to } -4.36^{\circ}\pm 3.17^{\circ})$, and there was no significant difference in AJLO changes between 3 months after surgery and 1 year after surgery (P = 0.551), indicating that AJLO did not change after 3 months after surgery (Fig. 4F).

MAD incrementally increased after surgery (9.83 \pm 1.44 cm to 11.04 \pm 2.88 cm), and there was no significant difference in MAD changes between 3 days after surgery and 3 months after surgery (P = 0.124). Therefore, MAD underwent constant change from preoperative time to

postoperative 3 days and from postoperative 3 months to postoperative 1 year (Fig. 4G).

To sum up, to understand the changes in imaging parameters of lower limbs after surgery, the data of postoperative 1 year should be integrated into the comparison with preoperative data (Table 1).

Preoperative vs Postoperative 1 Year

 Δ was used to represent the changes in radiographic parameters of the postoperative lower limb radiographs. The changes in imaging parameters 1 year after surgery were compared with those before surgery, and the differences of each parameter were found to be statistically significant (*P* < 0.05) (Table 2).

Correlation between Δ KJLO and Other Radiological Parameters

The correlation between postoperative changes in KJLO and other radiological parameters was analyzed, It is found that Δ KJLO bore a weak negative correlation with Δ HKA and Δ LDFA, and a weak positive correlation with Δ MAD and Δ AJLO (P < 0.05). No significant difference was found between Δ MPTA and Δ KJLTA (P > 0.05) (Table 3).

Discussion

O verall, this study confirmed that radiographic parameters of full-length lower extremities experienced changes within 1 year after TKA with MA. Imaging parameters underwent changed 1 year after surgery as compared with those before surgery and the differences were statistically significant. Different from the study of Zahn *et al.*,¹⁴ our analysis found significant differences in LDFA, MPTA and MAD even 1 year after surgery when compared with the data 3 months after surgery. We believe that the lower limbs are in an unnatural state within 1 year after TKA, and this unnatural state might be ascribed to soft tissue contracture and other factors. Therefore, imaging data beyond 1 year after surgery should be included in the study of changes of lower limb force lines after TKA.

Changes in Radiological Parameters

The data of KJLO showed that when the mechanical axis of the lower limb was varus, the knee line was not parallel to the horizontal line,¹⁹ which was consistent with the results by Ji *et al.*²⁰ Δ MPTA and Δ LDFA can well explain the changes of Δ HKA. However, Δ MPTA is 5.13° and Δ KJLO is 1.55°, which is less than half of Δ MPTA.²¹ KJLTA showed that the preoperative angle of the knee line relative to the ankle line was varus, while the postoperative angle of the knee line relative to the ankle line changed to valgus and was close to 0°. AJLO was -5.38° before surgery; AJLO was -4.36° 1 year after surgery; Δ AJLO was 1.01°, indicating that the angle of the ankle joint line relative to the horizontal line was both valgus before and after surgery, and TKA reduced AJLO while correcting the lower limb force line.²²

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TABLE 1 Preoperative and postoperative radiographic data (Mean \pm SD)										
Radiographic parameters	Postop 1 year (N = 121)	Postop 3 month (N = 121)	Postop 3 day (N = 121)	Preop (N = 121)	ťª	P value ^a	ť ^b	P value ^b	ť°	P value ^c
HKA, deg	$\textbf{2.04} \pm \textbf{1.81}$	$\textbf{2.36} \pm \textbf{1.60}$	$\textbf{2.87} \pm \textbf{2.26}$	9.17 ± 5.12	1.423	0.157	1.996	0.048	14.908	0.000
LDFA, deg	-2.18 ± 1.53	-1.74 ± 1.45	-1.57 ± 2.03	$\textbf{0.64} \pm \textbf{2.96}$	2.191	0.030	0.746	0.457	9.100	0.000
MPTA, deg	-0.45 ± 1.45	$\textbf{0.03} \pm \textbf{1.26}$	$\textbf{0.76} \pm \textbf{1.75}$	$\textbf{4.68} \pm \textbf{3.77}$	2.840	0.005	3.532	0.001	11.538	0.000
KJLO, deg	-4.58 ± 1.85	-4.59 ± 1.54	-3.50 ± 1.93	-3.03 ± 2.83	-0.054	0.957	4.913	0.000	1.716	0.089
MAD, cm	$\textbf{11.04} \pm \textbf{2.88}$	10.10 ± 2.03	$\textbf{10.46} \pm \textbf{1.85}$	$\textbf{9.83} \pm \textbf{1.44}$	-2.711	0.004	1.548	0.124	-3.168	0.002
KJLTA, deg	-0.24 ± 3.77	$\textbf{0.72} \pm \textbf{4.55}$	-1.60 ± 4.36	$\textbf{2.36} \pm \textbf{5.19}$	1.792	0.076	-4.136	0.000	10.417	0.000
AJLO, deg	-4.36 ± 3.17	-4.67 ± 4.81	-1.93 ± 4.55	-5.38 ± 6.35	0.082	0.551	3.592	0.000	-6.747	0.000

Abbreviations: AJLO, Ankle joint line orientation; HKA, Hip-knee-ankle angle; KJLO, Knee joint line orientation; KJLTA, the knee joint line relative to ankle joint line angle; LDFA, Lateral distal femoral angle; MAD, Midpoints of the ankle distance; MPTA, Medial proximal tibial angle.; ^aPostop 1 year vs Postop 3 month.; ^bPostop 3 month vs Postop 3 day.; ^cPostop 3 day vs Preop.

TABLE 2 Mean and standard deviation postop 1 year vs preop changes of radiographic parameters							
Changes of parameters (N $=$ 121)	$\text{Mean} \pm \text{SD}$	t	P value				
Δ HKA, deg	$\textbf{7.13} \pm \textbf{5.35}$	14.655	0.000				
Δ LDFA, deg	$\textbf{2.83} \pm \textbf{3.54}$	8.771	0.000				
Δ MPTA, deg	5.13 ± 4.17	13.545	0.000				
ΔKJLO, deg	1.55 ± 3.33	5.135	0.000				
Δ MAD, cm	$\textbf{1.21}\pm\textbf{3.26}$	-3.942	0.000				
Δ KJLTA, deg	$\textbf{2.59} \pm \textbf{6.18}$	4.620	0.000				
ΔAJLO, deg	1.01 ± 6.94	-1.616	0.019				

TABLE 3 Correlation coefficients and P values of Δ KJLO and other radiographic parameters								
Correlation between	ΔΗΚΑ	ΔLDFA	ΔΜΡΤΑ	ΔMAD	ΔKJLR-A	ΔAJLO		
Spearman's correlation coefficient (r) P value	-0.311 0.001	-0.505 0.000	0.157 0.085	0.421 0.000	0.011 0.906	0.421 0.000		

Correlation among Radiological Parameters

In this study, it has a weak negative correlation with Δ HKA and Δ LDFA, and a weak positive correlation with Δ MAD and Δ AJLO. There was no significant difference between Δ MPTA and Δ KJLR-A. In summary, this study suggested that the tibial side overall shifted to the lateral limb after TKA, resulting in in post-TKA changes in the lower limb force line.

Establishment of Tibial Model

On the basis of this assumption, a simple tibial model was established (Fig. 5), taking into account the changes of imaging parameters of the full length of the lower limbs. We assumed that the tibia swung from cd to cd1. Given possible angle measurement error, we assumed that the postoperative MPTA was 90°, so Δ MPTA = 4.68° and the angle of the swing was $\angle C = \Delta$ MPTA- Δ KJLO \approx 3°. Through this model, we calculated the lateral movement distance of the midpoint of the ankle joint and the postoperative AJLO compared with the measured value to verify the model. Tibial length L = cd; According to the tibia height calculation formula: female

Y = 4.61L + 5; Male Y = 4.53L + 5, Y = 121 the average height of patients was 160 cm, $L = 33.6 \sim 34.2$ was calculated, since the patients included both males and females, the length of tibia L = 34cm; according to the imaging data of preoperative and postoperative full-length x-ray films of lower limbs, dd1 is the chord length of $\angle C = 2^*L^*sin$ $(\angle C/2) = 1.78^\circ$, $\angle D = \angle A + \angle B - \angle C/2 = 6.18^\circ$. By using the Pythagorean theorem, the distance of the midpoint of the ankle of the operative limb moving to the lateral of the limb after TKA could be determined: the horizontal movement distance $L1 = L^* \cos(\angle D) = 1.76 \text{ cm}$; The vertical movement distance $L2 = L^* \sin(\angle D) = 0.19$ cm. In this study, $\triangle MAD$ after TKA was 1.21 cm, which was roughly identical to L1 of the horizontal movement distance of the midpoint of the ankle joint as calculated by the model, considering flexion contracture and measurement error of the affected limb before surgery. The vertical upward movement distance of the midpoint of the tibia plateau, as represented by L2 is virtually marginal and could be ignored, which may explain why post-TKA patients do not feel the length discrepancy of the limb



Fig. 5 The tibia is simplified as a two-dimensional graph, where ab is the extension line of the tibial plateau after TKA, c is the midpoint of the tibial plateau, d is the midpoint of the ankle point before TKA, d1 is the assumed midpoint of the postoperative ankle point, e is the intersection point of the horizontal line between the tibial plateau and the original midpoint of the ankle joint after TKA, a1b1 is the extension line of the tibial plateau after TKA, and tibial length L = cd = cd1. $\angle A$ is the preoperative KJLO, $\angle B$ is the preoperative MPTA, $\angle C$ is the angle of lower limb swing, and $\angle D = edd1$

on the operative side.^{23–25} According to this model, AJLO = $\angle B \cdot \angle A \cdot \angle C$ = -4.68° after operation could be calculated, which was roughly equivalent to AJLO = -4.36° after operation. Thus, it was verified that the angle of swing angle $\angle C$ = Δ MPTA- Δ KJLO \approx 3°. At this time, this model could explain the situation where Δ KJLO was much less than Δ MPTA after TKA, and the situation in which AJLO changed, from -5.38° before TKA to -4.36° after TKA, with ankle joint experiencing no changes. Thus, the hypothesis that the whole tibia moving to the lateral limb after TKA results in the change of the lower limb force line after TKA was verified.

Strengths and Limitations

Strengths of this study included: first, postoperative and postoperative x-ray films were taken by the same machine in our hospital and the imaging images were digitized and uploaded to the PACS system. These methods greatly reduce the observation error. Second, the changes in imaging parameters before, 3 days, 3 months and 1 year after TKA were systematically observed and analyzed. Third, the post-TKA changes in imaging parameter were further confirmed by a tibia model.

Some limitations of this study need to be mentioned. First, all full-length lower limb radiographs were taken at once

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by a radiographer blinded to the study, which rendered it impossible to control for operation errors. Preoperative fulllength radiographs of the lower extremity might be affected by knee flexion contracture. The second limitation is whether the imaging parameters of full-length lower extremity radiographs including ankle and knee positions change after postoperative 1 year.²⁶ In this study, only the full-length radiographs of lower limbs within 1 year after surgery were compared with those before surgery, and it remains unclear whether these imaging parameters continued to change 1 year after surgery.²⁷ The third limitation is that this imaging study is of a static nature and only reflects the lower limb force lines of patients in the static standing position after TKA. The results of this study provide a reasonable explanation for the KJLO changes after TKA. However, some studies suggest that the tibial plateau is parallel to the horizontal line during walking after TKA.^{19,28,29} The static nature of the study might have a great impact on imaging parameters due to an unnatural state of ankle and knee within 1 year after TKA. Therefore, we believe that it is necessary to conduct further dynamic studies through gait analysis, to verify the conclusions of this study by examining the changes in the relative positions of ankle and knee joints, and to accurately study the changes in lower limb force lines.^{30,31}

Conclusion

After total knee arthroplasty with mechanical alignment, the lower extremities may be in an unnatural state within 1 year after surgery due to soft tissue contracture. Therefore, imaging data of more than 1 year after surgery should be integrated into the study on the changes of lower limb force lines after TKA. Tibial model showed that the postoperative changes in the lower extremity force line were actually the results of the gradual adaptation of the lower extremities to TKA and the postoperative limb swing to the lateral 3°. However, the changes of lower limb force lines after TKA warrant further dynamic studies involving gait analysis.

Author Contribution

Conception and design: Long Cheng, Peng Ren, Qingyuan Zheng and Guo-Qiang Zhang. Analysis and interpretation of the data: Long Cheng, Peng Ren, Qingyuan Zheng, Yi-Ming Wang, Ming Ni, Lei Geng and Guo-Qiang Zhang. Drafting of the article: Long Cheng, Peng Ren and Qingyuan Zheng. Critical revision of the article for important intellectual content: Long Cheng, Peng Ren, Ming Ni and Guo-Qiang Zhang. Final approval of the article: Long Cheng, Peng Ren, Qingyuan Zheng and Guo-Qiang Zhang. The work was performed at the Chinese PLA General Hospital.

Ethics Statement

The study protocol was approved by the ethics committee of Chinese PLA General Hospital (No. S2021-094-01) and informed consents were obtained from all patients.

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