Higher Pelvic Incidence Was Associated with a Higher Risk of Sagittal Malposition of Femoral Component and Poor Outcomes of Primary Total Knee Arthroplasty: A Retrospective Cohort Analysis

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Abstract

Spine–pelvis–lower extremity sagittal alignment is regarded as a global sagittal balance. Currently, there are few studies evaluating the pelvic and femoral sagittal alignment during total knee arthroplasty (TKA). This retrospective study aims to elucidate how pelvic and femoral sagittal alignment affect clinical outcomes of primary TKA for osteoarthritis (OA) and determine the proper range of femoral sagittal alignment. Patient-reported outcome measures (PROMs), including the Knee Society Score (KSS), Western Ontario and McMaster Universities (WOMAC), and patient satisfaction scores, and clinician-reported outcomes (CROs), including range of motion (ROM) and pelvic and femoral sagittal parameters, of 67 cases were evaluated (89 knees) before and 1 year after TKA. The angle between the distal femur anterior cortex line and flange of the femoral component (FC) was defined as the $\alpha$ angle. Correlations between the $\alpha$ angle and PROM and CRO were investigated using multivariate and secondary regression analyses. Patients were further divided into four cohorts (A, B, C, and D) according to the $\alpha$ angle, and comparisons of their postoperative PROM and ROM scores were performed. Postoperative PROM and ROM scores improved significantly compared with the preoperative scores ($p < 0.01$). Only the $\alpha$ angle was significantly associated with postoperative knee extension among all PROM and CRO indexes ($p = 0.001$). Secondary regression demonstrated a convex upward function, and the scores were the highest at $\alpha$ angles of 0.57, 0.96, and $-1.42$ degrees for postoperative KSS, satisfaction, and range of knee extension, respectively ($p < 0.01$).

Keywords

► osteoarthritis
► total knee arthroplasty
► sagittal alignment
► femoral component

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Total knee arthroplasty (TKA) is an imperative treatment for the majority of patients with end-stage osteoarthritis (OA) of the knee joints. \(^1\) Alignment of the knee components is critical in ensuring patient satisfaction and functional ability after TKA. \(^2\) Compared with the attention focused on the balance of prosthetic knees in the coronal plane by TKA alignment research, \(^3\) less attention has been given to the balance of the sagittal plane. Moreover, because of femur bowing and deviation of the femoral intramedullary alignment rod, \(^4\) the probability of sagittal malposition of the femoral component (FC) is higher than that of coronal alignment during TKA. \(^5\) Additionally, overextension of the FC could lead to notching of the anterior femoral cortex, and too much flexion of the FC may result in overstuffing of the anterior cortex–FC interface gap and knee extension limitations, especially during posterior stabilized (PS) TKA because of anterior impingement between the posterior and intercondylar notch. \(^6\) Therefore, poor sagittal alignment of the FC is a cause of discomfort, pain, and inadequate range of motion (ROM), and it can lead to the need for revision surgery. \(^7\)

Normal sagittal spine–pelvis–lower extremity alignment is crucial in humans for maintaining the balance of motion, including motion of the spine, hip, knee and ankle joints. \(^8\) Previous research has suggested that sagittal alignment comprises the spine, pelvis, and lower extremity, and the integrity of each part affects the others. \(^9\) Weng reported that severe OA of the knee could have a significant influence on the sagittal alignment of the spine–pelvis–lower extremity. \(^10\) Sagittal malalignment of the TKA components could unbalance other segments, resulting in compensatory changes in the spine and pelvis and, possibly, knee–spine syndrome. \(^11\) Based on the compensatory mechanism, however, disparities in the spinal or pelvic sagittal alignment could also influence the sagittal alignment of the lower extremity or TKA components.

Nevertheless, to the best of our knowledge, few studies have focused on the correlations among pelvic and femoral sagittal alignment parameters (such as pelvic incidence [PI], sacral slope [SS], pelvic tilt [PT], pelvic femoral angle [PFA], sacrum femoral angle, femoral inclination [FI], femoral anterior bowing angle [FABA], distal femoral flexion angle [DFFA], and others) and sagittal alignment of the FC. Moreover, it is difficult to achieve accurate neutral sagittal alignment of the FC; therefore, an acceptable range of the distal femoral anterior cortex (DFAC)–FC interface angle (defined as \(\alpha\) angle) is needed for reference. However, this range has not been fully elucidated. Previously, we have reported that the plane of the DFAC could be a useful index for FC rotation during TKA. \(^12\) Recent findings showed that the DFAC might have an impact on sagittal alignment of the FC during TKA. \(^13\) Therefore, the role of the \(\alpha\) angle in sagittal alignment of the FC was further explored during this study. Collectively, this study aimed to evaluate the correlation between pelvic and femoral sagittal alignment parameters (especially FC-associated parameters), investigating how the sagittal parameters affect the clinical outcomes of patients with OA who underwent primary PS TKA surgery, and identify the appropriate range of the \(\alpha\) angle.

**Methods**

**Patients**

This retrospective study was approved by the First Affiliated Hospital of Sun Yat-sen University Clinical Research Ethics Committee (Guangzhou, China; Institutional Review Board [IRB] no.: 2013–032). All patients in the study submitted signed informed consent. Data used for our study were accessed from the database of the Joint Replacement Registry from the hospital. The inclusion criteria were age 65 years or older, diagnosis of end-stage OA of the knee joints (Kellgren–Lawrence classification grade IV, \(^14\) regardless of nonsurgical interventions), and primary TKA performed using a PS knee prosthesis (Smith & Nephew Inc., London, United Kingdom). The exclusion criteria were as follows: body mass index (BMI) >35 kg/m\(^2\); traumatic arthritis, rheumatoid arthritis, gouty arthritis, or suppurative arthritis; severe osteoporosis; a history of hip, ankle, or spine disorder; revision surgery; deep vein thrombosis, incision infection, or delayed healing; and peri-prosthetic joint infection. A total of 67 consecutive qualified Chinese patients (89 knees) were enrolled in our study in 2018; there were 16 men and 51 women with a mean age of 70.5 (range: 65–87) years. According to the epidemiology of knee osteoarthritis, the gender proportion (male vs. female) is approximately 1:2 to 1:4, \(^15\) which is consistent with our study (16 men vs. 51 women). Therefore, there is no obvious bias of gender proportion in this study. The mean BMI of all patients was 25.6 (range: 17.6–34.5) kg/m\(^2\).
Clinical Study

Patient-reported outcome measures (PROMs) included the Knee Society Score (KSS), the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index, and patient satisfaction score (0–10 points; high scores indicate a high degree of satisfaction). PROMs were evaluated before surgery and 1 year after surgery.

Radiographic Study

Clinician-reported outcomes (CROs) included ROM and pelvic and femoral–sagittal parameters. ROM was evaluated by clinicians using a handheld goniometer before surgery and 1 year after surgery. In our study, radiographic measurements were performed before surgery and 1 year after surgery. We had performed radiographic measurements immediately after surgery in some patients; however, some patients could not stand up straight because of postoperative pain of incision. And this could influence the quality of radiographic measurements. Prosthetic loosening had not been found in 1-year follow-up in our study. Therefore, we performed radiographic measurements before surgery and one year after surgery for accurate evaluation.

Surgimap software (Nemaris Inc., New York, NY) was used to investigate the sagittal parameters. Before surgery, the following parameters were measured: PI (defined as the angle between the line perpendicular to the sacral plate at its midpoint and the line connecting this point to the center of the axis of the femoral heads). SS (defined as the angle between the superior plate of sacral vertebrae 1 [S1] and a horizontal reference on sagittal plane of S1). PT (defined as the angle between the line perpendicular to the center of the axis of the femoral heads and the line connecting this point to the sacral plate at its midpoint). PFA (defined as the angle between the femoral longitudinal axis and the line connecting the center of the femoral head to the sacral plate at its midpoint). SAC (defined as the angle between the femoral longitudinal axis and the posterior tangent line of the sacral plate). FI (defined as the angle between the vertical line and the femoral axis), and FABA (defined as the angle between the medullary lines of the proximal and distal femur). The proximal medullary line was....
drawn as the line connecting the two points 10- and 15-cm distal to the proximal end of the femoral head. The distal medullary line connected the two points 5- and 10-cm proximal to the distal end of the medial femoral condyle.\textsuperscript{16} DF PA (defined as the angle between the centroid line of the distal third of the femur and the mechanical axis in the plane perpendicular to the epicondylar axis), and distal femoral anterior cortex angle (DFACA; defined as the angle between the longitudinal axis of the distal femur anterior cortex and the sagittal femoral mechanical axis).

One year after surgery, the following parameters were measured: femoral prosthesis flexion angle (FPFA; defined as the angle between the femoral mechanical axis and the longitudinal axis of the femoral component), $\alpha$ angle (defined as the angle between a line parallel to the distal cement interface of the FC and the femoral mechanical axis), and $\gamma$ angle (defined as the proximal angle between a line drawn perpendicular to the distal cement interface of the FC and the femoral anatomical axis; \textsuperscript{27}Fig. 1). A negative value of the $\alpha$ angle denoted flexion of the FC, whereas a positive value of the $\alpha$ angle denoted flexion of the FC. A negative value in the range of extension denoted flexion deformity of knee, whereas a positive value in the range of extension denoted extension of the knee.

### Statistical Analysis

To minimize interobserver errors in the measurements of the sagittal parameters, all parameters were measured by two authors at various times. The intraobserver and interobserver differences were evaluated by performing a Bland–Altman analysis. To identify the acceptable range of the $\alpha$ angle, patients were further divided into the following four cohorts according to the value of the $\alpha$ angle:\textsuperscript{8} cohort A, $\alpha$ angle $< 0$ degrees; cohort B, 0 degrees $\leq \alpha$ angle $\leq 3$ degrees; cohort C, 3 degrees $< \alpha$ angle $\leq 7$ degrees; and cohort D, $\alpha$ angle $> 7$ degrees (\textsuperscript{27}Fig. 2). SPSS version 20.0 (IBM Co., Armonk, NY) were used to analyze data. A multivariate regression analysis, secondary regression analysis,\textsuperscript{17} $\chi^2$ tests, and t-tests were used to compare differences between cohorts and means. To further explore the specific association between

### Results

At 1 year after surgery, PROM (including KSS, functional scores, and satisfaction scores) scores were higher than those evaluated before surgery ($p < 0.01$); however, the WOMAC Osteoarthritis Index scores were much lower than those

### Table 1 Comparisons of preoperative and postoperative PROM and ROM

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>Postoperative</th>
<th>$p$-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROM Score (mean ± SD)</td>
<td>60.3 ± 18.4</td>
<td>88.2 ± 4.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Functional score</td>
<td>38.7 ± 10.9</td>
<td>56.6 ± 10.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WOMAC</td>
<td>47.1 ± 6.4</td>
<td>27.1 ± 4.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Satisfaction score</td>
<td>4.5 ± 1.7</td>
<td>7.5 ± 1.2</td>
<td>0.008</td>
</tr>
<tr>
<td>ROM Degrees (mean ± SD)</td>
<td>109.1 ± 12.7</td>
<td>116.7 ± 14.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Knee flexion (degree)</td>
<td>109.1 ± 12.7</td>
<td>116.7 ± 14.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Knee extension (degree)</td>
<td>−0.6 ± 5.2</td>
<td>−2.5 ± 3.6</td>
<td>0.006</td>
</tr>
</tbody>
</table>

### Abbreviations: KSS, Knee Society Score; PROM, patient-reported outcome measure; ROM, range of motion; SD, standard deviation; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

### Table 2 Preoperative and postoperative values of sagittal alignment parameters

<table>
<thead>
<tr>
<th>Sagittal alignment parameters</th>
<th>Degree (mean ± SD)</th>
<th>Range (degrees)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvic incidence</td>
<td>56.9 ± 14.1</td>
<td>30.2–94.6</td>
</tr>
<tr>
<td>Pelvic tilt</td>
<td>18.0 ± 10.2</td>
<td>0.3–45.5</td>
</tr>
<tr>
<td>Sacral slope</td>
<td>39.0 ± 10.0</td>
<td>10.4–61.2</td>
</tr>
<tr>
<td>Pelvic femoral angle</td>
<td>11.4 ± 9.9</td>
<td>0.3–35.2</td>
</tr>
<tr>
<td>Sacral femoral angle</td>
<td>58.6 ± 13.3</td>
<td>17.9–102.0</td>
</tr>
<tr>
<td>Femoral inclination</td>
<td>15.2 ± 8.9</td>
<td>1.2–62.2</td>
</tr>
<tr>
<td>Femoral anterior bowing angle</td>
<td>10.8 ± 3.9</td>
<td>3.2–20.7</td>
</tr>
<tr>
<td>Distal femoral flexion angle</td>
<td>3.3 ± 1.8</td>
<td>0.3–8.5</td>
</tr>
<tr>
<td>Distal femoral anterior cortex angle</td>
<td>2.7 ± 2.1</td>
<td>0.1–10.2</td>
</tr>
<tr>
<td>Postoperative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femoral prosthesis flexion angle</td>
<td>6.7 ± 5.6</td>
<td>0.4–22.4</td>
</tr>
<tr>
<td>$\alpha$ angle</td>
<td>1.9 ± 3.9</td>
<td>−7.3 to 10.0</td>
</tr>
<tr>
<td>$\beta$ angle</td>
<td>84.6 ± 10.6</td>
<td>63.8–113.3</td>
</tr>
<tr>
<td>$\gamma$ angle</td>
<td>6.8 ± 5.4</td>
<td>0.0–19.0</td>
</tr>
</tbody>
</table>

### Abbreviation: SD, standard deviation.
before surgery ($p < 0.001$). The ROM of patients improved significantly after surgery ($p < 0.01$; Table 1).

There were no significant differences between the intraobserver and interobserver measurement of the sagittal parameters ($p > 0.05$). Subsequently, multivariate regression analyses were performed among the PROM, ROM, and pelvic and femoral sagittal parameters (Table 2). Among all these indexes before or after surgery, only the $\alpha$ angle was found to be significantly associated with postoperative knee extension ($p = 0.001$). Moreover, the secondary regression equations showed a convex upward function of the $\alpha$ angle ($p < 0.01$). The $\alpha$ angles that demonstrated the best postoperative KSS, satisfaction score, and knee extension were 0.57, 0.96, and $-1.42$ degrees, respectively. However, the equation showed a concave upward pelvic incidence in the $\alpha$ angle, and the $\alpha$ angle that demonstrated the lowest pelvic incidence was $0.33$ degrees ($p < 0.001$; Fig. 3).

There were no significant differences in age, sex, or BMI among the four cohorts ($p > 0.05$). A Bonferroni’s paired comparison indicated that the postoperative KSS and patient satisfaction scores of cohort B were better than those of any other cohorts ($p < 0.0125$; Table 3). However, no significant differences between the postoperative PROM and ROM of the other three cohorts were found ($p > 0.0125$). Because the PI and FABA data had normal distributions ($p > 0.05$), the Pearson’s correlation analysis was used and a moderate positive correlation was found ($r = 0.3749$; $p = 0.0003$; Fig. 4).

Fig. 3  Secondary regression analyses of the $\alpha$ angle and postoperative KSS, satisfaction scores, and knee extension and pelvic incidence. (A) The fitting curve demonstrated a correlation between the $\alpha$ angle and postoperative KSS ($y = -0.088x^2 + 0.101x + 89.695; R^2 = 0.124$; vertex: 0.57 degrees; $p = 0.003$). (B) The fitting curve showed a correlation between the $\alpha$ angle and postoperative satisfaction scores ($y = -0.036x^2 + 0.069x + 8.057; R^2 = 0.298$; vertex: 0.96 degrees; $p < 0.001$). (C) The fitting curve demonstrated a correlation between the $\alpha$ angle and postoperative knee extension ($y = -0.056x^2 - 0.159x - 1.102; R^2 = 0.194$; vertex: $-1.42$ degrees; $p < 0.001$). (D) The fitting curve demonstrated a correlation between the $\alpha$ angle and pelvic incidence ($y = 0.374x^2 - 0.245x + 50.282; R^2 = 0.274$; nadir: 0.33; $p < 0.001$). KSS, Knee Society Score.
### Table 3 Comparisons of general characteristics and postoperative scores of the four different cohorts

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>A (α &lt; 0 degrees)</th>
<th>B (0 degrees ≤ α ≤ 3 degrees)</th>
<th>C (3 degrees &lt; α ≤ 7 degrees)</th>
<th>D (α &gt; 7 degrees)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee joints (n)</td>
<td>24</td>
<td>26</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>Age (y)</td>
<td>70.50 ± 6.1</td>
<td>70.46 ± 5.71</td>
<td>70.68 ± 5.04</td>
<td>70.40 ± 5.28</td>
</tr>
<tr>
<td>BMI</td>
<td>26.12 ± 4.44</td>
<td>25.32 ± 3.34</td>
<td>26.02 ± 3.83</td>
<td>25.04 ± 4.29</td>
</tr>
<tr>
<td>KSSa</td>
<td>87.40 ± 3.83³</td>
<td>91.50 ± 4.23³</td>
<td>87.35 ± 4.57</td>
<td>85.75 ± 4.59</td>
</tr>
<tr>
<td>Functional scorea</td>
<td>57.29 ± 12.33</td>
<td>58.65 ± 13.38</td>
<td>55.26 ± 6.12</td>
<td>54.25 ± 6.54</td>
</tr>
<tr>
<td>WOMACa</td>
<td>27.96 ± 3.88</td>
<td>26.81 ± 5.64</td>
<td>26.89 ± 4.38</td>
<td>26.70 ± 4.51</td>
</tr>
<tr>
<td>Satisfaction scorea</td>
<td>7.17 ± 1.20³</td>
<td>8.19 ± 1.20³</td>
<td>7.32 ± 0.95</td>
<td>7.20 ± 1.15</td>
</tr>
<tr>
<td>Knee flexiona</td>
<td>113.54 ± 14.48</td>
<td>116.46 ± 13.99</td>
<td>118.58 ± 15.53</td>
<td>118.80 ± 13.74</td>
</tr>
<tr>
<td>Knee extensiona</td>
<td>−2.38 ± 3.76</td>
<td>−1.77 ± 3.49</td>
<td>−3.58 ± 3.96</td>
<td>−2.50 ± 3.17</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; KSS, Knee Society Score; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Note: Because of the heterogeneity of variance among the four groups, the Kruskal–Wallis test was used. The significance level of the Bonferroni paired comparison was adjusted to 0.0125.

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**Fig. 4** Correlation between the femoral anterior bowing angle and pelvic incidence. Scatter plot demonstrates the Pearson’s correlation analysis of the femoral anterior bowing angle and pelvic incidence ($r = 0.3749; p = 0.0003$)

### Discussion

Proper sagittal alignment of the FC during TKA involves compromise to avoid notching of the femoral prosthetic and overstuffing of the trochlea, both of which can affect the clinical outcomes. Hence, we studied the possible impact of the associated sagittal alignment parameters on the position of the FC and clinical outcomes of primary PS TKA for patients with OA. The principal findings of our study were that an extreme $\alpha$ angle was associated with poorer clinical outcomes and 0 to 3 degrees (neutral to mild flexion of the FC) might be the acceptable range of the $\alpha$ angle. Some researchers determined the variant morphology of the distal femur and unsatisfactory deviation from the actual size of the FC measured by the DFAC; however, according to the results of our study and other previous research, the DFAC could be a proper anatomic landmark that could be used to make adjustments to achieve correct sagittal alignment of the FC.

Among all these indexes and parameters in our study, only the $\alpha$ angle was found to be significantly associated with postoperative outcomes. Furthermore, PI was found to be closely associated with the $\alpha$ angle. Hence, the correlation between PI and the $\alpha$ angle was studied subsequently. We found that higher pelvic incidence might be associated with a higher $\alpha$ angle of FC. Because PI is a fixed sagittal parameter in adults, the reasons for our findings remain elusive. A cadaveric specimens study reported a significant correlation between higher PI and OA of the hip joint. A possible explanation could be that patients with increased PI tend to lose the anterior covering of the acetabulum due to excessive PT with aging. However, the possible explanation for our findings could be that PI was likely associated with sagittal femoral curvature. Our study revealed a moderate positive correlation between FABA and PI which suggested that higher PI might be associated with increased sagittal femoral curvature. Moreover, numerous studies have demonstrated that patients with increased femoral anterior bowing were at higher risk for sagittal malalignment during navigated TKA. Therefore, we hypothesized that, as a compensatory mechanism, higher PI is associated with an increased sagittal femoral curvature which probably increases the risk of sagittal malalignment of the FC during TKA.

Our research found that a neutral $\alpha$ angle indicated high postoperative KSS and patient satisfaction scores, subsequently indicating a favorable prognosis. Regarding the normal range of knee movement, particularly extension, as a benchmark to evaluate the postoperative prognosis, Kang et al reported that excessive flexion of the FC can lead to trochlea overstuffing. However, too much flexion of the FC...
can result in knee extension limitations. \(^6\) Interestingly, consistent with these study results, a multivariate regression analysis of our study showed that the \(\alpha\) angle was closely related to postoperative extension of the knee joints. Our findings suggested that a decreased \(\alpha\) angle was probably associated with neutral extension of the postoperative knee joints, whereas an increased \(\alpha\) angle could probably result in limited extension of the knee joints.

Kang et al also found that overextension of the FC during PS TKA can cause notching of the DFAC. \(^8\) The \(\alpha\) angle could be a key parameter for assessing the postoperative sagittal position of the FC. Therefore, we further investigated the ideal range of the \(\alpha\) angle. According to the cohort study, we found that patients with neutral to mild flexion of the FC (0 degrees \(\leq\) \(\alpha\) angle \(\leq\) 3 degrees) could probably achieve better clinical outcomes than patients with other \(\alpha\) angle ranges which is consistent with the results of the secondary regression analyses in our study and previous research. \(^2\) Our findings indicated that clinical outcomes can be significantly affected by the proper sagittal alignment of the FC which can be evaluated by the \(\alpha\) angle. Most importantly, our findings could indicate how to achieve and evaluate sagittal balance of the FC based on the reference index of the DFAC and the proper range of the \(\alpha\) angle during PS TKA.

**Limitations**

This work had several limitations. The conclusions of this retrospective, two-dimensional imaging study are limited to posterior stabilized prostheses and the Chinese population. Furthermore, the results are probably surgeon specific. Therefore, our findings should be verified by further studies with larger sample sizes.

**Conclusion**

In conclusion, increased PI might be associated with a higher risk of sagittal malposition of the FC during PS TKA. The DFAC could be a landmark for surgeons attempting to achieve proper sagittal alignment of the FC. Patients with neutral-to-mild flexion of the FC (0 degrees \(\leq\) \(\alpha\) angle \(\leq\) 3 degrees) might be more likely to achieve favorable clinical outcomes. Based on our findings, we suggest surgeons should pay more attention to the sagittal alignment of FC in patients with increased PI, the DFAC is recommended as an anatomic landmark for sagittal alignment balance of FC and 0 to 3 degrees might be “safe zones” of the sagittal flexion of FC (\(\alpha\) angle) in TKA.

**Ethics Approval**

This retrospective study was approved by the First Affiliated Hospital of Sun Yat-sen University Clinical Research Ethics Committee (Guangzhou, China, Institutional Review Board [IRB] no. 2013–032).

**Authors’ Contributions**

H.L. conceived, designed, performed research, and prepared manuscript. F.Z. conceived, designed, and performed clinical follow-up. S.L. collected clinical data and performed clinical follow-up. X.W. collected clinical data and performed clinical follow-up. X.W. contributed with analysis and interpretation of the data and prepared table and figures. X.Z. collected clinical data and performed clinical follow-up. W.L. supervised the study and revised manuscript. Z.Z. conceived, designed, supervised the study, and revised manuscript. H.L. and F.Z. are regarded as co–first authors. Z.Z. is regarded as the corresponding author.

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**Conflict of Interest**

None declared.

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