CLINICAL ARTICLE

Sagittal Parameters of Spine-Pelvis-Hip Joints in Patients with Lumbar Spinal Stenosis

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Objective: To explore sagittal compensation characteristics, including extra spinal-pelvic parameters and distal hip parameters, for analysis in middle-aged to the older patients with lumbar spinal stenosis (LSS) without spinal deformity and clarify the fitting relationship between the main sagittal parameters.

Methods: This retrospective single-center study included 205 patients with LSS in our department from January 2016 to December 2018, including 153 women (74.6%), with an average age of 67.6 ± 7.1 years. Sagittal parameters were obtained on the whole spinal lateral radiograph. Spinal parameters include thoracic kyphosis (TK), thoracolumbar kyphosis (TLK), and lumbar lordosis (LL). Pelvic parameters include pelvic incidence (PI), pelvic tilt (PT), and sacral slope (SS). Hip parameters include pelvic rotation (PR) and hip inclination angle (HIA). Spine-pelvic parameter is spino-sacral angle (SSA). Sagittal balance parameter is sagittal vertical axis (SVA). PI-LL, PT, SVA, HIA, and TLK were regarded as primary results, and the others were secondary outcomes. The independent sample t-test was used to compare gender. Pearson correlation analysis was used to evaluate the correlation between primary results and secondary results. We take PI-LL, PT, SVA, and TLK as dependent variables and include relevant factors for analysis.

Results: In the case of gender, PI, PI-LL, and PT were found smaller in men than women, but TK is greater in men than women (27.3° ± 6.1° vs 23.3° ± 7.7°, p = 0.033). PI-LL was positively correlated with PT (r = 0.608, p < 0.001) and negatively correlated with HIA (r = −0.193, p = 0.010); PT was negatively correlated with HIA (r = −0.289, p < 0.01). As to the relationship between primary and secondary results, HIA was positively correlated with SS and PR (p < 0.01). SVA was positively correlated with SSA (r = 0.341, p = 0.010). The positive influencing factors and risk factors of SVA were SSA, and PI-LL played a negative regulatory role through proximal TK, the distal PT plays a positive regulatory role. The regulation of PI-LL was compensated through both TK and PT, with a fitting relationship of PI-LL = 0.5 × PT − 0.2 × JK.

Conclusion: There was a close interaction among spine-pelvic-hip sagittal parameters. We found the matching of PI-LL in the domestic middle-aged and elderly LSS population is regulated by thoracic spine and pelvis.

Key words: degenerative thoracic kyphosis; lumbar spinal syndrome; lumbar stenosis syndrome; pelvic incidence; spino-pelvic-hip parameters

Introduction

The human spine is closely correlated with biomechanical function: the normal spine has several physiological curvatures in the sagittal plane to maximize efficiency by adjusting the center of gravity in the area between the feet and minimizing the impact on joints, muscles, and ligaments. For the whole spinal alignment, the most common method is to measure the overall sagittal vertical axis (SVA). SVA has high practicability in sagittal balance evaluation. The spinal-pelvic sagittal sequence describes the ideal balance in the sagittal position due to the interaction between different parts. Any cause that breaks the balance will cause

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sagittal deformities and trigger the compensatory mechanism. Loss of sagittal sequence is widespread in many spine-pelvic diseases and is essential for evaluating the load of the patient's spine.\(^2\) Duboussé\(^{et\ \text{al.}}\) proposed that the pelvis is the cornerstone of the spine sagittal sequence, and the emergence of pelvic tilt (PT) established a possible compensatory mechanism for spinal imbalance; Duval-Beaupère clarified the geometric meaning of pelvic incidence (PI), pelvic tilt (PT), and sacral slope (SS): where $PI = PT + SS$.\(^{4,5}\) The pelvis will have morphological changes during the growth and upright in childhood, which is mainly reflected in the changes of PI. Before PI stabilized in early puberty, there was a significant linear correlation between age and PI. The increase in PI varies with the leveling of the sacrum and the development of LL in early childhood, which is essential for standing on both feet and keeping them upright. PT and LL increase with age in childhood to fully move the body's center of gravity forward, while SS is not affected by age. Due to the limited movement of the sacroiliac joint, PI in adults is considered to be a fixed anatomical parameter, while the emergence of PT establishes a possible compensatory mechanism for spinal imbalance and quantifies the degree of pelvic rotation around the femoral head. Sacral inclination lays the foundation for lumbar kyphosis. That is, small SS is associated with small LL, but because of pelvic pronation, SS changes in patients with sequence loss, so SS is not suitable to guide orthopaedic strategies. PI is the only morphological parameter of an individual and has a strong positive correlation with LL.\(^6\) PI-LL was used to quantify the matching between pelvic shape and lumbar lordosis, and scholars usually determined the PI-LL <10° threshold as the standard for spine-pelvic sagittal fit; Schwab\(^{et\ \text{al.}}\) proposed a correction formula $LL = (PI + TK)/2 + 10$, which cleverly correlated extra parameters to fit a more realistic sagittal sequence.

Compensation mechanisms are the body’s response to sagittal sequence loss. For mild sequence loss, these mechanisms usually start in relatively flexible segments with a high range of motion and gradually extend distally to the hip joint and lower extremities. The body is compensated by moving the center of gravity back and forth, starting by the extension of thoracic vertebrae and then by pelvic pronation, supination, and flexion and extension of the knee and ankle joints.

Although Schwab\(^{et\ \text{al.}}\) determined the cutoff values of the sagittal parameters (SVA, PI-LL, and PT),\(^8\) others like lifestyle habits, musculoskeletal tissue, and nervous system also change with age. Thus, Schwab\(^{et\ \text{al.}}\) studied the effect of age on the spine-pelvic sequence;\(^9\) Lafage\(^{et\ \text{al.}}\) believed that the ideal sagittal parameters should consider age factors, and younger patients need more stringent matching standards.\(^{10}\) The compensation mechanism usually starts from the flexible segment with greater mobility and gradually extends distally to the hip joint.\(^{11}\) The body compensates by moving the center of gravity back and forth, initially compensating by stretching the thoracic spine,\(^{12}\) and then adjusting by pelvic rotation and hip-knee flexion. Therefore, it is not enough to evaluate the spine and pelvis; compensation such as the hip joint and even the lower limbs should be considered. Previous studies included few sagittal parameters, and there were fewer studies on the distal hip.

Changes in the thoracolumbar and lumbar spine are the leading cause of sagittal sequence loss and vary in different populations.\(^1\) In middle-aged and elderly people, the overall sagittal position is significantly forward with SVA increases and LL decreases. With improved quality of life, middle-aged and elderly patients’ exposure rate and attendance rate are increasing. The adjustment of sagittal parameters of this population changes by lumbar spinal stenosis (LSS) because many LSS patients have forward bending postures to increase the volume of the central canal and intervertebral foramen to reduce nerve compression.\(^13\) Such postures affect the sagittal parameters, making LSS patients not applicable to the previous conclusions drawn for asymptomatic middle-aged and elderly people.

To explore sagittal compensation characteristics, we include extra spinal-pelvic parameters and distal hip parameters for analysis, aiming at (i) analyzing the correlation between the spine-pelvis-hip joint parameters in middle-aged and elderly patients with LSS without spinal deformity; (ii) clarifying the fitting relationship between the main sagittal parameters; and (iii) exploring the differences of parameters in different gender groups.

**Methods**

**Patient Enrollment**

This retrospective single-center study was approved by the ethical committee of our institution [No. 2018PHC076]. We enrolled LSS patients with no spinal deformities in our department from January 2016 to December 2018. The diagnosis of LSS is mainly based on the symptoms, signs, and auxiliary examinations, which are repeated lower extremity radiating pain with or without low back pain, numbness, chills, and muscle weakness in the lower extremities, and intermittent claudication, CT, or MRI suggest signs of lumbar spinal stenosis.

The inclusion for selecting the subjects was as follows: (i) patients diagnosed with LSS and no spinal deformities; (ii) aged >55 years, with stand radiographs of lumbar and the whole spine; (iii) ineffective in conservative treatment for more than 6 months. The exclusion criteria were: (i) those with scoliosis or imbalance in the coronal position; (ii) those with local kyphosis or abnormal lordosis in the sagittal position; (iii) those who have undergone previous spinal surgery; (iv) those with neurofibromatosis or other muscle diseases; (v) patients with thoracic spinal stenosis, vertebral fractures, and other diseases.

**Spinal Alignment Evaluation**

The preoperative sagittal parameters were obtained on the full-length X-ray of the spine, including spinal parameters, pelvic parameters, hip joint parameters, spine-pelvic parameters, and sagittal balance parameters.
TK: the sagittal angle between the superior endplate of T5 and the inferior endplate of T12, which was a positive value in kyphosis patients.

TLK: the sagittal angle between the superior endplate of T10 and the inferior endplate of L2.

LL: the sagittal angle between the superior endplate of L1 and the inferior endplate of S1, which was a positive value in lordosis patients.

PT: the angle between the line from the center of the femoral head to the upper endplate of S1 and the plumb line.

SS: The angle between the upper endplate of S1 and the horizontal line.

PI: Draw a vertical line through the midpoint of the upper endplate of S1 and the femoral head center.

Hip inclination angle (HIA): The angle between the femur’s anatomical axis and the vertical line connecting the anterior superior iliac spine and the posterior superior iliac spine, normally 20°.

Pelvic rotation (PR): The angle between the line of the anterior superior iliac spine and the posterior superior iliac spine and the horizontal line, normally from 10° to 40°. HIA also reflects the relative relationship between PR and the anatomical axis of the femur. Therefore, this study uses PR as a hip joint parameter.

Spino-sacral angle (SSA): The angle between the line between the center of the C7 vertebral body and the midpoint of the S1 endplate and the S1 endplate.

SVA: Draw a plumb line through the midpoint of the C7 vertebral body. The distance from the upper back corner of S1 to the straight line.

Fig. 1 Illustration of the spine-pelvis-hip joint sagittal parameter. TK: the angle between T5 and T12; TLK: the angle between T10 and L2; LL: the angle between L1 and S1. PT: the angle between the line from the center of the femoral head to the upper endplate of S1 and the plumb line; SS: the angle between the upper endplate of S1 and the horizontal line; PI: draw a vertical line through the midpoint of the upper endplate of S1 and the femoral head center. HIA: the angle between the femur’s anatomical axis and the vertical line connecting the anterior superior iliac spine and the posterior superior iliac spine. PR: the angle between the line of the anterior superior iliac spine and the posterior superior iliac spine and the horizontal line. SSA: the angle between the line between the center of the C7 vertebral body and the midpoint of the S1 endplate and the S1 endplate. SVA: draw a plumb line through the midpoint of the C7 vertebral body. The distance from the upper back corner of S1 to the straight line.

Statistical Analysis
All measurement data was expressed by mean ± standard deviation. The independent sample t-test was used to compare gender. Pearson correlation analysis was used to evaluate the correlation between primary results and secondary results. We took PI-LL, PT, SVA, and TLK as dependent variables and include relevant factors for analysis. The statistical analysis was performed by SPSS 22.0 (International Business Machines Corporation), and statistical significance was defined as \( p < 0.05 \).

Results
Eventually, 205 patients were recruited, including 153 women (74.6%) and 52 men (25.4%) with an average age of 67.6 ± 7.1 years (55–83 years) and a BMI of 26.1 ± 3.2 kg/m² (20.1–34.4 kg/m²).

The Value and ICC of all Radiological Parameters
Intra-observer reproducibility and inter-observer reliability using ICC for all radiological parameters showed good to excellent agreement (Table 1). Specifically, PI-LL, PT, and SVA are 8.6° ± 11.0°, 19.8° ± 8.4° and 27.1 ± 31.1 mm, and
Table 1: Primary results and secondary results

| Primary results | Mean ± SD  | ICC  | Secondary results | Mean ± SD  | ICC  |
|----------------|-----------|------|------------------|-----------|------|
| TLK, °         | 7.2 ± 6.3 | 0.78 | TK, °            | 24.2 ± 7.6 | 0.88 |
| SVA, mm        | 27.1 ± 31.1 | 0.91 | PR, °            | 14.1 ± 7.7 | 0.79 |
| HIA, °         | 18.3 ± 6.6 | 0.72 | SSA, °           | 57.6 ± 8.4 | 0.84 |
| PLL, °         | 8.6 ± 11.0 | 0.77 | LL, °            | 41.7 ± 10.9 | 0.81 |
| PT, °          | 19.8 ± 8.4 | 0.93 | PI, °            | 50.7 ± 10.4 | 0.77 |

Abbreviations: HIA, hip inclination angle; ICC, intraclass correlation coefficient; LL, lumbar lordosis; PI, pelvic incidence; PR, pelvic rotation; PT, pelvic tilt; SSA, spino-sacral angle; SVA, sagittal vertical axis; TLK, thoracolumbar kyphosis.

Table 2: Pearson correlation analysis of main results and age

|         | PI-LL    | PT       | HIA      | SVA      | TLK      |
|---------|----------|----------|----------|----------|----------|
| r       | p        | r        | p        | r        | p        |
| PT      |          |          |          |          |          |
| HIA     | −0.193   | 0.010    | −0.289   | <0.001   |          |
| SVA     | 0.238    | 0.019    | −0.070   | 0.497    | 0.088    |
| TLK     | −0.037   | 0.630    | −0.082   | 0.286    | −0.155   |
| Age     | 0.027    | 0.715    | 0.065    | 0.381    | −0.020   |

Abbreviations: HIA, hip inclination angle; LL, lumbar lordosis; PI, pelvic incidence; PT, pelvic tilt; SVA, sagittal vertical axis; TLK, thoracolumbar kyphosis.

The Relationship among the Spinal Sagittal Parameters

In this population, PI-LL was positively correlated with PT (17.2° vs 23.3°, p < 0.01), PT was positively correlated with SS and PR (Beta = 0.228, p < 0.001), SVA is correlated with PI-LL and PT as the dependent variable and the above-mentioned related factors as independent variables. Through collinearity judgment, the independent variables can exist at the same time (tolerance >0.1). The positive influencing factors and risk factors of SVA were SSA (p < 0.001), and PI-LL played a negative regulatory role through proximal TK (Beta = −0.228, p = 0.011), and PT plays a positive regulatory role (Beta = 0.520, p < 0.001), the fitting relationship is: PI-LL = 0.5 × PT-0.2 × TK; and HIA is not an influencing factor of the three (Table 2, Fig. 5).

Discussion

Generally, there was a close interaction among spine-pelvis-hip sagittal parameters. Firstly, it found PI, PI-LL, and PT are smaller in males than in females, while the TK is greater in males than in females. Then the parameters mentioned by Schwab (PI-LL, PT and SVA) closely interacted. With the initial change of loss of lumbar lordosis, there was a series of compensation chain by spino-pelvic-hip parameters. What's more, the compensation of parameters existed in real-time from stasis to dynamic status.

Spino-Pelvic Sagittal Alignment

The spino-pelvic sagittal alignment plays an essential role in the maintenance of the normal function and guidance for surgical reconstruction. The degeneration of spinal deformity...
consumes plenty of energy and probably accelerates the pro-
gress of spinal diseases. Therefore, many studies attempted
to quantify the spine-pelvic parameters to provide specific
clinical evidence. Schwab et al. outlined the matching condi-
tion between the pelvis and lumbar spine with PI-LL <10°
as the standard for spino-pelvic adaption. In addition, patients
with high TK also need a larger LL than theoretical value to
compensate for thoracic kyphosis with LL = (PI + TK)/2.
When the factor of age was taken into consideration, Lafage
et al. believed that elderly patients had more compensation,
more severe LL loss, and more trunk tilt. As the most
important joint of the spino-pelvis, the hip enables the over-
all sagittal balance, LSS is often combined with lower
extremity symptoms that may affect hip motion, making it
necessary to include hip parameters, but it is seldom con-
tained as an essential parameter in spino-pelvic analysis.

**PI-LL, PT, and SVA Closely Interacted**

This study, pooling spino-pelvic-hip parameters, found that
the sagittal parameters closely interacted, which confirmed
the biomechanical chain between various parts from the tho-
aric spine to the hip. The reasons for concentrating middle-
aged and elderly LSS patients without spinal deformity were
as follows. Firstly, LSS was the most common type of degen-
erative spinal disease in middle-aged and elderly people. Sec-
ondly, a large number of LSS patients, some with deformity,
required surgical treatment. Reconstruction of the sagittal
alignment and quantifying the parameters with normal
sequence can provide guidance for surgical strategies.
Thirdly, LSS often combines lower extremity symptoms, which may affect the biomechanical chain of the hip joint
and it should be taken into consideration. Furthermore, at
present, sagittal parameters were fitted for almost all

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**Table 3**: Pearson correlation analysis of secondary results and age

|      | TK | PR | SSA  |
|------|----|----|------|
| PR   | 0.126 | -0.304** | 0.279** |
| SSA  | 0.304** | -0.031 | 0.064 |
| Age  | 0.031 | 0.064 | 0.143 |

Abbreviations: PR, pelvic rotation; SSA, spino-sacral angle; TK, thoracic kyphosis.; **p < 0.01.
asymptomatic adults, while LSS patients need to fine tune these parameters to eliminate neurological symptoms, which may be in disparity with the healthy group.16

This study showed that the sagittal parameters PI, PI-LL, and PT were smaller in males than females. For the value of PI, the males have an average decrease by 5°–7° than females (p < 0.01) in the two age groups (40–49 and 70–79). Yukawa et al. included 626 asymptomatic adults and found gender-difference in SVA, PI, and PT (p < 0.05). Anatomically, there are significant gender differences in pelvic size and shape, and the pelvic range of motion was lesser in the male group compared with the female group. Therefore, we considered that the ideal value of PI-LL may vary by gender.17

The SRS-Schwab classification characterized the parameters of PI-LL, PT, and SVA in ASD patients. The lumbar spine sequence is the initial for the study of lumbar spine degeneration and reconstruction. Mangione et al.5 believe that to maintain a balanced posture with minimal consumption the optimal alignment of the lumbar spine mainly depended on PI, and consequently, PT also established a compensatory mechanism for spinal balance by the rotation of pelvis. This study addressed PI-LL, PT, and SVA as the main results, showing that PI-LL was positively correlated with PT, consistent with previous studies. SVA had high sensitivity and practicality in the evaluation of sequence loss, but SVA can be affected by the patient position and pelvic rotation.18 In our data, the increase of PI-LL led to an increase of SVA. For patients with small lumbar lordosis, according to Rousouly classification,19 the vertebral at the proximal thoracic and lumbar was relatively horizontal, so the proximal hyperextension is not adequately compensated, causing the trunk to lean forward. In this condition, the hip joint extended to compensate for the pelvic retroversion and to maintain the balance of the overall spine.

The Spino-Pelvic-Hip Compensation Chain with Less LL

Previous studies believed that PI was closely correlated to SS and LL, and LL was also associated with SS. In the case of decreased lumbar lordosis, the spine and pelvis may be compensated by increasing PT and decreasing TK to maintain sagittal balance, where the parameters, except for PI, need to be adjusted for compensation.13 When there was lumbar hypolordosis, the sacrum would become horizontal while the pelvis retroverted, so PI-LL was negatively correlated with PR and SS. SVA enabled quantifying the displacement distance of the cervical spine to the pelvis, which was the compensating role for LL loss together with pelvic rotation.20 The increase of SVA forced the body to appear positively imbalanced, ensuing the trunk tilted forward and the SSA increased. When the LL remained unchanged and the thoracic kyphosis increased, the upper lumbar spine consequently increased. To maintain PI-LL matching, the body will compensate by leveling the sacrum, pelvic ante-rotation, and the flexion of the hip. None of these parameters had an identified correlation with age, which was possibly attributed to the narrower age range of the participants.

In ASD, the lumbo-pelvic parameter was of great importance. A large number of previous studies have focused on the adjustment of distal lumbo-pelvic adaptation. However, the proximal compensation mechanism has been gradually emphasized and quantified. Some scholars addressed that...
PI + (TK – LL) > 45° was a risk factor for poor postoperative sagittal balance (SVA) \( (p = 0.009) \), but the studies mainly aimed at asymptomatic people and neglected the impact of the hip. This study quantified the fitting relationship between PI-LL and pelvis as well as proximal thoracic spine tightly to clinical practice. When patients attend the clinic, the sagittal morphology has been dually affected by the deformity and compensation.

**The Compensation of Parameters from Stasis to Dynamic Status**

When the lumbar spine was instrumented, PI-LL was relatively fixed and sagittal adjustment need to start from pelvic rotation. Once the pelvis uncompensated adequately, the fixation of the proximal thoracic spine possibly caused proximal junctional kyphosis (PJK). Hey et al. have shown that the SVA would gradually increase from an upright position or a straight sitting position, to a relaxed sitting position, where LL would decrease progressively. When LL was overcorrected (PI-LL close to \(-9^\circ\)) and exceeded the compensatory capacity of the thoracic spine, PJK was prone to appear in a sitting position. Therefore, in order to avoid the occurrence of PJK, it was necessary to select UIV seriously and to confine lumbar lordosis to a reasonable range. Given that when all lumbar spine was fused by long-segment fixation and LL was excessively restored, the UIV would terminate at the thoracolumbar segment. When the patient was in sitting posture, with the undercompensation of pelvic retroversion, the stress on TK and TLK would sharply increase, meaning that the PJK or PJF was inevitable in the elderly patients with osteoporosis (Fig. 6). By understanding this relationship in this study, physicians can guide patients to undertake functional exercises and adjust their posture independently to avoid biomechanical complications.

**Limitations**

The limitation of this study is that the hip joint parameters only include the hip joint inclination angle. Although this parameter reflects both the pelvic inclination angle and hip joint flexion angle, fewer parameters are included. The research parameters are all standard stance parameters, while dynamic parameters can be a better reflection. There are differences between the patient’s motion status and neurological function, static parameters, and dynamic parameters, and further study is needed. Affected by the total spine X-ray, this study only includes the hip joint parameters for research, while the distal knee and ankle joints are also involved in essential adjustments. A large sample of in-depth research is needed; this study only proposes the fitting relationship of parameters for patients.

### TABLE 5 Multiple linear regression analysis of main results

| Dependent variables | Unstandardized Beta | Standardized Beta | T | \( p \) | Tolerance | VIF |
|--------------------|---------------------|-------------------|---|-----|-----------|-----|
| PT                 | Constant            | 18.575            | 5.768 | 3.220 | 0.002     |     |
| PR                 | −0.177              | 0.104             |     |     |           |     |
| SVA                | Constant            | 1.744             | 16.329 | −0.184 | −1.699 | 0.093 | 1.342 |
| SSA                |                      | 1.254             | 0.265 | 0.341 | 0.107 | 0.915 |     |
| PI-LL              | Constant            | 3.307             | 5.1 | −0.228 | 2.611 | 0.011 | 1.000 |
| TK                 | −0.341              | 0.131             |     |     |           |     |
| PT                 | 0.672               | 0.117             | 52 | 5.764 | <0.001 | 0.928 | 1.078 |
| HIA                | −0.014              | 0.131             | −0.01 | −0.106 | 0.916 | 0.926 | 1.079 |

Abbreviations: HIA, hip inclination angle; LL, lumbar lordosis; PI, pelvic incidence; PR, pelvic rotation; PT, pelvic tilt; SSA, spine-sacral angle; SVA, sagittal vertical axis; TK, thoracic kyphosis; VIF, variance inflation factor.

**Fig. 5** When the physiological curvature of the lumbar spine decreases, PI-LL increases, PT increases, and TK decreases; and when LL increases, PT decreases, and TK increases. LL, lumbar lordosis; PI, pelvic incidence; PT, pelvic tilt; TK, thoracic kyphosis.
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Conclusion
In total, there was a close interaction among spine-pelvic-hip sagittal parameters. PI, PI-LL, and PT are smaller in women than in men, while the TK value is greater in men than in women; PI-LL has a clear correlation with PT, SVA, and hip inclination; SVA has a clear correlation with SSA, while TLK has an exact apparent influencing factor. The matching of PI and LL is adjusted by the thoracic spine and pelvis, which aligns with the fitting relationship of the domestic middle-aged and elderly LSS population as PI-LL = 0.5 × PT – 0.2 × TK. These conclusions supply the specific evidence for the whole spina-pelvic-hip sagittal biomechanics. Furthermore, by this fitting formula, physicians can guide the patients to undertake functional exercises and adjust their posture individually to avoid biomechanical complications.

Author Contributions
Conceptualization: Haiying Liu, Shuai Xu; Data Curation: Shuai Xu, Chen Guo; Formal Analysis: Shuai Xu, Chen Guo, Yan Liang; Investigation: Yan Liang; Methodology: Shuai Xu; Chen Guo, Yan Liang; Project Administration: Haiying Liu, Yan Liang; Resources: Shuai Xu; Yan Liang; Software: Shuai Xu, Chen Guo, Zhenqi Zhu; Validation: Chen Guo; Visualization: Haiying Liu, Zhenqi Zhu; Writing & Editing: Haiying Liu, Shuai Xu, Chen Guo, Yan Liang.

Conflict of Interest
The authors declare no conflict of interest.

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