Clinical Article

The Standing and Sitting Spino-Pelvic Sagittal Alignment in Patients with Instrumented Lumbar Fusion Might Correlate with Adjacent Segment Degeneration

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Objectives: Sitting is a common weight-bearing posture, like standing, but there still lacks enough understanding of sagittal alignment in sitting position for patients after lumbar fusion. This study aimed to investigate the accommodation of fixed spine from standing to sitting position and its influence on unfused segments.

Methods: Sixty-two patients after lumbar fusion (test group) and 40 healthy volunteers (control group) were recruited in this research. All subjects underwent lateral radiographs of entire spine in the standing and sitting positions. The spinopelvic parameters including sagittal vertical axis (SVA), T1 pelvic angle (TPA), lumbar lordosis (LL), thoracic kyphosis (TK), and pelvic tilt (PT) were measured. The changes in parameters of patients between two positions were compared with control group, and patients were divided in different groups based on fusion level and their parameters were compared.

Results: When changing from standing to sitting positions, a forward-moving SVA and TPA were observed in both patients and control groups, accompanied by the decrease in LL, TK and increase in PT, but the changes of patients were smaller in TPA, LL, and TK (6.5°/C14/C6 7.2°/C14 vs 9.7°/C14/C6 6.0°/C14, 7.7°/C14/C6 8.3°/C14 vs 13.6°/C14/C6 8.5°/C14, 2.2°±6.5° vs 5.4°±5.1°, respectively, p<0.05). Increase of PT in the lumbosacral fixation group was lower than that in the control group (4.4°/C14/C6 9.1°/C14 vs 8.3°/C14, p<0.05). Patients who had adjacent segments degeneration (ASD) showed more kyphosis in unfused lumbar segments than the other patients (16.4°±10.7° vs −1.0°±4.8°, p<0.05) from standing to sitting.

Conclusions: The spine straightens in lumbar and thoracic curve, combined with forward-moving axis and pelvic retroversion when changing to the sitting position. However, these changes are relatively limited in patients after lumbar fusion, so the adjacent unfused lumbar segments compensate to stress during sitting and this may be related to ASD.

Key words: Adjacent segment degeneration; Correction surgery; Lumbar fusion; Sagittal alignment; Sitting

Introduction

Spinal fusion is a useful surgical technique when dealing with spinal disorders, since it can render the spine fixed in a suitable curvature and provide stability. Recently, this curvature is modeled after a typical spine in standing posture.1-4 However, sitting is also a weight-bearing posture as common as standing in our daily life5 and the dynamic is different between the two positions.6,7 Therefore, after fusion, the fixed standing spine cannot change to the suitable alignment in sitting position, which may make the spine bear...
abnormal stress in the sitting position and lead to surgical complications.

Previous literature has reported that the sagittal alignment significantly changed from standing to sitting in children with scoliosis, healthy young adults, and elderly persons, which was represented by a forward-moving sagittal vertical axis (SVA), decreased lumbar lordosis (LL), thoracic kyphosis (TK), and sacral slope (SS), as well as increased pelvic tilt (PT). Hey et al. demonstrated that with standing posture as a reference, LL and TK decreased 24.6° ± 12.7° and 8.6° ± 7.2°, respectively, followed by SVA increasing 6.4 ± 3.9 cm and PT increasing 13.8° ± 10.2° in young adults. Zhou et al. have investigated the standing and sitting sagittal alignment of 235 healthy volunteers aged 19 to 71 years. They reported that age could influence the reduction in LL and PT during the change from standing to sitting positions, indicating that the spinal straightening and pelvic retroversion in sitting position was smaller in an older population. These results indicate that the sitting position requires a different sagittal alignment from the standing position, and it should be valued when planning spinal fusion surgery.

However, little is known about the fixed spine after fusion when moving from standing to sitting positions. This post-fusion adaptation of the spine in different positions should be elaborated to design the suitable sagittal alignment accounting for both positions. Some researchers have investigated postoperative adaptation in patients after fusion surgery. Zhu et al. documented that thoracic fusion could diminish the decrease in LL (14.0%) and SS (13.9%) during sitting position, compared with the preoperative status (42.1% decrease in LL and 31.1% decrease in SS) for adolescent idiopathic scoliosis (AIS). A biomechanical study using human thoracolumbar spine specimens has reported that sagittal parameters often were partially preserved in the fused cranial segment situation including lumbosacral fixation and adjacent segment degeneration (ASD). Therefore, this study was designed to elaborate on the adaptation that occurred during sitting position in patients after lumbar fusion in the first. Second, the influences of fusion segments on the changes when moving from standing to sitting positions were further explored. Finally, the relationship between ASD and lumbar curve compensative changes in two positions will be explored. These findings could explain how the surgical fusion technology impacted the spinal alignment and its regulatory mechanism, which served as a reference for planning surgery.

Materials and Methods

Study Design
This comparative study was approved by Peking University Third Hospital Ethics Committee and was conducted according to the principles of the Declaration of Helsinki (IRB00006761-2015150). All volunteers were fully informed about the methods, purposes, and risks involved in the study protocol and signed the informed consent.

Patients
To evaluate the effects of lumbar fusion on the spinal sagittal alignment and leave enough time for patients to adapt to the lumbar fusion in their daily life, we recruited 86 patients who underwent posterior instrument and fusion surgery for lumbar spinal stenosis in our hospital from 2010 to 2012. All patients underwent a comprehensive history taking and physical examination before participating in this study. Then, X-ray imaging of the lumbar extension and flexion position was used to evaluate the fusion, and if the fusion situation was difficult to judge on X-ray, the computed tomography (CT) scan was taken. Magnetic resonance imaging (MRI) was performed to help assess the adjacent segment. Finally, 62 patients were included in this study based on the inclusion and exclusion criteria.

The inclusion criteria were: (1) lumbar spinal stenosis patients with lower instrumented vertebra located in the lumbar vertebrae or the sacrum; (2) with no rod or screw breakage; (3) with no other spinal surgery.

The exclusion criteria were: (1) hip or knee joint contracture; (2) severe osteoporosis or vertebral fracture; (3) neuromuscular disorder; (4) suspected or confirmed nonunion based on radiographic findings; and (5) with severe pain which influenced the standing and sitting positions.

Among the test group, patients were divided into different subgroups based on lumbosacral fixation and adjacent segment situation including lumbosacral fixation group vs lumbosacral non-fixation group and ASD group vs non-ASD group. ASD was diagnosed at last follow-up according to following criteria without preoperative presentation: (1) disc degeneration; (2) listhesis of more than 4 mm; (3) the adjacent bodies angle changed more than 10°; (4) spinal stenosis aggravation; (5) hypertrophic facet arthropathy; (6) osteophyte more than 3 mm; (7) scoliosis; and (8) compression vertebra fracture.

For the control group, 40 healthy middle-aged and elderly people (age ≥ 45 years) who met the following inclusion criteria were included: (1) no history of back or leg pain; (2) no history of spinal disorders or spinal surgery; (3) no history of hip or knee diseases; and (4) no history of neuromuscular disease were recruited.

Surgical Procedures
The posterior midline approach was applied in all patients. After the internal pedicle screw fixation, the patients underwent decompressive laminectomy, while the observation of traversing nerve roots was considered the standard of complete decompression on the lateral extent. The lamina and spinous process were partially preserved in the fused cranial
## TABLE 1 The sagittal parameters in standing and sitting position of 62 patients and 40 healthy people (mean ± SD)

| Sagittal parameters | Standing       | Sitting        | Differences   | t value  | p value |
|---------------------|----------------|---------------|---------------|----------|---------|
| Global balance      |                |               |               |          |         |
| SVA (mm)            | 22.0 ± 34.2    | 41.2 ± 27.2*  | 19.2 ± 33.6   | -4.517   | <0.001  |
| TPA (°)             | 3.8 ± 27.8     | 25.1 ± 26.3*  | 21.3 ± 31.8   | -4.239   | <0.001  |
|                     | 13.1 ± 6.3     | 19.6 ± 9.4*   | 6.5 ± 7.2     | -7.126   | <0.001  |
|                     | 8.4 ± 7.5      | 18.1 ± 8.4*   | 9.7 ± 6.0     | -10.302  | <0.001  |
| Local curvature     |                |               |               |          |         |
| LL (°)              | -41.2 ± 14.5   | -33.5 ± 15.2* | 7.7 ± 8.3     | -7.253   | <0.001  |
| TK (°)              | -47.4 ± 12.7   | -33.9 ± 13.2* | 13.6 ± 8.5    | -10.133  | <0.001  |
|                     | 31.0 ± 12.2    | 28.8 ± 12.9*  | -2.2 ± 6.5    | 2.679    | 0.009   |
|                     | 33.2 ± 7.9     | 27.8 ± 9.2*   | -5.4 ± 5.1    | 6.752    | <0.001  |
| Spinopelvic parameters |              |               |               |          |         |
| PI (°)              | 47.5 ± 9.6     | -            | -             | -        | -       |
| PT (°)              | 16.6 ± 7.0     | 22.3 ± 10.6*  | 5.8 ± 8.3     | -5.475   | <0.001  |
| SS (°)              | 12.6 ± 7.8     | 20.9 ± 9.3*   | 8.3 ± 7.1     | -7.436   | <0.001  |
|                     | 30.9 ± 9.3     | 26.1 ± 10.4*  | -4.9 ± 7.7    | 4.962    | <0.001  |
|                     | 33.0 ± 8.9     | 25.6 ± 8.9*   | -7.4 ± 7.0    | 6.746    | <0.001  |

Note: Data in the upper and lower lines present the parameters of patients and the control group, respectively. The negative values represent backward translation in balance and lordosis in curvature. “*” means compared with the standing position, \( p < 0.05 \).
vertebra, combined with the protection of the capsule in a cranial facet joint. The autologous graft was obtained from the resected lamina and processed with a cage.

**Radiographic Examination**

All subjects underwent anteroposterior and lateral radiographs of the whole spine and pelvis in the standing position and the lateral radiograph of the whole spine and pelvis in the sitting position. Before performing the X-ray, the VAS score of patients was less than 3 to reduce the influence of pain on their position.

The standing position procedure was performed by requesting subjects to stand as straight as possible, not to lean forward or backward, and then the fingers should be placed on their collar bones.

Regarding the sitting position, subjects were required to flex their hips and knees to 90°. A height-adjustable stool without a back was offered to the subjects so they could adjust the height to reach a standardized posture and put their feet on the ground. Then, they were instructed to sit as straight as possible, without leaning forwards or backwards, and put their fingers on their collar bones.

**Radiographic Evaluation**

Two orthopaedic specialists who were not otherwise involved in this study performed all measurements, and the average of their measurements was recorded. The parameters were measured using the Picture Archiving and Communication System (PACS; GE healthcare, Mount prospect, IL, USA) as follows:

1. Global parameters: SVA, T1 pelvic angle (TPA, the angle between the line from the femoral head axis to the

| TABLE 2 The general data of 37 patients with lumbosacral fixation and 25 patients without lumbosacral fixation |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| General information | With lumbosacral fixation | Without lumbosacral fixation | t value | p value |
| Age (years) | 64.9 ± 8.6 | 63.9 ± 8.3 | 0.460 | 0.647 |
| Male/female | 15/22 | 12/13 | - | 0.561 |
| BMI (kg/m²) | 26.0 ± 3.2 | 25.6 ± 2.4 | 0.537 | 0.593 |
| Fusion segments | 2.5 ± 1.1 | 2.2 ± 1.2 | 1.160 | 0.251 |

Abbreviation: BMI, body mass index.

| TABLE 3 The sagittal parameters in standing and sitting position of 37 patients with lumbosacral fixation and 25 patients without lumbosacral fixation (mean ± SD) |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Sagittal parameters | Standing | Sitting | Differences | t value | p value |
| Global balance | | | | | |
| SVA (mm) | 25.5 ± 37.4 | 42.5 ± 26.5 | 17.0 ± 31.8 | -0.640 | 0.524 |
| 16.7 ± 28.9 | 39.3 ± 28.7 | 22.6 ± 365 | | |
| TPA (°) | 13.1 ± 5.4 | 18.0 ± 9.4 | 4.9 ± 7.9* | -2.183 | 0.033 |
| 13.2 ± 7.6 | 22.1 ± 9.0 | 8.8 ± 5.2 | | |
| Local curvature | | | | | |
| LL (°) | -39.6 ± 14.5 | -32.7 ± 16.3 | 6.9 ± 9.3 | -0.889 | 0.377 |
| -43.5 ± 14.5 | -34.7 ± 13.6 | 8.8 ± 6.6 | | |
| TK (°) | 30.5 ± 11.0 | 27.9 ± 12.3 | -2.6 ± 6.5 | -0.588 | 0.559 |
| 31.6 ± 14.0 | 30.0 ± 13.9 | -1.6 ± 6.4 | | |
| Spinopelvic parameters | | | | | |
| PI (°) | 46.0 ± 10.1 | - | - | - | |
| 49.8 ± 8.7 | - | - | | |
| PT (°) | 16.2 ± 6.5 | 20.6 ± 10.5 | 4.4 ± 9.1 | -1.644 | 0.105 |
| 17.1 ± 7.8 | 28.0 ± 10.5 | 7.8 ± 6.6 | | |

Note: The data in the upper line present the parameters in lumbosacral fixation group and that in the lower line presents the parameters in lumbosacral non-fixation group. The negative values represent backward translation in balance and lordosis in curvature. "*" means the comparison with the patients who did not have lumbosacral fixation, p < 0.05.
FIGURE 2 From standing to sitting posture, forward-moving SVA, pelvic retroversion and spinal straightening occurred in both the patients and control groups. However, the ability of pelvic retroversion and spinal straightening was relatively limited in the patients.

FIGURE 3 In patients who had fusion in L4-S1, the unfused area compensated to kyphosis more in sitting position.
centroid of T1 and the line from the femoral head axis to the middle of the S1 endplate,\textsuperscript{16} which accounted for both truncal inclination and pelvic retroversion).

2. Local curvature: LL (the angle between the upper endplate of L1 and sacral endplate), TK (the angle between the upper endplate of T4 and the lower endplate of T12), lordosis of L4-S1 (the angle between the upper endplate of L4 and sacral endplate).

3. Pelvic parameters: pelvic incidence (PI), which reflected the relative position between femoral head and sacrum, PT, and sacral slope (SS), which reflected pelvic retroversion.

**Statistical Analysis**

All the collected data were analyzed using the SPSS version 19.0 (SPSS Inc., Chicago, IL, USA). Continuous radiological parameters were compared in the standing and sitting positions using the paired t-tests. Differences in the sagittal alignment between patients and the control group were compared using independent sample t-tests. Differences in sagittal parameters between patients with ASD and without ASD were compared using nonparametric test. Statistical significance was set at a level of $p < 0.05$.

**Results**

**General Profiles**

Patients comprised 27 men and 35 women, with an average age of 64.5 (range, 45–81) years. The mean follow-up time was 82.4 (range, 68–96) months. The average number of fusion segments was 2.4 (range, 1–5). The average body mass index (BMI) was $25.9 \pm 2.9$ kg/m$^2$. Thirty-five of the patients had ASD based on the diagnostic criteria. However, no patients with ASD received the revision surgery during the follow-up. The average Oswestry Disability Index (ODI) in patients was $19.8 \pm 14.0$, and the average Visual Analog Score (VAS) of leg and back pain was $2.2 \pm 3.0$ and $3.4 \pm 2.8$, respectively.

The control group included 14 men and 26 women, with an average age of 60.0 (range, 46–81) years. The mean BMI of the control group was $24.4 \pm 3.0$ kg/m$^2$. The baseline information was comparable between the patient group and the control group.

**Sagittal Alignment in Standing and Sitting Positions**

As shown in Table 1, when patients moved from standing to a sitting position, their body’s center of gravity moved forward with the significant increase in SVA ($p < 0.001$) and TPA ($p < 0.001$), accompanied by a significant decrease in LL ($p < 0.001$) and TK ($p < 0.01$), indicating that the spine became straight in sitting position. The significant increase in PT ($p < 0.001$) demonstrated pelvic retroversion in the sitting position.

Compared with the control group, the trend of changes from standing to sitting was similar in patients, as shown in Figure 1; however, the degree of changes was smaller in TPA ($6.5^\circ$ vs $9.7^\circ$, $p < 0.05$), LL ($7.7^\circ$ vs $13.6^\circ$, $p < 0.01$), TK ($2.2^\circ$ vs $5.4^\circ$, $p < 0.01$), and PT ($5.8^\circ$ vs $8.3^\circ$, $p = 0.11 > 0.05$).

**FIGURE 4** These images presented the situation of adjacent segment in the same patient shown in Figure 3. (A) presented the preoperative MR image and (B) presented the MR image during the last follow-up, which indicated that the patient had ASD.
The present study

Recent studies have demonstrated that the sagittal alignment of the spine was affected by spinal degeneration. Therefore, we hypothesized that the spinal sagittal alignment was significantly different between patients with and without ASD, and the unfused segments might compensate for changing more in sitting position to balance the spine. Since lumbosacral fusion limited the pelvic retroversion and spinal straightening in sitting position, we hypothesized that the spinal sagittal alignment might account for both standing and sitting positions, we needed to know how the sagittal spinal alignment changed after fusion surgery when moving from standing to sitting, and this result could provide important information for clinical practice.

### Discussion

Since spinal sagittal alignment was reported to be significantly associated with the health-related quality of life (HRQOL) in lumbar degenerative disease, many studies have been conducted to investigate the prognostic and therapy-guided effects of sagittal alignment. However, most of the studies only focused on the standing sagittal alignment, neglecting that sitting was as common a posture as standing in daily life. Recent studies have demonstrated that the spinal sagittal alignment was significantly different between standing and sitting positions, and ignoring these differences in the current correction strategy might be responsible for the increasing surgical complication. To determine the optimal sagittal alignment, which accounted for both standing and sitting positions, we needed to know how the sagittal spinal alignment changed after fusion surgery when moving from standing to sitting, and this result could provide important information for clinical practice.

### Postoperative Changes when Moving from Standing to Sitting in Spinal Sagittal Parameters

When moving from standing to sitting position, previous studies reported that the spine went straight in a lumbar and thoracic curve, combined with pelvic retroversion and the forward-moving center of gravity. The present study agreed with these studies, as we found that the increase in SVA and PT, decrease in LL and TK occurred in both the control group (healthy elderly volunteers) and test group (patients after lumbar fusion) during the sitting position. These results indicated that sitting required a certain change in spinal sagittal alignment to maintain the balance and this change also happened in a fused spine. However, the degree of changes in sagittal parameters including LL and TK were significantly smaller in the patient group than in the control group due to lumbar fusion.

### The Influence of Lumbosacral Fixation

In addition, we found that the increase in PT of lumbosacral fixation group was 50% less than lumbosacral non-fixation group when moving from standing to sitting positions, and it was also significantly smaller than that of the control group. This finding indicates that lumbosacral fixation might limit pelvic retroversion and spinal straightening in sitting position.

### Comparison between Groups with and without Lumbosacral Fixation

The patients were divided into two groups: lumbosacral fixation group consisted of 37 patients and lumbosacral non-fixation group consisted of 25 patients. The general data of the two groups were comparable (p > 0.05), as listed in Table 2.

As shown in Table 3, compared with lumbosacral non-fixation group, increased PT (4.4° vs 7.8°) and TPA (4.9° vs 8.8°) were approximately 50% lower in lumbosacral fixation group during the change of positions. They were also significantly lower than the increase in the control group (4.4° vs 8.3°, p < 0.05), indicating that lumbosacral fixation might hamper pelvic retroversion.

In lumbosacral non-fixation group, the increase in PT was closely similar to the control group (7.8° vs 8.3°), but the decrease in LL and TK was significantly smaller than that in the control group (p < 0.05).

### The Change in Unfused Segments

Since lumbosacral fusion limited the pelvic retroversion and sitting required some changes in lumbosacral alignment to maintain sagittal balance in this position, we hypothesized that the unfused segments might compensate for changing more in sitting position to balance the spine.

When looking into the patients with fusion in L4-S1, we found that the lordosis of the unfused area above fusion segments in these patients decreased 64% more than the same area in the control group (Table 4), which was consistent with our speculation that the unfused segments might compensate for changing more in sitting position to balance the spine. Then we speculated that the compensation would put abnormal stress on the adjacent segments and might be related to adjacent segments degeneration. Therefore, we divided the patients with fusion in L4-S1 into two groups based on the situation of adjacent segments. As shown in Figures 2 and 3, we found that the decreased lordosis of unfused segment was greater from standing to sitting position in ASD group than non-ASD group. This finding indicated that the compensation might stress the unfused segments and be related to ASD (Figure 4).

| Table 5 The comparison between patients with ASD and without ASD (mean ± SD) |
|-----------------|-----------------|-----------------|-----------------|
| Sagittal parameters | Non-ASD Group (N = 7) | ASD group (N = 6) | Z value | p value |
| PI (°) | 50.5 ± 10.5 | 52.0 ± 11.7 | -0.429 | 0.731 |
| LL (°) | -50.7 ± 12.3 | -44.9 ± 10.7 | -0.429 | 0.731 |
| Residual lordosis above (°) | -19.1 ± 10.8 | -18.7 ± 10.8 | -0.072 | 0.945 |
| Δ Residual lordosis above (°) | 1.0 ± 4.8 | 16.4 ± 10.7 | -2.571 | <0.05 |

Note: Residual lordosis above = LL – lordosis of L4-S1, Δ Residual Lordosis above = Residual lordosis above in sitting – Residual lordosis above in standing.
positions. Zhu et al. also reported that nonselective thoracic fusion would diminish spinal straightening and pelvic retroversion during sitting.

Lazennec et al. reported that patients with post-fusion pain in sitting position showed a small PT, while those with pain in standing position had a large PT. Our results might explain this phenomenon. The sitting position required a higher degree of pelvic retroversion, but the process was limited by lumbosacral fixation, so the patients with small PT could not increase their PT to the optimal value during sitting, which might be related to pain. Therefore, both standing and sitting spinopelvic sagittal alignment should be considered preoperatively. For example, patients who presented a large difference in PT between standing and sitting position (large PT in sitting and small PT in standing) preoperatively might need a relatively modest PT postoperatively (not too small).

**The Relationship between Postoperative Compensation and Degeneration in Adjacent Segments**

Meanwhile, we found that in patients with fusion in L4-S1, the residual LL compensated for decreasing by 64% more than the same area in the control group while sitting. Sitting required pelvic retroversion and spinal straightening, but the changes did not occur in fused segments, so the adjacent unfused segments changed more to compensate. However, as shown in Table 5, patients with ASD showed significantly more decrease in residual lumbar lordosis than those without ASD (16.4° vs. 1.0°), indicating that this compensation might exert more pressure in adjacent segments and be related to ASD. Previous studies also reported that an abnormal lordosis distribution index (LDI) could increase the stress of adjacent segments. Zheng et al. found that patients with moderate postoperative LDI showed the lowest risk to develop ASD after L4-S1 posterior lumbar interbody fusion, while the patients with low LDI were at higher risk to develop ASD. Consistent with our findings, the overcompensation of adjacent segments in sitting positions could also influence the lordosis distribution and increase the stress in the adjacent segments, resulting in ASD.

**Limitations and Strengths**

There were a few limitations to this study. First, our sample size was relatively small. Second, we lacked the preoperative standing and sitting whole spine radiographs compared with the postoperative situation. However, the preoperative standing and sitting sagittal alignment could not present the primary situation of the spine under the influence of severe preoperative pain. Thus, this study included the healthy people as a control group to be compared with the patients, and we found that the fixed spine similarly changed from standing to sitting position as the control group. Despite these limitations, this study demonstrated that apart from standing, sitting should also be taken into consideration before surgery since the spine needed a different sagittal alignment in this position to maintain balance. If we fixed the spine in the position only accounting for the standing alignment, the unfused area compensated for changing more during sitting position, which might be related to adjacent segments degeneration, or the patients had to bear an unsuitable alignment in sitting position, which might be related to post-fusion pain. A prospective study with a larger sample is needed for further exploring the relationship between clinical symptoms, complications, and sitting sagittal alignment.

**Conclusion**

A forward-moving center of gravity and straightening in the lumbar and thoracic spine, accompanied by pelvic retroversion, were observed in the control group when moving from standing to sitting position. In the fixed spine of patients group, similar adaption happened but with less magnitude since lumbosacral fixation would limit pelvic retroversion and spinal straightening in the sitting position. However, the adjacent unfused segments compensated for changing more during sitting position, which might be related to ASD.

**Authorship declaration**

Weishi Li conceived the project. Siyu Zhou and Woquan Zhong analyzed the data. All authors contributed towards the interpretation and the collection of the data. All authors wrote and approved the final manuscript.

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**Conflicts of Interest**

The authors declare that they have no conflict of interest.

**Author’s Contribution**

Weishi Li conceived the project. Siyu Zhou and Woquan Zhong analyzed the data. All authors contributed towards the interpretation and the collection of the data. All authors wrote and approved the final manuscript.

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