A 540° posterior-anterior-posterior approach for 360° fused rigid severe cervical kyphosis: patient series

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BACKGROUND Treatment of severe rigid 360° fused cervical kyphosis (CK) is challenging and often requires a combined approach for ankylosis release, establishment of sagittal balance, and fixation with fusion.

OBSERVATIONS Four patients with iatrogenic 360° fused severe rigid CK (Cobb angle $\geq 40^\circ$) were enrolled for this retrospective analysis. All patients in the case series were female, with an average age of 27 years. All patients previously underwent posterior laminectomy/laminoplasty and cervical tumor resection when they were children (13–17 years). They underwent correction surgery with a 540° posterior-anterior-posterior approach. Preoperative and final follow-up radiography and computed tomography (CT) were used to evaluate kyphosis correction, internal fixation implants, and bone fusion. The preoperative and final follow-up average C2–7 Cobb angles were $-32.4^\circ \pm 12.0^\circ$ and $5.3^\circ \pm 7.1^\circ$, respectively. Preoperative and final follow-up CK angles averaged $-47.2^\circ \pm 7.4^\circ$ and $-0.9^\circ \pm 16.1^\circ$, respectively. The mean correction angle was $46.3^\circ \pm 9.6^\circ$. At final follow-up, CT showed stable fixation and solid bone fusion.

LESSONS The rare iatrogenic severe kyphosis with 360° ankylosis requires a combined approach. The 540° posterior-anterior-posterior approach can completely release the bony fusion, and the CK can be corrected using an anterior plate. This technique can achieve good results and is an effective strategy.

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KEYWORDS fixed cervical kyphosis; circumferential ankylosis; posterior-anterior-posterior; 540°; procedure; cervical deformity correction; pedicle screw fixation

The etiological factors of cervical kyphosis (CK) deformity are wide ranging and include congenital, iatrogenic, neoplastic, and other factors.^{1,2} The most common cause is multilevel laminectomy,² after which the incidence of CK is approximately 21%.³ After laminectomy, the posterior tension bands were destroyed, leading to CK.⁴ Laminoplasty has been suggested to help reduce the risk of CK by preserving the posterior column structures;⁵ however, the incidence of CK after laminoplasty remains high (up to 10%).⁶ The incidence, degree, and rate of progress of CK in adolescents after cervical surgery are higher than those in adults because of the incomplete ossification of the vertebral body, weakness of the neck extensors, and propensity for ligamentous stretching.^{7–9} Once CK

has progressed to severe kyphosis (Cobb angle $\geq 40^\circ$), it leads to severe nerve compression; therefore, surgical correction remains the primary treatment option. The goal of surgery is to decompress the cervical cord, restore cervical and global sagittal balance, achieve spinal fusion,^{1,2,10} and improve the patient's appearance and symptoms.

Currently, the classification and treatment protocols of CK remain controversial, and the surgical technique for severe fixed CK (Cobb angle $\geq 40^\circ$) with circumferential ankylosis (360° fusion) is yet to be established. In this retrospective study, we discuss the strategy of a 540° posterior-anterior-posterior approach for four young patients with rare cases of 360° fused severe CK

ABBREVIATIONS ACCF = anterior cervical corpectomy and fusion; ACDF = anterior cervical discectomy and fusion; CBVA = chin–brow vertical angle; CK = cervical kyphosis; CL = cervical lordosis; CT = computed tomography; JOA = Japanese Orthopaedic Association; MRI = magnetic resonance imaging; SVA = sagittal vertical axis; T1S = T1 slope.

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after laminectomy/laminoplasty, and we review the 540° cervical correction surgery.

Study Description

Patient Population

From June 2018 to June 2020, four patients with 360° fused severe iatrogenic CK (after laminectomy/laminoplasty) were treated with a 540° posterior-anterior-posterior surgery at our institute. They were all female and aged 16–34 years and had undergone cervical tumor resection in local hospitals when they were 13–17 years old. Cervical medullary hemangioblastoma recurrence in situ was observed in two patients.

Clinical Presentation

All four patients showed numbness and weakness in their upper limbs. Two patients developed lower limb numbness, and one patient developed neck pain. Physical examination revealed obvious limitation of cervical movement, tendon hyperreflexia, and positive pathological signs in four patients (Table 1).

Radiological Examination and Measurement

Radiological measurements included global cervical curvature, local CK angle, correction angle, chin–brow vertical angle (CBVA), T1 slope (T1S), C7 sagittal vertical axis (SVA), and C2–7 SVA. The global cervical curvature and local CK angle were measured using the Cobb method. The former ranged from the C2 to the C7 inferior endplate, and the latter from the most cranial to caudal ends of the vertebrae in kyphosis segments. A lordotic alignment was defined as a negative angle, whereas a kyphotic alignment was reported as a positive angle. The straight cervical spine was defined as -4° to $+4^\circ$, kyphosis as greater than $+4^\circ$, and lordosis as less than -4° .¹¹ The correction angle was calculated as follows: postoperative local CK angle minus preoperative local CK angle. Intervertebral movement and deformity reduction were assessed using extension radiographs.

Preoperative intervertebral ankylosis (intervertebral space and facet joints), previous implants, and postoperative bone fusion status were evaluated using computed tomography (CT) and reconstructive

methods. A solid fusion was determined when both criteria, including no continuous radiolucent lines/area across the fusion site and presence of bridging trabeculae across the fusion site, were met.

CT angiography was used to exclude vertebral artery abnormalities. Magnetic resonance imaging (MRI) was used to assess the shape of the spinal cord and tumor residual or recurrence. Whole-spine plain radiographs were used to measure C7 SVA to assess the overall sagittal balance of the spine (Fig. 1).

Surgical Strategy

Because of the rigid kyphosis, preoperative cervical traction was not performed.² The surgical strategy was a 540° posterior-anterior-posterior sequence. Somatosensory and motor evoked potentials were used intraoperatively for neurophysiological monitoring. The surgical strategy employed in case 2 is cited as an example (Fig. 2).

Posterior Facet Release and Pedicle Screw Implantation

With the patient in the prone position, a posterior approach was employed. Dissection exposed C2–6 from the medial stump of the lamina to the lateral margin of the facet on both sides and revealed incomplete absorption of the lamina with the fusion of C2–5 bilateral lateral masses into a column. We removed the previous implants and performed laminectomy. After removal of the ligamentum flavum, the spinal cord was decompressed. The position of the C2–6 pedicles was explored with a nerve dissector, and the fused bone between the lateral masses was removed by drilling between the adjacent pedicles. Under C-arm fluoroscopy, pedicle screws were inserted from C2 to C6. The wound was closed temporarily.

Anterior Cervical Discectomy and Fusion (ACDF), Bone Grafting, and Correction with an Anterior Plate

The patient was securely flipped to the supine position. We started with a left-sided anterior Smith-Robinson approach between C2 and C6. The surfaces of the C2–5 vertebral bodies were fused. Under C-arm fluoroscopy, the position of the intervertebral space was determined, and the bone on the disc surface was removed by drilling. Under the microscope, the intervertebral disc and cartilaginous endplate

TABLE 1. Clinical data obtained after admission in all patients undergoing 540° posterior-anterior-posterior approach for 360° fused rigid severe cervical kyphosis

Case No.	Sex/Age (yrs)	Clinical Presentation	Pathology	Neoplasm Recurrence	Surgical History	Postoperative Duration (yrs)
1	F/34	Left upper limb weakness, limitation of cervical movement, hyperreflexia, positive pathological signs	Schwannoma	No	Tumor resection by laminectomy (C1–5)	20
2	F/30	Right limb pain, limitation of cervical movement, hyperreflexia, positive pathological signs	Cervical cord arteriovenous malformation	No	Tumor resection by replacement of vertebral lamina (laminoplasty) (C3–5)	12
3	F/16	Right limb weakness, 4/5 muscle strength of upper limbs, gait disturbance, thenar muscle atrophy, limitation of cervical movement, hyperreflexia, positive pathological signs	Cervical cord hemangioblastoma	Yes	Tumor resection by replacement of vertebral lamina (laminoplasty) (C2–3)	7
4	F/28	Left upper limb weakness, limitation of cervical movement, hyperreflexia, positive pathological signs	Cervical cord hemangioblastoma	Yes	Tumor resection twice by laminectomy (C2–5)	11

FIG. 1. Preoperative assessment of case 2. **A:** Lateral cervical spine radiograph reveals severe local cervical kyphosis angle (50.4°) with an apex centered over C3–4. **B:** Radiographs in flexion show no reduction of the kyphosis deformity. **C:** Sagittal CT reconstruction reveals the incomplete interbody fusion between C2 and C5. **D and E:** CT three-dimensional reconstruction shows the fixed nature of the deformity with circumferential ankylosis between C2 and C5. **F:** Sagittal MRI reveals draping of the spinal cord over the posterior aspect of the vertebral bodies. **G:** Whole-spine plain radiograph shows the translation of the cervical spine in the sagittal plane. TIA = thoracic inlet angle; PT = pelvic tilt; PI = pelvic incidence; SS = sacral slope; LL = lumbar lordosis.

were removed, and the fused posterior margin of the vertebral body to the posterior longitudinal ligament and fused uncinat joints were removed with a high-speed burr. After the posterior longitudinal ligament was resected, a suit-sized cage filled with an autogenous iliac cancellous bone was placed in the intervertebral space. Subsequently, a plate was implanted on the C2–6 vertebral bodies. The cervical curvature was corrected to normal lordosis using the lifting force generated by gradually tightening the screws.

Posterior Rod Assembly

The patient was again placed in the prone position. Rods were shaped into a suitable curvature, which was secured into the C2–6 screw heads on both sides. A negative pressure drainage tube was placed in the operative area, and the posterior incision was permanently closed.

Follow-Up

The patients were evaluated at 6 months and 1 year postoperatively. The Japanese Orthopaedic Association (JOA) scale improvement rate was calculated as (last follow-up JOA – preoperative JOA)/(17 – preoperative JOA) × 100% to assess neurological function.

Statistical Methods

Preoperative and latest follow-up JOA and radiological measurements were recorded, as well as the intraoperative fusion span in this operation and the resection span in the previous laminectomy/laminoplasty. The mean ± standard deviation for the normally distributed data and median (interquartile range) for the nonnormally distributed data were calculated.

Surgical Outcome

All patients underwent 540° correction (combined with intraspinal tumor resection in two patients) under a single episode of anesthesia in one stage. The mean operative time was 667 ± 268 min. The average amount of bleeding was 500 ± 258 ml. Patient 3 underwent subsequent intracranial tumor resection after recovery.

Clinical Outcome

Patient 2 developed postoperative dysphagia, which was relieved 3 days later. The follow-up period ranged from 12 to 24 months. All patients showed remission of symptoms at the last follow-up. The JOA improvement rate was 45.63% ± 37.00%.

FIG. 2. Intraoperative images of case 2. **A:** Ponte osteotomy is used to release ankylosing facet joints. **B and C:** Posterior pedicle screw implantation. **D:** The intervertebral space has been fused during the anterior approach. **E:** With the help of C-arm fluoroscopy, the release of intervertebral space fusion was performed after the position of the intervertebral space was determined. **F:** Anterior cervical plate implantation. **G:** Cervical lordosis was corrected by an anterior plate and screws. Posterior rods were assembled.

Patient 1 had residual upper limb weakness. Patient 2 showed complete remission. Patient 3 had residual gait instability and limited upper limb movement at the last follow-up. Patient 4 had residual upper limb sensory and motor disorders.

Radiographic Outcome

Preoperative

The preoperative mean global cervical curvature was $-32.4^\circ \pm 12.0^\circ$. The preoperative local CK angle averaged $-47.2^\circ \pm 7.4^\circ$. Patient 1 had an obvious upward gaze. Patients 1 and 4 had C7 SVA ≤ 50 mm. All had a normal C2–7 SVA (Table 2).

Follow-Up

The mean postoperative C2–7 Cobb angle was $-5.3^\circ \pm 7.1^\circ$. Two patients had a lordotic alignment, and the other two presented with a straight alignment. The postoperative local CK angle averaged $0.9^\circ \pm 16.1^\circ$. The mean correction angle was $-46.3^\circ \pm 9.6^\circ$.

Global spinal balance was improved in all patients with C7 SVA falling within 50 mm of the posterosuperior aspect of the sacrum (Fig. 3). However, case 3 (Supplemental Fig. 1) had anterior cervical translation (C2–7 SVA >40 mm) after surgery (Table 2).

Spinal fusion was achieved in all patients at the last follow-up.

Discussion

CK is divided into flexible and fixed deformities according to whether it can be reduced by extension movement or traction.^{2,12} Flexible CK is reducible with the help of hyperextension and traction; however, fixed CK is associated with anterior or posterior ankylosis,

and no improvement is observed after extension and traction. Therefore, ankylosis should be released to restore the normal curvature.^{2,13} In 2014, Hann et al.¹² proposed the basic strategies for surgical correction of cervical deformity. They stated that correction of anterior fused and posterior fused rigid kyphosis should be performed by using the anterior-posterior and posterior-anterior-posterior approaches, respectively. However, guidelines for the rare 360° fused rigid kyphosis have not been established. Local release and correction by a single approach is mostly ineffective because of its extensive circumferential fusion area. Furthermore, the correction angle of a single approach is limited.^{1,12} Thus, a combined approach is required for both circumferential lysis and ideal correction angle for iatrogenic, circumferentially fused, severe CK ($\geq 40^\circ$). We review the 540° correction procedure and present our strategy.

Observations

Characteristics of CK

There is no accepted range of parameters for cervical deformity; however, the available evidence suggests that T1S minus cervical lordosis (CL) $<15^\circ$, C2–7 SVA <40 mm, and CBVA between -10° and $+20^\circ$ are generally acceptable ranges.¹⁴ We summarize the characteristics of CK of the patients as follows: a 360° fused fixed CK with a severe kyphosis angle $\geq 40^\circ$; round CK with smooth curvature and retained vertebral body height, as well as the intervertebral space; severe anterior surface fusion of the vertebral bodies; deformed posterior structure; the cervical sagittal balance not translated, with C2–7 SVA <40 mm; most patients having the normal preoperative CBVA; most patients having the compensatory decreased T1S. This patient

TABLE 2. Preoperative and postoperative assessment of all patients undergoing 540° posterior-anterior-posterior approach for 360° fused rigid severe cervical kyphosis

Case No.	Preoperative Kyphosis Level	Fusion Level During Operation	Preoperative/Postoperative Global Cervical Curvature (°)*		Preoperative/Postoperative Cervical Kyphosis Angle (°)		Preoperative/Postoperative CBVA (°)†		Preoperative/Postoperative C7 SVA (mm)‡		Preoperative/Postoperative T1S (°)		Preoperative/Postoperative T1S Minus Cervical Lordosis (°)¶		Preoperative/Postoperative C2-7 SVA (mm)**		Preoperative/Postoperative mJOA Score	
			Preoperative	Postoperative	Preoperative	Postoperative	Preoperative	Postoperative	Preoperative	Postoperative	Preoperative	Postoperative	Preoperative	Postoperative	Preoperative	Postoperative	Preoperative	Postoperative
1	C3-5	C2-7	27.1/-8.9	27.1/-8.9	42.0/-17.4	42.0/-17.4	-21.6/-4.0	-21.6/-4.0	-84.8/-41.6	-84.8/-41.6	-1/10.2	-1/10.2	26.1/1.3	26.1/1.3	6.3/-10.8	6.3/-10.8	13/14	13/14
2	C3-5	C2-6	28.6/-12.4	28.6/-12.4	50.4/10.3††	50.4/10.3††	2.2/9.1	2.2/9.1	-25.2/-30.2	-25.2/-30.2	6.2/15.0	6.2/15.0	34.8/2.6	34.8/2.6	-24/-1.5	-24/-1.5	12/17	12/17
3	C2-5	C2-6	23.8/-3.9	23.8/-3.9	40.3/-7.4	40.3/-7.4	-1.5/-2.4	-1.5/-2.4	10.3/8.4	10.3/8.4	24.8/21.4	24.8/21.4	48.6/17.5	48.6/17.5	33.5/42.3	33.5/42.3	9/12	9/12
4	C3-6	C2-7	50.1/3.9	50.1/3.9	56.0/17.9	56.0/17.9	-3.2/-6.6	-3.2/-6.6	-54.1/-36.6	-54.1/-36.6	7.0/11.4	7.0/11.4	46.1/15.3	46.1/15.3	29.8/18.1	29.8/18.1	12/14	12/14

mJOA = modified Japanese Orthopaedic Association scale.

* Lordosis is defined as negative and kyphosis as positive.

† When the head is tilted down, the CBVA is positive; when the head is tilted up, the CBVA is negative.

‡ When the C7 sagittal vertical axis is in front of the posterior-superior aspect of the sacrum, the C7 SVA is positive and vice versa.

§ When the T1 superior endplate is tilted down, the T1S is positive; when the T1 superior endplate is tilted up, the T1S is negative.

¶ When the spine was lordotic, T1S minus cervical lordosis (CL) was calculated as follows: T1S - C2-7 Cobb angle; when the spine was kyphotic, T1S minus cervical lordosis (CL) was calculated as follows: T1S + C2-7 Cobb angle.

** When C2 sagittal vertical axis is in front of C7 sagittal vertical axis, C2-7 SVA is positive and vice versa.

†† Wedged vertebra.

population is unique because of their young age, due to which their compensatory capacity is greater. In addition, their horizontal gaze function and sagittal cervical balance (C2-7 SVA <40 mm) were retained in the long-term history of the illness. Despite kyphosis progression, most developed cervicothoracic hyperlordosis (T1S decreased) to maintain a C2-7 SVA <40 mm. This sagittal cervical balance saves energy expenditure while maintaining the horizontal gaze function. That is, to maintain an effortless horizontal gaze, hyperlordosis at the cervicothoracic junction compensates kyphosis at the cervical spine. Laminectomy at a high level of the cervical spine (C1-4) is usually associated with changes in kyphosis, whereas a low level (C5-7) increases lordosis.¹⁵ Abnormal cervicothoracic hyperlordosis may also be associated with increased lordosis resulting from C5 (low level) laminectomy/laminoplasty.

Previous 540° Correction Surgery Reported in the Literature

O'Shaughnessy et al.,² Hann et al.,¹² and Lee et al.¹⁶ performed posterior-anterior-posterior correction surgery to treat cervical kyphosis (Supplemental Table 1). The main correction procedure is anterior; therefore, pedicle screws are not necessary. The steps include posterior release and screw placement, anterior release and ventral reduction technology to correct the curvature, and finally posterior rod assembly. O'Shaughnessy et al. proposed the following advantages: The posterior corrective approach at the end of the operation can help provide direct observation of the lamina and nerve root state and avoid nerve injury, and, after posterior release, it is easier to perform anterior release; the disadvantage is the possible displacement of anterior bone grafts during the final posterior approach.²

Abumi et al.,¹³ Sin et al.,¹⁷ Yoshihara et al.,¹⁸ Garg et al.,¹⁹ Funayama et al.,²⁰ and Srivastava et al.²¹ performed anterior-posterior-anterior correction surgery (Supplemental Table 2). The most important operation is the posterior approach; therefore, pedicle screws are necessary. The first step is anterior release. Because posterior fusion is not released, it is impossible to select the appropriate cage. During the subsequent posterior release, temporary fixation rods are required when both sides are released. Correction is performed by posterior manual manipulation of the Mayfield clamp or loading compression force and other posterior reduction techniques. Finally, a structural intervertebral graft is performed using the final anterior approach. Yoshihara et al.¹⁸ proposed the advantage as the possible prevention of anterior graft displacement when using the anterior approach at the end of the surgery and the disadvantage as the increased risk of posterior pharyngeal wall edema and airway obstruction by the two consecutive anterior exposures.

Compared with the anterior-posterior-anterior approach, the strength of the anterior correction by distraction, bone grafting, and the application of a multilevel anterior plate in the posterior-anterior-posterior procedure is higher than that of the posterior internal fixation system under the condition of circumferential release; hence, the corrective effect is higher. The primary correction procedure for the anterior-posterior-anterior surgery is loading the posterior screw compression. Because the screw rod in the posterior approach is fixed, the effect of anterior intervertebral space distraction and bone graft reduction may not be ideal; hence, the corrective effect is slightly poor.

Lessons

Posterior-Anterior-Posterior Approach

Due to the powerful corrective effect of lifting each vertebra with a plate after intervertebral release and dilation, our treatment

FIG. 3. Cervical and global balance images at the 9-month follow-up of case 2. **A:** Postoperative lateral radiograph reveals satisfactory correction. **B:** Sagittal CT reconstruction shows a solid fusion. **C:** Sagittal MRI shows no compression of the spinal cord. **D:** Whole-spine plain radiograph shows good sagittal globe spine balance. **E and F:** Photographs reveal the patient's good condition with no deformity. PT = pelvic tilt; PI = pelvic incidence; SS = sacral slope; LL = lumbar lordosis.

strategy was to release the circumferential bony fusion and subsequently to use an anterior plate to correct kyphosis. Thus, we chose the posterior-anterior-posterior sequence. The first step was to release the facet joints using the Ponte osteotomy technique during the posterior approach. The second step was to release all vertebral segments through the anterior intervertebral space. The CK was corrected using intervertebral distraction and the lifting effect of the anterior plate. The stability of the cervical spine is greatly influenced by the 360° release. In order to avoid failure of the anterior fixation system and improve the fusion rate, the third step was to use the posterior pedicle screw for posterior fixation with fusion.

The first and second stages of the surgery were the most critical. In the first step of Ponte osteotomy, the bony fusion facet joints were completely ground to achieve the release. Stewart et al.²² reported the application of a Cobb periosteal elevator in the anterior intervertebral space to fracture the fused facet joints by rotating and stretching, thus achieving posterior release. However, this technique was not considered feasible, because the facet joints were completely fused into a columnar shape.

The second step of the operation was to release the anterior column through the intervertebral space. Most scholars have adopted anterior cervical corpectomy and fusion (ACCF) for anterior release.^{13,17–19,21} For patients with angular CK or complete intervertebral fusion, where intervertebral release is not possible, the ACCF technique is a reasonable choice to relieve spinal cord compression. However, in round CK cases where the intervertebral space is still retained, multilevel intervertebral release and distraction can provide better corrective results because ACDF can achieve better

release of the fused uncinate joints on both sides of the intervertebral space than ACCF. Moreover, the risk of fusion cage collapse of ACDF is also significantly lower than that of ACCF.¹⁰ With five levels of ACDF, the cervical spine can be realigned with a cumulative correction of approximately 30°. However, the difficulty of performing ACDF in this group was indistinguishable intervertebral spaces due to the anterior complete surface fusion. Intraoperatively, C-arm fluoroscopy was performed to identify the intervertebral spaces to remove the fused bone and uncinate joints. Attention should be paid to avoid endplate injury and cage collapse caused by the deviation of the drill from the intervertebral space, as well as vertebral artery injury on both sides.

Fassett et al.⁴ suggested that the application of the anterior plate is optional because it increases stability. However, in our practice, we consider the anterior plate to be necessary because it provides not only more stability but also a strong corrective effect and higher corrective angles after intervertebral release, dilation, and cage implantation.

The final step was assembly of the posterior rods to strengthen stability. The biomechanical properties of pedicle screws were better than those of lateral mass screws, which fixed the three-column structure of the spine and had a pullout resistance four times higher than that of lateral mass screws.²³

The combined approach has higher rates of complications and mortality.¹ The patients in our series recovered well without any complications. It can be inferred that the 540° posterior-anterior-posterior sequence is an effective method for the treatment of 360° fused CK. At the latest follow-up, case 3 presented with T1S minus CL >15° accompanied by C2–7 SVA >40 mm, which was considered to be caused by the short segment and insufficient prebending of the anterior plate. We believe that the recovery of T1S minus CL <15° is the key to surgical correction for patients with normal CBVA. For patients without small T1S (case 3), the anterior corrective segment and curvature of the plate should be increased appropriately to correct the CL to a larger range in order to avoid postoperative sagittal cervical translation (C2–7 SVA >40 mm); for patients with compensatory decreased T1S (except case 3), the achievement of CL is not demanding, because preoperative sagittal cervical balance was not translated (C2–7 SVA <40 mm).

In summary, rare iatrogenic severe kyphosis with 360° ankylosis requires a combined approach. The 540° posterior-anterior-posterior approach can completely release the bony fusion, and the CK can be corrected using an anterior plate. This technique can achieve good results and is an effective strategy.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Chen, Qiang Jian. Acquisition of data: Chen, Liu, Duan, Fengzeng Jian. Analysis and interpretation of data: Chen, Liu. Drafting the article: Qiang Jian, Liu. Critically revising the article: Liu, Duan, Guan, Fengzeng Jian. Reviewed submitted version of manuscript: Duan. Statistical analysis: Qiang Jian. Administrative/technical/material support: Liu. Study supervision: Chen, Duan.

Supplemental Information

Online-Only Content

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