Factors associated with improvement in sagittal spinal alignment after microendoscopic laminotomy in patients with lumbar spinal canal stenosis

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OBJECTIVE Little is known about the relationship between sagittal spinal alignment in patients with lumbar spinal canal stenosis (LSS) and objective findings such as spinopelvic parameters, lumbar back muscle degeneration, and clinical data. The purpose of this study was to identify the preoperative clinical and radiological factors that predict improvement in sagittal spinal alignment after decompressive surgery in patients with LSS.

METHODS The records of 61 patients with LSS who underwent microendoscopic laminotomy and had pre- and post-operative clinical data collected were retrospectively reviewed. Spinopelvic parameters, including sagittal vertical axis (SVA), lumbar lordosis (LL), sacral slope, pelvic tilt, and pelvic incidence (PI), were evaluated. On T2-weighted MRI, the cross-sectional area and the percentage of fat infiltration of the paravertebral muscles (PVMs) before surgery were calculated. For patients with preoperative SVA > 40 mm (n = 30), the correlation between SVA improvement and preoperative clinical and radiographic parameters was calculated.

RESULTS SVA improvement correlated with preoperative LL (r = −0.39) and PI − LL (r = 0.54). Multiple regression analysis showed that preoperative PI − LL (beta = 0.62; p < 0.01) and symptom duration (beta = −0.40; p < 0.05) were independently associated with SVA improvement. The percentage of fat infiltration of the PVM at L4–5 was significantly greater in patients with preoperative SVA ≥ 40 mm than in those patients with SVA < 40 mm.

CONCLUSIONS Preoperative PI − LL and symptom duration were independently associated with SVA improvement in LSS patients with forward-bending posture. PVM degeneration at the lower lumbar level was significantly greater among patients with preoperative SVA ≥ 40 mm than in patients with SVA < 40 mm.

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KEY WORDS microendoscopic lumbar decompression; sagittal vertical axis; C-7 plumb line; spinopelvic parameter; paravertebral muscle degeneration; fat infiltration

SAGITTAL balance of the spine is important in the management of lumbar diseases and low-back pain (LBP).^{1,9,10} The sagittal vertical axis (SVA) (Fig. 1)—defined as the deviation of the C-7 plumb line from the posterior corner of the sacrum—has been associated with health-related quality of life (QOL).^{7,16} In patients with lumbar spinal canal stenosis (LSS), symptomatic relief is obtained by standing or walking with lumbar flexion.²⁰ A correlation has been reported between sagittal spinal alignment and clinical outcome in patients with lumbar disease.^{5,19} We previously reported that a preop-

erative forward-bending posture was associated with LBP before and after microendoscopic laminectomy (MEL) in patients with LSS.⁴

Evaluation of the lumbar back muscles is also important when treating lumbar diseases because LBP and spinopelvic imbalance are associated with back muscle degeneration.^{3,12,14} Moreover, QOL is related to back muscle strength, and poor functional performance in patients with LSS is related to fatty degeneration of the paravertebral muscles (PVMs).²

Spinopelvic parameters, including SVA, lumbar lordo-

ABBREVIATIONS CSA = cross-sectional area; JOA = Japanese Orthopaedic Association; LBP = low-back pain; LL = lumbar lordosis; LSS = lumbar spinal canal stenosis; MEL = microendoscopic laminectomy; PI = pelvic incidence; PT = pelvic tilt; PVM = paravertebral muscle; QOL = quality of life; SS = sacral slope; SVA = sagittal vertical axis; VAS = visual analog scale; %FI = percentage of fat infiltration.

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FIG. 1. Illustration showing the sagittal spinopelvic parameters, including SVA, LL, SS, PT, and PI.

sis (LL), sacral slope (SS), pelvic tilt (PT), and pelvic incidence (PI) (Fig. 1), have been used in the management of adult spinal deformity. However, in patients with LSS, little is known about the relationship between sagittal spinal alignment and objective findings, such as spinopelvic parameters, degeneration of the lumbar back muscles, and clinical data. The present study aimed to determine whether any preoperative clinical and radiological factors predict improvement in sagittal spinal alignment after decompressive surgery in patients with LSS. We also evaluated differences in PVM degeneration according to preoperative SVA.

Methods

This study was approved by the Institutional Review Board of Osaka City University Graduate School of Medicine.

The records of 73 patients who underwent MEL for LSS at our institution between August 2008 and October 2012 were retrospectively reviewed. All patients had experienced lower-extremity pain and/or numbness. The minimum duration of clinical and radiological follow-up was 1 year. Of the 73 patients considered for inclusion in the analysis, 12 were excluded: 7 were lost to follow-up, 4 had a history of previous spinal surgery, and 1 had a vertebral fracture. The remaining 61 patients (30 men and 31 women), with a mean age of 69.4 years (range 47–86 years), were included in this study. The mean duration of symptoms before surgery was 3.8 years (range 4 months to 20 years), and patients were observed for a mean duration of 19.1 months after surgery (range 12–48 months).

Twenty-three patients had degenerative spondylolisthesis (> 3 mm), and 12 had scoliotic disc wedging ($> 3^\circ$) at the affected level. The exclusion criteria for the use of this surgical procedure in patients with degenerative spon-

dylolisthesis were percent slip $> 25\%$ and segmental kyphosis in flexion $> 5^\circ$. Exclusion criteria in patients with degenerative lumbar scoliosis were a Cobb angle $> 25^\circ$, severe LBP, changes in segmental disc wedging between standing and prone position $> 5^\circ$, and lateral disc slippage > 3 mm.⁴

Fifty-seven patients underwent decompression at a single level (49 patients at L4–5, 7 patients at L3–4, and 1 patient at L5–6), and 4 patients underwent decompression at 2 levels (3 patients at L3–5 and 1 patient at L2–4).

Clinical Evaluation

Surgical outcomes were evaluated using the Japanese Orthopaedic Association (JOA) score for LBP. The JOA score and visual analog scale (VAS) ratings for LBP, leg pain, and leg numbness were collected before surgery and at the final follow-up. The VAS rating for pain or numbness intensity ranged from 0 to 100 and was anchored by “no pain or numbness” (score 0) and “worst imaginable pain or numbness” (score 100). These data were collected at standardized times: before surgery and at 6 months, 1 year, and 2 years after surgery. The JOA score improvement ratio was calculated as (postoperative JOA score – preoperative JOA score) / (29 – preoperative JOA score) $\times 100$ (%). The VAS score improvement (mm) was calculated as (preoperative VAS score) – (postoperative VAS score).

Radiological Evaluation

Three authors (S.D., H. Toyoda., and T.M.) measured the images and were blinded to outcomes. SVA, LL, SS, PT, and PI were measured on lateral standing radiographs of the entire spine that were obtained before surgery and at the final follow-up, as described by Jackson and McManus.⁹ The mean time to obtaining the lateral standing radiographs at the final follow-up was 29.9 ± 14.8 months. Improvement in SVA and PT were calculated as (value before surgery) – (value at final follow-up), and LL improvement was calculated as (value at final follow-up) – (value before surgery).

Evaluation of PVM on MR Images

Axial T2-weighted MR images were chosen for PVM evaluation. The bilateral PVM volume was calculated by aggregating the cross-sectional area (CSA) of the multifidus and erector muscles before surgery at L2–3, L3–4, and L4–5 using ImageJ 1.48 (released by the National Institutes of Health) (Fig. 2). The percentage of fat infiltration (%FI) was assessed using a previously reported threshold technique.^{12,18} CSA and %FI of the PVM were statistically compared between patients with SVA ≥ 40 mm and those with SVA < 40 mm.

Factors Associated With Improvement in Sagittal Spinal Alignment

Improvement in SVA was defined as the difference between SVA before surgery and the final follow-up: (SVA before surgery) – (SVA at the latest follow-up). For patients with a preoperative SVA ≥ 40 mm ($n = 30$), the relationship between SVA improvement and preoperative

FIG. 2. Magnetic resonance image showing the measurement of the CSA of the PVM (dotted circle).

clinical data and radiographic parameters was analyzed using multiple regression analysis.

Deformity Subgroup Analyses

Patients with a preoperative SVA ≥ 40 mm were divided into 2 groups: the deformity group (Group D: degenerative spondylolisthesis [> 3 mm] or scoliotic disc wedging [$> 3^\circ$] at the affected level) and the no deformity group (Group N). Sixteen patients were allocated to Group D (6 male and 10 female patients) and 14 patients to Group N (7 male and 7 female patients). Clinical outcomes were statistically compared between the 2 groups.

Clinical Outcomes According to the Change in SVA

We grouped patients according to the change in the SVA after MEL: the SVA-improved group (postoperative – preoperative value < 0) and the SVA-increased group (postoperative – preoperative value ≥ 0). The JOA score improvement ratio and VAS improvements in LBP, leg pain, and leg numbness were statistically compared between the 2 groups.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics (version 19, IBM SPSS Inc.), and p values < 0.05 were considered statistically significant. To evaluate the reliability of the CSA and %FI measurements of the PVM, intra- and interobserver variabilities were evaluated. Two spine surgeons (S.D. and S.T.), who were blind to the patients' clinical data, independently measured the parameters. After each surgeon had measured a parameter twice, the intra- and interobserver variabilities were evaluated as the intraclass coefficient of correlation. Parametric analyses were performed with the Student t -test or paired t -test. Nonparametric analyses were performed using the Mann-Whitney U -test. Categorical variables were analyzed using the chi-square test.

For patients whose preoperative SVA values were > 40 mm, the Pearson product moment correlation coefficient

TABLE 1. Radiographic and clinical data

Variable	Preop*	At Latest Follow-Up*	p Value
SVA (mm)	45.5 $\pm$ 37.4	36.7 $\pm$ 36.9	0.082
LL ($^\circ$)	25.6 $\pm$ 16.0	28.0 $\pm$ 16.4	0.038
SS ($^\circ$)	29.7 $\pm$ 7.9	30.1 $\pm$ 10.2	0.607
PT ($^\circ$)	19.4 $\pm$ 8.1	19.4 $\pm$ 9.9	0.957
PI ($^\circ$)	48.9 $\pm$ 9.5	49.3 $\pm$ 10.1	0.251
PI – LL ($^\circ$)	23.2 $\pm$ 15.0	21.3 $\pm$ 15.3	0.100
JOA score (points)	14.0 $\pm$ 4.4	25.1 $\pm$ 3.6	< 0.01
VAS score			
LBP	45.7 $\pm$ 30.4	15.7 $\pm$ 22.5	< 0.01
Leg pain	61.6 $\pm$ 28.0	17.3 $\pm$ 27.8	< 0.01
Leg numbness	48.8 $\pm$ 29.2	24.3 $\pm$ 28.2	< 0.01

* Values are shown as the mean $\pm$ SD.

was calculated between SVA improvement and the following variables obtained before surgery: age, symptom duration, JOA score, VAS score (LBP, leg pain, and numbness), LL, SS, PT, PI, PI – LL, CSA of PVM, and %FI of PVM. Multiple regression analysis was used to evaluate the factors independently associated with SVA improvement. Variables included in the multivariate model were those with a p value < 0.2 in the univariate analysis.

Results

The SVA decreased in 39 of 61 patients (69.3%) who underwent MEL. Twenty-two patients (36.1%) had an increase in SVA. The mean SVA value decreased from 45.5 mm (range -36 to 162 mm) before surgery to 36.7 mm (range -43 to 49 mm) at the latest follow-up; however, the difference was not significant ($p = 0.082$). LL increased in 33 of 61 patients (54.1%) who underwent MEL. LL significantly increased from 25.6 $^\circ$ (range -45° to 50 $^\circ$) to 28.0 $^\circ$ at the latest follow-up (range -31° to 49 $^\circ$; $p = 0.038$). There were no significant differences between pre- and postsurgical values for SS, PT, PI, or PI – LL. The JOA and VAS scores for LBP, leg pain, and numbness significantly improved after MEL (Table 1).

Among patients with a preoperative SVA ≥ 40 mm ($n = 30$), 2 of 7 patients with a preoperative SVA ≥ 95 mm and 8 of 23 patients with a preoperative SVA between 40 and 95 mm had improvement in SVA to < 40 mm (Table 2).

SVA improvement in the patients with preoperative SVA ≥ 40 mm (20.4 $\pm$ 44.7) was significantly higher than those of the patients with preoperative SVA < 40 mm (-2.4 ± 28.9 ; $p = 0.02$). LL improvement in the patients with preoperative SVA ≥ 40 mm (4.6 $\pm$ 7.8) tended to be higher than those of the patients with preoperative SVA < 40 mm (0.3 $\pm$ 9.6; $p = 0.06$) (Table 3).

CSA and %FI of the PVM

The intraobserver intraclass coefficient of the correlation values for the CSA and %FI of PVM were 0.94 and 0.88, respectively; the interobserver values were 0.94 and 0.83, respectively, indicating that the measurements were

TABLE 2. Number of patients according to SVA before surgery and at the latest follow-up

SVA at Latest Follow-Up (mm)	Preop SVA (mm)		
	<40	40–95	>95
<40	27	8	2
40–95	3	13	3
>95	1	2	2

reliable.¹¹ The CSA of the PVM at L4–5 tended to be low in patients with preoperative SVA ≥ 40 mm (40.7 ± 9.8 cm²) compared with those with SVA < 40 mm (45.3 ± 10.4 cm²). The %FI of the PVM at L4–5 was significantly higher in patients with a preoperative SVA ≥ 40 mm ($33.0 \pm 11.1\%$) than in those with SVA < 40 mm ($26.0 \pm 12.3\%$). The CSA and %FI of the PVM at L2–3 and L3–4 were not significantly different between the groups that were divided according to preoperative SVA (Table 3).

Factors Associated With Improvement in Sagittal Spinal Alignment

SVA improvement was significantly greater in patients with preoperative SVA ≥ 40 mm (20.4 ± 44.7 mm) than in patients with preoperative SVA < 40 mm (-2.4 ± 28.9 mm). SVA improvement in patients with preoperative SVA ≥ 40 mm correlated with preoperative LL ($r = -0.39$; $p < 0.03$) and PI – LL ($r = 0.54$; $p < 0.01$) (Table 4). Multiple regression analysis showed that preoperative PI – LL ($\beta = 0.62$; $p < 0.01$) and symptom duration ($\beta =$

TABLE 3. Radiographic improvement and CSA and %FI of PVM according to preoperative SVA

Variable	Preop SVA*		p Value
	≥ 40 mm (n = 30)	< 40 mm (n = 31)	
Age (yrs)	71.9 ± 9.3	66.9 ± 9.2	0.04
Male/female (no.)	13/17	17/14	0.45
SVA improvement (mm)†	20.4 ± 44.7 §	-2.4 ± 28.9	0.02
LL improvement (°)‡	4.6 ± 7.8 §	0.3 ± 9.6	0.06
PT improvement (°)†	0.3 ± 4.5	-0.4 ± 5.0	0.60
CSA of PVM (cm ²)			
L2–3	42.9 ± 9.5	44.9 ± 11.6	0.46
L3–4	43.6 ± 11.1	45.9 ± 10.8	0.43
L4–5	40.7 ± 9.8	45.3 ± 10.4	0.08
L2–5	42.4 ± 8.6	45.2 ± 9.9	0.25
%FI of PVM (%)			
L2–3	17.4 ± 7.3	15.2 ± 9.4	0.32
L3–4	21.8 ± 7.7	20.6 ± 11.7	0.66
L4–5	33.0 ± 11.1	26.0 ± 12.3	0.03
L2–5	20.8 ± 10.2	24.0 ± 7.5	0.17

* Values are shown as mean $\pm$ SD.

† (Value before surgery) – (value at final follow-up).

‡ (Value at final follow-up) – (value before surgery).

§ Significantly different before versus after surgery ($p < 0.01$).

TABLE 4. Variables correlating with SVA improvement in patients with preoperative SVA ≥ 40 mm

Preop Variable	r	p Value
Age	0.07	0.73
Symptom duration	-0.29	0.12
LL (°)	-0.39	0.03
SS (°)	0.04	0.82
PT (°)	0.16	0.40
PI (°)	0.16	0.40
PI – LL (°)	0.54	<0.01
JOA score (points)	0.04	0.83
VAS score		
LBP	0.13	0.50
Leg pain	-0.03	0.86
Leg numbness	-0.34	0.07
CSA of PVM (L4–5)	-0.21	0.28
%FI of PVM (L4–5)	0.10	0.60

-0.40; $p < 0.05$) were independently associated with SVA improvement in patients with preoperative SVA ≥ 40 mm (Table 5).

Deformity Subgroup Analyses

The preoperative clinical characteristics of Groups D and N are summarized in Table 6. The preoperative JOA score and VAS score for LBP, leg pain, and leg numbness were not significantly different between the groups. At the final follow-up evaluation, the mean JOA score was 24.8 ± 3.5 points in Group D and 22.9 ± 4.1 points in Group N; the mean VAS score for LBP was 21.2 ± 28.5 mm in Group D and 25.1 ± 27.7 mm in Group N; the mean VAS score for leg pain was 20.2 ± 30.2 mm in Group D and 26.4 ± 37.3 mm in Group N; and the mean VAS score for leg numbness was 22.3 ± 33.2 mm in Group D and 22.1 ± 26.2 mm in Group N (Figs. 3 and 4). These values were not significantly different between groups.

Clinical Outcomes According to the Change in SVA

Table 7 shows the clinical results for the SVA-improved and SVA-increased groups. There were no statistically significant differences in the JOA score improvement ratio or the improvements in the VAS scores for LBP, leg pain, and leg numbness between the 2 groups.

TABLE 5. Multiple regression analysis of SVA improvement in patients with preoperative SVA ≥ 40 mm*

Variable	B	SE B	Beta	p Value
PI – LL	1.78	0.42	0.62	<0.001
Symptom duration	-0.48	0.17	-0.4	0.011

B = partial regression coefficient; Beta = standardized partial regression coefficient; SE = standard error of estimate.

* $R = 0.67$; $r^2 = 0.45$; adjusted $r^2 = 0.41$.

TABLE 6. Preoperative clinical characteristics in patients with a preoperative SVA ≥ 40 mm

Variable	Group D (n = 16)*	Group N (n = 14)*	p Value
SVA (mm)	79.3 $\pm$ 30.5	68.3 $\pm$ 32.7	0.35
Age (yrs)	74.5 $\pm$ 9.5	68.9 $\pm$ 8.3	0.10
JOA score (points)	15.4 $\pm$ 5.3	12.4 $\pm$ 4.8	0.12
VAS			
LBP	43.6 $\pm$ 30.8	48.7 $\pm$ 32.7	0.66
Leg pain	65.5 $\pm$ 31.7	58.9 $\pm$ 27.5	0.55
Leg numbness	44.6 $\pm$ 29.1	41.4 $\pm$ 26.6	0.76

* Values are shown as mean $\pm$ SD.

Discussion

MEL has several advantages over other microsurgical procedures for posterior soft tissues. It is minimally invasive to the paraspinal muscles because the tubular retractor enables gentle tissue dissection and minimizes retraction of the paraspinal muscles.^{8,13,15} The radiographic changes that occur after this procedure are similar to those that occur naturally over time in LSS.²² Therefore, clinical outcomes after this procedure can provide useful information about the pathology of LSS.

In the current study, we made 2 important clinical observations. First, preoperative PI – LL and symptom duration were independently associated with SVA improvement in LSS patients with preoperative SVA ≥ 40 mm. Second, PVM degeneration at L4–5 was significantly greater in patients with preoperative SVA ≥ 40 mm than in patients with SVA < 40 mm.

The finding that preoperative PI – LL was independently associated with SVA improvement in LSS patients with preoperative SVA ≥ 40 mm indicates that SVA improvements after MEL tend to be better when preoperative PI – LL is large. According to the Scoliosis Research Society–Schwab classification, a large PI – LL value in patients with adult spinal deformity indicates sagittal imbalance.¹⁷ However, in patients with degenerative lumbar

FIG. 4. Bar graphs showing the VAS scores for LBP, leg pain, and leg numbness in the patients in Groups D and N at the final follow-up evaluation. Error bars indicate the standard deviation.

disease such as LSS, anterior displacement of the C-7 plumb line and the loss of lordosis occur as a protective mechanism to avoid neurological symptoms.¹ In patients with LSS in the present study, the anterior shift of the C-7 plumb line did not likely result from severe structural deformity. Thus, the high PI – LL value in LSS patients likely resulted from an abnormal posture used to avoid neurological symptoms. Decompression surgery without corrective fusion surgery can improve sagittal spinal alignment in patients with LSS.⁶

We also found that SVA improvement after MEL in patients with preoperative SVA ≥ 40 mm tended to be worse in patients who had symptoms for a long duration. Abnormal spinal alignment in the sagittal plane while standing is influenced by decreased paraspinal muscle strength, lumbar lordosis, and spinal mobility.²¹ Continuous extension of the paraspinal muscles caused by long-term forward-bending posture increases pressure on those muscles and promotes local ischemia.²¹ Thus, we speculate that long periods of positioning in a forward-bending posture

FIG. 3. JOA scores for patients in Groups D and N at the final follow-up evaluation (p = 0.21). N.S. = not significant.

TABLE 7. Clinical outcomes grouped according to change in SVA

Variable	SVA-Improved Group (n = 39)*	SVA-Increased Group (n = 22)*	p Value
Age (yrs)	69.0 $\pm$ 10.7	70.1 $\pm$ 8.2	0.71
Improvement ratio of JOA score (%)†	76.2 $\pm$ 19.1	70.2 $\pm$ 29.1	0.38
Improvement of VAS score (mm)‡			
LBP	31.7 $\pm$ 35.5	27.7 $\pm$ 26.2	0.68
Leg pain	44.1 $\pm$ 43.2	45.4 $\pm$ 38.5	0.91
Leg numbness	18.5 $\pm$ 37.2	32.3 $\pm$ 37.7	0.21

* Values are shown as mean $\pm$ SD.

† JOA score improvement ratio (%) = (postoperative – preoperative score) / (29 – preoperative score) $\times$ 100.

‡ VAS improvement (mm) = preoperative – postoperative value.

to avoid neurological symptoms can make SVA improvement after decompression surgery less likely.

PVM degeneration at L4–5 was significantly greater in patients with preoperative SVA ≥ 40 mm than in patients with SVA < 40 mm. According to the Scoliosis Research Society–Schwab classification, 40 mm is a cutoff SVA value for modifier grades, indicating outcome scores that have been demonstrated to have a strong clinical impact.¹⁷ Lee et al. reported that fat infiltration into the PVM was higher in patients with a degenerative flat back than in normal controls, and this change was more significant in the lower lumbar back.¹² In contrast, PVM degeneration was most prominent at the level of the affected nerve root and 1 level below in patients with neurological symptoms.¹⁸ In this study, all but 1 patient underwent surgery at L3–4 and/or L4–5. For these structural and neurological reasons, PVM degeneration at L4–5 was more marked in patients with forward-bending posture than in patients without forward-bending posture.

In patients with adult spinal deformity, progressive positive sagittal spinal alignment resulted in increasing PT, or pelvic retroversion, to compensate for the anterior translation of the spine.¹⁶ In this study, PT did not significantly decrease after surgery, despite SVA improvement. This finding indicates that compensation by pelvic retroversion did not occur in LSS patients before surgery. It is possible that the mechanism and pathology of forward-bending posture in LSS patients is different from that in adult spinal deformity patients. Similarly, it appears that the significance of PI – LL is different in patients with LSS versus those with adult spinal deformity.

The current study yielded important findings. Our study revealed that improvement in forward-bending posture, which is associated with health-related QOL and LBP, can be predicted from PI – LL and symptom duration. This information can help clinicians predict SVA improvement after decompression surgery in LSS patients based on a few preoperative radiological and clinical factors.

This study has 3 limitations. First, this was a retrospective study, and the indications for this surgical procedure were limited in patients with degenerative spondylolisthesis or degenerative lumbar scoliosis. Second, the sample size in each group was not sufficient to yield substantial effects. Further studies based on a larger sample size should be performed to confirm the present results. Third, the timing of the lateral standing radiographs after surgery was relatively late. In this study, the mean timing of lateral standing films at the final follow-up was approximately 30 months after surgery. Various factors are affected by the passage of time. Earlier timing of radiographs would make it possible to more directly evaluate the effect of decompression surgery on spinopelvic parameters.

Conclusions

This study showed that preoperative PI – LL and symptom duration were independently associated with SVA improvement in LSS patients with forward-bending posture, and PVM degeneration at the lower lumbar level was significantly greater in patients with preoperative SVA ≥ 40 mm than in patients with SVA < 40 mm.

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Disclosures

The authors report no conflict of interest concerning the materi-

als or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Dohzono. Acquisition of data: Toyoda, Dohzono, Matsumoto. Analysis and interpretation of data: Dohzono. Drafting the article: Dohzono. Critically revising the article: Toyoda. Reviewed submitted version of manuscript: Toyoda. Approved the final version of the manuscript on behalf of all authors: Toyoda. Statistical analysis: Dohzono, Takahashi. Administrative/technical/material support: Takahashi, Suzuki, Terai. Study supervision: Nakamura.

Supplemental Information

Previous Presentations

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