Retrospective Review

The Role of the Ligamentum Flavum Area as a Morphological Parameter of Lumbar Central Spinal Stenosis

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Background: Hypertrophy of the ligamentum flavum (LF) has been considered as a major cause of lumbar central spinal stenosis (LCSS). Previous studies have found that ligamentum flavum thickness (LFT) is correlated with aging, disc degeneration, and lumbar spinal stenosis. However, hypertrophy is different from thickness. Thus, to evaluate hypertrophy of the whole LF, we devised a new morphological parameter, called the ligamentum flavum area (LFA).

Objectives: We hypothesized that the LFA is a key morphologic parameter in the diagnosis of LCSS.

Study Design: Retrospective observational study.

Setting: The single center study in Seoul, Republic of Korea.

Methods: LF samples were collected from 166 patients with LCSS, and from 167 controls who underwent lumbar magnetic resonance imaging (MRI) as part of a routine medical examination. T1-weighted axial MR imageswere acquired at the facet joint level from individual patients. We measured the LFA and LFT at the L4-L5 intervertebral level on MRI using a picture archiving and communications system. The LFA was measured as the cross-sectional area of the whole LF at the L4-L5 stenotic level. The LFT was measured by drawing a line along the side of the ligament facing the spinal canal and along the laminar side of the ligament curve and then measuring the thickest point at the L4-L5 level.

Results: The average LFA was 96.56 ± 30.74 mm^2 in the control group and 132.69 ± 32.68 mm^2 in the LCSS group. The average LFT was 3.61 ± 0.72 mm in the control group and 4.24 ± 0.97 mm in the LCSS group. LCSS patients had significantly higher LFA ($P < 0.001$) and LFT ($P < 0.001$). Regarding the validity of both LFA and LFT as predictors of LCSS, Receiver Operator Characteristics (ROC) curve analysis showed that the best cut-off point for the LFA was 105.90 mm^2, with 80.1% sensitivity, 76.0% specificity, and area under the curve (AUC) of 0.83 (95% CI, 0.78 – 0.87). The best cut off-point of the LFT was 3.74 mm, with 70.5% sensitivity, 66.5% specificity, and AUC of 0.72 (95% CI, 0.66 – 0.77).

Limitations: The principal methodological limitation was the retrospective observational nature. Anatomically, degenerative lumbar spinal stenosis can involve the central canal, foramina, and lateral recess. However, we focused on LCSS only.

Conclusions: Although the LFT and LFA were both significantly associated with LCSS, the LFA was a more sensitive measurement parameter. Thus, to evaluate LCSS patients, the treating doctor should more carefully analyze the LFA than LFT.

Institutional Review Board (IRB) approval number: S2015-1328-0001

Key words: Ligamentum flavum, ligamentum flavum area, ligamentum flavum thickness, lumbar central spinal stenosis, hypertrophy of the ligamentum flavum, morphological parameter, cross-sectional area, optimal cut-off point

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Lumbar central spinal stenosis (LCSS) is a multifactorial spinal disorder with a prevalence of 27.2% (1-3). It is more common in elderly individuals (4). LCSS typically causes low back or buttock pain, sensory and motor disturbances, and neurogenic intermittent claudication in the lower extremities (3,5). LCSS can be defined as a decrease in the size of the dural sac and spinal canal caused by arthritic changes of the facet joints, disc herniation combined with osteophytes, and spinal nerve root compression (3,6). Hypertrophy of the ligamentum flavum (LF) has also been considered as a major cause of LCSS (7). Thickening of the LF can compress the dural sac and nerve root, reducing the diameter of the spinal canal, and contributing to the above symptoms (8). Previous studies have demonstrated that ligamentum flavum thickness (LFT) is associated with aging, disc degeneration, and lumbar spinal stenosis (4,9). However, hypertrophy is somewhat different from thickness. LFT may increase by buckling in the mass of the LF without a change (7,8). Thus, for evaluating hypertrophy of the whole LF, we devised a new morphological parameter, called ligamentum flavum area (LFA). In contrast to the LFT, the LFA measures the cross-sectional area of the whole LF. We hypothesized that the LFA is a key morphologic parameter in the diagnosis of LCSS. Therefore, we compared the LFA and LFT between LCSS patients and normal controls via magnetic resonance imaging (MRI).

Methods

Patients

This study was registered at the University of Ulsan, College of Medicine, Asan Medical Center, Republic of Korea (S2015-1328-0001). The Institutional Review Board (IRB) approved the research protocol.

Table 1. *Comparison of the characteristics of control and LCSS groups.*

Variable	Control Group n = 167	LCSS Group n = 166	Statistical significance
Gender (male/female)	85 / 82	54 / 112	NS
Age (yrs)	69.20 ± 8.04	68.69 ± 7.38	NS
LFT (mm)	3.61 ± 0.72	4.24 ± 0.97	$P < 0.001$
LFA (mm^2)	96.56 ± 30.74	132.69 ± 32.68	$P < 0.001$

Data represent the mean ± standard deviation (SD) or the numbers of patients. LFT, ligamentum flavum thickness; LFA, ligamentum flavum area; NS, not statistically significant ($P > 0.05$).

We reviewed retrospectively each patient who visited the Asan Spine Center from 2010 to 2015 and who were diagnosed with LCSS. Inclusion criteria were defined as follows: 1) MR images taken within 12 months of the diagnosis of LCSS and available for review; 2) clinical symptoms and signs compatible with LCSS, such as leg or low back pain aggravated by walking; 3) patients older than 60 years of age; 4) the most stenotic level was located at L4-L5. Exclusion criteria were defined if they had any one of the following conditions: 1) previous spinal injury; 2) history of prior lumbar spine surgery; 3) history of prior spinal interventions, such as kyphoplasty or vertebroplasty; and 4) any congenital spine disorder or defect that could affect pain severity.

A total of 166 individuals who met specified criteria for inclusion were enrolled after the diagnosis of LCSS was confirmed by an experienced board-certified neuroradiologist. There were 54 (32.5%) men and 112 (67.5%) women with a mean age of 68.69 ± 7.38 years (range, 60 to 88 years) (Table 1). Each patient underwent lumbar spine MRI. To compare the LFA and LFT between patients with and without LCSS, we also enrolled a control group who underwent lumbar MRI as part of a routine medical examination from June 2013 to September 2015. We only enrolled patients in the control group who did not have LCSS-related symptoms. The control group consisted of 167 participants (85 men and 82 women) with a mean age of 69.20 ± 8.04 years (range, 60 to 86 years). The LFT and LFA in the control group were also examined at the L4-L5 level.

Image Processing and Analysis

MRI data were obtained on 1.5 T Avanto (Siemens Medical Solutions, Erlangen, Germany) and 1.5 T Intera (Philips Medical Systems, Eindhoven, Netherlands) scanners. For all MRI examinations, we acquired T1-weighted axial and sagittal images with < 3 mm slice thickness, 0.9-mm intersection gap, 30-cm field of view, > 3 echo train length (ETL), and 448 × 314 matrix.

Image Analysis

T1-weighted axial MR images were acquired at the level of facet joint for individual patient data. We measured the LFA and LFT at the L4-L5 intervertebral level on MRI using a picture archiving and communications system (Fig. 1). The LFA was measured as the cross-sectional area of the whole LF at the L4-L5 stenotic level. The LFT was measured by drawing a line along the side of the ligament facing the spinal canal and along the

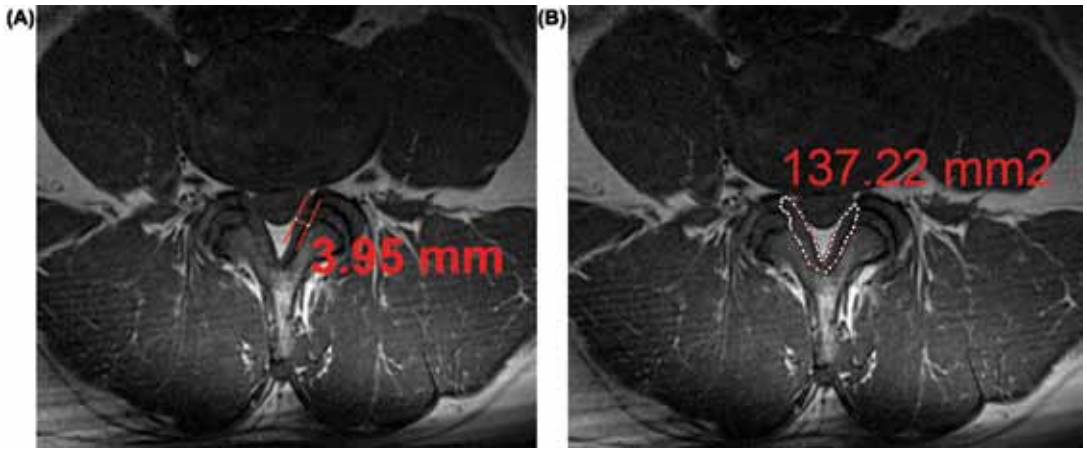


Fig. 1. *Measurement of both the ligamentum flavum thickness (A) and the ligamentum flavum area (B) was carried out at the facet joint level on T1-weighted MRIs.*

laminar side of the curve of the ligament and recording the thickest point at the L4-L5 level.

Statistical Analysis

We compared the LFA and LFT between the control and LCSS groups using unpaired t-tests. The data are expressed as mean ± standard deviation (SD). The validity of the LFA and LFT for diagnosis of disease was estimated by Receiver Operator Characteristics (ROC) curves, area under the curve (AUC), cut-off values, specificity, and sensitivity with 95% confidence intervals (CIs). The statistically significant differences were set at a P-value of less than 0.05. SPSS version 21 for Windows (IBM SPSS, IBM Corp., Armonk, NY) was used for the statistical analysis.

Results

The average LFA was 96.56 ± 30.74 mm2 in the control group and 132.69 ± 32.68 mm2 in the LCSS group. The average LFT was 3.61 ± 0.72 mm in the control group and 4.24 ± 0.97 mm in the LCSS group. LCSS patients had significantly greater LFA ($P < 0.001$) and LFT ($P < 0.001$) than controls (Table 1). Regarding the validity of both the LFA and LFT as predictors of LCSS, ROC curve analysis showed that the optimal cut-off point of the LFA was 105.90 mm2, with 80.1% sensitivity, 76.0% specificity (Table 2), and AUC of 0.83 (95% CI, 0.78 – 0.87) (Fig. 2). The optimal cut-off point of the LFT was 3.74 mm, with 70.5% sensitivity, 66.5% specificity (Table 3), and AUC of 0.72 (95% CI, 0.66 – 0.77) (Fig. 2).

Table 2. *Sensitivity and specificity of each cut-off point of the LFT.*

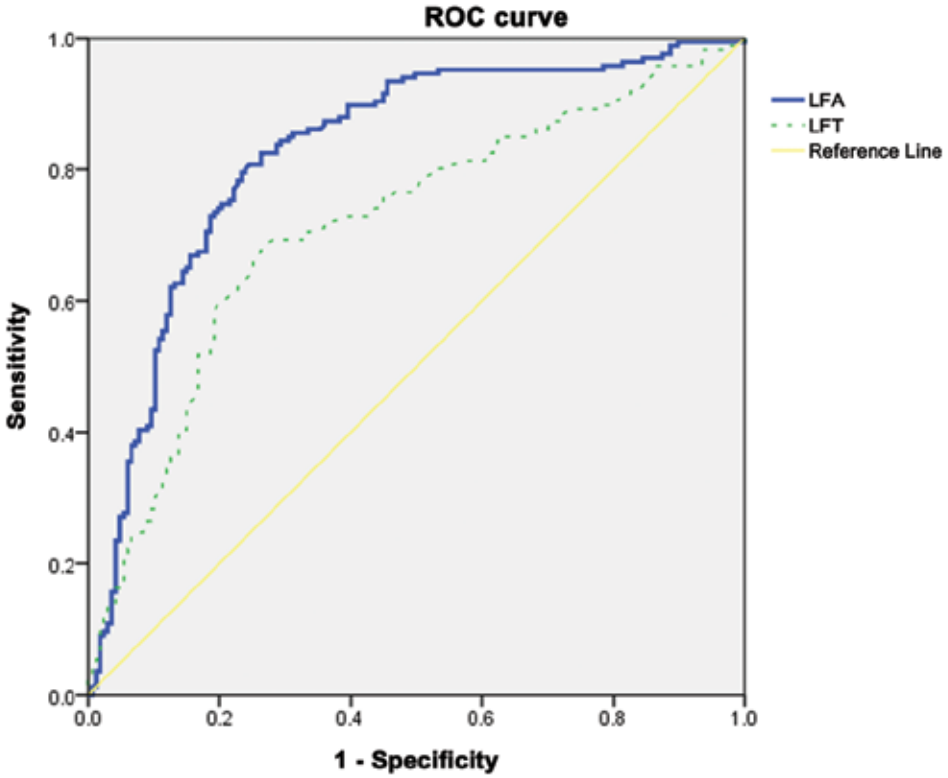
LFT (mm)	Sensitivity (%)	Specificity (%)
1.87	99.4	0
3.03	90.4	20.1
3.36	83.7	37.7
3.74*	70.5	66.5
4.64	28.3	90.1
6.26	2.4	100

*The best cut-off point on the receiver operating characteristic (ROC) curve; LFT, ligamentum flavum thickness.

Table 3. *Sensitivity and specificity of each cut-off point of the LFA.*

LFA (mm^2)	Sensitivity (%)	Specificity (%)
41.75	100	0
94.71	90.4	56.3
100.16	85.5	68.9
105.90*	80.1	76.0
135.76	43.4	90.2
282.91	0	100

*The best cut-off point on the receiver operating characteristic (ROC) curve; LFA, ligamentum flavum area.



LFA AUC (95% CI) = 0.83 (0.78 – 0.87). LFT AUC (95% CI) = 0.72 (0.66 – 0.77). AUC, area under the curve

Fig. 2. *Receiver operating characteristic (ROC) curve of ligamentum flavum area (LFA) and ligamentum flavum thickness (LFT) for prediction of lumbar central spinal stenosis. The best cut off point of LFA was 105.90 mm2 versus 3.74 mm of LFT, with sensitivity 80.1% versus 70.5%, specificity 76.0% versus 66.5% and AUC 0.83 versus 0.72, respectively.*

Discussion

The most common spinal disorder in elderly patients is LCSS, which causes intermittent neurogenic claudication and low back pain (3,5,10). LCSS results from a decrease in the transversal, anteroposterior, or combined diameter secondary to hypertrophy of the facet joints, disc height loss with or without herniation of the intervertebral disc, and the LF hypertrophy (11). The role of the LF is to protect the fat tissue that keeps the dural sac activity and maintains spinal stability and nerves within a certain range (12,13). The thickness of the LF differs significantly between the L2-L3, L3-L4, L4-5, and L5-S1 levels, and it is thickest at the L4-L5 level (8). Thus, we measured the LFA and LFT at the L4-5 level to obtain the most accurate measurement of thickness. We strictly controlled for age (all patients were older than 60 years) because many studies have found that the LF becomes thicker with age (4). The normal LF is a well-defined structure with 20% collagen fibers and 80% elastic fibers (7,14). The LF is a yellow, segmentally ligamentous structure that connects the adjacent vertebrae laminae in the spinal canal (13). In LCSS patients, the LF shows an increase in collagen fibers and a loss of elastic fibers, resulting in fibrosis. The contribution of mechanical factors to LF hypertrophy has been assessed in a previous study. Transforming growth factor beta is related to the stimulation of fibrosis. The process of LF thickening begins with mechanical stress, which induces inflammation, tissue damage, scarring, and finally, fibrosis (15). Abnormal movement can cause mechanical stress and inflammation, although the pathogenesis of the inflammatory reaction in LF ap-

pears to be multifactorial (15,16). Many studies have evaluated the associations between the LFT on MRI and the signs and symptoms of LCSS (4,17). Park et al (9) indicated that the LF is significantly thinner in patients with a herniated intervertebral disc than in those with lumbar spinal stenosis. Altinkaya et al (8) demonstrated that thickening of the LF is correlated with age, disc degeneration, and body mass index. Karabekir et al (18) demonstrated that contralateral disc herniation is related to a hypertrophied and asymmetrical LF. However, Abbas et al (4) emphasized that "LF hypertrophy" and "LF thickness" are not the same thing. Although the LFT may increase by infolding or buckling of the LF without a change in mass (4), LFT and LF hypertrophy are often used interchangeably in the literature. Previous studies have focused only on the LFT. We hypothesized that the cross-sectional area of the whole LF may predict LCSS because we previously found a positive association between Oswestry Disability Index scores and the LFA (19). Our interpretation of this association is that whole enlargement of the LF was related to chronicity (disability or persistent symptoms), which could diminish quality of life. In the current study, we found that the LFA had 80.1% sensitivity, 76.0% specificity, and AUC of 0.83 (95% CI, 0.78 – 0.87) to predict LCSS. In contrast, the LFT had 70.5% sensitivity, 66.5% specificity, and AUC of 0.72 (95% CI, 0.66 – 0.77). These findings suggest that the LFA is a better predictor of LCSS than the LFT. We also identified several problems associated with the measurement of the LFT. Previous studies have assessed the LFT by using a single measurement method at the approximate "middle" of the LF. However, Munns et al (15) demonstrated differences between the medial and lateral LFT, and emphasized that single measurements ignore possible differences in the location and laterality of stenosis. In addition, enlargement of the LF is sometimes unilateral as a result of asymmetrical mechanical stress (20,21). Thus, measurement error could occur at any time. Safak et al (20) reported a significant difference in the LFT between each side of the LF at the same facet joint level. They explained that the irregular mechanical stress borne by the LF during a lifetime may lead to asymmetrical hypertrophy. This asymmetry is suggested to be the consequence of the individual's preferred side. Abbas et al (4) reported that the LF is significantly thicker on the right side than the left, whereas Kolte et al (21) reported that the left LF is thicker than the right LF at each spinal level. In contrast to the LFT, the LFA does not suffer from this measurement error because the LFA measures the cross-sectional area of the whole LF. We found that the LFA is better than the LFT as a morphologic parameter of LCSS.

The current study has several limitations. Anatomically, degenerative lumbar spinal stenosis can involve the central canal, foramina, and lateral recess (11). However, we focused on LCSS only. Second, several different methods to evaluate LCSS, such as sedimentation sign or morphologic grading, have been shown to be effective at discriminating LCSS (22,23). However, we only assessed the measurement of LFA and LFT, so our results may have some limitations regarding measurement of epidural pressure or morphologic change. Third, there might be errors associated with measuring the LFA and LFT on MRI. Although we measured these morphologic parameters in the T1-weighted axial image that best showed the LF at the level of the facet joints, the T1-weighted axial images we analyzed to measure the variables could be inhomogeneous because of differences in the cutting angle or level in MRI resulting from technical causes and individual anatomic variation. In addition, a 3.0-mm slice of axial T1-weighted MR image is thicker than the ideal slice. Fourth, the principal methodological limitation was the retrospective observational nature.

Conclusion

Although the LFT and LFA were both significantly associated with LCSS, the LFA was a more sensitive measurement parameter for LCSS than was the LFT. We identified the best cut-off value of the LFA as 105.90 mm^2, with 80.1% sensitivity and 76.0% specificity. The best cut-off value of the LFT was 3.74 mm, with 70.5% sensitivity and 66.5% specificity. When evaluating patients with LCSS, physicians should carefully assess the LFA rather than the LFT.

References

1. Kalichman L, Cole R, Kim DH, Li L, Suri P, Guermazi A, Hunter DJ. Spinal stenosis prevalence and association with symptoms: The Framingham Study. *Spine J* 2009; 9:545-550.
2. Haig AJ, Tomkins CC. Diagnosis and management of lumbar spinal stenosis. *JAMA* 2010; 303:71-72.
3. Manchikanti L, Kaye AD, Manchikanti K, Boswell M, Pampati V, Hirsch J. Efficacy of epidural injections in the treatment of lumbar central spinal stenosis: A systematic review. *Anesth Pain Med* 2015; 5:e23139.
4. Abbas J, Hamoud K, Masharawi YM, May H, Hay O, Medlej B, Peled N, Hershkovitz I. Ligamentum flavum thickness in normal and stenotic lumbar spines. *Spine (Phila Pa 1976)* 2010; 35:1225-1230.
5. Manchikanti L, Cash KA, McManus CD, Damron KS, Pampati V, Falco FJ. A randomized, double-blind controlled trial of lumbar interlaminar epidural injections in central spinal stenosis: 2-year follow-up. *Pain Physician* 2015; 18:79-92.
6. Park CH, Lee SH, Jung JY. Dural sac cross-sectional area does not correlate with efficacy of percutaneous adhesiolysis in single level lumbar spinal stenosis. *Pain Physician* 2011; 14:377-382.
7. Yabe Y, Hagiwara Y, Ando A, Tsuchiya M, Minowa T, Takemura T, Honda M, Hatori K, Sonofuchi K, Kanazawa K, Koide M, Sekiguchi T, Itoi E. Chondrogenic and fibrotic process in the ligamentum flavum of patients with lumbar spinal canal stenosis. *Spine (Phila Pa 1976)* 2015; 40:429-435.
8. Altinkaya N, Yildirim T, Demir S, Alkan O, Sarica FB. Factors associated with the thickness of the ligamentum flavum: Is ligamentum flavum thickening due to hypertrophy or buckling? *Spine (Phila Pa 1976)* 2011; 36:E1093-E1097.
9. Park JB, Chang H, Lee JK. Quantitative analysis of transforming growth factor-beta 1 in ligamentum flavum of lumbar spinal stenosis and disc herniation. *Spine (Phila Pa 1976)* 2001; 26:E492-E495.
10. Manchikanti L, Falco FJ, Pampati V, Cash KA, Benyamin RM, Hirsch JA. Cost utility analysis of caudal epidural injections in the treatment of lumbar disc herniation, axial or discogenic low back pain, central spinal stenosis, and post lumbar surgery syndrome. *Pain Physician* 2013; 16:E129-E143.
11. Genevay S, Atlas SJ. Lumbar spinal stenosis. *Best Pract Res Clin Rheumatol* 2010; 24:253-265.
12. Losiniecki AJ, Serrone JC, Keller JT, Bohinski RJ. Lumbar ligamentum flavum: Spatial relationships to surrounding anatomical structures and technical description of en bloc resection. *J Neurol Surg A Cent Eur Neurosurg* 2013; 74:388-392.
13. Li S, Xia H, Han C. Retrospective analysis on correlation factors of preserving the ligamentum flavum in microendoscopic discectomy. *Clin Neurol Neurosurg* 2015; 139:46-50.
14. Viejo-Fuertes D, Liguoro D, Rivel J, Midy D, Guerin J. Morphologic and histologic study of the ligamentum flavum in the thoraco-lumbar region. *Surg Radiol Anat* 1998; 20:171-176.
15. Munns JJ, Lee JY, Espinoza Orias AA, Takatori R, Andersson GB, An HS, Inoue N. Ligamentum flavum hypertrophy in asymptomatic and chronic low back pain subjects. *PLoS One* 2015; 10:e0128321.
16. Sairyo K, Biyani A, Goel V, Leaman D, Booth R, Jr., Thomas J, Gehling D, Vishnubhotla L, Long R, Ebraheim N. Pathomechanism of ligamentum flavum hypertrophy: A multidisciplinary investigation based on clinical, biomechanical, histologic, and biologic assessments. *Spine (Phila Pa 1976)* 2005; 30:2649-2656.
17. Okuda T, Baba I, Fujimoto Y, Tanaka N, Sumida T, Manabe H, Hayashi Y, Ochi M. The pathology of ligamentum flavum in degenerative lumbar disease. *Spine (Phila Pa 1976)* 2004; 29:1689-1697.
18. Karabekir HS, Yildizhan A, Atar EK, Yaycioglu S, Gocmen-Mas N, Yazici C. Effect of ligamenta flava hypertrophy on lumbar disc herniation with contralateral symptoms and signs: A clinical and morphometric study. *Arch Med Sci* 2010; 6:617-622.
19. Kim YU, Kong YG, Lee J, Cheong Y, Kim SH, Kim HK, Park JY, Suh JH. Clinical symptoms of lumbar spinal stenosis associated with morphological parameters on magnetic resonance images. *Eur Spine J* 2015; 24:2236-2243.
20. Safak AA, Is M, Sevinc O, Barut C, Eryoruk N, Erdogmus B, Dosoglu M. The thickness of the ligamentum flavum in relation to age and gender. *Clin Anat* 2010; 23:79-83.
21. Kolte VS, Khambatta S, Ambiye MV. Thickness of the ligamentum flavum: Correlation with age and its asymmetry - an magnetic resonance imaging study. *Asian Spine J* 2015; 9:245-253.
22. Barz T, Melloh M, Staub LP, Lord SJ, Lange J, Merk HR. Increased intraoperative epidural pressure in lumbar spinal stenosis patients with a positive nerve root sedimentation sign. *Eur Spine J* 2014; 23:985-990.
23. Lonne G, Odegard B, Johnsen LG, Solberg TK, Kvistad KA, Nygaard OP. MRI evaluation of lumbar spinal stenosis: Is a rapid visual assessment as good as area measurement? *Eur Spine J* 2014; 23:1320-1324.