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Clinical Study

Migration patterns of herniated disc fragments: a study on 1,020 patients with extruded lumbar disc herniation

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Abstract

BACKGROUND CONTEXT: Herniated disc fragments are known to migrate in various directions within the spinal canal. To date, no comprehensive studies have been undertaken to examine the migration patterns of herniated disc material using a standard nomenclature and classification system.

PURPOSE: To report migration patterns of extruded lumbar disc fragments.

STUDY DESIGN: A review of magnetic resonance (MR) images.

PATIENT SAMPLE: A total of 1,020 consecutive Azeri patients with symptomatic extruded lumbar intervertebral disc herniation.

OUTCOME MEASURES: Migration patterns of extruded lumbar disc fragments in vertical and horizontal planes and their association with age, gender, body mass index (BMI), and the level of herniation.

METHODS: High-quality axial and sagittal MR images of the lumbar spine were used. Disc material that was displaced away from the site of extrusion, regardless of continuity, was considered "migrated." The migration patterns observed were rostral or caudal in the vertical plane and central, paracentral, subarticular, foraminal, or extraforaminal in the horizontal plane.

RESULTS: In the vertical plane, rostral and caudal migrations were observed in 27.8% and 72.2% of the patients, respectively. The number of rostral migrations increased significantly with increasing age and in higher levels in the lumbar spine (p<.001 for both). Radiculopathy was significantly more frequent in caudal migrations than in rostral migrations (78.9% vs. 65.1%, p<.001). There was no significant association between gender or BMI and migration patterns in the vertical plane. In the horizontal plane, central, paracentral, subarticular, foraminal, and extraforaminal migrations were reported in 17.3%, 74.2%, 4.3%, 2.5%, and 1.8% of the patients, respectively. The youngest (median age 39 years, interquartile range [IQR] 13 years) and the oldest (median age 55 years, IQR 15 years) groups of patients (p<.001) had the most formainal and extraforaminal migrations, respectively. Radiculopathy was present in 66.5%, 76.8%, 88.6%, 96%, and 27.8% of the patients with central, paracentral, subarticular, foraminal, and extraforaminal migrations, respectively (p<.001). No significant association was found between gender, BMI, or the level of herniation and migration pattern in the horizontal plane.

CONCLUSIONS: Caudal and paracentral migrations are the most common patterns of migration in patients with extruded lumbar disc herniation in the vertical and horizontal planes, respectively.

FDA device/drug status: Not applicable.

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Keywords:

Lumbar disc herniation; Extrusion; Migration pattern; Age; Gender; Body mass index; Level of herniation

Introduction

When the intervertebral disc (IVD) material, including the nucleus, cartilage, fragmented bone, annular tissue, or any combination thereof, is displaced locally beyond the limits of the IVD, a disc herniation occurs [1]. Herniated disc fragments are known to migrate within the spinal canal and in rostral, caudal, or lateral directions [2,3].

The ability to identify a disc fragment that has migrated is essential for an appropriate management and surgical planning [4–9] because those migrated fragments may mimic tumors (such as neurofibroma and meningioma), hematomas, and abscesses [10]. Magnetic resonance imaging (MRI), and contrast-enhanced sequences in particular, has been suggested as the method of choice for evaluating migrated disc material [11–13].

Despite the importance of migration of disc fragments in patients with disc herniation, no comprehensive studies have been reported that have focused on the patterns of this migration. Inappropriate and/or inconsistent nomenclature and classification systems, small sample sizes, flawed methodology, and confounding factors have made it difficult to draw concrete conclusions from the current literature [5,14–16].

The objectives of the present study were to examine migration patterns of disc fragments in symptomatic patients with extruded lumbar disc herniation and to examine possible contributing roles played by age, gender, body mass index (BMI), and the level of herniation.

Materials and methods

Study design and population

After receiving approval from the local institutional review board, lumbar spine MR images of a total of 1,048 Azeri patients with symptomatic extruded lumbar disc herniation were reviewed consecutively from April 2005 to October 2011 at a teaching MRI center.

Of these, 28 subjects were excluded for the following reasons: combined end-plate fracture (n=17), history of back surgery (n=7), segmental instability on dynamic radiography (n=2), and concurrent spinal abnormalities other than lumbar disc herniation (n=2). Written informed consent was obtained from the participants before enrollment.

MRI technique and definitions

High-quality axial and sagittal T1- and T2-weighted MR images of the lumbar spine were obtained using a 0.3-T scanner (MRP7000; Hitachi Corp., Tokyo, Japan). The images

were reviewed independently by two skilled neuroradiologists with more than 15 years of experience in neurologic MRI interpretation.

A herniated disc was considered as a localized displacement of nucleus, cartilage, fragmented epiphyseal bone, or fragmented annular tissue beyond the IVD space. The IVD space was defined by the vertebral body end plates (craniad and caudad) and the edges of the vertebral ring apophyses, exclusive of osteophytic formations, peripherally [1].

Extrusion was present when any single distance between the edges of the disc material beyond the disc space was greater than the distance between the edges of the base measured in the same plane or when no continuity existed between the disc material beyond the disc space and that within the disc space. Disc material that was displaced away from the site of extrusion, regardless of continuity, was called "migrated." Extruded disc material that had no continuity with the disc of origin was defined a "sequestrated" disc [1,6].

Migration of disc material was reported in both horizontal and vertical planes. From central to lateral in the horizontal (axial) plane, migration was defined as "central," "paracentral," "subarticular," "foraminal," and "extraforaminal" (Figs. 1 and 2). From the disc level upward or downward in the vertical (sagittal) plane, migration was defined as "rostral" or "caudal," respectively [1,17] (Figs. 1 and 2).

Inter- and intraobserver agreements were acceptable [18] between the two neuroradiologists (Cohen kappa=0.83 and 0.89, respectively). In the case of disagreement in interpretation between them, a third neuroradiologist arbitrated.

Statistical analysis

SPSS software version 19.0 (IBM Corp., New York, NY, USA) was used for statistical analyses. Distribution of the data was analyzed using Kolmogorov-Smirnov analysis and QQ plots. Contingency tables (chi-square or Fisher exact test, where appropriate), independent sample *t* test, Mann-Whitney *U* test, or one-way analysis of variance/Kruskal-Wallis test with an appropriate post hoc analysis was used. The logistic regression test was performed in multivariate analysis. The paired inter- and intraobserver comparisons were analyzed using Cohen kappa coefficient. A significance level of $p \le .05$ was used.

Results

The study population included 633 men (62.1%) and 387 women (37.9%), with a mean age of 46.52 ± 12.42 (range 21–84) years. The male and female patients were comparable



Fig. 1. Classification of horizontal (Left) and vertical (Right) migrations of herniated disc fragments.

in terms of age $(46.69\pm13.21 \text{ and } 45.08\pm14.12 \text{ years, respectively; independent samples } t \text{ test, } p=.89)$. The mean BMI of the patients was $27.49\pm8.87 \text{ kg/m}^2$ (range 24–35, median 27).

Rostral and caudal migrations were observed in 284 (27.8%) and 736 (72.2%) cases, respectively, in the vertical plane. In the horizontal plane, we observed 176 cases (17.3%) with central migration, 757 cases (74.2%) with

paracentral migration, 44 cases (4.3%) with subarticular migration, 25 cases (2.5%) with foraminal migration, and 18 cases (1.8%) with extraforaminal migration. In the horizontal plane, right- and left-sided migrations were observed in 446 and 398 patients with noncentral herniations, respectively.

The patient demographic data and MRI findings are summarized in Table 1. The migration patterns of the herniated disc fragments in the vertical and horizontal planes



Fig. 2. Sagittal (A and B) and axial (C–G) magnetic resonance images of the lumbar spine in patients with extruded lumbar disc herniation (arrows). Rostral (A) and caudal (B) migrations of herniated disc fragments in the vertical plane. Central (C), paracentral (D), subarticular (E), foraminal (F), and extraforaminal (G) migration of herniated disc fragments in the horizontal plane.

Table 1

Characteristics and general data of the study population with extruded lumbar disc herniation

| Characteristics | |
|--------------------------------------|-------------|
| Gender | |
| Male | 633 (62.1) |
| Female | 387 (37.9) |
| Age (y) | 46.52±12.42 |
| Age groups (y) | |
| 20–29 | 62 (6.1) |
| 30–39 | 239 (23.4) |
| 40–49 | 340 (33.3) |
| 50–59 | 217 (21.3) |
| 60–69 | 107 (10.5) |
| 70+ | 55 (5.4) |
| Body mass index (kg/m ²) | 27.49±8.87 |
| Clinical manifestations | |
| Low back pain | 1,020 (100) |
| Radiculopathy | 766 (75.1) |
| Sensory deficit | 203 (19.9) |
| Motor deficit | 53 (5.2) |
| Level of disc herniation | |
| L1–L2 | 12 (1.2) |
| L2–L3 | 54 (5.3) |
| L3–L4 | 107 (10.5) |
| L4–L5 | 495 (48.5) |
| L5-S1 | 352 (34.5) |
| Migration | |
| Vertical plane | |
| Rostral | 284 (27.8) |
| Caudal | 736 (72.2) |
| Horizontal plane | |
| Central | 176 (17.3) |
| Paracentral | 757 (74.2) |
| Right | 395 (52.2) |
| Left | 362 (47.8) |
| Subarticular | 44 (4.3) |
| Right | 26 (59.1) |
| Left | 18 (40.9) |
| Foraminal | 25 (2.5) |
| Right | 16 (64) |
| Left | 9 (36) |
| Extraforaminal | 18 (1.8) |
| Right | 9 (50) |
| Left | 9 (50) |

Note: Data are shown as the mean ± standard deviation and frequency (%).

are summarized in Table 2. No significant association was found between the migration patterns in the vertical and horizontal planes (chi-square test, p=.12).

Migration in the vertical plane

Rostral and caudal migrations of herniated disc fragments were present in 12 (19.4%) and 50 (80.6%) patients in the 20- to 29-year age group; 48 (20.1%) and 191 (79.9%) patients in the 30- to 39-year age group; 80 (23.5%) and 260 (76.5%) patients in the 40- to 49-year age group; 71 (32.7%) and 146 (67.3%) patients in the 50- to 59-year age group; 49 (45.8%) and 58 (54.2%) patients in the 60to 69-year age group; and 24 (43.6%) and 31 (56.4%) patients in the 70+ year age group, respectively. A progressive and significant increase was observed in the number of

Table 2

Migration direction of extruded lumbar disc fragments in vertical and horizontal planes

| Migration direction | Horizontal plane | | | | |
|---------------------|------------------|-------------|--------------|-----------|----------------|
| | Central | Paracentral | Subarticular | Foraminal | Extraforaminal |
| Vertical pl | ane | | | | |
| Rostral | 58 (20.4) | 206 (72.5) | 10 (3.5) | 3 (1.1) | 7 (2.5) |
| Caudal | 118 (16) | 551 (74.9) | 34 (4.6) | 22 (3) | 11 (1.5) |

Note: Data are presented in terms of raw numbers and frequency (%).

rostral migrations with increasing age (Pearson chi-square test, p<.001, Fig. 3).

The median age of patients with rostral migration was higher than in those with caudal migration (50 years, interquartile range [IQR]=19 vs. 43 years, IQR=19; Mann-Whitney U test, p < .001).

The two groups with rostral and caudal migrations were comparable in terms of gender (176 men, 62% and 108 women, 38% vs. 457 men, 62.1% and 279 women, 37.9%, respectively; chi-square test, p=.97) and mean BMI (27.03±6.48 vs. 27.64±8.79 kg/m², respectively; independent samples *t* test, p=.43).

Rostral and caudal migrations were documented in 5 (41.7%) and 7 (58.3%) cases with herniation at L1–L2; 30 (55.6%) and 24 (44.4%) cases with herniation at L2–L3; 45 (42.1%) and 62 (57.9%) cases with herniation at L3–L4; 129 (26.1%) and 366 (73.9%) cases with herniation at L4–L5; and 75 (21.3%) and 277 (78.7%) cases with herniation at L5–S1, respectively.

The number of rostral migrations decreased significantly at lower levels in the lumbar spine (Pearson chi-square test, p<.001, Fig. 4). Radiculopathy was significantly more frequent in cases with caudal (581 cases, 78.9%) compared with rostral (185 cases, 65.1%) migrations (chi-square test, p<.001).

Based on the results of the logistic regression analysis, although both age and the level of herniation were independently associated with the migration patterns in the vertical plane (p<.001 with exp B=0.78 and p=.03 with exp B=1.34, respectively), no significant difference was found



Fig. 3. Percentage of migrated disc fragments in the vertical plane stratified by patient age.



Fig. 4. Percentage of migrated disc fragments in the vertical plane stratified by the level of herniation.

between rostral and caudal migrations in terms of the frequency of radiculopathy (p=.25 with exp B=1.25).

Migration in the horizontal plane

In the 20- to 29-year age group, there were 16 cases (9.1%) with central, 34 cases (4.5%) with paracentral, 6 cases (13.6%) with subarticular, and 6 cases (24%) with foraminal migration. There were 48 cases (27.3%) with central, 177 cases (23.4%) with paracentral, 5 cases (11.4%) with subarticular, and 9 cases (36%) with foraminal migration in the 30- to 39-year age group. Central, paracentral, subarticular, foraminal, and extraforaminal migrations were present in 47 (26.7%), 263 (34.7%), 19 (43.2%), 10 (40%), and 1 (5.6%) cases in the 40- to 49year age group, respectively. We observed 36 cases (20.5%) with central, 162 cases (21.4%) with paracentral, 7 cases (15.9%) with subarticular, and 12 cases (66.7%) with extraforaminal migration in the 50- to 59-year age group. A total of 18 cases (10.2%) with central, 83 cases (11%) with paracentral, 5 cases (11.4%) with subarticular, and 1 case (5.6%) with extraforaminal migration were observed in the 60- to 69-year age group. In the 70+ year age group, central, paracentral, subarticular, and extraforaminal migrations were documented in 11 (6.2%), 38 (5%), 2 (4.5%), and 4 (22.2%) cases, respectively. A significant difference was found between the age groups and frequency of each migration path in the horizontal plane (chi-square test, p<.001, Fig. 5).

The median ages of the patients with central migration were 44 (IQR=19) years, 45 (IQR=15) years with paracentral migration, 45 (IQR=18) years with subarticular migration, 39 (IQR=13) years with foraminal migration, and 55 (IQR=15) years with extraforaminal migration (Kruskal Wallis test, p<.001). The results of post hoc analysis (Bonferroni corrected) showed that the lowest and the highest median ages were found in the patients with foraminal and extraforaminal migrations, respectively (for all paired comparisons, p<.01).

Regarding gender and migration type, central, paracentral, subarticular, foraminal, and extraforaminal migrations were



Fig. 5. Percentage of migrated disc fragments in the horizontal plane stratified by patient age.

observed in 104 men (59.1%)/72 women (40.9%), 483 men (63.8%)/274 women (36.2%), 22 men (50%)/22 women (50%), 16 men (64%)/9 women (36%), and 8 men (44.4%)/10 women (55.6%), respectively (chi-square test, p=.15).

Mean BMI values for the same migration types were 27.03 ± 7.48 , 27.43 ± 8.25 , 27.59 ± 6.16 , 27.41 ± 7.33 , and 27.48 ± 8.56 kg/m², respectively (one-way analysis of variance, p=.87).

At L1–L2, we observed four cases (33.3%) with central and eight cases (66.7%) with paracentral migration. At L2-L3, 13 cases (24.1%) with central, 38 cases (70.4%) with paracentral, 2 cases (3.7%) with subarticular, and 1 case (1.9%) with extraforaminal migration were seen. At L3-L4, we saw 22 cases (20.6%) with central, 73 cases (68.2%) with paracentral, 8 cases (7.5%) with subarticular, 2 cases (1.9%) with foraminal, and 2 cases (1.9%) with extraforaminal migration. At L4-L5, we observed 76 cases (15.4%) with central, 375 cases (75.8%) with paracentral, 19 cases (3.8%) with subarticular, 10 cases (2%) with foraminal, and 15 cases (3%) with extraforaminal migration. At L5–S1, we saw 61 cases (17.3%) with central, 263 cases (74.7%) with paracentral, 15 cases (4.3%) with subarticular, and 13 cases (3.7%) with foraminal migration (chisquare test, p=.08, Fig. 6).



Fig. 6. Percentage of migrated disc fragments in the horizontal plane stratified by the level of herniation.

Radiculopathy was present in 117 cases (66.5%) with central, 581 cases (76.8%) with paracentral, 39 cases (88.6%) with subarticular, 24 cases (96%) with foraminal, and 5 cases (27.8%) with extraforaminal migration. There was a significant difference among the groups in terms of the frequency of radiculopathy (chi-square test, p < .001).

Discussion

Migration of extruded disc material within the spinal canal can take place in any direction—rostrally into the space behind the adjacent vertebral body or foramen, caudally into the lateral recess or further, and laterally in the horizontal plane [7,17].

In the present study, rostral and caudal migrations of herniated disc fragments were observed in 27.8% and 72.2% of the study population, respectively.

According to the previous studies, the incidence of rostral and caudal migrations of herniated lumbar disc material varies between 40% and 78% and 40% and 50%, respectively [4,5,7–9,11,12,14–16].

Although one of these studies reported an equal chance of rostral and caudal migrations [4], others reported a higher incidence of rostral [14] and caudal [15,16] migrations in cases with extruded or sequestered herniated lumbar discs.

The anterior epidural space (AES) is a well-defined space that is delimited by the posterior longitudinal ligaments (PLL) and lateral membrane; the AES is attached medially to the free edge of the PLL and stretches laterally to the wall of the spinal canal [19].

Fries et al. [14] hypothesized that a higher incidence of rostral migration of herniated disc fragments in the vertical plane may be because of greater space available to accommodate herniated nucleus pulposus (HNP) in the AES. In contrast, Schellinger et al. [4] suggested that because the configuration of the AES is identical at both superior and inferior halves of the vertebral body, the HNP appears to have an equal chance of moving rostrally or caudally.

A large sample size empowered the present study to reliably analyze possible influences of the level of herniation and patient age, gender, and BMI on the direction of migrated disc fragments. Although no significant association was found for gender and BMI, both age and the level of herniation were significantly associated with rostral and caudal migrations of herniated disc material. Accordingly, the frequency of caudal migrations declined with increasing patient age and at higher segments in the lumbar spinal column (Figs. 3 and 4).

A significant correlation between age and the level of herniation in the lumbar spine has been previously reported [20]. In the present study, however, the results of an appropriate model of multivariate analysis confirmed that both age and the level of herniation were independently associated with the direction of migrated disc fragments in the vertical plane.

Previous reports have shown great variation in epidural anatomy in association with both age and the vertebral level [21,22]. In support of our finding, a higher incidence of more cephalad lumbar herniations has been reported in older patients [23].

According to the results of another study by Igarashi et al. [24], the extradural space at the L2–L3 interspace becomes widely patent and the fatty tissue in the extradural space diminishes with increasing age. These age-related changes in the AES along with other senile degenerations may contribute to the higher incidence of rostral migration of the HNP in the elderly. In addition, a sedentary lifestyle in the elderly could predispose them to a higher incidence of rostral migration of herniated disc fragments compared with their more active younger counterparts. An attenuated effect of gravity on herniated material, along with an augmented compressive effect of the structures surrounding the lower lumbar region in sitting or lying positions, may explain this finding in older subjects.

Some migration patterns of herniated disc fragments at spinal levels may be explained by variability in the points of bony attachment of the PLL. The deep and superficial layers of the PLL attach to a midline bony septum on the posterior surface of the vertebral body. The central band of the PLL has a wider attachment to the IVD [25,26]. There is a considerable variation within the lumbar region, where the central fibers and "fanlike" IVD attachment of the PLL portion appear to decrease in width between L1 and L5 [27]. Throughout the lumbar spine, lateral fibers attach to the annulus fibrosus and the rim of the adjacent vertebrae. Additionally, medial fibers attach to the posterior wall of the vertebral bodies, bridging the basivertebral foramina. Because these foramina become enlarged in the caudal portions of the vertebral column, the number of attachment points at the posterior wall of the vertebral bodies decreases caudally [28]. This peculiar anatomic condition may account for the tendency of caudal migration of the herniated disc fragments in the lower segments of the lumbar spine (ie, L4–S1).

In the horizontal plane, central, paracentral, subarticular, foraminal, and extraforaminal migrations were found in 17.3%, 74.2%, 4.3%, 2.5%, and 1.8% of study patients, respectively.

There is a paucity of similar studies in the literature. In a series by Ebeling and Reulen [2], 131 patients with lumbar disc herniation were studied. Herniated disc fragments were located mediolaterally in 64%, laterally in 20%, within or lateral to the intervertebral compartment in 12%, and centrally in 5%. Barlocher et al. [29] reported a lower incidence of central lumbar disc herniation in comparison with the more common occurrence of paramedian or posterolateral disc herniations.

In a report by Sipko et al. [30], the directions of disc herniations in 40% of 39 patients with lumbar disc herniation were distributed as follows: central, 22.5% central right sided, 15% central left sided, 20% central bilateral, and 2.5% right sided. In other studies, far lateral (extraforaminal) discs constituted 7% to 12% of all lumbar disc herniations [31–33].

We found no significant association between the direction of migrated disc fragments in the horizontal plane and other variables including gender, BMI, and the level of herniation. In terms of age, however, foraminal and extraforaminal migrations were observed in the youngest and the oldest groups, respectively (Fig. 5). This result was statistically significant.

Similar to our findings, previous reports have shown no gender difference regarding the direction of migrated disc fragments in the horizontal plane. In addition, previous authors have also reported a higher incidence of far lateral herniations in older patients [23,31,32,34].

Anatomic and structural changes during aging may explain the connection between age and the location of migrated disc fragments in the horizontal plane. Normally, a sagittal midline septum (septum posticum) separates the AES into two compartments and limits lateral migration. The epidural membrane is another lateral barrier that is attached to the PLL medially and to the wall of the spinal canal laterally. The midline and lateral dural Hoffmann ligaments, which connect the anterior dural surface to the PLL and posterior vertebral periosteum, may also play an important role in preventing axial migration [35].

Age-related changes in these structures and other anatomic elements such as epidural vessels, fat, and nerve roots are critical in making individuals vulnerable to migration of herniated disc materials in the horizontal plane [26].

It is important to consider that migration patterns of extruded disc contents may be influenced by other factors such as preexisting status of the trunk muscles [36], degree of lordosis [37], distribution of intervertebral stress [38], previous asymptomatic disc herniation(s) [2,4], anatomic variations [39], and facet tropism [40]. Many of these factors are even interrelated [41], adding further complexity to the issue.

Interestingly, and contrary to some previous reports [4,11], no bidirectional migration in the vertical plane or sequestrated herniated disc fragment was observed in the present study. Although the exact etiology is unclear, racial and ethnic differences may explain this discrepancy [42–44].

The aspects of the disc herniation (protrusion or extrusion) and its size are not the only predictors of nerve root compression. Although the rostral migration of herniated disc fragments may compress the ganglion against the pedicle, migration in the opposite direction into the confined space of the lateral recess more likely leads to traversing nerve root compression [17]. This is most likely why the rate of radiculopathy was significantly higher in our patients with caudal migrations than in those with rostral migrations (65.1% vs. 78.9%).

In the horizontal plane, radiculopathy was found in 66.5%, 76.8%, 88.6%, 96%, and 27.8% of the cases with central, paracentral, subarticular, foraminal, and extraforaminal migration, respectively. Whereas the central region is a roomy canal and the extraforaminal region lacks dense nerve roots and ganglia, the lateral recess, including subarticular and foraminal regions, is a very confined space with traversing nerve roots [17]. Lateral disc herniations usually irritate and compress the ganglia of the dorsal root, provoking radiculopathy with intense pain [45]. Most foraminal disc herniations are accompanied by radiculopathy, typically referred to as acute radicular syndromes. This radiculopathy originates from the compression on the longitudinal emerging root in the extracanal portion of the medullary canal [46]. These anatomic considerations can explain the high incidence of radiculopathy in subarticular and foraminal regions in our population.

From a clinical standpoint, the location of migrated disc fragments may be defined in four zones depending on the direction and distance from the disc space. This classification can serve as a yardstick for preoperative evaluation of patients with migrated disc material and in selecting the most appropriate surgical approach [9]. Our findings may be useful for physicians and surgeons in improving their ability to identify the location of extruded discs or remnant(s) during epidural exploration at different lumbar levels.

To the best of our knowledge, this is the first study that has comprehensively investigated the migration directions of disc material in a large sample of symptomatic patients with extruded lumbar disc herniation in terms with a standard nomenclature and classification system derived by multispecialty combined task force [1]. Although the roles of some variables such as age, gender, BMI, and the level of herniation were examined, additional factors, as described previously, deserve further study. The effect of racial and ethnical differences and the connection between these anatomic data with outcomes of treatment are other potential avenues for future research.

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