Studies in Failures of Discectomies

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Thesis Title

Studies in failures of discectomies

Thesis Abstract

The different discectomy techniques for symptomatic lumbar disc herniation (LDH) patients provide excellent short-term clinical outcomes. However, a high rate of recurrence or complications is observed, which represents a significant burden on healthcare systems worldwide.

This thesis presents series of studies investigating a hierarchy of complication rates following different discectomy techniques, and then explores factors like surgical technique variations, altered tissue molecular markers, and disc height (DH) measurements in the context of discectomy. The findings revealed that a plethora of techniques used for measuring disc height index (DHI) were never subjected to the proper evaluation.

First, a meta-analysis and network meta-analysis was performed by ranking of complications hierarchy and then evaluating their rates following different discectomy techniques. The findings revealed a 20% complication rates and 10% reoperation rates. Percutaneous endoscopic lumbar discectomy (PELD) had the lowest ranking for complication rates.

Subsequently, an online survey of orthopaedic surgeons and neurosurgeons in Australia and New Zealand (ANZ) was conducted. The findings revealed that surgeons' annual practice volume had important implications in the perception of surgical complications when treating primary LDHs, but there was no significant difference in the selection of surgical techniques.

A clinical study demonstrated an association between poor clinical outcome and inflammatory dysregulation in subcutaneous fat overlying the back region.

Another systematic review of observational studies to access the pre-post changes in DH showed that discectomy produces significant and quantifiable reductions in DH. A strong association between the reduction in DH and the decrease in LBP after discectomy was observed.

Finally, an intra- and inter-rater agreement and reliability on seven previously reported DHI measurement methods revealed four of them as sensitive and valid tools.

In summary, PELD offers the lowest complication rates, however, it has a learning curve, that surgeons in ANZ do not have any variation in practice that may impact outcomes of primary discectomy. The subcutaneous fat of patients with poorer outcomes has evidence of inflammation, that DH diminishes after discectomy. In case DH has to be used for a clinical trial evaluating annular closures or nucleus replacement, the issue of concern is the method of reliable measurement.

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I confirm that where I have used a publication in lieu of a chapter, the listed publication(s) above meet(s) the requirements to be included in the thesis. I also declare that I have complied with the Thesis Examination Procedure.

Abstract

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List of Abbreviations

AF	Annulus fibrosis
ANZ	Australia and New Zealand
Arg-1	Arginase-1
BDNF	Brain-derived neurotrophic factor
BMI	Body mass index
CES	Cauda equina syndrome
CI	Confidence interval
CSA	Cross-sectional area
CT	Computed tomography
DH	Disc height
DHI	Disc height index
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ICC	Intra-class correlations
IGF-1	Insulin-like growth factor
I^2	Chi-squared
IL-1β	Interleukin-1β
IQR	Interquartile range
IVD	Intervertebral disc
LDH	Lumbar disc herniation
LMM	Lumbar multifidus muscle
LOA	Limits of Agreement

MCDC	Modified Clavien-Dindo classification
MD	Microdiscectomy
MDs	Mean differences
MED	Microendoscopic discectomy
MRI	Magnetic resonance imaging
NMA	Network meta-analysis
NOS	Newcastle-Ottawa Scale
Nos-2	Nitric oxide synthase 2
NP	Nucleus pulposus
NPS	Numeric rating pain scale
NSAIDs	Nonsteroidal anti-inflammatory drugs
OD	Open discectomy
ODI	Oswestry disability index
OR	Odds ratio
PELD	Percutaneous endoscopic lumbar discectomy
PFS	Physical functioning scale
PICO	Patient, interventions, comparator, and outcome
PLDD	Percutaneous laser disc decompression
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PROSPERO	International Prospective Register of Systematic Reviews Number
qPCR	Quantitative polymerase chain reaction
RCTs	Randomized controlled trials
rLDH	Recurrent lumbar disc herniation

RR	Risk ratio
SD	Standard deviation
SEM	Standard error of measurement
SMD	Standardise mean difference
SoFs	Summary of findings
SUCRA	Surface under cumulative ranking curve
TGF-β1	Transforming growth factor beta 1
TNF	Tumor necrosis factor
VAS	Visual analogue scale

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Thesis Related Journal Publications

1. **Chen XL**, Chamoli U, Fogel H, Diwan AD. Clinicians' perceptions around discectomy surgery for lumbar disc herniation: a survey of orthopaedic and neurosurgeons in Australia and New Zealand. Archives of Orthopaedic and Trauma Surgery, 2021; doi: 10.1007/s00402-021-04019-3
2. **Chen XL**, Sandhu HS, Castillo JV, Diwan AD. The association between pain scores and disc height change following discectomy surgery in lumbar disc herniation patients: A systematic review and meta-analysis. Eur Spine J, 2021; doi: 10.1007/s00586-021-06891-4
3. **Chen XL**, Hodges PW, James G, Diwan AD. Do markers of inflammation and/or muscle regeneration in lumbar multifidus muscle and fat differ between individuals with good or poor outcome following microdiscectomy for lumbar disc herniation? Spine, 2021; 46(10):678-686. doi: 10.1097/BRS.0000000000003863
4. **Chen XL,** Chamoli U, Castillo JV, Ramakrishna VAS, Diwan AD. Complication rates of different discectomy techniques for symptomatic lumbar disc herniation: A systematic review and meta-analysis. Eur Spine J, 2020; doi: 10.1007/s00586-020-06389-5
5. **Chen XL,** Chamoli U, Lapkin S, Castillo JV, Diwan AD. Complication rates of different discectomy techniques for the treatment of lumbar disc herniation: a network meta-analysis. Eur Spine J, 2019; 28:2588-2601. doi: 10.1007/s00586-019-06142-7

Thesis Related Manuscripts (Under Review)

1. **Chen XL**, Sima S, Kuan J, Diwan AD. Radiographic evaluation of lumbar intervertebral disc height index: an intra and inter-rater agreement and reliability study. The Spine Journal, 2021; under review

Other Journal Publications During Candidature

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Conference Presentations

1. **XL Chen**, U Chamoli, AD Diwan. Lumbar Canal Stenosis - Pathology and Natural History. Sydney Spinal Symposium 2018, Sydney, Australia, 6th September 2018
2. **XL Chen**, PW Hodges, G James, JA Umali, U Chamoli, AD Diwan. What factors differ between individuals with either good or poor outcome following microdiscectomy for lumbar disc herniation: an investigation of inflammatory and muscle regeneration markers in the lumbar multifidus muscle. 46th ISSLS annual meeting, 2019, Kyoto, Japan, 4th June 2019
3. **XL Chen**, AD Diwan. Clinical traveling fellowship report. 46th ISSLS annual meeting, 2019, Kyoto, Japan, 4th June 2019
4. **XL Chen**, U Chamoli, AD Diwan. Studies in Discectomy Complications. St George and Sutherland Clinical School Research in Progress Meetings. Sydney, Australia, 21st August 2019
5. **XL Chen**, U Chamoli, AD Diwan. Variations in Primary Discectomy and Revision Surgery for Lumbar Disc Herniations: An Online Survey of Neuro- and Spine Surgeons in Australia and New Zealand. Proceeding of the 2020 Spine Society of Australia Virtual Meeting, Australia, 27th November 2020
6. **XL Chen**, U Chamoli, AD Diwan. Complication rates of different discectomy techniques for the treatment of lumbar disc herniation: A network meta-analysis. SpineWeek 2020. Melbourne, Australia, 27th April 2020

7. **XL Chen**, U Chamoli, AD Diwan. Complication rates of different discectomy techniques for symptomatic lumbar disc herniation: A systematic review and meta-analysis. SpineWeek 2020. Melbourne, Australia, 27th April 2020

Conference Posters

1. **XL Chen**, PW Hodges, G James, AD Diwan. Can molecular changes in multifidus muscle predict outcomes of microdiscectomy? A study of mRNA in muscles of patients undergoing microdiscectomy. Sydney Spinal Symposium 2019. Sydney, Australia, 19th September 2019
2. **XL Chen**, U Chamoli, S Lapkin, JV Castillo, AD Diwan. Complication rates of different discectomy techniques for the treatment of lumbar disc herniation: a network meta-analysis. Sydney Spinal Symposium 2019. Sydney, Australia, 19th September 2019
3. **XL Chen**, U Chamoli, H Fogel, AD Diwan. Clinicians' perceptions around discectomy surgery for lumbar disc herniation: a survey of orthopaedic and neurosurgeons in Australia and New Zealand. Sydney Spinal Symposium 2020. Sydney, Australia, 11st September 2020

Chapter 1. Herniated Lumbar Intervertebral Disc

Low back pain is the greatest cause of disability and loss of productivity worldwide. Over 80% of the population suffers an episode of low back pain once during their lifetime [1]. Low back pain incurs an annual cost exceeding A$5 billion in Australia and US$100 billion in the United States of America due to its high prevalence and significant contribution to disability [2-4]. Within the vast differential of low back pain, the common source is the defects or failures of the intervertebral disc leading to lumbar disc herniation nearly in 85% of cases [5]. Herniation refers to the displacement of intervertebral disc material beyond the normal margins of disc space, which often occurs in sciatic nerve due to the inflammatory changes by the mechanical compression to the nerve root. Different etiological factors that may explain the occurrence of lumbar intervertebral disc herniation include strenuous activities, cigarette smoking, genetic, and environmental factors. Thus, an effective understanding of lumbar disc herniation, its origins, and how to appropriately treat herniation is of substantial importance.

Not all herniated intervertebral discs necessarily cause pain. Conservative treatment is an alternative approach for most patients with symptomatic lumbar disc herniation which is the onset of low back pain or sciatica for six weeks in the absence of a major neurologic deficit [6]. Surgical intervention is recommended for symptomatic lumbar disc herniation patients who are non-responsive to at least six weeks of non-surgical treatment or/and had a progressive neurological impairment.[7]. Open discectomy and several minimally invasive discectomy techniques have been reported as a good short-term clinical outcome for symptomatic lumbar disc herniation [8-11]. However, dissatisfaction following discectomy is observed in almost 30% of patients and rates of

revision surgery have been reported up to 20% [12, 13], which ultimately impacts socioeconomic factors affecting the patient and the healthcare system. Therefore, an understanding of the resultant list and hierarchy of different discectomy techniques regarding complication rates, and the investigation of additional factors that impact the occurrence of complications and post-operative outcomes are required.

1.1 Anatomy of Intervertebral Disc

The intervertebral disc (IVD) lies between adjacent vertebrae in the vertebral column, which is composed of an inner nucleus pulposus (NP) and outer annulus fibrosis (AF). The NP is a gelatinous structure of collagen secretion and contains an abundance of proteoglycans, which acts as a shock absorber for axial forces and facilitates water retention [14-16]. The three-dimensional network AF is composed of primarily concentric type I collagen fibers (70% of overall dry weight), low proteoglycan (25% of total dry weight), and lower water retention and it surrounds the NP and helps stabilize the vertebral bodies [14-16]. Lumbar disc herniation (LDH) consists of the displacement of the content of NP through the outer AF in different forms, such as the protrusion of NP incomplete through AF, extrusion of the NP through the AF though still maintaining continuity with the disc or complete loss of continuity and sequestration of a free fragment [17]. Several changes in biology and mechanics in IVD are considered as the main contribution to LDH. These include reduced water imbibition in the NP [15, 18, 19], degradation of matrix and inflammation [20, 21], the transformation of fibrous, and reduced load carrying capacity [17].

1.2 Pathology of Disc Degeneration

Acute injury, chronic degeneration, and genetic predisposition are considered as the main situations causing the displacement of disc material and localized displacement of NP, cartilage, fragmented apophyseal bone, or fragmented AF beyond the margins of IVD space. When acute injury or trauma is applied across IVD, the intradiscal pressure increases, leading to AF damage and displacement of NP out of its normal location[22, 23]. However, the incidence of traumatic LDH is relatively rare with a reported prevalence of 0.4% [24].

The chronic degeneration of the intervertebral disc leads to a reduced ability of the NP to maintain water[15]. Consequently, the disc height is decreased, and the load-carrying capacity of the spine is reduced. At the degenerative disc, there is degradation of the extracellular matrix materials of the AF and NP involving an increased synthesis of type I collagen, decreased synthesis and accumulation of proteoglycans, and decreased secretion of type II collagen. [20, 21, 25, 26]. These changes result in the AP becoming thinner and more irregular, eventually cracking, and tearing [27]. Upregulation of the degradation process such as inflammatory pathways, apoptosis, and matrix metalloproteinases further increase the degeneration of the intervertebral disc [25, 28-31]. The border between AF and NF becomes more unclear, with the NP gradually becoming fibrous and the AF developing fissures. If the fissures reach the periphery of the NP, the nuclear material will pass through as a disc herniation [32]. Genetic factors are considered as the main important cause of disc herniation. Herniation disc is accompanied by dehydration and immunoreaction [33-37], biomechanical changes [22, 38-48], and an acidic environment.

1.3 Epidemiology of Lumbar Disc Herniation

LDH is the most common degenerative condition of the spine with a reported prevalence of 2 to 3% in general populations and 4.86 per 1000 person-years in young population, with the highest prevalence among people aged 40-50 years. Almost 5% of males and 2.5% of females experience sciatica at some time in their lifetime [5]. Most LDH occurs at the segment of L4-5 and L5-S1 (90%-97%). Various risk factors have been attributed to the pathogenesis and progression of LDH, such as inflammation and gene polymorphisms [14, 15, 49-51], axial overloading (e.g., spinal alignment) [52, 53], smoking [54-56], and obesity [57, 58].

1.4 Clinical Presentation

The typical signs and symptoms of LDH include radicular pain, weakness, and numbness in a myotomal or dermatomal distribution [59, 60]. Local paresis, restricted trunk flexion, increased radicular pain with leg straight up and sneezing and coughing by increased abdominal pressure indicate LDH. Supine straight leg raises, Lasegue sign, crossed Lasegue sign, sensory testing, and manual muscle testing are strongly recommended tests for the LDH patients [7]. Cauda equina syndrome (CES) is a rare but devastating consequence following a large, herniated disc, which is usually characterised by some so-called “red flag” symptoms, such as saddle and/or genital sensory disturbance, and/or bladder, bowel, and sexual dysfunction [61]. In CES surgical treatment is strongly recommended.[62].

There are many factors leading to LDH related symptoms, such as occupation-related risk factors, trauma, inflammation, age-related, genetic variants, psychosocial factors, and spinal alignment. Although there are several studies that have focused on multi-susceptible genes for herniation disc [25-37], few studies were performed to clarify the

relationship among these multiple genes [33-37]. Although functional studies indicate how the susceptible genes work in the pathogenesis of herniation disc and whether the susceptible genes affect the clinical symptoms, such studies are very difficult to perform, yet they are very important for the understanding of the pathology. In the meanwhile, a large body of evidence has shown how psychiatric conditions (e.g., depression, anxiety) and psychological factors and process (e.g., fear of pain, self-efficacy) contribute to the onset and maintenance of LDH related syndromes [4-7, 39, 40]. It is well known that these factors play an important role in the development of LBP and/or radicular pain in patients with LDH, but psychological aspects also predict pain and disability after disc surgery at short-term and long-term follow-up. Abnormal spinal alignment (e.g., sagittal spinal alignment, coronal spinal alignment, and spinopelvic alignment) could cause persistent LBP in LDH. Patients with LDH accompanied by radicular pain sometimes present a forward-bending posture while walking based on protective mechanisms [4-7].

1.5 Diagnostics Test

Plain radiographs are the first-line imaging modality used to evaluate the degree of degeneration and the role of instability in the LDH patients' symptoms. Magnetic resonance imaging (MRI) is proven to be the most appropriate imaging to confirm the presence of LDH with a diagnostic accuracy of 97% [7, 63]. When MRI is contraindicated or inconclusive to the patients, computed tomography (CT) and CT myelography are the most appropriate examinations to confirm the herniation disc [7].

1.5.1 Diagnostic guidelines

Herniation disc often occurs without symptoms, as revealed by MRI or CT in asymptomatic people. North American Spine Society's Evidence-Based Guideline Development Committee defined the symptomatic LDH as the displacement of NP beyond the normal range of the intervertebral disc resulting in LBP and/or sciatica, sensory abnormalities, and weakness [7]. Symptoms, signs, and physical examination findings should be consistent with imaging findings to diagnose asymptomatic LDH [7].

1.6 Treatment

1.6.1 Conservative treatment

Conservative treatments for symptomatic LDH are the main choice for the majority of patients, who reported a high percentage of recovery and substantial pain improvement in six weeks [6]. Therapies aimed at managing sciatic pain and restoring physical functioning. Conservative management consists of a multimodal treatment including analgesics, education, physical therapy, exercise training, manual therapies/manipulation, massage, McKenzie, and traction [64]. While some conservative management improve symptoms, there is no evidence of changing the natural history of disc herniation. Nonsteroidal anti-inflammatory drugs (NSAIDs) are proved to manage LBP and sciatic pain caused by LDH. The NSAIDs can slightly reduce some of the LBP in short term [65], but the treatment for sciatica pain is not clear [66]. Randomized controlled trials (RCTs) on NSAIDs and RCTs to assess the use of other analgesics in LDH patients with sciatica are few. Compared to placebo, RCTs show that corticosteroid therapy, the use of opioids and epidural corticosteroid injection do not have a significant benefit in relieving pain or reducing the rate of subsequent surgical intervention [67, 68]. Trials to assess the efficacy of antidepressants, muscle

relaxants, antiepileptic drugs, and physical therapy and exercise in LDH patients with sciatica are lacking. There is still a controversy on the efficacy of herbal supplementation, acupuncture, and manipulation in the treatment of LDH [69].

Conservative treatment of LDH has unique advantages, with the clinical symptoms of most patients diminished or even completely gone within a few weeks. Advances in radiological examination have revealed evidence that conservative treatment allows resorption of the herniated disc [5,6]. Previous studies found that the overall incidence of LDH reabsorption was around 66.66% [5,6]. In Japan, the resorption rate was 62.58%, which is close to the average level. In the United Kingdom, the incidence was much higher, at 82.94%. The medical standards of the countries may have an impact on the incidence of LDH reabsorption with conservative treatment. LDH amount and type were identified as predictive factors associated with disc resorption and this information should be factored into prognosis and informed decision-making in treatment selection as most patients were unaware of the fact that disc resorption may occur spontaneously [6].

1.6.2 Surgical intervention

To prevent or improve the dysfunction caused by the further aggravation of LDH, surgical interventions are used to treat LDH patients who are nonresponsive to at least six weeks of non-surgical treatment [7]. Bowel or bladder incontinence and progressive lower extremity weakness/ progressive neurological deficits are the absolute surgical indications for LDH, which are most associated with CES [70]. For the properly enrolled patients (e.g., nonresponsive to at least six weeks of non-surgical treatment), surgical intervention for symptomatic LDH shortens sciatica pain duration and fastens

patients return to work, although it has little effect on relieving back pain [71-73]. Compared with conservative treatment, surgical treatment has been consistently showing faster relief of pain [71-73]. The choice of surgical techniques for patients with LDH is attributed to a variety of factors including the surgical learning curve, surgeon's experience, level of training, the frequency of use, economic status, and the medical standards of the countries (health care system).

1.6.2.1 Discectomy and microdiscectomy

Discectomy and microdiscectomy are considered the main surgeries to treat symptomatic LDH patients. In 1934, William J. Mixter first elucidated discectomy to treat symptomatic LDH [74]. This technique had undergone only subtle alteration until the late 1960s when a less invasive microsurgical dissection was introduced. The first publications of microsurgical discectomy procedures were in 1977. Yasargil [75] in Switzerland and Caspar [76] in Germany reported their experience with operating a microscope for enhanced visualisation of the operative field for lumbar disc disease. This new operation was described as lumbar microdiscectomy as it was performed through a visual device and with less dissection than open lumbar discectomy [77]. Microdiscectomy is generally regarded as the most common technique for symptomatic LDH patients which provide excellent outcomes [9, 78-80]. However, the subperiosteal approach require the incision of midline ligamentous structures and detachment of the paraspinal muscles from the spinous process. The surgical trauma of paravertebral supporting structures could lead to post-operative back pain, spinal instability, and even the failed back surgery syndrome [81, 82], with a reported 10% of re-herniation rate and 20% of reoperation rate [13, 83].

1.6.2.2 Minimally invasive surgery

More recently, there has been a trend towards minimally invasive procedures (Table 1.1). Minimally invasive surgeries use different techniques to reduce surgical trauma, potentially reducing recovery time. The first generation of minimally invasive surgeries includes chemonucleolysis, percutaneous nucleotomy [84], automated percutaneous nucleotomy [85], and percutaneous laser disc decompression (PLDD) [86]. More new technologies have been used such as endoscope, tubular, and cannula. The percutaneous approach accompanied by an endoscope, and cannula assembly, a working channel scope, or use of an oval cannula, became routine in the 1990s, and these methods comprise the percutaneous endoscopic lumbar discectomy (PELD) [87, 88]. Microendoscopic discectomy (MED) techniques employ a longitudinal paramedian incision through which a sheath is placed via a transforaminal approach, extraforaminal approach, or interlaminar approach and visualization is achieved through an endoscope [89]. MED has less post-operative pain and a more rapid return to work compared with conventional microdiscectomy [90-92]. However, the main limitation of MED was that a small operation field was visualized through a cylindrical tubular retractor. For better visualization, the tubular retractors systems were combined with the use of the microscope [10]. Tubular microdiscectomy surgeries use a small-diameter tubular retractor that was placed over sequential dilators that create a surgical pathway to the lumbar spine in between fascicles of the lumbar paraspinal muscles, avoiding the traditional detachment of the multifidus muscles from the spine [10, 91].

1.6.2.3 Other surgeries

Total disc replacement, fusion, and nucleus pulposus replacement are considered optional treatments [93, 94]. Although these surgical treatments can achieve significant clinical outcomes, they are not suitable for all types of LDH patients due to strict surgical indications. Total disc replacement is only used to treat LDH patients whose herniation disc could be removed from the anterior. Fusion surgery is considered for LDH patients with spinal instability and those who may have segmental instability due to extensive decompression. In theory, the nucleus pulposus replacement device is an implant designed to provide stable motion, maintain the physical height of intervertebral disc space, and relieve shear forces on the AF, facet joints, and stabilizing ligamentous structures.

1.7 Clinical Results

1.7.1 Surgical treatment versus conservative treatment

Results of meta-analysis and network meta-analysis show that discectomy is more effective than conservative treatment in improving physical functions and alleviating symptoms in LDH [95, 96]. Clinical studies also support that surgical treatment is superior to conservative treatment in improving short-term pain in LDH patients [97-99], with 46-75% success rates at six to eight weeks and 78-75% success rates at one to two years following discectomy [100]. Previous clinical data suggested ongoing disability and residual pain following discectomy surgery were the main issues for LDH patients, with 30–70% of the LDH patients reported to experience residual pain.

Table 1.1 Comparison of open discectomy, microdiscectomy, percutaneous endoscopic lumbar discectomy (PELD), microendoscopic discectomy (MED) and tubular discectomy

	Open Discectomy	**Microdiscectomy**		**PELD**	**MED**	**Tubular discectomy**
Magnification	No	Loupes	Microscope	Endoscope	Endoscope	Microscope/loupes
Illumination	External	Not parallel to line of vision (paraxial), external	Parallel to line of vision (coaxial) and strong, Optical light fibers, external	Fiber optics and "cold light" (heat shield placed around the bulb), internal	Fiber optics and "cold light" (heat shield placed around the bulb), internal	Parallel to line of vision (coaxial) and strong, Optical light fibers, internal
Access	With any retractor, VERSA-TRAC or equivalent	Retractor or equivalent	Retractor or equivalent	Sheath or tube	Tube	Tube
Visualization	Direct	2.5X, limited and fixed	4X, relatively unlimited	3D imaging from tiny video camera	4X or 2.5X	3D imaging from tiny video camera

1.7.2 Pairwise comparison of different techniques

Microdiscectomy and open discectomy are the traditional surgical interventions that produce excellent outcomes in more than 75% of LDH patients [9, 80]. Compared with open discectomy/microdiscectomy, the results of pairwise comparisons of different discectomy techniques showed that the minimally invasive surgeries were associated with shorter hospital stay and time of return to work [101-106]. In theory, minimally invasive surgeries should achieve better clinical outcomes. However, previous studies

of specific types of minimally invasive discectomy surgery for the management of LDH have not yielded conclusive results [107-124].

1.7.3 Complications following discectomy

The utility of any procedure is a complex mix of safety, efficacy, and cost. A procedure that has fewer complications will have a superior clinical utility as it directly impacts efficacy and cost. A high incidence of complications following discectomy surgery will significantly increase the patients' suffering, medical service, and social-economic burdens. Only a few publications currently consider the complications and side effects following different discectomy surgeries for LDH; these topics are mainly found in books by personal surgeon experience. Not surprisingly, the few publications have led to wide variations in the treatment rendered for LDH. Therefore, mastering the epidemiological data, previous literature data, and related risk factors of complications helps take relevant measures to prevent and reduce the incidence of complications following different discectomy surgeries. In the United States of America, more than 300 000 lumbar discectomies with a cost of U$50 billion are performed annually, making it the most common spinal procedure. Database studies reported that complications rates range from 8-30% [12], primary admission rates following a lumbar discectomy range from 5.7-50.3% [13] and reoperation rate up to 20% [83].

1.7.4 Definition of complications following discectomy

Although different discectomy techniques for LDH provide excellent outcomes, they still carry approximately 20% risk of complications [13] such as nerve root injury, new or worsening neurological deficit, medical complications, surgical errors, durotomy, hematoma, wound complications, reherniation, and reoperation [125]. One study

reported that 0.6 deaths per 1000 procedures occurred 60 days after spine surgery [126]. A systematic review indicated that nerve root injury occurred in 1 to 2%, new or worsening neurologic deficits occurred in 1 to 3%, incidental durotomy occurred in approximately 3%, and wound complications occurred in 1 to 2% [125]. Most patients with LDH have negative perceptions of the surgical treatment, with the "fear of reherniation and revision surgery". Based on previously published literatures on the definition of reherniation, the occurrence of herniated disc material at the same level in a patient who has undergone discectomy was the most commonly used definition [13, 125, 126]. As the most common problems following different discectomy surgeries, reherniation rate of disc herniation is reported at 2% to 25% according to different definition [13, 125]. Revision surgery, for various reasons, occurred in about 6% at 1 year following discectomy and in almost 13% at 4 years follow-up [127]. Previous studies have reported the incidence rate of various surgical complications in the treatment of LDH following different discectomy surgeries [107-117, 119-124, 128-147], however, these results showed mixed findings due to inconsistent classification of complications.

1.7.5 Classification of complications following discectomy

Although quality assessment has been widely used in clinical research, there is still no consensus on formulating a standard to define and classify surgical complications. The various discectomy surgeries make complication assessment difficult. Similarly, the definition of what constitutes a complication varies widely within personal specialty surgical literature and between different neurosurgeons and spine surgeons. Surgeons routinely divide complications into intraoperative and post-operative, major and minor,

medical and surgical, and five grades following modified Clavien-Dindo classification [148-155].

The general classification divided the complications into intraoperative and post-operative, according to the time when they are apparent [151]. It may be useful for the management of complications to have clear guidelines for symptoms. Therapeutic consequences have been recommended as a way of classifying complications in spine surgery [148, 149]. Modified Clavien-Dindo classification for complications is based on the management required for each complication, which can guide the surgeons to choose the suitable surgical strategy according to the severity of surgical complications.

The complication rates associated with different discectomy approaches affect the surgeon's ability to choose the most suitable surgical plan. However, there is no consensus about how to define and grade complications following spine surgery. Previous studies have shown that surgeons routinely classify complications as major and minor, intraoperative and post-operative, medical and surgical, and into five grades following modified Clavien-Dindo classification [148-155]. Although these classification schemes are commonly used, there are no objective criteria for assigning a specific complication into any category of these classifications. Standardization of the reported outcomes following discectomy for LDH will help surgeons identify, manage, and avoid perioperative and post-operative complications.

1.7.6 Previous studies on discectomy complications

1.7.6.1 Minimally invasive surgery versus open discectomy/microdiscectomy

Minimally invasive surgical approaches and instruments have been introduced for the surgical management of symptomatic LDH, in theory, utilizing technological advancements to reduce complication rates and improve recovery. However, previous studies of specific types of minimally invasive discectomy surgery for the management of LDH have not yielded conclusive results [102, 156]. Rasouli *et al* found that minimally invasive surgeries were associated with a lower risk of surgical site infections, but a higher risk of readmission due to reherniation. Chang *et al* and Lau *et al* showed that there was no significant difference in complications between minimally invasive discectomy and open discectomy/microdiscectomy surgeries [106, 156].

1.7.6.2 Microendoscopic discectomy versus open discectomy/microdiscectomy

Due to the reduction of soft tissue trauma and improvement of visualization of the operative field, MED was associated with a lower risk of post-operative complications than open discectomy/microdiscectomy [109, 115, 122].

1.7.6.3 Percutaneous endoscopic lumbar discectomy versus open discectomy/microdiscectomy

The percutaneous procedure caused less damage to surrounding tissues and obtained a good operative field through an endoscope, posited as the main cause of PELD's lower overall complication rate. However, the limitation of surgical field-of-view through endoscope might restrain the surgeon from obtaining adequate decompression following PELD. There is insufficient evidence to judge the complication rates of PELD compared with open discectomy/microdiscectomy for LDH.

1.7.6.4 Tubular discectomy open discectomy/microdiscectomy

While there were differences in complication rates following tubular discectomy and open discectomy/microdiscectomy, none reached statistical significance. In theory, the tubular discectomy retractor is associated with fewer complications than the conventional open approach. This, however, was not observed in previous studies [10, 121, 144, 147]. Previous studies reporting on the safety and efficacy of different lumbar discectomy surgeries for LDH have not yielded conclusive results due to the pairwise nature of the comparisons [10, 91, 101-106, 157-159]. There are still many problems to be solved. Complication rates related to different discectomy surgeries are typically analyzed by an institutional or individual surgeon [107-117, 119-124, 128-147]. There is currently no study of the accurate knowledge of complications rates following different discectomy techniques and a lack of information as to which disc removal technique has the least complications.

1.7.7 Risk factors of complications

Dissatisfaction (persistent pain and disability) following discectomy for LDH is about 30% and revision surgery rate is 20% in a 7-year survivorship analysis [12, 13]. In the cases of discectomy for LDH, a question remains as to why some patients experience persistent post-operative pain and others do not, after a relatively simple standard operation and rehabilitation, even when performed under the same circumstances by the same surgeon. Complications as the main reason for the dissatisfaction following discectomy affect the psychological state of patients and place a significant burden on the health care system. Therefore, it is important to find out the potential risk factors and identify these LDH patients who may be at an increased risk of surgical complications, as well as the best practices regarding its management to decrease the

cost and morbidity associated with this condition. Many studies are on the surgeon, patient, intervertebral disc, and paraspinal tissues.

1.7.7.1 Confirmed factors

Clinical risk factors such as age (unchangeable factor), gender (unchangeable factor), lower level of education, longer duration of symptoms, lower work satisfaction, higher level of pre-operative pain, higher level of psychological problems, longer duration of pre-operative leg pain, higher level of passive, inappropriate patient selection/diagnosis, iatrogenic instability, smoking status, diabetes, and body mass index (BMI) are associated with the reherniation [160-169].

1.7.7.2 Unconfirmed factors

One risk factor is the surgeon. Despite the availability of various evidence-based guidelines, there is a lack of consensus amongst orthopaedic surgeons and neurosurgeons on the surgical management of LDH due to the potential deviation among surgeons on the surgical learning curve, surgeon's experience, level of training, and the frequency of use. Therefore, identifying factors that influence surgeons' decision-making on choosing a surgical technique for LDH is required. The second factor is paraspinal tissues. Changes in the paraspinal muscles after surgery include a loss of muscle thickness, oedematous and fatty changes observed in MRI, but underlying molecular changes and mechanisms are poorly understood [170, 171]. In animal models, these structural alterations have been proposed to be promoted by molecular pathways regulating inflammation [172, 173]. However, is it unknown if the expression of these molecules is dysregulated following LDH and if their expression may differ between individuals with good and poor outcomes following

microdiscectomy for LDH (Chapter 5). Final risk factor is disc height. Disc height loss was reported as a main risk factor for reherniation following discectomy surgery [174]. In theory, removal of herniated nucleus material during discectomy procedure leads to immediate loss of disc height. One study found that degenerative discs with preserved disc height had latent instability compared to collapsed discs [175]. When the disc height was reduced by 50%, the re-stabilization stage began to increase the intradiscal pressure [176]. These biomechanical changes result in the incidence of reherniation. Partial removal of the NP within the IVD increases the exposure of the annulus to shear stresses, which leads to accelerated degeneration of the AF, further decreasing its ability to resist shear forces. However, there is a paucity of information regarding disc height changes following discectomy and its clinical significance, especially using different methods to estimate the DH (Chapter 6 and Chapter 7).

1.8 Aims and Objectives

The utility of any procedure is a complex mix of safety, efficacy, and cost. A procedure that has fewer complications will have a superior clinical utility as it directly impacts efficacy and cost. A high incidence of complications following discectomy surgery will significantly increase the patients' suffering, medical service, and social-economic burdens. Therefore, mastering the epidemiological data, previous literature data, and related risk factors of complications can better take relevant measurements to prevent and reduce the incidence of complications following different discectomy surgeries. There are still questions that need to be resolved and they appear below with a proposed strategy to answer them as part of this work (Chapter 1).

Question 1: The complication rates associated with different discectomy approaches affect the surgeon's ability to choose the most suitable surgical plan. Complication reporting follows different formats, during or following discectomy for lumbar disc herniation. Further, there is a lack of information on pairwise comparisons of complication rates between different discectomy techniques. A systematic review and meta-analysis reported the complication rates of different discectomy techniques for symptomatic LDH using two classification schemes (a general classification that includes intraoperative and post-operative complications and modified Clavien-Dindo classification) and pairwise comparisons of complication rates between different discectomy techniques (Chapter 2).

Question 2: There is substantial evidence regarding the hierarchy of different discectomy techniques regarding complication rates. Network meta-analysis is a technique for comparing multiple treatments simultaneously in a single analysis by combining direct and indirect evidence within a network of randomized controlled trials. Network meta-analysis may assist assessing the comparative effectiveness of different treatments regularly used in clinical practice, and therefore has become attractive among clinicians. A network meta-analysis of all complications reported in discectomy studies to compare the complication rates of different discectomy techniques using two classification schemes (a general classification that includes intraoperative and post-operative complications and modified Clavien-Dindo classification) was performed (Chapter 3).

Question 3: Lumbar disc herniation is one of the most common conditions treated by a spine surgeon or a neurosurgeon. If a patient fails non-operative management, lumbar discectomy is the surgical treatment of choice. Despite its frequent usage, there are

variations in the technique used and the complications encountered when performing lumbar discectomy for primary or recurrent lumbar disc herniation. Whether the surgical training and experience and surgical specialty of spine surgeons and neurosurgeons influence a surgeons' decision-making for symptomatic primary and recurrent lumbar disc herniation in Australia and New Zealand? An online survey was conducted to estimate the variation in techniques used by surgeons for primary and recurrent lumbar disc herniation and to evaluate the main perceived complications of the various discectomy techniques for primary and recurrent lumbar disc herniation (Chapter 4).

Question 4: Lumbar multifidus muscle changes lead to different expressions of inflammatory and muscle regeneration markers in lumbar disc herniation animal models and in human low back pain trials, which provide a basis for the question "What is the molecular change for lumbar disc herniation individuals with healthier lumbar multifidus muscle having a better chance for recovery following discectomy than those accompanied with alterations in multifidus muscle". A clinical study was performed to demonstrate the difference of inflammatory and muscle regeneration markers in lumbar multifidus muscle between individuals with good and poor outcome following microdiscectomy for lumbar disc herniation (Chapter 5).

Question 5 and 6: In theory, removal of herniated nucleus material during discectomy procedure leads to loss of disc height immediately. There is a paucity of information regarding disc height changes following discectomy and it´s clinical significance, especially using different methods to estimate the disc height (Chapter 6 and Chapter 7).

Understanding the resultant list and hierarchy of different discectomy techniques regarding complication rates is critical to reducing unwarranted variation in the delivery of spinal care. Identifying the potential risk factors that influence the occurrence of complications and dissatisfaction following discectomy in the symptomatic lumbar disc herniation will offer useful insights for developing guidelines for selecting the safest and most cost-effective procedure.

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Chapter 2. Do Different Discectomy Techniques for Symptomatic Lumbar Disc Herniation Incur or Have Different Rates of Complication? A Systematic Review and Meta-Analysis

In the previous chapter an overview of the pathological, epidemiological, diagnostic, treatment, and complications related to lumbar disc herniation were discussed. Various discectomy procedures provide excellent short-term clinical outcomes, however, up to a 20% complication rate is observed. It is still unknown whether one discectomy technique is better (or inferior) than another one. There is a lack of information on pairwise comparisons of complication rates between different discectomy surgeries for symptomatic lumbar disc herniation.

2.1 Introduction

Symptomatic lumbar disc herniation (LDH) usually manifests as low back pain (LBP) and/or sciatica with a reported prevalence of 1-3% [1]. Treatment for LDH represents a significant burden on healthcare services and the economy worldwide [2, 3]. Surgical intervention is recommended for LDH patients who are non-responsive to at least six weeks of non-surgical treatment [4]. Open discectomy and microdiscectomy are surgical interventions to relieve nerve root compression and improve its function. The two are quite similar procedures with the only variation is the use of visual enhancement such as a microscope or loupes in microdiscectomy. Collectively, open discectomy/microdiscectomy are the most common surgical interventions for symptomatic LDH that produce excellent short-term clinical outcomes in the majority

of patients [5, 6]. However, the rate of re-herniation following open discectomy/microdiscectomy is as high as 10% [7], the incidence of LBP following surgery is almost 30% [8], and rates of revision surgery have been reported up to 20% [9].

Minimally invasive surgeries have been developed in order to reduce tissue trauma and decrease complication rates in symptomatic LDH patients [10, 11]. Percutaneous lumbar laser disc decompression (PLDD), as the first generation of minimally invasive surgery, achieved good clinical results [12-14]. Since then, the development of newer technologies has resulted in adapted approaches including endoscopic, tubular, cannula, and so on. The percutaneous approach, which became routine in the 1990s, includes an endoscope and cannula assembly, or use of an oval cannula. These methods comprise percutaneous endoscopic lumbar discectomy (PELD) [15, 16]. Microendoscopic discectomy (MED) techniques employ a longitudinal paramedian incision through which a sheath is placed via a transforaminal approach, extraforaminal approach, or interlaminar approach and visualization is achieved through an endoscope [17]. MED resulted in less post-operative pain and a quicker return to work compared with microdiscectomy [18-20]. However, a significant limitation of this technique is the size of the visualized operating field. In order to obtain better visualization, the tubular retractors systems were combined with the use of the microscope in tubular microdiscectomy surgery [21].

These minimally invasive surgical interventions provide similar clinical outcomes to open discectomy; however, approximately one in five cases still encounter complications [22] such as hematoma formation, durotomy, infection, and nerve root injury [23, 24]. Previous pairwise studies have not conclusively yielded that minimally

invasive discectomy techniques result in lower complication rates when compared with open discectomy/microdiscectomy for symptomatic LDH patients [10, 13, 25-27].

The complication rates associated with different discectomy techniques may influence a surgeon's decision to choose the most suitable surgical plan. However, there is a lack of consensus on how to define and grade complications following spine surgeries. Previous studies have shown that surgeons routinely classify complications as major and minor, intraoperative and post-operative, and into five grades following the modified Clavien-Dindo classification scheme [24, 28-30]. Although these classification schemes are commonly used for tabulating and reporting data on adverse events, surgeons often find it difficult to assign a specific complication to overlapping categories within these schemes. Standardization of the reported outcomes following discectomy for LDH will help surgeons identify, manage, and avoid intraoperative and post-operative complications.

Many complications and different reoperation rates have been reported. However, there is a lack of information on pairwise comparisons of complication rates between different discectomy techniques. We therefore performed a systematic review and meta-analysis of all complications reported in discectomy studies to compare open discectomy/microdiscectomy with MED, PELD, PLDD, and tubular discectomy using two commonly implemented complication classification schemes (general classification that includes intraoperative and post-operative complications, and modified Clavien-Dindo classification (MCDC)).

2.2 Methods

2.2.1 Search strategy

Online databases EMBASE, MEDLINE, and Cochrane Central Register of Controlled Trials were searched in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines to identify all relevant studies published between January 1977 (microdiscectomy first reported) and June 2019 [31]. The search included the following terms: “lumbar spine”, “intervertebral disc”, “herniation”, “discectomy”, “microdiscectomy”, “minimally invasive surgery”, “endoscopic”, “laser”, and “percutaneous discectomy”, with appropriate combinations of operators “AND”, “OR”, and “NOT”. The reference lists of relevant studies were evaluated for the purposes of the present study. The language of the included studies was restricted to English. The review protocols are registered on PROSPERO (International Prospective Register of Systematic Reviews number, CRD42020150582).

2.2.2 Inclusion criteria

1) Randomized controlled trials (RCTs) and cohort studies.

2) Studies which reported the comparisons between any of the minimally invasive surgeries (MED, PELD, PLDD, and tubular discectomy as comparator group) and open discectomy/microdiscectomy (as control group) for symptomatic LDH patients.

3) Studies which reported at least one of the following outcomes:

i. Primary outcomes including the overall complication rate and complications in two different classification schemes (General classification and MCDC).

   Overall complications were defined as complications related to various discectomy surgeries.

General classification divides the complications into intraoperative and post-operative complications. Intraoperative general complications included mortality, thrombosis, and hepatitis; intra-operative specific complications included durotomy, bleeding, nerve root injury, and surgical error; post-operative general complications included urinary tract infection, miction disturbances (catheter required), pulmonary complications, and deep venous thrombosis; post-operative specific complications included infection superficial or deep, hematoma, re-herniation, neurologic problems (post-operative weakness, altered sensitivity), skin problems, and psychological and coping problems.

MCDC scheme includes five types of complications:

Type I: normal recovery without intervention or pharmacologic treatment.

Type II: pharmacologic treatment needed.

Type III: invasive intervention under general anesthesia needed.

Type IV: intensive care unit admission needed.

Type V: death.

ii. The reoperation rate was included as a secondary outcome.

2.2.3 Exclusion criteria

1) Studies which compared discectomy procedures with other spinal surgeries, such as chemical nucleolysis, intradiscal electrothermal annuloplasty, and surgeries involving the use of an implant.

2) Case reports, reviews, and conference reports.

3) *In vitro* biomechanical studies and computational modelling studies.

2.2.4 Selection of studies

Two reviewers (Xiaolong Chen and Jose Vargas Castillo from Spine Service, Department of Orthopaedic Surgery, St. George Hospital Campus, New South Wales, Australia) independently reviewed all titles and abstracts that were identified in the initial online search of databases. Full-text articles and reference lists were reviewed for the relevant abstracts. When consensus could not be reached between the reviewers, a third reviewer (Ashish D. Diwan) was consulted to resolve the disagreement.

2.2.5 Data extraction

Two reviewers (Xiaolong Chen and Jose Vargas Castillo) extracted data independently. The reviewers collected the following data: methods (study design, sample size, inclusion and exclusion criteria, study period, mean duration of follow-up), participants (number of participants, age, gender), interventions (surgical procedure), and outcomes (for each primary outcome: number of subjects and occurrence rate in general complication classification and MCDC, and revision surgery rate).

2.2.6 Quality assessment

The 13 criteria recommended in the Cochrane Back and Neck Group guidelines [32] were used to assess the risk of bias of RCTs that were included in this meta-analysis. “Low risk,” “high risk,” or “unclear risk,” were used to score the risk of bias for individual criteria. Thereafter, for the overall risk of bias evaluation, a “low overall risk” of bias was attributed to the study when seven or more of the 13 criteria were

considered low risk [32]. Studies with six or less low-risk criteria were considered as having a “high overall risk” of bias.

The Newcastle-Ottawa Scale (NOS) was used to assess the methodological quality of the included cohort studies [33]. The “star system” of NOS ranges from 0 to 9, which is judged on three broad perspectives: selection of the study, comparability, and the ascertainment of the outcome of interest. In this meta-analysis, a study awarded seven or more stars was regarded as high-quality.

A sensitivity analysis was conducted to assess the impact of including studies with a high overall risk of bias. Controversial scores were resolved by the third reviewer (Ashish D. Diwan).

2.2.7 Statistical analysis

We performed two separate meta-analyses (one for the RCTs and the other for the cohort studies) to examine the consistency of various studies with different potential biases.

Pooled mean complication rates were calculated by the summation of total complication events divided by the overall number of patients included in the studies reporting that specific complication. Interstudy median and interquartile range (IQR), which ranged from the first to the third quartile (Q1–Q3), were used to assess the variations in specific cross-study complication rates. The pooled estimates of risk ratio (RR) and 95% confidence intervals (CI) for direct comparisons were reported. Chi-squared (I^2) statistic was used to measure heterogeneity among the trials. $I^2 < 50\%$ implied homogeneity and the analysis included a fixed-effects model by the Mantel-Haenszel method. $I^2 > 50\%$

indicated heterogeneity and, consequently, a random-effects model was used according to the DerSimonian-Laird method. Meta-analyses results were also assessed using forest plots. Risk of publication bias was evaluated using the Begg-Mazumdar test. The statistical significance was set at 5% (α =0.05).

This meta-analysis was performed according to the Quality of Reporting of Meta-analyses group and the Meta-analysis of Observational Studies in Epidemiology group recommendations for improving the quality of reporting of meta-analyses of clinical RCTs and observational studies, respectively [34, 35]. RevMan (Review Manager 5.3 version. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.) was used to evaluate the risk of bias in RCTs and STATA software (release 15, StataCorp LLC, TX) was used for the statistical analyses.

2.2.8 Evaluating the quality of evidence

The quality of the evidence informing this meta-analysis was assessed using Grading of Recommendations Assessment, Development and Evaluation (GRADE) scale, which rated evidence quality as high, moderate, low, or very low using factors such as the risk of bias, inconsistency, indirectness, imprecision, and publication bias [36] (**Table 2.1**). The summary of findings (SoFs) table presents the endpoint of the GRADE evidence summary (**Table 2.2**).

Table 2.1 Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for rating the quality of estimates of treatment effect [36]

GRADE Assessment
Ratings **High quality** (⊕⊕⊕⊕)—We are very confident that the true effect lies close to that of the estimate of the effect **Moderate quality** (⊕⊕⊕O)— We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low quality** (⊕⊕OO)— Our confidence in the effect estimates is limited: The true effect may be substantially different from the estimate of the effect **Very low quality** (⊕OOO)— We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
Down rating The quality rating may be rated down by −1 (serious concern) or −2 (very serious concern) for the following reasons • Risk of bias (such as failure to conceal random allocation or blind participants in randomised controlled trials or failure to adequately control for confounding in observational studies) • Inconsistency (such as heterogeneity of estimates of effects across trials) • Indirectness (such as surrogate outcomes, study populations or interventions that differ from those of interest, or intransitivity) • Imprecision (for example, 95% confidence intervals are wide and include or are close to null effect) • Publication bias
Up rating Rating up is typically applied only to observational studies, the most common reason is for a large or very large effect seen over a short period of time and altering a clear downward trajectory

Note: In the GRADE approach, RCTs start as high-quality evidence and cohort studies as low-quality evidence.

Table 2.2 Summary of findings (SoFs) table template in meta-analysis [36]. SoFs table included PICO information, data presentation, ranking treatments, and interpretation of findings.

Patient or population: **Interventions:** **Comparator (reference):** **Outcome:** **Setting(s):**						
Total study: Total participants:	**Relative effect (95% CI)**	**Estimated risks * (95% CI)**			**Quality of the evidence (GRADE)**	**Interpretation of Findings**
		Control risk	**Intervention risk**	**Difference**		
SoFs table definitions * Estimated risks compare two risks by calculating the difference between the risk of the comparator group (PELD, PLDD, MED, and tubular discectomy) with the risk of the control group (open discectomy/microdiscectomy).						
GRADE working group grades of evidence (or certainty in the evidence) High quality: We are very confident that the true effect lies close to that of the estimate of the effect Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different Low quality: Our confidence in the effect estimates is limited: The true effect may be substantially different from the estimate of the effect Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect						

PICO = patient, interventions, comparator, and outcome; CI = confidence interval; GRADE = Grading of Recommendations Assessment, Development, and Evaluation

2.3 Results

2.3.1 Study selection

The literature search is illustrated in the PRISMA flow diagram (**Figure 2.1**). Thirty-seven studies met the selection criteria for the purposes of the present review, which included 17 RCTs [13, 14, 25-27, 37-48] and 20 cohort studies [49-68].

2.3.2 Quality assessment

The detailed risk of bias in RCTs is summarized in **Figure 2.2**. Two of the 17 studies had a high overall risk of bias [43, 47]. Five studies were classified as having a high risk of selection bias [37, 40, 41, 45, 46]. Ten studies were deemed to have a high-risk of performance bias [13, 14, 25, 26, 38, 40, 41, 45, 46, 48], and seven studies were assessed as unclear [27, 37, 39, 42-44, 47]. We assessed all the studies as having low attrition bias except three studies that did not clearly report [37, 39, 47]. Five studies were assessed as having a high risk of detection bias [38, 45-48]. None were assessed as having a reporting bias or other biases.

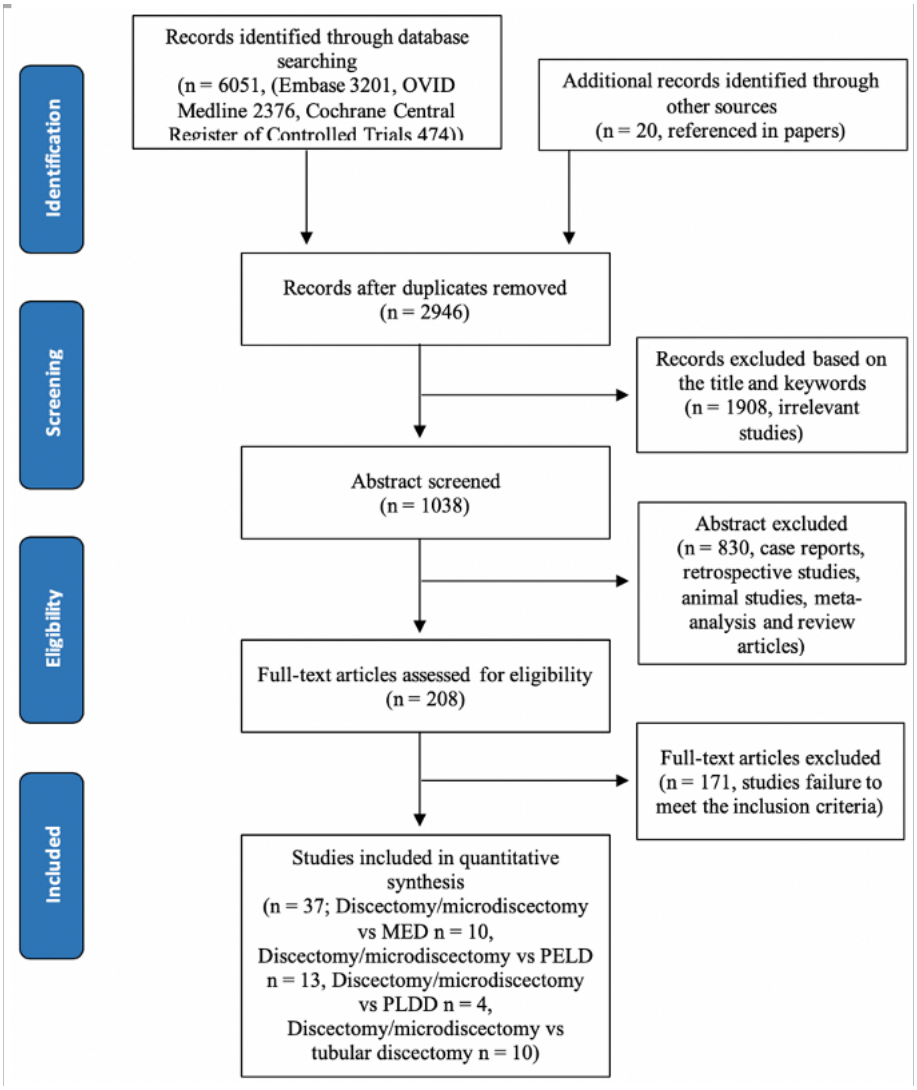

Figure 2.1 Flow chart showing the procedure and results of the literature search in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [31]. MED = microendoscopic discectomy, PELD = percutaneous endoscopic lumbar discectomy, PLDD = percutaneous laser disc decompression

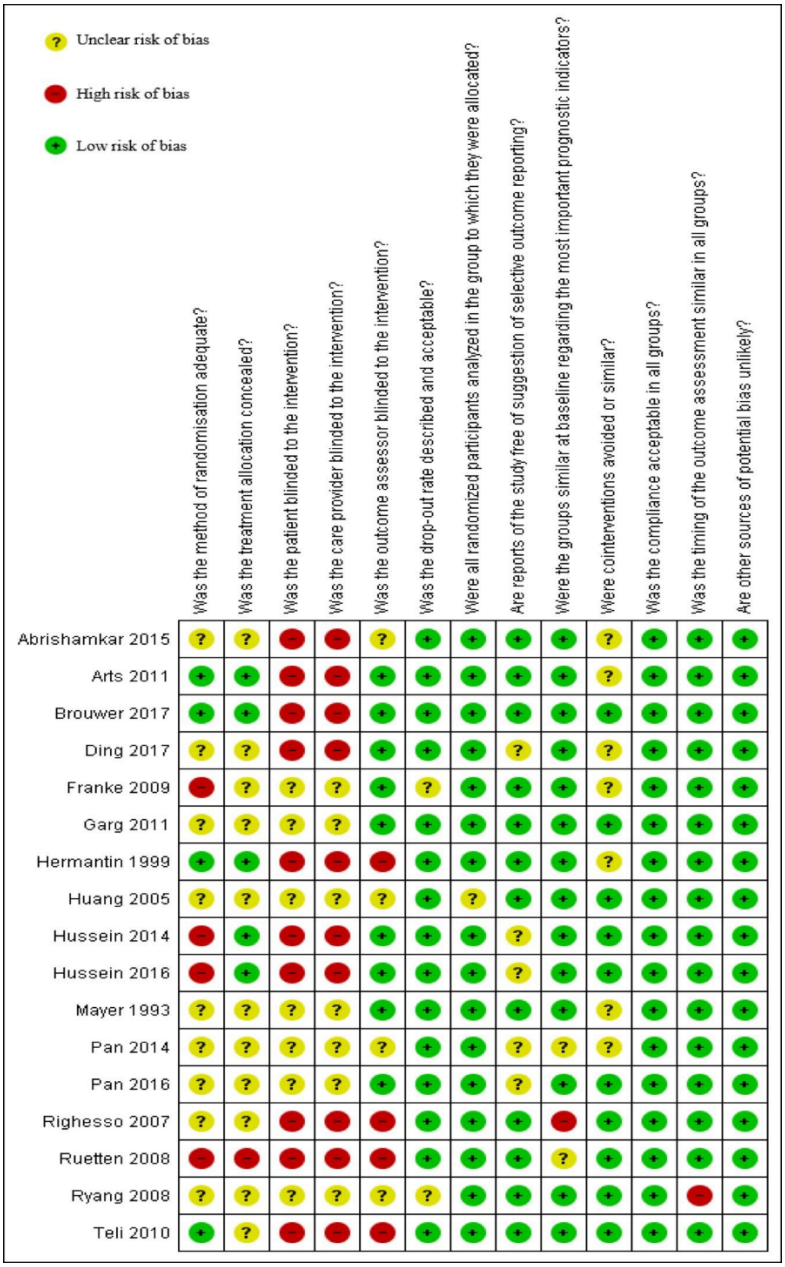

Figure 2.2 Risk of bias summary: review authors' judgements about each risk of bias item for each randomized controlled trial included in this review.

The methodological quality of cohort studies was assessed using NOS. All cohort studies were awarded more than seven stars, which demonstrated high-quality (**Table 2.3**).

Demographic data, surgical technique, and surgery-related complications from the 37 included studies are provided in **Table 2.4**. The number of pairwise studies reporting complication rates for different discectomy techniques varied: MED versus open discectomy/microdiscectomy (n=10), PELD versus OD/MD (n=13), PLDD versus open discectomy/microdiscectomy (n=4), and tubular discectomy versus open discectomy/microdiscectomy (n=10) (**Table 2.5**).

Table 2.3 Assessment of the methodological quality of cohort studies according to the Newcastle-Ottawa Scale (NOS) [33]

Author	Year	Country	Surgical Procedures	Selection (/4)	Comparability (/2)	Outcome (/3)	Total Score (/9)
Liu	2010	China	MED vs OD/MD	4	2	3	9
Wu	2006	China	MED vs OD/MD	4	2	3	9
Schizas	2005	Switzerland	MED vs OD/MD	4	1	2	7
Nakagawa	2003	Japan	MED vs OD/MD	4	1	3	8
Liu	2018	China	PELD vs OD/MD	4	2	3	9
Ahn	2016	Korea	PELD vs OD/MD	4	2	2	8
Choi	2016	Korea	PELD vs OD/MD	4	2	2	8
Hsu	2013	China	PELD vs OD/MD	4	1	3	8
Yoon	2012	Korea	PELD vs OD/MD	4	2	3	9
Kim	2007	Korea	PELD vs OD/MD	4	2	3	9
Kleinpeter	1995	Australia	PELD vs OD/MD	4	0	3	7
Kim	2018	Korea	PLDD vs OD/MD	4	1	3	8
Tassi	2006	Italy	PLDD vs OD/MD	4	2	3	9
Bhatia	2016	India	Tubular vs OD/MD	4	2	3	9
Cahill	2013	USA	Tubular vs OD/MD	4	2	3	9
Lau	2012	USA	Tubular vs OD/MD	4	2	3	9
Lee	2011	USA	Tubular vs OD/MD	4	2	3	9
Bennis	2009	France	Tubular vs OD/MD	4	2	3	9
German	2008	USA	Tubular vs OD/MD	4	2	3	9
Choi	2006	Korea	Tubular vs OD/MD	4	2	3	9

MED = microendoscopic discectomy, PELD = percutaneous endoscopic lumbar discectomy, OD = open discectomy, MD = microdiscectomy, PLDD = percutaneous laser disc decompression, vs = versus, USA = United States of America; A study awarded seven or more stars was regarded as a high-quality study.

Table 2.4 Demographic data, surgical technique, and surgery-related complications for the selected studies.

Study ID	Study design	Study location	Surgical Procedures	Sample Size	Gender (M/F)	Age (y)	Follow-up (m)	No. of Complications							
								Total No.	Intra-op		Post-op		Modified Clavien-Dindo Classification			No. of Re-op
									General	Specific	General	Specific	Type I	Type II	Type III	
MED VS OD/MD																
Hussein 2016	RCT	Egypt	MED	37	20/17	30.5	25.5	6		1	2	3	3	1	2	3
			MD	36	21/15	31.9	26.2	11		2	2	7	4	3	4	7
Hussein 2014	RCT	Egypt	MED	95	58/42	30.2	104.2	20		6	3	11	10	3	7	7
			OD	90	54/46	31.5	101.3	23		5	1	17	8	5	10	10
Garg 2011	RCT	India	MED	55	36/19	37	12	12		5	4	3	11		1	1
			OD	57	44/13	38	12	15		5	9	1	11	3	1	0
Teli 2010	RCT	Italy	MED	70	45/25	39	26	19		8		11	11	1	8	8
			OD/MD	142	94/48	79	26	17		4		12	3	7	7	7
Righesso 2007	RCT	Brazil	MED	21	10/11	42	24	3		1		2	2	1		1
			OD	19	13/6	46	24	1				1		1		1
Huang 2005	RCT	China	MED	10	6/4	39.2	18.9	1		1				1		0
			OD	12	9/3	39.8	18.9	1				1		1		0
Liu 2010	Cohort	China	MED	82	47/35	42.0	77	2				2	2			2
			OD	104	73/31	42.9	80	0								8
Wu 2006	Cohort	China	MED	873	535/338	41.5	28	55	2	14	7	32	17	18	20	20
			OD	358	230/128	43.8	31	19		8	3	8	11	8		0
Schizas 2005	Cohort	Switzerland	MED	14	9/5	43	12	2		1	1			2		0
			MD	14	6/8	41.5	12	0								0
Nakagawa 2003	Cohort	Japan	MED	30	8/22	42.9	34.1	3		1		3	2		1	1
			MD	30	15/15	36.6	69.5	0								0
PELD VS OD/MD																
Ding 2017	RCT	China	PELD	50	30/20	41.3	12	1				1	1			0
			OD	50	27/23	43.9	12	3				3		3		0
Pan 2016	RCT	China	PELD	48	26/22	39.5	16.7	3				3	3			0
			OD	58	31/27	42.8	17.3	12		2	4	6	12			0
Pan 2014	RCT	China	PELD	10	5/5		6	1				1		1		0
			OD	10	5/5		6	0								0
Ruetten 2008	RCT	Germany	PELD	100	42/58	43	24	9				9	3		6	6
			MD	100	42/58	43	24	17			3	14	12		5	5
Hermantin 1999	RCT	USA	PELD	30	22/8	39	32									1
			OD	30	17/13	40	31	1		1					1	1
Mayer 1993	RCT	Germany	PELD	20	12/8	39.8	24	1				1			1	3
			MD	20	14/6	42.7	24	1				1			1	1
Liu 2018	Cohort	China	PELD	60	31/29	36.2	7.4	5		0		5	2		3	3
			MD	69	36/33	34	6.3	5		2		3	2	3		0
Choi 2016	Cohort	Korea	PELD	20	14/6	33.9	27.5	1				1			1	2
			OD	23	13/10	38	27.5	1				1			1	1

Ahn 2016	Cohort	Korea	PELD	32	32/0	22.4	13.7	5	1				3	2	1		1
			MD	34	34/0	22.2	13.4	5		1			3	2	1	1	1
Hsu 2013	Cohort	China	PELD	57	38/19	44.2	20.4	4					4	2		2	6
			MD	66	45/21	50.4	20.4	1					1		1		4
Yoon 2012	Cohort	Korea	PELD	37	16/9	45.9	20	4		1			3	3	1		0
			MD	35	13/13	56.5	20	4		1			3	4			0
Kim 2007	Cohort	Korea	PELD	295	188/107	34.9	23.6	23		3			20	7		16	28
			OD	607	392/215	44.4	23.6	38		6			32	10		28	38
Kleinpeter 1995	Cohort	Austria	PELD	13	8/5	50	21.2	5					5			5	5
			OD	313	166/147	36	21.2	34				2	32	7		27	27
PLDD VS OD/MD																	
Brouwer 2017	RCT	Netherlands	PLDD	55	36/19	43.2	24	6					6			6	29
			MD	57	33/24	43.7	24	7					7			7	12
Abrishamkar 2015	RCT	Iran	PLDD	100	82/18	39.7	12	7					7			7	7
			OD	100	78/22	40.2	12	8					8			8	8
Kim 2018	Cohort	Korea	PLDD	40	22/18	40.4	9.9	3					3		3		0
			MD	40	20/20	57.4	12.4	3					2		2		0
Tassi 2006	Cohort	Italy	PLDD	500	253/247	49	24	16					16			16	16
			MD	500	261/239	47	24	46					46	3		43	43
Tubular discectomy VS OD/MD																	
Arts 2011	RCT	Netherlands	Tubular	166	84/82	41.6	24	58	2	18	3		35	42		16	23
			MD	159	88/71	41.3	24	40		15	3		22	30		10	14
Franke 2009	RCT	Germany	Tubular	52	31/21		12	4		2			2	2		2	2
			MD	48	29/19		12	8		3			5	3		5	5
Ryang 2008	RCT	Germany	Tubular	30	19/11	39.1	16	2					2			2	2
			MD	30	13/17	38.2	16	6		2			3	2		4	4
Bhatia 2016	Cohort	India	Tubular	102	64/38	41.8	13	15		9			6	9	1	5	5
			MD	46	29/17	41.7	19	5		3			2	5			0
Cahill 2013	Cohort	USA	Tubular	48	25/23	50		2		1			1	1	1		0
			OD	33	16/17	45		3		1			2	1	1	1	0
Lau 2012	Cohort	USA	Tubular	20	10/10	44.6	8.2	4		2			2	4			0
			OD	25	12/13	42.2	8.2	6		4			3	5	1		0
Lee 2011	Cohort	USA	Tubular	64	46/18	45.9		8		6			2	6		2	2
			MD	45	22/23	44.6		6		3			3	3		3	3
Bennis 2009	Cohort	France	Tubular	57	38/29	42	3	7		5			2		5	2	2
			MD	26	17/9	43	3	4		3			1		3	1	1
German 2008	Cohort	USA	Tubular	49	22/27	47.5	36	5		4			1	4		1	1
			MD	123	75/48	41.8	36	6		6				6			0
Choi 2006	Cohort	Korea	Tubular	22	11/11	44.1	12	1					1			1	1
			OD	39	32/7	37.5	12	8					8	6		2	2

RCT = randomized controlled trials, MED = microendoscopic discectomy, PELD = percutaneous endoscopic lumbar discectomy, PLDD = percutaneous laser disc decompression, OD = open discectomy, MD = microdiscectomy, M = male, F = female, Intra-op = intraoperative, post-op = post-operative, Re-op = re-operation. None of the 37 studies reported the incidence of type IV and type V complications (per the modified Clavien-Dindo classification scheme).

Table 2.5 Number of randomized controlled trials (RCTs) and cohort studies included in the meta-analysis

Pairwise comparison	Type of study	Number of studies
MED vs OD/MD	RCTs	6
	Cohort studies	4
PELD vs OD/MD	RCTs	6
	Cohort studies	7
PLDD vs OD/MD	RCTs	2
	Cohort studies	2
Tubular discectomy vs OD/MD	RCTs	3
	Cohort studies	7

MED = microendoscopic discectomy, PELD = percutaneous endoscopic lumbar discectomy, PLDD = percutaneous laser disc decompression, OD = open discectomy, MD = microdiscectomy.

2.3.3 Meta-analysis of RCTs

2.3.3.1 Complication rates

Complications were calculated from the 17 RCTs for a total of 1967 patients with a mean follow-up duration of 24.2 months [13, 14, 25-27, 37-48], which included 1018 open discectomy/microdiscectomy patients with a mean follow-up duration of 33.2 months, 288 MED patients with a mean follow-up duration of 35.1 months, 258 PELD patients with a mean follow-up duration of 19.1 months, 155 PLDD patients with a mean follow-up duration of 18 months, and 248 tubular discectomy patients with a mean follow-up duration of 17.3 months (**Table 2.4 and Table 2.6**). Studies reporting open discectomy/microdiscectomy, MED, PELD, PLDD, and tubular discectomies had

overall complication rates (pooled mean) of 16.8% and 16.1%, 21.2%, 5.8%, 8.4%, and 25.8%, respectively.

Open discectomy/microdiscectomy, MED, PELD, PLDD, and tubular discectomy were associated with intraoperative complications rates of 6.4%, 6.8%, 7.6%, 0.0%, and 8.1%, respectively; and post-operative complications occurred in 10.2%, 11.4%, 10.4%, 6.6%, and 8.4%, respectively.

The rate of occurrence of Type 1 (per MCDC) events in open discectomy/microdiscectomy, MED, PELD, PLDD, and tubular discectomy were 10.8%, 12.2%, 13.3%, 0.0% and 3.5%, respectively. Type II complications rates were 5.5% following open discectomy/microdiscectomy, 2.4% following MED, and 0.0% following PLDD, PELD, and tubular discectomy. Type III complications rates were 7.2% following open discectomy/microdiscectomy, 7.0% following MED, 4.7% following PELD, 8.4% following PLDD, and 8.1% following tubular discectomy.

Incidence of durotomy was reported in 4.6% of open discectomy/microdiscectomy, 6.8% of MED, 0.0% of PELD, and 6.5% of tubular discectomy. Open discectomy/microdiscectomy, MED, PELD, PLDD, and tubular discectomy studies reported reherniation rates of 5.5%, 4.7%, 5.8%, 8.4%, and 7.3%, respectively. Studies performing open discectomy/microdiscectomy, MED, PELD, PLDD, and tubular discectomy resulted in reoperation rates of 8.4%, 4.7%, 6.7%, 23.2%, and 11.7%, respectively (**Figure 2.3**).

2.3.3.2 MED versus open discectomy/microdiscectomy

The level of evidence was of low-quality due to lack of precision in the data and lack of blinding [40, 41, 45, 48]. No significant difference was found in the overall complication rates, intraoperative complication rates, post-operative complication rates, occurrence rate of Type I to Type III complications (per MCDC), durotomy rates, and incidence of reherniation and reoperation between the two procedures (**Table 2.6**).

2.3.3.3 PELD versus open discectomy/microdiscectomy

Based on six studies, there was moderate-quality evidence of a lower risk of overall complications (RR = 0.52, 95% CI = 0.29-0.94) and high-quality evidence of a lower risk of Type I complications per MCDC (RR = 0.37, 95% CI = 0.16-0.81) for PELD versus open discectomy/microdiscectomy (**Table 2.6, Figure 2.4, and Figure 2.5**). No significant difference was found in the intraoperative complication rates, post-operative complication rates, occurrence rates of Type I and Type III complications (per MCDC), incidence of durotomy, reherniation, and reoperation between the two procedures. We rated all the level of evidence as moderate-quality due to imprecision in the reported data and lack of blinding in estimates [26, 38, 42-44, 46].

2.3.3.4 PLDD versus open discectomy/microdiscectomy

Based on two studies, there was low-quality evidence of no statistically significant difference between PLDD and open discectomy/microdiscectomy for overall complication rates, post-operative complication rates, the occurrence rate of Type III complications (per MCDC), incidence of reherniation, and reoperation rates (**Table 2.6**) [13, 14]. We rated the quality of evidence as low due to the lack of precision in data and lack of blinding.

2.3.3.5 Tubular discectomy versus open discectomy/microdiscectomy

The level of evidence was of low-quality for lack of precision in data and lack of blinding [25, 37, 47]. No significant difference was found in intraoperative complication rates, post-operative complication rates, occurrence rates of Type I and Type III complications (per MCDC), durotomy rates, reherniation and reoperation rates between the two procedures (Table 2.6). Additionally, inconsistency in findings, lack of blinding, and lack of precision in the reported data downgraded the quality of evidence for overall complication rates to very low.

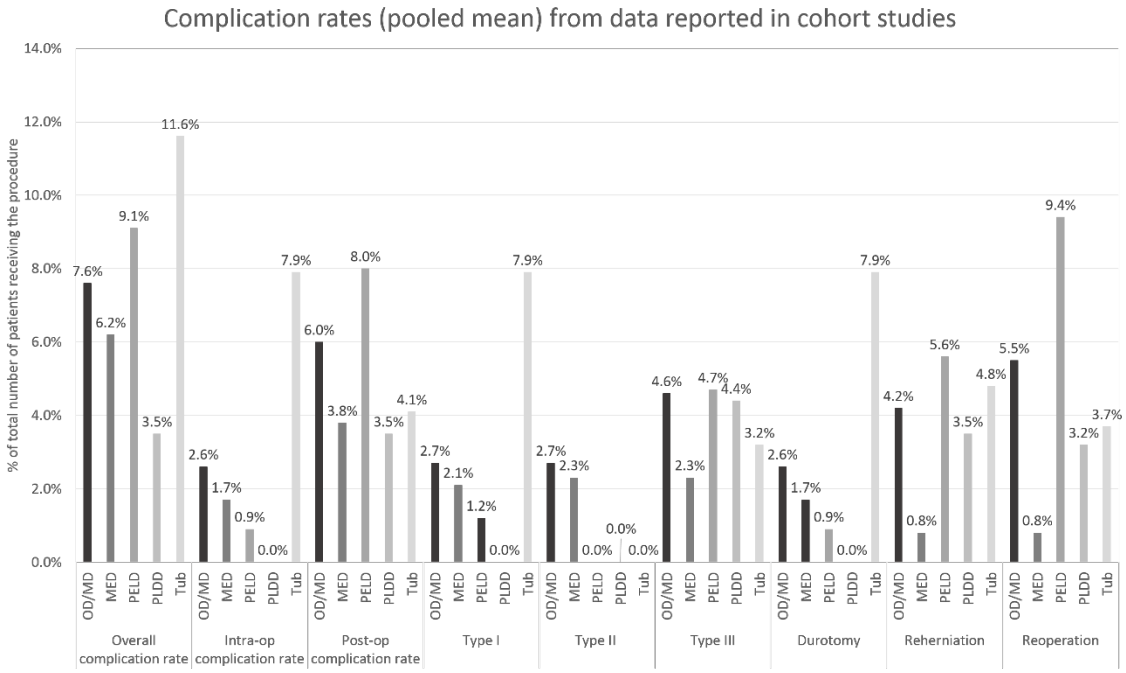

Figure 2.3 Unweighted averages of complication rates of discectomy/microdiscectomy (OD/MD), microendoscopic discectomy (MED), percutaneous endoscopic lumbar discectomy (PELD), percutaneous laser disc decompression (PLDD), and tubular discectomy for symptomatic lumbar disc herniation (LDH) using two different classification schemes (General classification and modified Clavien-Dindo classification) from randomized controlled trials (RCTs). The number of patients in each discectomy technique is mentioned in **Table 2.3**.

Table 2.6 Different pairwise comparison results from randomized controlled trials. The table presents a detailed summary of the evidence, including the number of studies feeding data for each pairwise comparison, total patients included in these studies, number of patients in each complication event, interstudy median rate of each complication, risk ratio and associated confidence intervals (CI), tests of homogeneity, publication bias (Begg's test), and the certainty of the evidence

	Pairwise comparison	No. of	Total number of patients		Number of complications (rate*)		Interstudy median rate (IQR)		Statistical Model		Homogeneity		Begg's *P*
	(Comparator vs Control)	studies	Comparator group	Control Group	Comparator group	Control Group	Comparator group	Control Group	RR	95% CI	*P*	I^2 (%)	
Overall complications	MED vs OD/MD [L 1,2]	6	288	356	61 (21.2%)	68 (19.1%)	18.6% (13.2%-23.1%)	18.8% (7.6%-27.4%)	1.07	0.78 to 1.46	0.19	32	0.85
	PELD vs OD/MD [M 2]	6	258	268	15 (5.8%)	34 (12.7%)	5.6% (1.5%-9.3%)	5.5% (2.5%-17.9%)	0.52	0.29 to 0.94[a]	0.84	0	0.26
	PLDD vs OD/MD [L 1,2]	2	155	157	13 (8.4%)	15 (9.6%)	9.0% (-)	10.1% (-)	0.89	0.44 to 1.81	0.98	0	1.00
	Tub vs OD/MD [VL 1,2,3]	3	248	237	64 (25.8%)	54 (22.8%)	7.7 % (6.7%-34.9%)	16.7% (16.7%-25.2%)	1.08	0.78 to 1.50	0.10	55[c]	0.30
Intraoperative complications	MED vs OD/MD [L 1,2]	6	288	356	22 (7.6%)	16 (4.5%)	7.7% (4.2%-10.4%)	4.2% (0%-6.4%)	1.59	0.88 to 2.88	0.53	0	0.85
	PELD vs OD/MD [H 1,4]	2	78	88	0	3 (3.4%)	0% (-)	3.4% (-)	0.29	0.03 to 2.54	0.88	0	1.00
	Tub vs OD/MD [L 1,2]	3	248	237	20 (8.1%)	20 (8.4%)	3.8% (0%-10.8%)	6.7% (6.3%-9.4%)	0.95	0.53 to 1.72	0.48	0	0.30
Post-operative complications	MED vs OD/MD [L 1,2]	6	288	356	30 (10.4%)	40 (11.2%)	8.8% (4.1%-12.6%)	8.7% (4.4%-19.0%)	0.95	0.61 to 1.47	0.33	13	1.00
	PELD vs OD/MD [L 1,2]	5	228	238	15 (6.6%)	24 (10.1%)	6.3% (3.5%-9.5%)	6.0% (2.5%-12.2%)	0.68	0.37 to 1.26	0.87	0	0.46
	PLDD vs OD/MD [L 1,2]	2	155	157	13 (8.4%)	15 (9.6%)	9.0% (-)	10.1% (-)	0.89	0.44 to 1.81	0.98	0	1.00
	Tub vs OD/MD [L 1,2]	3	248	237	39 (16.5%)	30 (12.7%)	6.7% (3.8%-21.1%)	10.4% (10.0%-13.8%)	1.19	0.76 to 1.86	0.25	28	1.00
Modified Clavien-Dindo classification (Type I)	MED vs OD/MD V[L 1,2,3]	5	278	344	37 (13.3%)	26 (7.6%)	10.5% (8.8%-17.9%)	8.9% (1.1%-15.2%)	1.56	0.99 to 2.46	0.09	51[c]	0.47
	PELD vs OD/MD [H 2,4]	3	198	208	7 (3.5%)	24 (11.5%)	3.0% (2.0%-6.3%)	12% (0%-20.7%)	0.37	0.16 to 0.81[a]	0.39	0	0.30
	Tub vs OD/MD [L 1,2]	3	248	237	44 (17.7%)	35 (14.8%)	3.8% (0%-25.3%)	6.7% (6.3%-18.9%)	1.15	0.77 to 1.72	0.39	0	0.30
Modified Clavien-Dindo classification (Type II)	MED vs OD/MD [M 1,2,4]	6	288	356	7 (2.4%)	20 (5.6%)	2.9% (1.1%-6.1%)	5.4 % (5.2%-8.3%)	0.44	0.19 to 1.02	0.90	0	1.00
	MED vs OD/MD [L 1,2]	4	257	325	18 (7.0%)	22 (6.8%)	6.4% (2.7%-10.4%)	8.0% (2.5%-11.1%)	1.03	0.58 to 1.85	0.30	19	0.73

Modified Clavien-Dindo classification (Type III)	PELD vs OD/MD [L 1,2]	3	150	150	7 (4.7%)	7 (4.7%)	5.0% (0%-6.0%)	5.0% (3.3%-5.0%)	1.00	0.37 to 2.68	0.77	0	0.30
	PLDD vs OD/MD [L 1,2]	2	155	157	13 (8.4%)	15 (9.6%)	9.0% (-)	10.1% (-)	0.89	0.44 to 1.81	0.98	0	1.00
	Tub vs OD/MD [L 1,2]	3	248	237	20 (8.1%)	19 (8.0%)	6.7% (3.8%-9.6%)	10.4% (6.3%-13.3%)	1.01	0.55 to 1.85	0.23	32	1.00
Durotomy	MED vs OD/MD [L 1,2]	4	278	344	19 (6.8%)	16 (4.7%)	6.3% (3.7%-8.8%)	5.6 % (1.4%-7.2%)	1.38	0.74 to 2.58	0.63	0	1.00
	PELD vs OD/MD [M 1,2,4]	3	98	108	0	4 (3.7%)	0%	3.4% (3.3%-5.0%)	0.30	0.05 to 1.83	0.99	0	1.00
	Tub vs OD/MD [L 1,2]	3	248	237	16 (6.5%)	12 (5.1%)	3.8% (0%-8.4%)	6.3% (4.4%-6.7%)	1.24	0.60 to 2.56	0.26	25	0.30
Reherniation	MED vs OD/MD [L 1,2]	5	278	344	13 (4.7%)	11 (3.2%)	2.7% (2.0%-8.1%)	3.5% (1.7%-5.4%)	1.58	0.75 to 3.30	0.46	0	0.81
	PELD vs OD/MD [L 1,2]	2	120	120	7 (5.8%)	5 (4.2%)	5.5% (-)	2.5% (-)	1.34	0.46 to 3.93	0.61	0	1.00
	PLDD vs OD/MD [L 1,2]	2	155	157	13 (8.4%)	15 (9.6%)	9.0% (-)	10.1% (-)	0.89	0.44 to 1.81	0.98	0	1.00
	Tub vs OD/MD [L 1,2]	3	248	237	18 (7.3%)	16 (6.8%)	3.3% (1.9%-9.6%)	8.3% (5.7%-10.0%)	1.07	0.55 to 2.06	0.14	49	1.00
Reoperation	MED vs OD/MD [L 1,2]	5	278	344	13 (4.7%)	11 (3.2%)	7.4 % (3.3%-9.8%)	5.3% (2.5%-15.3%)	0.99	0.58 to 1.71	0.29	20	0.81
	PELD vs OD/MD [L 1,2]	3	150	150	10 (6.7%)	7 (4.7%)	6.0% (3.3%-15%)	5.0% (3.3%-5.0%)	1.39	0.54 to 3.57	0.78	0	1.00
	PLDD vs OD/MD [L 1,2]	2	155	157	36 (23.2%)	20 (12.7%)	29.9% (-)	14.5% (-)	1.57	0.95 to 2.59	0.17	48	1.00
	Tub vs OD/MD [L 1,2]	3	248	237	29 (11.7%)	23 (9.7%)	6.7% (3.8%-15.1%)	10.4% (8.8%-13.3%)	1.18	0.70 to 1.99	0.15	47	1.00

RCT = randomized controlled trial, Intra-op = intraoperative, post-op = post-operative, MED = microendoscopic discectomy, PELD = percutaneous endoscopic lumbar discectomy, PLDD = percutaneous laser disc decompression, OD = open discectomy, MD = microdiscectomy, Tub = tubular discectomy, RR = risk ratio, CI = confidence interval, IQR = interquartile range.

* Pooled mean complication rates

IQR ranged from the first to the third quartile (Q1-Q3); Control group includes OD/MD; Comparator group includes PELD, PLDD, MED, and tubular discectomy.

$$\text{RR} = \frac{risk\ of\ complication\ in\ the\ comparator\ group}{risk\ of\ complication\ in\ the\ control\ group}$$

RR lower than one favors the former technique and greater than one favors the latter technique; Statistical model includes random-effects model and fixed-effects model.

[a] If the 95% CI range included one, no statistical significance could be concluded; [b] $P < 0.05$ indicated significance; [c] $I^2 > 50\%$ implied heterogeneity.

Quality of evidence: [H] high, [M] moderate, [L] low, [VL] very low.

[1]-rated down for imprecision, [2]-rated down for risk of bias (lack of allocation concealment or lack of blinding), [3]-rated down for inconsistency, [4]-rated up for large magnitude of effect (Strong evidence of association—significant relative risk of > 2 (< 0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+1); Very strong evidence of association—significant relative risk of > 5 (< 0.2) based on direct evidence with no major threats to validity (+2)).

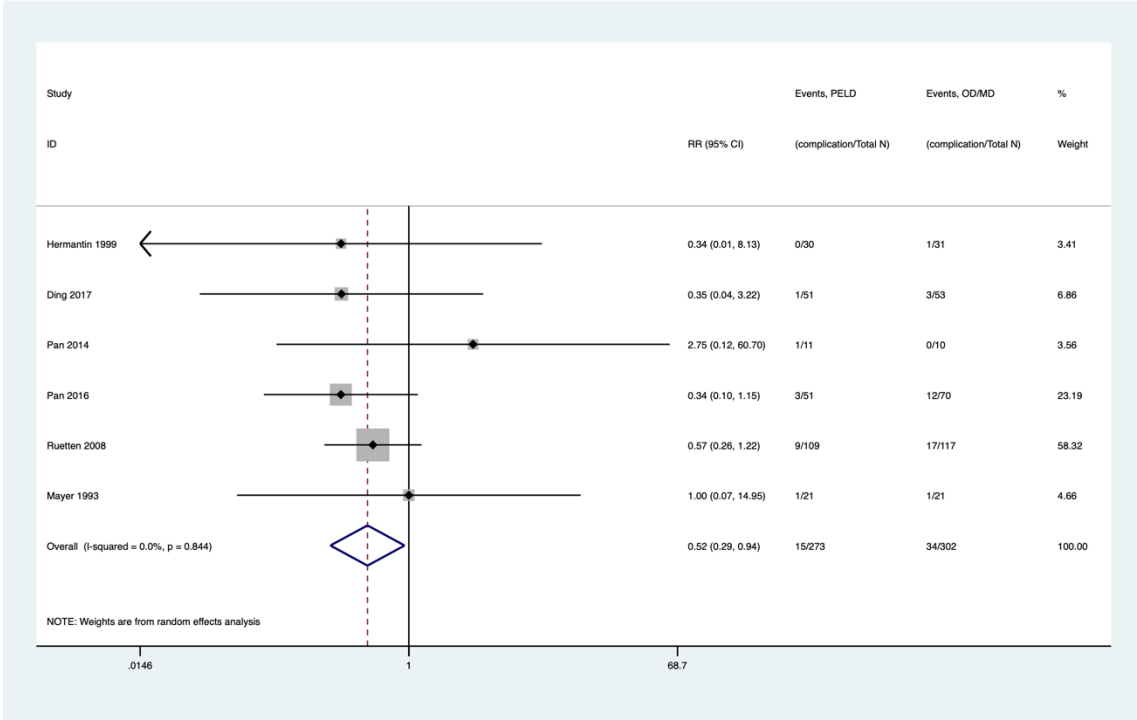

Figure 2.4 Risk ratio (RR) with 95% confidence intervals (CI) of the overall complications between percutaneous endoscopic lumbar discectomy (PELD) and open discectomy/microdiscectomy (OD/MD) from randomized controlled trials were used to measure relative efficacy. PELD was associated with lower risk of overall complication rates versus OD/MD (RR = 0.52, 95% CI = 0.29-0.94). RR lower than one favors the former technique and greater than one favors the latter technique. If the 95% CI range included one, no statistical significance could be concluded. $I^2 > 50\%$ implied heterogeneity.

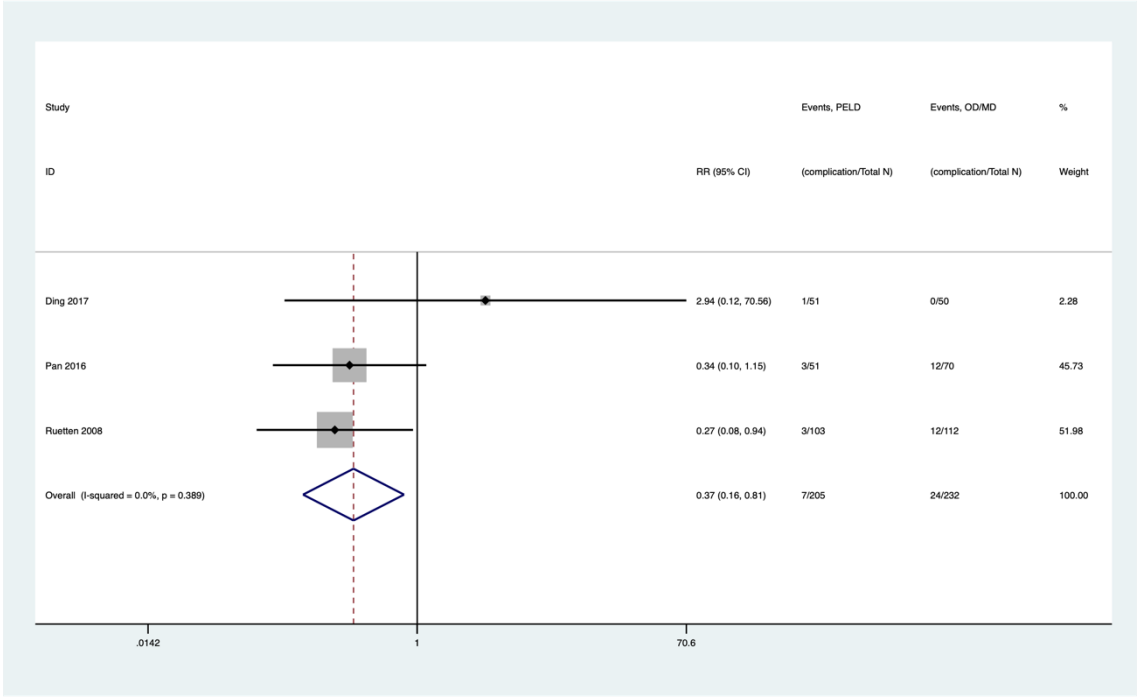

Figure 2.5 Risk ratio (RR) with 95% confidence intervals (CI) of the occurrence of Type I complications per modified Clavien-Dindo classification between percutaneous endoscopic lumbar discectomy (PELD) and open discectomy/microdiscectomy (OD/MD) from randomized controlled trials were used to measure relative efficacy. PELD was associated with lower risk for Type I complications per modified Clavien-Dindo classification versus OD/MD (RR = 0.37, 95% CI = 0.16-0.81). RR lower than one favors the former technique and greater than one favors the latter technique. If the 95% CI range included one, no statistical significance could be concluded. $I^2 > 50\%$ implied heterogeneity.

2.3.4 Meta-analysis of cohort studies

2.3.4.1 Complication rates

Complications were calculated from 4945 patients with a mean follow-up duration of 19.9 months from the 20 cohort studies [49-68], including 2530 open discectomy/microdiscectomy patients with a mean follow-up duration of 20.2 months, 999 MED patients with a mean follow-up duration of 37.8 months, 514 PELD patients with a mean follow-up duration of 19.1 months, 540 PLDD patients with a mean follow-up duration of 17 months, and 362 tubular discectomy patients with a mean follow-up duration of 10.3 months (**Table 2.4 and Table 2.6**). Studies reporting open discectomy/microdiscectomy, MED, PELD, PLDD, and tubular discectomies had overall complication rates (pooled mean) of 7.6%, 6.2%, 9.1%, 3.5%, and 11.6%, respectively.

Open discectomy/microdiscectomy, MED, PELD, PLDD, and tubular discectomy were associated with intraoperative complications rates of 2.6%, 1.7%, 0.9%, 0.0%, and 7.9%, respectively. Post-operative complications occurred in 6.0%, 3.8%, 8.0%, 0.0%, and 3.5% of LDH patients who underwent open discectomy/microdiscectomy, MED, PELD, PLDD, and tubular discectomy, respectively.

The occurrence of Type I complications (per MCDC) in open discectomy/microdiscectomy, MED, PELD, PLDD, and tubular discectomies were 2.7%, 2.1%, 1.2%, 0.0%, and 7.9%, respectively. The occurrence of Type II complications was 2.7% following open discectomy/microdiscectomy, 2.3% following MED, and 0.0% following PLDD, PELD, and tubular discectomy. Similarly, Type III complications were 4.6% following open discectomy/microdiscectomy, 2.3% following

MED, 4.7% following PELD, 4.4% following PLDD, and 3.2% following tubular discectomy.

Incidence of durotomy was reported in 2.6% of open discectomy/microdiscectomy, 1.7% of MED, 0.9% of PELD, 0.0% of PLDD, and 7.9% of tubular discectomy patients. Open discectomy/microdiscectomy, MED, PELD, PLDD, and tubular discectomy studies reported reherniation rates of 4.2%, 0.8%, 5.6%, 3.5%, and 4.8%, respectively. Studies reporting data for open discectomy/microdiscectomy, MED, PELD, PLDD, and tubular discectomies had reoperation rates of 5.5%, 0.8%, 9.4%, 3.2%, and 3.7%, respectively (**Figure 2.6**).

2.3.4.2 MED versus open discectomy/microdiscectomy

Based on four studies, there was moderate-quality evidence of a higher risk of Type III complications (per MCDC) (RR = 10.83, 95% CI = 1.29-91.18) (**Figure 2.7**) for MED versus open discectomy/microdiscectomy [51, 63, 65, 67]. The large magnitude of effect upgraded the low-quality evidence from cohort studies to moderate quality. However, inconsistency in findings, high risk of bias of cohort studies, and lack of precision in the reported data downgraded the quality of no statistically significant difference between MED and open discectomy/microdiscectomy for the different complication rates, except for the occurrence rate for Type III complications, to very low.

2.3.4.3 PELD versus open discectomy/microdiscectomy

There was low-quality evidence for a higher risk of reherniation (RR = 1.67, 95% CI = 1.05-2.64) (**Figure 2.8**) and reoperation (RR = 1.75, 95% CI = 1.20-2.55) (**Figure 2.9**)

for PELD versus open discectomy/microdiscectomy [49, 50, 57, 58, 60, 64, 68]. We rated the quality of other complication rates with no statistical significance as very low due to high risk of bias and limited precision in estimates.

2.3.4.4 PLDD versus open discectomy/microdiscectomy

Based on two studies, there was low-quality evidence of a lower risk of overall complication rates (RR = 0.42, 95% CI = 0.25-0.70) (**Figure 2.10**), post-operative complication rates (RR = 0.42, 95% CI = 0.25-0.70) (**Figure 2.11**), Type III complications (per MCDC) (RR = 0.39, 95% CI = 0.22-0.69) (**Figure 2.12**), and reoperation rates (RR = 0.39, 95% CI = 0.22-0.69) (**Figure 2.13**) for PLDD versus open discectomy/microdiscectomy [59, 66]. We rated the quality of evidence as low due to high risk of bias, inconsistency in findings, and publication bias. However, there was no large magnitude of effect to upgrade the very low-quality evidence of a lower risk of reherniation (RR = 0.56, 95% CI = 0.33-0.97) (**Figure 2.14**) for PLDD versus open discectomy/microdiscectomy.

2.3.4.5 Tubular discectomy versus open discectomy/microdiscectomy

The quality of evidence comparing tubular discectomy versus open discectomy/microdiscectomy was very low due to imprecision in the reported data and high risk of bias. No significant difference between the complication rates per the two complication classification schemes (**Table 2.7**) was found between these two procedures [52-56, 61, 62].

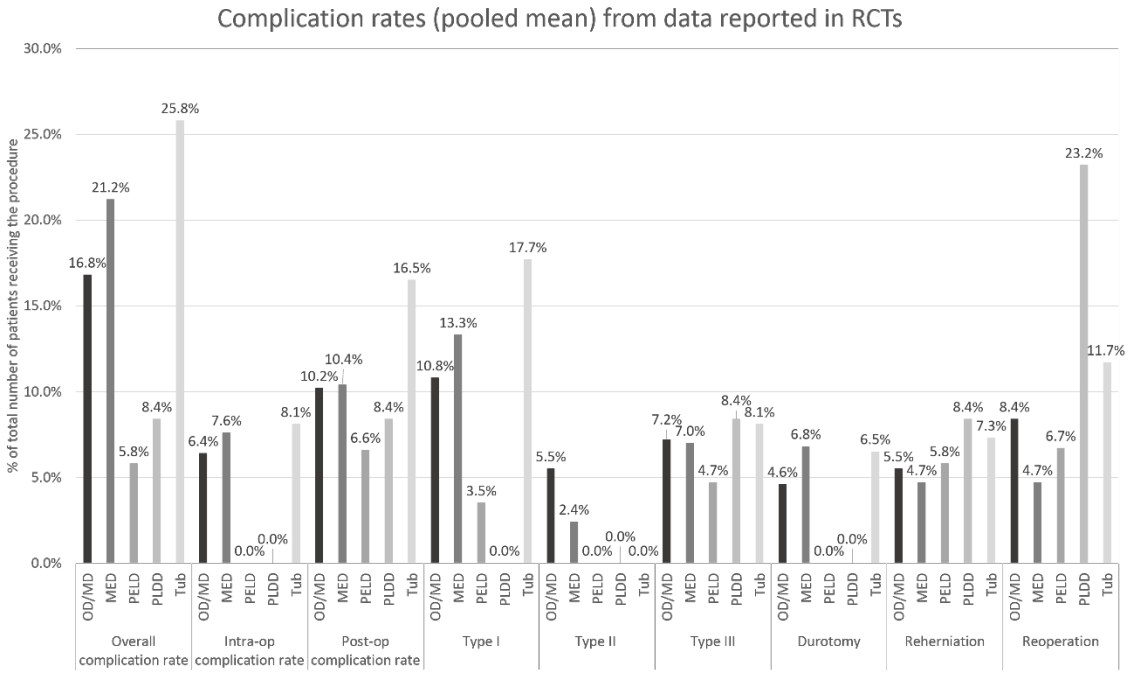

Figure 2.6 Unweighted averages of complication rates for discectomy/microdiscectomy (OD/MD), microendoscopic discectomy (MED), percutaneous endoscopic lumbar discectomy (PELD), percutaneous laser disc decompression (PLDD), and tubular discectomy for symptomatic lumbar disc herniation (LDH) using two different classification schemes (General classification and modified Clavien-Dindo classification) from cohort studies.

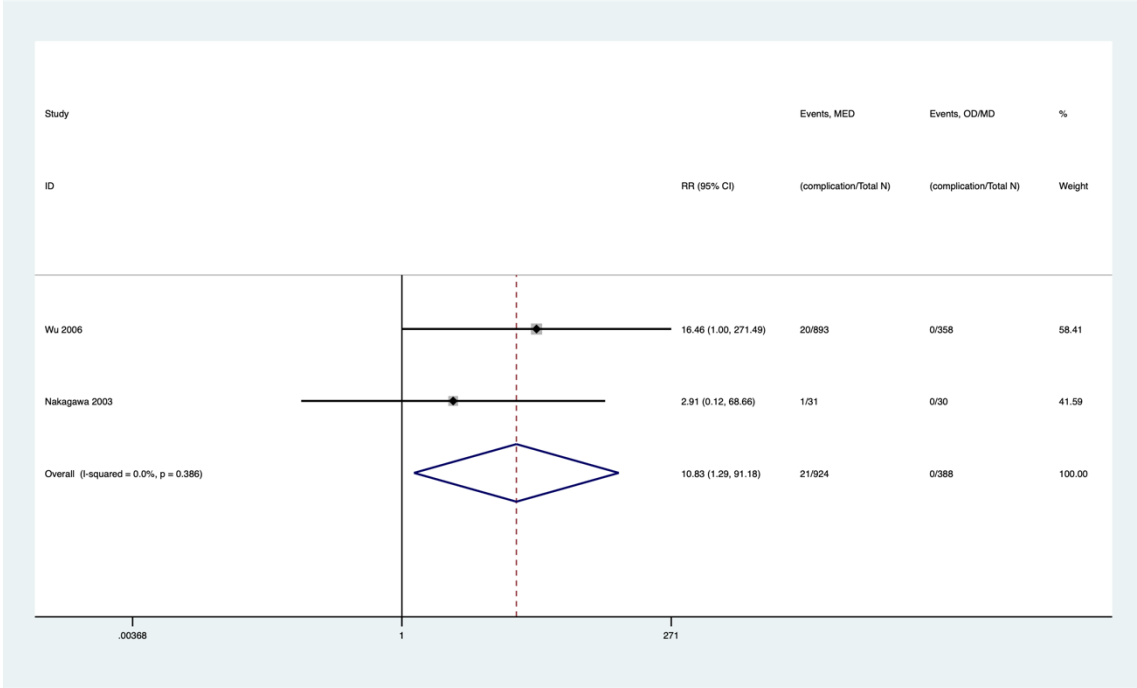

Figure 2.7 Risk ratio (RR) with 95% confidence intervals (CI) of the occurrence of Type III complications per modified Clavien-Dindo classification between microendoscopic discectomy (MED) and open discectomy/microdiscectomy (OD/MD) from cohort studies were used to measure relative efficacy. Compared with OD/MD, MED was associated with higher risk for Type III complications per modified Clavien-Dindo classification (RR = 10.83, 95% CI = 1.29-91.18). RR lower than one favors the former technique and greater than one favors the latter technique. If the 95% CI range included one, no statistical significance could be concluded. $I^2 > 50\%$ implied heterogeneity.

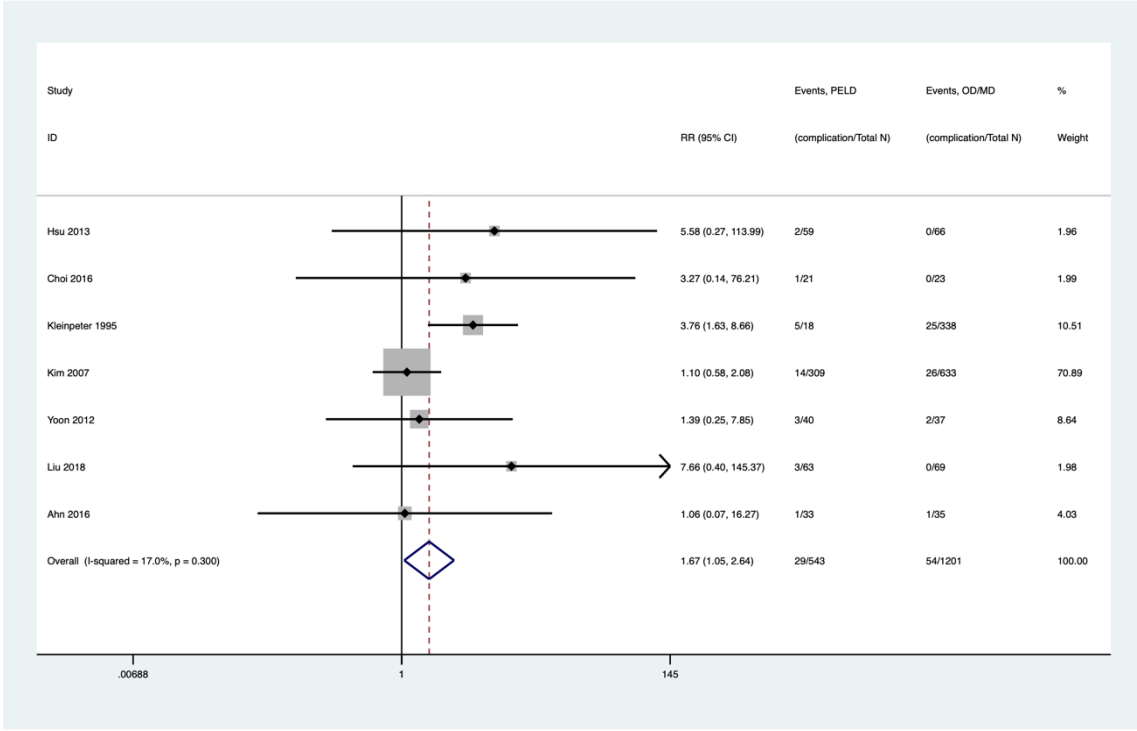

Figure 2.8 Risk ratio (RR) with 95% confidence intervals (CI) of the reherniation rates between percutaneous endoscopic lumbar discectomy (PELD) and open discectomy/microdiscectomy (OD/MD) from cohort studies were used to measure relative efficacy. There was higher risk of reherniation for PELD versus OD/MD (RR = 1.67, 95% CI = 1.05-2.64). RR lower than one favors the former technique and greater than one favors the latter technique. If the 95% CI range included one, no statistical significance could be concluded. I^2 > 50% implied heterogeneity.

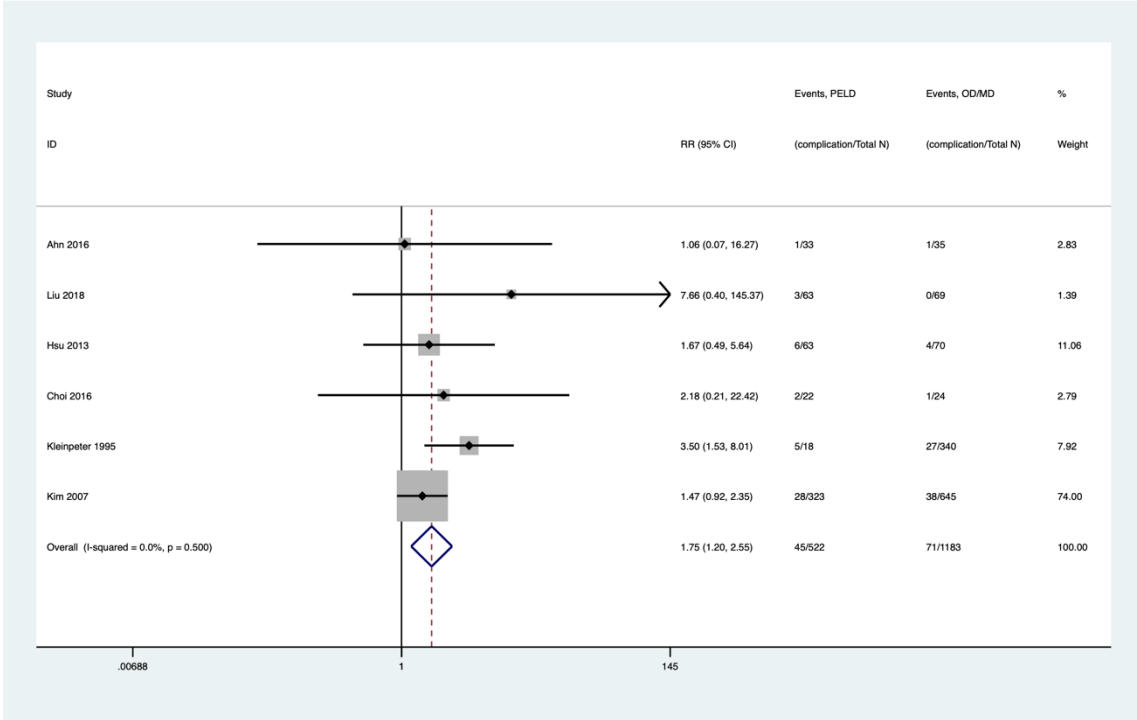

Figure 2.9 Risk ratio (RR) with 95% confidence intervals (CI) of the reoperation rates between percutaneous endoscopic lumbar discectomy (PELD) and open discectomy/microdiscectomy (OD/MD) from cohort studies were used to measure relative efficacy. There was higher risk of reoperations for PELD versus OD/MD (RR = 1.75, 95% CI = 1.20-2.55). RR lower than one favors the former technique and greater than one favors the latter technique. If the 95% CI range included one, no statistical significance could be concluded. I^2 > 50% implied heterogeneity.

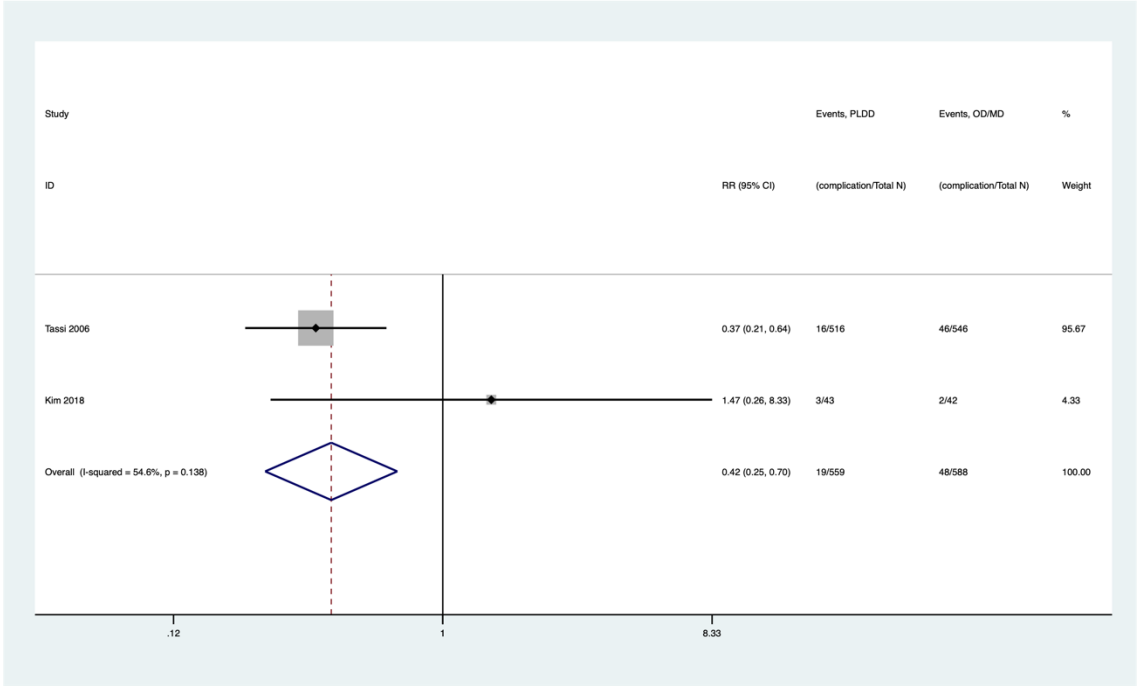

Figure 2.10 Risk ratio (RR) with 95% confidence intervals (CI) of the overall complications between percutaneous laser disc decompression (PLDD) and open discectomy/microdiscectomy (OD/MD) from cohort studies were used to measure relative efficacy. PLDD was associated with lower risk of overall complication rates versus OD/MD (RR = 0.42, 95% CI = 0.25-0.70). RR lower than one favors the former technique and greater than one favors the latter technique. If the 95% CI range included one, no statistical significance could be concluded. I^2 > 50% implied heterogeneity.

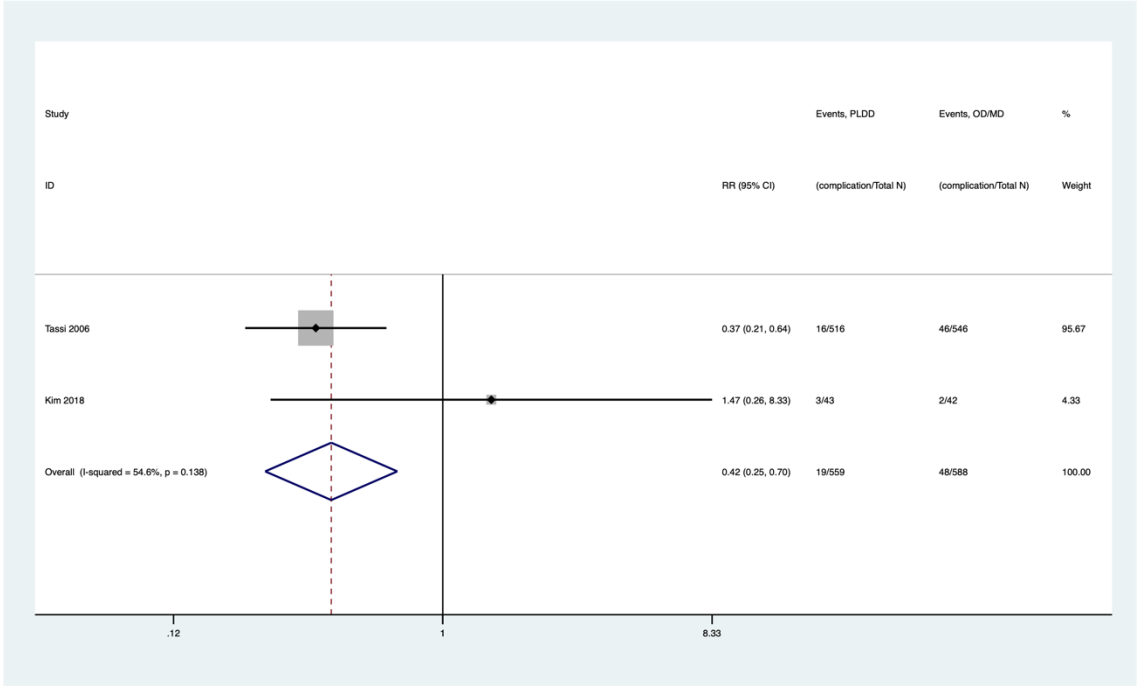

Figure 2.11 Risk ratio (RR) with 95% confidence intervals (CI) of the post-operative complications between percutaneous laser disc decompression (PLDD) and open discectomy/microdiscectomy (OD/MD) from cohort studies were used to measure relative efficacy. PLDD was associated with lower risk of post-operative complication rates versus OD/MD (RR = 0.42, 95% CI = 0.25-0.70). RR lower than one favors the former technique and greater than one favors the latter technique. If the 95% CI range included one, no statistical significance could be concluded. I^2 > 50% implied heterogeneity.

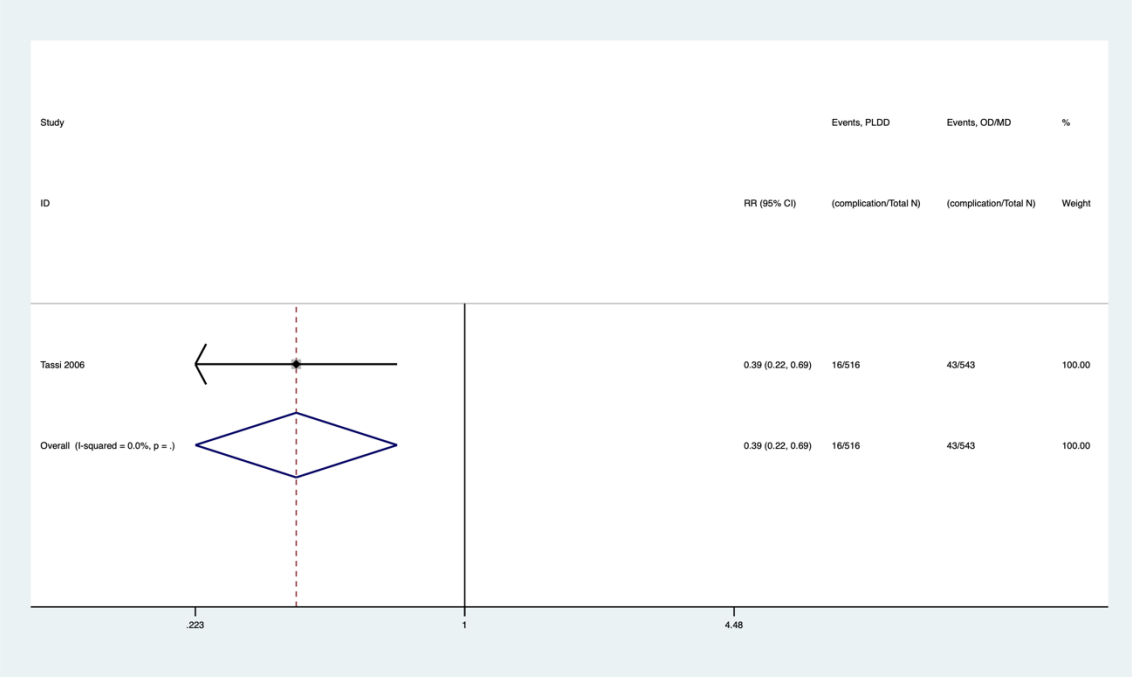

Figure 2.12 Risk ratio (RR) with 95% confidence intervals (CI) of the occurrence of Type III complications per modified Clavien-Dindo classification between percutaneous laser disc decompression (PLDD) and open discectomy/microdiscectomy (OD/MD) from cohort studies were used to measure relative efficacy. Compared with OD/MD, PLDD was associated with lower risk for Type III complications per modified Clavien-Dindo classification (RR = 0.39, 95% CI = 0.22-0.69). RR lower than one favors the former technique and greater than one favors the latter technique. If the 95% CI range included one, no statistical significance could be concluded. I^2 > 50% implied heterogeneity. Due to only one study included, the results are invalid.

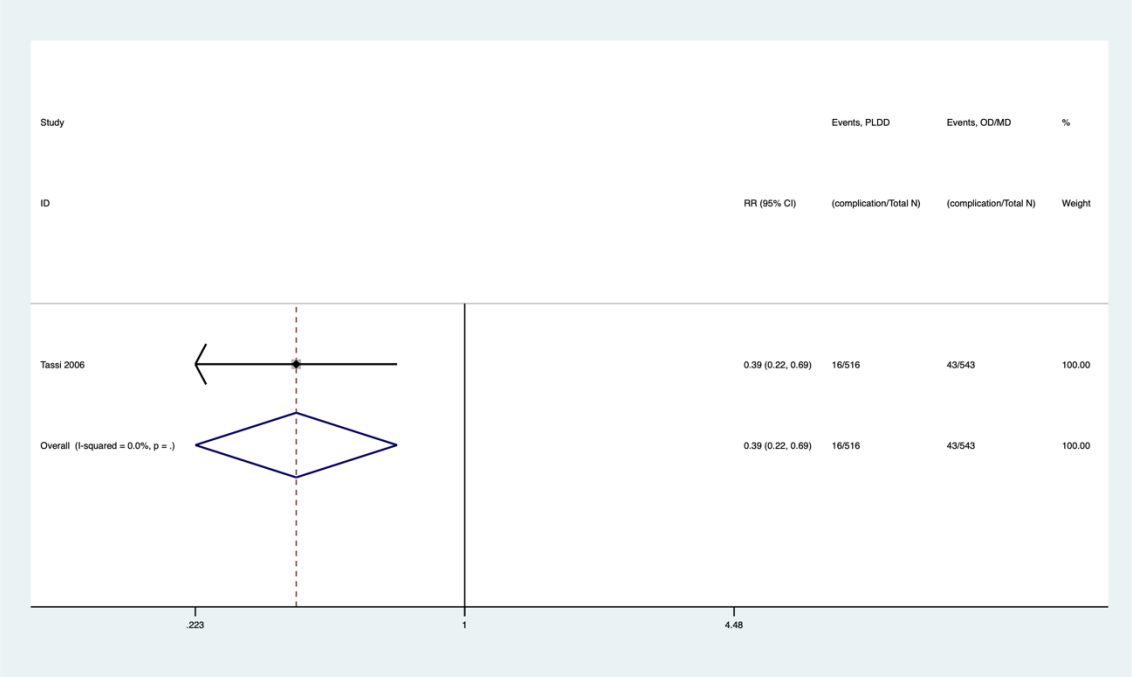

Figure 2.13 Risk ratio (RR) with 95% confidence intervals (CI) of the reoperation rates between percutaneous laser disc decompression (PLDD) and open discectomy/microdiscectomy (OD/MD) from cohort studies were used to measure relative efficacy. PLDD was associated with lower risk of reoperation rates versus OD/MD (RR = 0.39, 95% CI = 0.22-0.69). RR lower than one favors the former technique and greater than one favors the latter technique. If the 95% CI range included one, no statistical significance could be concluded. $I^2 > 50\%$ implied heterogeneity. Due to only one study included, the results are invalid.

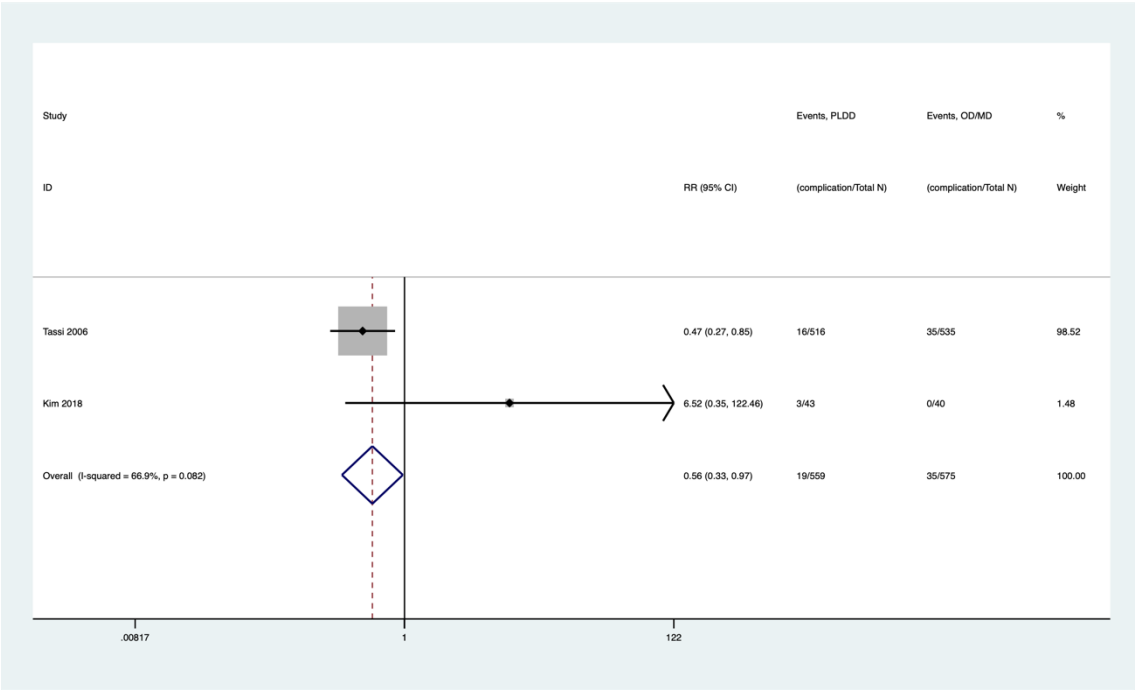

Figure 2.14 Risk ratio (RR) with 95% confidence intervals (CI) of the reherniation rates between percutaneous laser disc decompression (PLDD) and open discectomy/microdiscectomy (OD/MD) from cohort studies were used to measure relative efficacy. There was lower risk of reoperations for PLDD versus OD/MD (RR = 0.56, 95% CI = 0.33-0.97). RR lower than one favors the former technique and greater than one favors the latter technique. If the 95% CI range included one, no statistical significance could be concluded.

Table 2.7 Different pairwise comparison results of cohort studies. It presents a more detailed summary of the evidence, including the number of studies in each type of study, total patients included in these studies, number of patients in each complication event, interstudy median rate of each complication, risk ratio and associated confidence intervals (CI), tests of heterogeneity, publication bias (Begg's test), and the certainty of the evidence

	Pairwise comparison	No. of	Total number of patients		Number of complications (rate*)		Interstudy median rate (IQR)		Statistical Model		Heterogeneity		Begg's *P*
	(Comparator vs Control)	studies	Comparator group	Control Group	Comparator group	Control Group	Comparator group	Control Group	RR	95% CI	*P*	I^2 (%)	
Overall complications	MED vs OD/MD [VL1,2]	4	999	506	62 (6.2%)	19 (3.8%)	8.2% (3.4%-13.2%)	0.0% (0%-4.0%)	1.41	0.88 to 2.27	0.39	0	1.00
	PELD vs OD/MD [VL1,2]	7	514	1147	47 (9.1%)	88 (7.7%)	8.3% (7.0%-15.6%)	7.2% (4.3%-11.4%)	1.36	0.95 to 1.95	0.54	0	0.76
	PLDD vs OD/MD [L,2,3,5]	2	540	540	19 (3.5%)	48 (8.9%)	5.4% (-)	7.1% (-)	0.42	0.25 to 0.70[a]	0.14	55[c]	1.00
	Tub vs OD/MD [VL1,2]	7	362	337	42 (11.6%)	38 (11.3%)	12.3% (4.5%-14.7%)	13.3% (9.1%-20.5%)	0.94	0.61 to 1.46	0.63	0	0.04
Intraoperative complications	MED vs OD/MD [VL1,2]	3	917	402	16 (1.7%)	8 (2.0%)	3.3% (1.6%-7.1%)	0.0% (0%-2.2%)	0.90	0.41 to 1.96	0.52	0	0.60
	PELD vs OD/MD [VL1,2]	4	424	745	4 (0.9%)	10 (1.3%)	0.5% (0%-2.3%)	2.9% (1.5%-2.9%)	0.70	0.25 to 1.97	0.80	0	0.31
	Tub vs OD/MD [VL1,2]	6	340	298	27 (7.9%)	20 (6.7%)	8.8% (6.6%-9.5%)	6.6% (4.4%-12.7%)	1.12	0.63 to 2.00	0.93	0	0.13
Post-operative complications	MED vs OD/MD [VL1,2]	3	985	492	37 (3.8%)	8 (1.6%)	3.7% (2.4%-10.0%)	0.0% (0%-2.2%)	0.95	0.91 to 1.47	0.33	13	1.00
	PELD vs OD/MD [VL1,2]	7	514	1147	41 (8.0%)	75 (6.5%)	8.1% (6.8%-9.4%)	5.3% (4.3%-8.8%)	1.51	1.02 to 2.23	0.58	0	0.76
	PLDD vs OD/MD [L,2,3,5]	2	540	540	19 (3.5%)	48 (8.9%)	5.4% (-)	7.1% (-)	0.42	0.25 to 0.70[a]	0.14	55[c]	1.00
	Tub vs OD/MD [VL1,2]	7	362	337	15 (4.1%)	19 (5.6%)	3.5% (2.1%-5.9%)	6.1% (3.8%-12.0%)	0.73	0.36 to 1.46	0.64	0	0.76
Modified Clavien-Dindo classification (Type I)	MED vs OD/MD [VL1,2]	3	985	492	21 (2.1%)	11 (2.2%)	2.4% (1.9%-6.7%)	0.0% (0%-3.1%)	0.92	0.47 to 1.78	0.17	44	1.00
	PELD vs OD/MD [VL1,2]	6	494	1124	16 (1.2%)	25 (2.2%)	3.4% (1.8%-6.7%)	2.6% (1.2%-7.3%)	1.30	0.69 to 2.45	0.90	0	0.45
	Tub vs OD/MD [VL1,2]	6	305	311	24 (7.9%)	26 (8.4%)	8.5% (1.6%-12.0%)	8.8% (4.4%-16.5%)	0.93	0.53 to 1.61	0.73	0	0.26
Modified Clavien-Dindo classification (Type II)	MED vs OD/MD [VL1,2]	2	887	372	20 (2.3%)	8 (2.2%)	8.2% (-)	1.1% (-)	1.08	0.50 to 2.35	0.32	0	1.00
Modified Clavien-Dindo classification (Type III)	MED vs OD/MD [M2,5]	2	903	388	21 (2.3%)	0	2.8% (-)	0% (-)	10.83	1.29 to 91.18 [a]	0.39	0	1.00

	PELD vs OD/MD [VL1,2]	6	477	1112	27 (5.7%)	57 (5.1%)	5.0% (2.6%-13.7%)	3.6 % (0.0%-5.6%)	1.59	1.00 to 2.52	0.21	30	0.30
	PLDD vs OD/MD [L2,4,5]	1	500	500	16 (3.2%)	43 (8.6%)	1.6 (-)	4.3 (-)	0.39	0.22 to 0.69 [a]	-	-	-
	Tub vs OD/MD [VL1,2]	6	342	312	342 (3.2%)	7 (2.2%)	3.3% (1.5%-4.6%)	3.4% (0%-5.5%)	1.12	0.46 to 2.70	0.53	0	0.45
Durotomy	MED vs OD/MD [VL1,2]	2	917	402	16 (1.7%)	8 (2.0)	3.3% (1.6%-7.1%)	0.0% (0%-2.2%)	0.90	0.41 to 1.96	0.52	0	1.00
	PELD vs OD/MD [VL1,2]	4	424	745	4 (0.9%)	10 (1.3%)	0.5% (0%-2.3%)	2.9% (1.5%-2.9%)	0.70	0.25 to 1.97	0.78	0	0.31
	Tub vs OD/MD [VL1,2]	6	340	298	27 (7.9%)	20 (6.7%)	8.8% (6.6%-9.5%)	6.6 % (4.4%-12.7%)	1.12	0.63 to 2.00	0.94	0	0.13
Reherniation	MED vs OD/MD [VL1,2,5]	2	903	388	7 (0.8%)	0	2.0% (-)	0% (-)	4.30	0.50 to 37.04	0.78	0	1.00
	PELD vs OD/MD [L2]	7	514	1147	29 (5.6%)	54 (4.7%)	5.0% (3.5%-8.1%)	2.9% (0%-6.3%)	1.67	1.05 to 2.64 [a]	0.30	17	0.76
	PLDD vs OD/MD [VL2,3]	2	540	540	19 (3.5%)	35 (6.5%)	5.4% (-)	3.5% (-)	0.56	0.33 to 0.97 [a]	0.01	67 [c]	1.00
	Tub vs OD/MD [VL1,2]	2	84	70	4 (4.8%)	2 (2.9%)	6.6% (-)	3.1% (-)	1.82	0.35 to 9.45	0.76	0	1.00
Reoperation	MED vs OD/MD [VL1,2,3]	2	903	388	7 (0.8%)	0	2.4% (2.3%-3.3%)	0.0% (0%-7.7%)	1.92	0.75 to 4.89	0.03 [b]	73 [c]	1.00
	PELD vs OD/MD [L2]	6	477	1112	45 (9.4%)	71 (6.4%)	9.7% (4.5%-17.5%)	5.2% (2.2%-6.9%)	1.75	1.20 to 2.55 [a]	0.50	0	0.71
	PLDD vs OD/MD [L2,4,5]	1	500	500	16 (3.2%)	43 (8.6%)	1.6% (-)	4.3% (-)	0.39	0.22 to 0.69 [a]	-	-	-
	Tub vs OD/MD [VL1,2]	5	294	279	11 (3.7%)	6 (2.2%)	3.5% (2.6%-4.7%)	3.8% (0%-5.9%)	1.33	0.52 to 3.43	0.50	0	0.09

Intra-op = intraoperative, post-op = post-operative, MED = microendoscopic discectomy, PELD = percutaneous endoscopic lumbar discectomy, PLDD = percutaneous laser disc decompression, OD = open discectomy, MD = microdiscectomy, Tub = tubular discectomy, RR = risk ratio, CI = confidence interval, IQR = interquartile range.

* Pooled mean complication rates

IQR ranged from the first to the third quartile (Q1-Q3); Control group includes OD/MD; Comparator group includes PELD, PLDD, MED, and tubular discectomy.

$$\text{RR} = \frac{risk\ of\ complication\ in\ the\ comparator\ group}{ris\ of\ complication\ in\ the\ control\ group}$$

RR lower than one favors the former technique and greater than one favors the latter technique; Statistical model includes random-effects model and fixed-effects model.

[a] 95% CI including 1 means no statistical significance, while not including 1 means have statistical significance; [b] $P < 0.05$ indicated significance; [c] $I^2 > 50\%$ implied heterogeneity.

Quality of evidence: [H] high, [M] moderate, [L] low, [VL] very low.

[1]-rated down for imprecision, [2]-rated down for risk of bias (no RCT), [3]-rated down for inconsistency, [4]-rated down for publication bias, [5]-rated up for large magnitude of effect (Strong evidence of association—significant relative risk of > 2 (< 0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+1); Very strong evidence of association—significant relative risk of > 5 (< 0.2) based on direct evidence with no major threats to validity (+2)).

2.4 Discussion

In this study, we conducted a systematic review and meta-analysis of the complication rates associated with various discectomy techniques for symptomatic LDH. Complication rates in different classification schemes and reoperation rates were extracted from 17 RCTs and 20 cohort studies.

Although safety assessment has been widely used in lumbar spine surgeries and the complication rates of a procedure are paramount to said assessment, there is no standardized way of reporting surgical complications. The general classification divides the complications into intraoperative and post-operative complications, according to the time when they become apparent [24]. It may be useful for the management of spine surgery complications to have clear guidelines for symptoms. Therapeutic consequences have been recommended as a way of classifying complications in spine surgery [28, 29]. MCDC scheme is based on the management required for each complication, which can guide clinical decision-making based on the severity of complications. We used the general classification and MCDC to evaluate the complications following discectomy surgeries for symptomatic LDH.

The present systematic review and meta-analysis reports a comprehensive list of complication rates following different discectomy techniques and elucidate differences between open discectomy/microdiscectomy group and various minimally invasive discectomy techniques.

2.4.1 MED versus open discectomy/microdiscectomy

In our systematic review and meta-analysis, we identified a number of complications following open discectomy/microdiscectomy and MED from RCTs and cohort studies. There were differences in pooled mean complication rates following both surgical techniques. Previous studies reported that the incidence of nerve root injury, durotomy, and reoperation in MED group were higher than those in the open discectomy/microdiscectomy group [45, 48], which is supported by our meta-analysis results. A possible explanation is the poor perception of depth with microendoscopic surgery and the restricting surgical field, which limit surgeons to orientate surgical instruments. However, the complications data from RCTs did not reach statistical significance. The low quality of evidence across outcomes was due to imprecision in the reported data [40, 41, 45, 48] and poor allocation (four studies were assessed as having an unclear risk) [27, 39, 45, 48] or lack of blinding to intervention (two studies were assessed as having an unclear risk [27, 39] and four studies were assessed as having a high risk [40, 41, 45, 48]). Additionally, the inconsistency in Type I complications per MCDC (I^2=51% > 50%) downgraded the evidence to very low.

We only found that MED was associated with a lower risk of Type III complications per MCDC from cohort studies. The finding indicated that a good visualization of discectomy and enhanced identification of anatomical structures through microendoscope results in a low incidence of complications requiring surgical treatment. Due to the low-quality of cohort studies and large magnitude of effect, this result was assessed as moderate-quality evidence.

2.4.2 PELD versus open discectomy/microdiscectomy

Compared with open discectomy/microdiscectomy, PELD magnifies the operative field with a camera system so that the surgeon can identify and protect the dural sac and nerve roots. A meta-analysis showed a higher complication rate in the PELD group (4.69%) compared with the MD group (2.33%), but the differences were not significant [69]. In our meta-analysis, there was a difference in complication rates between the two groups when data from RCTs were pooled. We found that PELD was associated with a lower risk of overall complications and a lower risk of Type I complications per MCDC. We also found that PELD was associated with a lower risk of reherniations and reoperations from cohort studies. These findings are inconsistent with previously reported data [69-71], which may partly be due to differences in study selection and the classification of complications. The percutaneous procedure causes less damage to surrounding tissues and obtains a good operative field through an endoscope, which are posited as the primary reasons for the lower overall complication rates. In the GRADE approach, RCTs start as high-quality evidence and cohort studies as low-quality evidence, but both can be rated down if most of the relevant evidence comes from studies that suffer from a high risk of bias [72]. The lower risk of overall complications in the PELD group was rated moderate-quality due to poor allocation (one study was assessed as having high risk [46] and three studies were assessed as having unclear risk [42-44]) and lack of blinding (three studies were assessed as having high risk [26, 38, 46] and three studies were assessed as having unclear risk [42-44]) in the included studies. Additionally, a large magnitude of effect (RR=0.37<0.5) upgraded the lower risk of Type I complications per MCDC for PELD versus open discectomy/microdiscectomy to high-quality. The quality of all the complication rates from cohort studies rated low-quality or very low quality due to high risk of bias and/or some imprecision in estimates.

2.4.3 PLDD versus open discectomy/microdiscectomy

Advantages of PLDD over open discectomy/microdiscectomy are decreased tissue injury and fewer post-operative complications, such as bleeding, infection, and post-operative pain for soft tissue exposure [13], which were supported by our results. We also found that PLDD had a lower risk of post-operative complications (low-quality due to high risk of bias (cohort studies), inconsistency in findings (I^2=55) and large magnitude of effect (RR=0.42<0.5)), lower type III complications per MCDC (low-quality due to high risk of bias (cohort studies), publication bias (P=0) and large magnitude of effect (RR=0.39<0.5)), lower reherniation rate (very-low-quality due to high risk of bias (cohort studies) and inconsistency in findings (I^2=67)), and lower reoperation rate (low-quality due to high risk of bias (cohort studies), publication bias (P=0) and large magnitude of effect (RR=0.39<0.5)). However, the limited study sample (n=1) [66] leaves the inferences drawn open to question.

2.4.4 Tubular discectomy versus open discectomy/microdiscectomy

In theory, the tubular retractor with or without a microscope could help a surgeon gain better view of the operative field and result in less surgical trauma than the conventional open approach, all of which is expected to reduce intraoperative complications [19]. Compared with open discectomy/microdiscectomy, MED had a higher pooled mean intraoperative complication rate when data from cohort studies were pooled (8.4% in open discectomy/microdiscectomy group versus 8.1% in MED group). In contrast, MED had a lower complication rate when data from RCTs were pooled (6.7% in open discectomy/microdiscectomy group versus 7.9% in MED group). However, the differences in intraoperative complication rates between open

discectomy/microdiscectomy and MED showed no statistical significance, which is consistent with previously reported data [19].

Although the results of our systematic review and meta-analysis are comprehensive, there are certain limitations which must be noted. Firstly, the small sample size of direct comparisons from RCTs may have reduced the statistical robustness of the results. Secondly, there is substantive heterogeneity in the studies due to wide variation in the duration of follow-up, and some post-operative complications may have a gestation period. Thirdly, the inherent limitations exist on an individual study basis. Some complications and/or reoperations were not reported due to unknown reasons which might present a dilemma of the outcomes. Fourth, there is a learning curve associated with the adoption of any new technology and surgical technique, and chronologically older discectomy procedures may have an advantage over newer approaches in reduced complication rates. Finally, the primary literature is varied and does not routinely discuss age and surgical levels in reporting complications, which may increase heterogeneity and reveal inherent differences associated with complications. Further well-defined RCTs with large sample sizes are needed to improve the predictive strength of such pairwise comparisons.

2.5 Conclusion

Results of this pairwise meta-analysis suggest that for the surgical treatment of symptomatic LDH, PELD has a lower risk of overall complications and a lower risk of complications necessitating conservative compared to open discectomy/microdiscectomy. The resultant list of complication rates will provide a reasonable explanation for signing an informed consent form between a surgeon and a

patient, managing expectations while considering alternate surgical techniques. Due to the inherent limitations on the missing reported data on some special complications, the measurement bias is existed. It remains unknown which discectomy technique is the saftest or leads to least complications.

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Chapter 3. Which Discectomy Technique is the Saftest or Leads to the Lowest Complication Rate? A Network Meta-Analysis

Up to around 20% complication rate following different discectomy techniques for symptomatic lumbar disc herniation is reported in the previous chapter. However, with regard to existing meta-analyses, there is a lack of information as to which disc removal technique has the lowest complication rate.

3.1 Introduction

Discectomy/microdiscectomy is considered as the most common surgical technique to treat symptomatic lumbar disc herniation (LDH). However, the surgical trauma of spine and its supporting structures could lead to post-operative back pain, spinal instability, and sometimes recurrent herniation [1-3]. In order to reduce surgical related complications, further variants of minimally invasive surgical procedures have been developed to treat symptomatic LDH [4, 5] that allows less surgical trauma to the tissues and hence a faster recovery, such as percutaneous laser disc decompression (PLDD) [6], percutaneous endoscopic lumbar discectomy (PELD) [7], tubular discectomy [8], and microendoscopic discectomy (MED) [9].

Different surgical interventions for LDH provide excellent outcomes, although they still carry approximately 20% risk of complications [10] such as durotomy, nerve root injury, hematoma and post-operative pain [11, 12]. Previous studies reporting on the safety and efficacy of different lumbar discectomy surgeries for LDH have not yielded conclusive results due to the pairwise nature of the comparisons [13-23].

Network meta-analyses (NMAs) are becoming more influential in informing clinicians and decision-makers as they provide rigorous means for indirect or direct comparisons of multiple interventions or treatments for the same pathology via randomized clinical trials [24, 25]. Given the lack of substantial evidence regarding the hierarchy of different discectomy techniques regarding complication rates, we performed a NMA of all complications reported in discectomy studies to compare the complication rates of open discectomy/microdiscectomy, tubular discectomy, PLDD, PELD and MED using two classification schemes (general classification that includes intraoperative and post-operative complications, and modified Clavien-Dindo classification (MCDC)).

3.2 Methods

3.2.1 Search strategy

Online databases EMBASE, MEDLINE and Cochrane Central Register of Controlled Trials were searched in accordance with preferred reporting information for systematic reviews and meta-analyses (PRISMA) guidelines to identify all relevant studies published between January 1977 (microdiscectomy first reported) and January 2019 [26]. The search strategy consisted of keywords and commonly used synonyms including “lumbar spine”, “intervertebral disc”, “herniation”, “discectomy”, “microdiscectomy”, “minimally invasive surgery”, “endoscopic”, “laser”, and “percutaneous discectomy”, with appropriate combinations of operators “AND”, “OR”, and “NOT”. We also evaluated the reference lists of relevant studies and identified additional studies for the purposes of the present study. Only studies published in English were considered. The review protocols were registered on PROSPERO (International Prospective Register of Systematic Reviews number, CRD42019120163).

3.2.2 Inclusion criteria

1) Randomized controlled trials (RCTs).

2) Studies which reported the comparisons between any two discectomy techniques (e.g., open discectomy or microdiscectomy or PLDD or PELD or MED or tubular discectomy surgery) for symptomatic LDH patients.

3) Studies which reported at least one of the following outcomes:

Primary outcomes including overall complication rate and complications in two different classification schemes (General classification and MCDC). Overall complication included all the complications related to various discectomy surgeries. Intraoperative complications included mortality, thrombosis, and hepatitis; intra-operative specific complications include durotomy, bleeding, nerve root injury, surgical error; post-operative complications included urinary tract infection, miction disturbances (catheter required), pulmonary complication, deep venous thrombosis leg, infection superficial, infection deep, hematoma, re-herniation, neurologic problem, skin problem, psychological and coping problems. Modified Clavien-Dindo classification scheme includes five types of complications (type I: conservative treatment, without intervention or pharmacologic treatment; type II: pharmacologic treatment; type III: invasive intervention under general anesthesia; type IV: intensive care unit management; type V: death).

The secondary outcome included the reoperation rate.

3.2.3 Exclusion criteria

1) Studies which compared discectomy procedures with other spinal surgeries involving the use of an implant.

2) Case reports, retrospective studies, reviews, and conference reports; in vitro biomechanical studies, computer modelling studies.

3.2.4 Study selection

Two reviewers (Xiaolong Chen and Jose Vargas Castillo from Spine Service, Department of Orthopaedic Surgery, St. George Hospital Campus, New South Wales, Australia) independently reviewed all titles and abstracts that were identified in the initial online search of databases. Full-text articles were further reviewed for all the relevant abstracts. Disagreements between the reviewers in the selection process for studies were either resolved by consensus or with the help from a third reviewer (Ashish D. Diwan).

3.2.5 Data extraction

Two reviewers (Xiaolong Chen and Jose Vargas Castillo) extracted data independently using a standardized tool developed for this study. The reviewers collected the following data: methods (study design, sample size, inclusion and exclusion criteria, study period, mean duration of follow-up), participants (number of participants, age, gender), interventions (surgical procedure) and outcomes (for each primary outcome: number of subjects and occurrence rate in general complication classification, MCDC, and revision surgery rate).

3.2.6 Assessment of risk of bias included in studies

The 13 criteria recommended in the Cochrane Back and Neck Group guidelines [27] were used to assess the risk of bias. "Low risk," "high risk," or "unclear risk," was used to score the risk of bias for individual criteria. Thereafter, for the overall risk of bias evaluation, we considered a "low overall risk" of bias when seven or more of the 13 criteria were a low risk [27]. Studies with six or less low-risk criteria were considered a "high overall risk" of bias. We conducted a sensitivity analysis to assess the impact of including studies with a high overall risk of bias. As before, controversial scores were resolved by the third reviewer (Ashish D. Diwan).

3.2.7 Statistical analysis

Regular meta-analysis was performed with RevMan (Review Manager 5.3 version. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.). The chi squared (I^2) statistic was used to measure heterogeneity among the trials [28]. Statistical analysis software STATA (release 15, StataCorp LLC, TX) was used for performing the NMA [29]. We used the DerSimonian and Laird random-effects model to analyze data. The pooled estimates of odds ratio (OR) and 95% CI for direct comparisons and 95% credible intervals (CrI) for NMA results were reported. NMA results were also assessed by means of forest plots. The evaluation of inconsistency of treatment, which estimates whether the treatment effects from direct and indirect evidence are in agreement, is an important aspect of NMA. Node-splitting results were used to evaluate the consistency of each outcome between direct and indirect comparisons. The statistical significance was set at 5% (α =0.05). Surface under cumulative ranking curve (SUCRA) is a numeric presentation of the overall ranking of different techniques compared for hierarchical ordering. SUCRA results were used to evaluate the relative rank of each discectomy technique under different complication

outcomes. A higher SUCRA value corresponded to a higher ranking and a lower complication rate in each comparison.

3.2.8 Evaluating the quality of evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment rated the quality of evidence informing this NMA as high, moderate, low or very low across five components-study limitations, imprecision, inconsistency in results, indirectness, and publication bias [30, 31]. Based on GRADE guidelines for rating the certainty of evidence from NMA, NMA 'summary of findings (SoF)' tables were used to present NMA results.

3.3 Results

3.3.1 Selection, quality assessment and network structure

The selection process for studies is illustrated in the PRISMA flow diagram (**Figure 3.1**). A total of 1563 citations were identified through our literature search, and 12 from the review of the reference list. Of these, 255 studies were selected for abstract assessment after removal of duplicates, and then 60 studies were selected for full-text article assessment for eligibility. Finally, 18 RCTs met the inclusion criteria for the present study [32-49].

3.3.2 Risk of bias in included studies

We described the risk of selection bias for each study according to the Cochrane Back and Neck Group guidelines [27]. The summary of the risk of bias assessment is

presented in **Figure 3.2**. Two out of the 18 studies had a high overall risk of bias [36, 47].

1) Allocation: Five studies were assessed as having a high risk of selection bias [33, 50-53].

2) Blinding: Eleven studies [32, 35, 39, 48, 50-56] were deemed to have a high-risk and seven studies [33, 36, 37, 41, 43, 47, 57] were classified as unclear in terms of performance bias.

3) Incomplete outcome data: All the studies were assessed as having low attrition bias except three studies that did not clearly report [33, 47, 57].

4) Outcome assessment: Five studies were assessed as having a high risk of detection bias [39, 47, 52, 53, 56].

5) Selective reporting and other potential sources of bias: None were assessed as having a reporting bias or other bias.

Demographic data, surgical technique, and surgery-related complications from the 18 included studies are provided in **Table 3.1**. The number of studies reporting complications rates for different discectomy techniques varied: OD/MD (n=17), MED (n=7), tubular microdiscectomy (n=2), PLDD (n=2) and PELD (n=7). The network formed by the direct comparisons between various surgical discectomy techniques is shown in **Figure 3.3**.

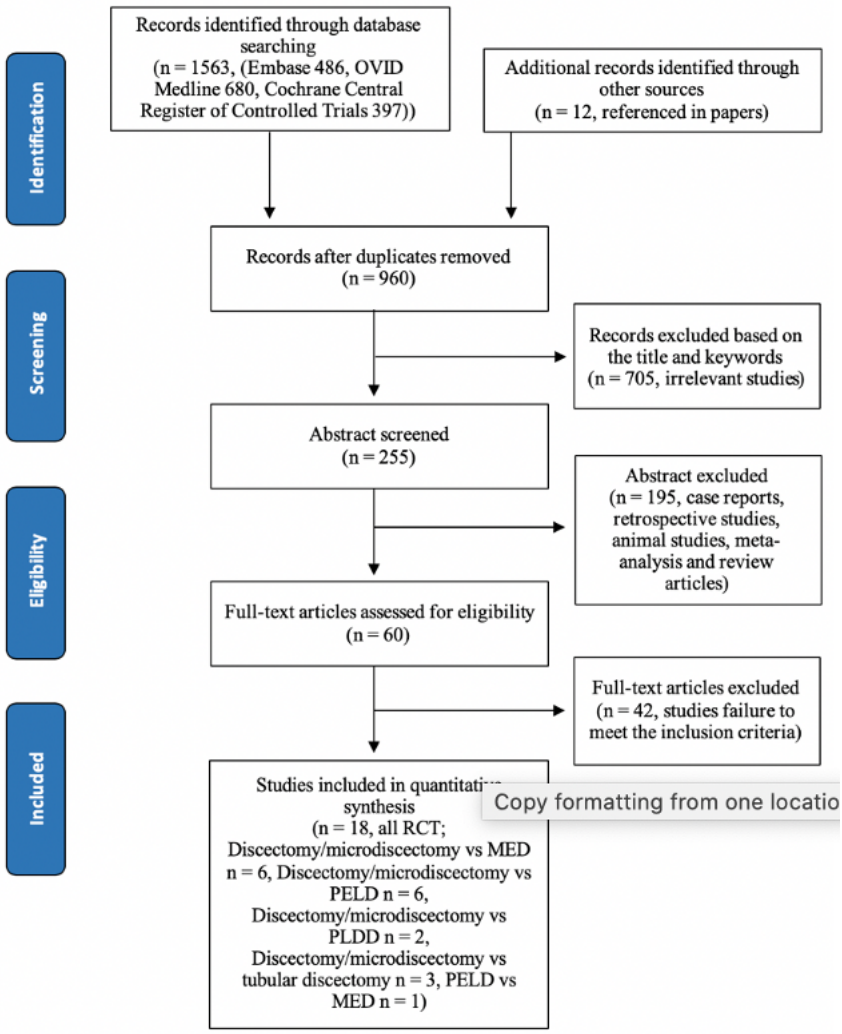

Figure 3.1 Flow chart showing the search strategy conducted in accordance with the preferred reporting information for systematic reviews and meta-analyses (PRISMA) guidelines, and the results [26]

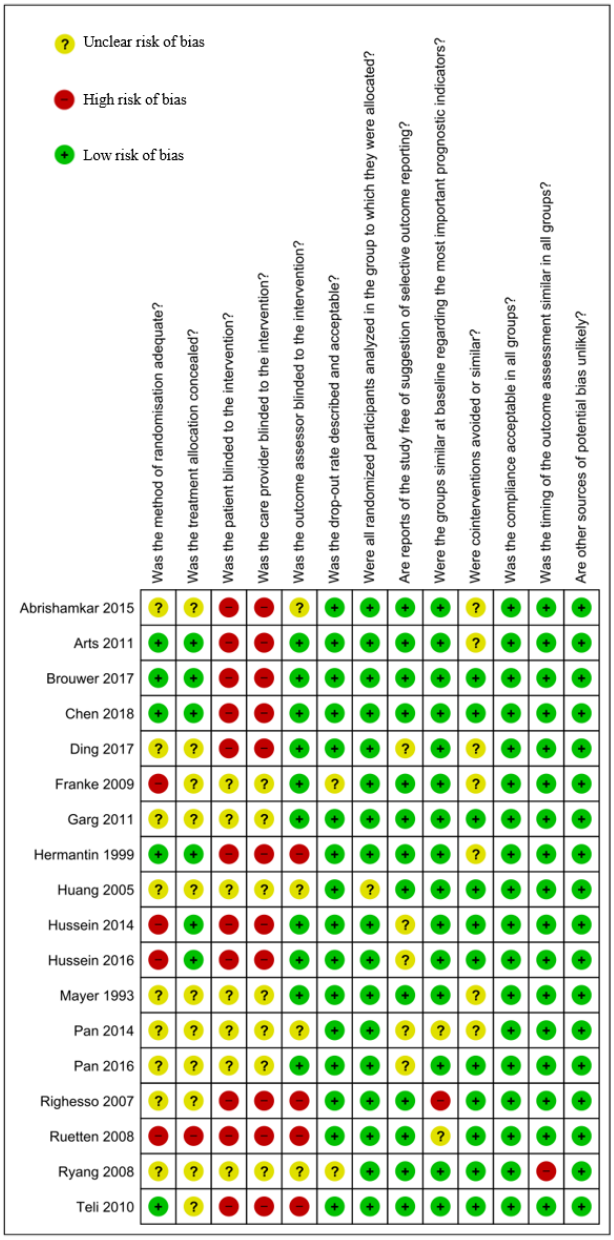

Figure 3.2 Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

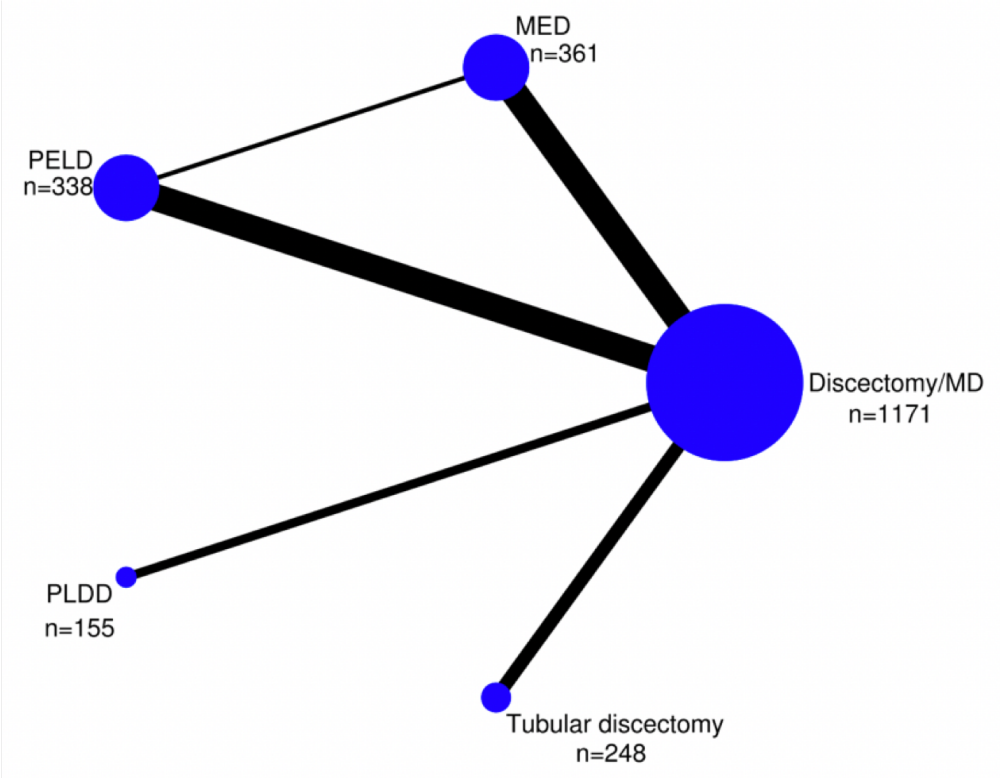

Figure 3.3 Network comparisons of different surgical discectomy techniques. Each node represents a discectomy technique, and the size of the node indicates the sample size of patients for which complications data could be extracted from the literature. The lines between any two nodes represent the existence of a direct correlation. The thickness of the solid line between any two nodes depicts the number of existing direct comparisons between the two interventions. MED = microendoscopic discectomy, PELD = percutaneous endoscopic lumbar discectomy, PLDD = percutaneous laser lumbar discectomy, MD = microdiscectomy

Table 3.1 Demographic data, surgical technique, and surgery-related complications for the selected studies

Study ID	Study design	Study location	Surgical	Sample Size	M/F	Age (y)	Follow-up (m)	Total No.	No. of Complications							No. of Re-op
									Intra-op		Post-op		Modified Clavien-Dindo Classification			
									General	Specific	General	Specific	Type I	Type II	Type III	
Garg 2011	RCT	India	MED	55	36/19	37	12	12		5	4	3	11		1	1
			Discectomy	57	44/13	38	12	15		5	9	1	11	3	1	0
Huang 2005	RCT	China	MED	10	6/4	39.2	18.9	1		1				1		0
			Discectomy	12	9/3	39.8	18.9	1				1		1		0
Hussein 2014	RCT	Egypt	MED	95	58/42	30.2	104.2	20		6	3	11	10	3	7	7
			Discectomy	90	54/46	31.5	101.3	23		5	1	17	8	5	10	10
Hussein 2016	RCT	Egypt	MED	37	20/17	30.5	25.5	6		1	2	3	3	1	2	3
			MD	36	21/15	31.9	26.2	11		2	2	7	4	3	4	7
Righesso 2007	RCT	Brazil	MED	21	10/11	42	24	3		1		2	2	1		1
			Discectomy	19	13/6	46	24	1				1		1		1
Teli 2010	RCT	Italy	MED	70	45/25	39	26 ±2	19		8		11	11	1	8	8
			MD	142	94/48	79	26	17		4		12	3	7	7	7
Hermantin 1999	RCT	USA	PELD	30	22/8	39	32									1
			Discectomy	30	17/13	40	31	1		1					1	1
Pan 2014	RCT	China	PELD	10	5/5		6	1				1		1		0
			Discectomy	10	5/5		6	0								0
Ruetten 2008	RCT	Germany	PELD	100	42/58	43	24	9				9	3		6	6
			MD	100	42/58	43	24	17			3	14	12		5	5
Mayer 1993	RCT	Germany	PELD	20	12/8	39.8	24	1				1			1	3
			MD	20	14/6	42.7	24	1				1			1	1
Pan 2016	RCT	China	PELD	48	26/22	39.5	16.7	3				3	3			0
			Discectomy	58	31/27	42.8	17.3	12		2	4	6	12			0
Ding 2017	RCT	China	PELD	50	30/20	41.3	12	1				1	1			0
			Discectomy	50	27/23	43.9	12	3				3		3		0
Abrishamkar 2015	RCT	Iran	Laser	100	82/18	39.7	12	7				7			7	7
			Discectomy	100	78/22	40.2	12	8				8			8	8
Brouwer 2017	RCT	Netherlands	Laser	55	36/19	43.2	24	6				6			6	29
			MD	57	33/24	43.7	24	7				7			7	12
Arts 2011	RCT	Netherlands	Tubular	166	84/82	41.6	24	58	2	18	3	35	42		16	23
			MD	159	88/71	41.3	24	40		15	3	22	30		10	14
Franke 2009	RCT	Germany	Tubular	52	31/21		12	4		2		2	2		2	2
			MD	48	29/19		12	8		3		5	3		5	5
Ryang 2008	RCT	Germany	Tubular	30	19/11	39.1	16	2				2			2	2
			MD	30	13/17	38.2	16	6		2		3	2		4	4
Chen 2018	RCT	China	PELD	80	52/28	40.2	12	11		4		7	6		5	5
			MED	73	37/36	40.7	12	12		1		10	6	1	3	3

None of the 18 RCT studies reported the incidence of type IV and type V complications according to the modified Clavien-Dindo classification. RCT = randomized controlled trials, MED = microendoscopic discectomy, PELD = percutaneous endoscopic lumbar discectomy, PLDD = percutaneous laser lumbar discectomy, MD = microdiscectomy, M = male, F = female, Intra-op = intraoperative, post-op = post-operative, Re-op = re-operation

3.3.3 Part 1: Pairwise comparisons using NMA

3.3.3.1 Overall complication rate, General classification of complications, MCDC and Reoperation rate related outcomes

The overall complication rates, durotomy rates, reherniation rates, intraoperative complication rates, post-operative complication rates, complication rates by MCDC scheme, and reoperation rates are presented in **Table 3.2** (direct pairwise comparisons) and **Table 3.3** to **Table 3.8** (all the comparisons between each pair of discectomy techniques) and the forest plots in **Figure 3.4** (NMA comparison). There was no significant difference in any of the pairwise comparisons.

Table 3.2 Results of direct pairwise meta-analysis for the overall complication rates, durotomy rates, reherniation rates, intraoperative complication rates, post-operative complication rates, complication rates by MCDC scheme, and reoperation rates

Comparisons	Odds Ratio (95% CI)	I^2	Number of studies
Overall complication			
MED vs MD/discectomy	1.07 (0.64, 1.79)	32.1%	6
PELD vs MD/discectomy	0.48 (0.26, 0.92)	0	6
PLDD vs MD/discectomy	0.88 (0.41, 1.92)	0	2
Tubular vs MD/discectomy	0.75 (0.29, 1.96)	57.9%	3
PELD vs MED	0.84 (0.35, 2.01)	100%	1
Durotomy			
MED vs MD/discectomy	0.71 (0.35, 1.40)	0	6
PELD vs MD/discectomy	1.66 (0.26, 10.44)	0	6
PLDD vs MD/discectomy	-	-	2
Tubular vs MD/discectomy	0.93 (0.30, 2.82)	27%	3
PELD vs MED	1.10 (0.07, 17.84)	100%	1
Reherniation			
MED vs MD/discectomy	0.61 (0.26, 1.39)	0	6
PELD vs MD/discectomy	0.74 (0.24, 2.33)	0	6
PLDD vs MD/discectomy	1.14 (0.52, 2.47)	0	2
Tubular vs MD/discectomy	1.40 (0.35, 5.65)	49.4%	3
PELD vs MED	0.66 (0.15, 2.85)	0	1
Intraoperative complication			
MED vs MD/discectomy	0.61 (0.32, 1.19)	0	6
PELD vs MD/discectomy	3.56 (0.38, 32.92)	0	6
PLDD vs MD/discectomy	-	-	2
Tubular vs MD/discectomy	0.93 (0.49, 1.77)	0	3

PELD vs MED	0.27 (0.03, 2.51)	0	1
Post-operative complication			
MED vs MD/discectomy	1.11 (0.71, 1.73)	0	6
PELD vs MD/discectomy	1.17 (0.34, 4.01)	56.2%	6
PLDD vs MD/discectomy	1.14 (0.52, 2.47)	0	2
Tubular vs MD/discectomy	0.99 (0.45, 2.21)	26.9%	3
PELD vs MED	1.57 (0.57, 4.33)	100%	1
Type I			
MED vs MD/discectomy	0.60 (0.26, 1.38)	49.8%	6
PELD vs MD/discectomy	3.04 (0.25, 7.40)	0	6
PLDD vs MD/discectomy	-	-	2
Tubular vs MD/discectomy	0.83 (0.51, 1.35)	0	3
PELD vs MED	1.10 (0.34, 3.55)	100%	1
Type II			
MED vs MD/discectomy	2.17 (0.88, 5.34)	0	6
PELD vs MD/discectomy	1.67 (0.08, 33.21)	44.6%	6
PLDD vs MD/discectomy	-	-	2
Tubular vs MD/discectomy	-	-	3
PELD vs MED	3.29 (0.13, 81.92)	100%	1
Type III			
MED vs MD/discectomy	0.97 (0.45, 2.08)	19.1%	6
PELD vs MD/discectomy	0.98 (0.34, 2.82)	0	6
PLDD vs MD/discectomy	1.14 (0.52, 2.47)	0	2
Tubular vs MD/discectomy	1.16 (0.45, 2.98)	32.6%	3
PELD vs MED	0.66 (0.15, 2.85)	0	1
Reoperation			
MED vs MD/discectomy	1.00 (0.48, 2.10)	20.1%	6
PELD vs MD/discectomy	0.72 (0.26, 1.98)	0	6
PLDD vs MD/discectomy	0.63 (0.23, 1.76)	60.1%	2

Tubular vs MD/discectomy	1.14 (0.43, 3.04)	40.7%	3
PELD vs MED	0.66 (0.15, 2.85)	0	1

CI = confidence interval; I^2 = chi-squared; Odds Ratio lower than 1 favors the former technique and over 1 favors the later technique. The 95% CI including 1 means no statistical significance.

Table 3.3 Network meta-analysis results for the overall complication rates reported for different discectomy procedures. Odds ratio (OR) with 95% credible intervals (CrI) were used to measure relative risk

Overall Complication	**PELD**	-	-	-	-
	0.64 (0.21,2.00)	**Tub**	-	-	-
	0.61 (0.17,2.19)	0.96 (0.25,3.73)	**PLDD**	-	-
	0.54 (0.24,1.23)	0.85 (0.30,2.40)	0.89 (0.27,2.92)	**MED**	-
	0.53 (0.26,1.11)	0.83 (0.35,1.99)	0.87 (0.31,2.47)	0.98 (0.55,1.74)	**MD/discectomy**

Table 3.4 Network meta-analysis results for durotomy rates reported for different discectomy procedures. Odds ratio (OR) with 95% credible intervals (CrI) were used to measure relative risk

Durotomy	**PELD**	-	-	-	-
	0.82 (0.23, 2.94)	**MD/discectomy**	-	-	-
	0.80 (0.04, 17.17)	0.98 (0.06, 15.86)	**PLDD**	-	-
	0.61 (0.13, 2.75)	0.74 (0.33, 1.65)	0.75 (0.04, 13.64)	**Tub**	-
	0.58 (0.15, 2.31)	0.71 (0.37, 1.38)	0.73 (0.04, 12.66)	0.96 (0.34, 2.73)	**MED**

Table 3.5 Network meta-analysis results for reherniation rates reported for different discectomy procedures. Odds ratio (OR) with 95% credible intervals (CrI) were used to measure relative risk

Reherniation	**PLDD**	-	-	-	-
	0.87 (0.35, 2.14)	**MD/discectomy**	-	-	-
	0.85 (0.20, 3.56)	0.98 (0.32, 2.97)	**Tub**	-	-
	0.62 (0.18, 2.11)	0.71 (0.31, 1.64)	0.72 (0.20, 2.58)	**MED**	-
	0.57 (0.16, 2.09)	0.66 (0.26, 1.67)	0.67 (0.16, 2.78)	0.93 (0.32, 2.70)	**PELD**

Table 3.6 Network meta-analysis results for the intra-operative complication rates and post-operative complication rates reported for different discectomy procedures. Odds ratio (OR) with 95% credible intervals (CrI) were used to measure relative risk

Post-op complications	**MD/discectomy**	0.99 (0.38, 2.61)	1.02 (0.06, 17.09)	1.11 (0.30, 4.01)	1.43 (0.69, 2.95)	**Intra-op complications**
	0.79 (0.40, 1.57)	**Tub**	1.03 (0.05, 20.29)	1.12 (0.23, 5.34)	1.44 (0.45, 4.57)	
	1.15 (0.52, 2.54)	1.46 (0.51,4.16)	**PLDD**	1.09 (0.05, 24.16)	1.40 (0.08, 25.80)	
	1.90 (1.12, 3.25)	2.41 (1.00, 5.82)	1.65 (0.64, 4.31)	**PELD**	1.29 (0.33, 5.01)	
	1.14 (0.74, 1.76)	1.45 (0.65, 3.22)	1.00 (0.40, 2.46)	0.60 (0.32, 1.11)	**MED**	

Table 3.7 Network meta-analysis results for the complication rates by modified Clavien-Dindo classification scheme reported for different discectomy procedures [12, 58-61]. Odds ratio (OR) with 95% credible intervals (CrI) were used to measure relative risk

Type I	**PELD**	1.61 (0.11, 22.65)	1.71 (0.08, 37.55)	1.68 (0.43, 6.46)	0.84 (0.18, 3.83)	**Type II**
	0.61 (0.13, 2.82)	**Tub**	1.06 (0.03, 38.52)	1.04 (0.11, 10.13)	0.52 (0.05, 5.93)	
	0.56 (0.03, 12.04)	0.92 (0.04, 21.32)	**PLDD**	0.98 (0.06, 15.86)	0.49 (0.03, 9.03)	
	0.57 (0.22, 1.47)	0.94 (0.29, 2.98)	1.02 (0.05, 18.92)	**MD/discectomy**	0.50 (0.21, 1.19)	
	0.40 (0.14, 1.16)	0.65 (0.16, 2.69)	0.71 (0.03, 14.61)	0.70 (0.32, 1.51)	**MED**	
Type III	**PLDD**	-	-	-	-	
	0.92 (0.27, 3.16)	**Tub**	-	-	-	
	0.89 (0.29, 2.67)	0.96 (0.33, 2.81)	**MED**	-	-	
	0.87 (0.36, 2.09)	0.95 (0.40, 2.26)	0.98 (0.50, 1.92)	**MD/discectomy**	-	
	0.76 (0.22, 2.64)	0.83 (0.24, 2.78)	0.86 (0.32, 2.27)	0.87 (0.36, 2.11)	**PELD**	

Table 3.8 Network meta-analysis results for reoperation rates reported for different discectomy procedures. Odds ratio (OR) with 95% credible intervals (CrI) were used to measure relative risk

Reoperation	**Tub**	-	-	-	-
	0.90 (0.25, 3.24)	**MED**	-	-	-
	0.87 (0.32, 2.41)	0.97 (0.44, 2.13)	**MD/discectomy**	-	-
	0.62 (0.15, 2.53)	0.69 (0.22, 2.10)	0.71 (0.26, 1.88)	**PELD**	-
	0.42 (0.10, 1.79)	0.47 (0.13, 1.74)	0.49 (0.17, 1.37)	0.69 (0.17, 2.88)	**PLDD**

3.3.4 Part 2: Ranking of discectomy techniques using NMA

3.3.4.1 SUCRA for ranking probability

SUCRA was evaluated in order to rationally rank the complication rates among the procedures studied (**Table 3.9**). According to the standing list of the primary outcomes, we found that PELD (SUCRA: 0.856) had the lowest overall complication rates, followed by tubular discectomy (SUCRA: 0.506), PLDD (SUCRA: 0.470), MED (SUCRA: 0.351) and MD (SUCRA: 0.316). PELD (SUCRA: 0.672) and PLDD (SUCRA: 0.696) ranked lowest for durotomy and reherniation rates respectively. Discectomy/microdiscectomy (SUCRA: 0.599) had the lowest reported incidence of intraoperative complications, and PELD (SUCRA: 0.939) had the lowest reported incidence of post-operative complications. Concerning modified Clavien-Dindo classification of complications, PELD (SUCRA: 0.803), MED (SUCRA: 0.730) and PLDD (SUCRA: 0.605) held the first ranking for the occurrence of type I, II and III, respectively. Tubular discectomy (SUCRA: 0.699) had the lowest reoperation rate, whereas PLDD (SUCRA: 0.163) had the highest.

3.3.5 Part 3: Inconsistency test and evaluating the quality of evidence from NMA

Node-splitting results (**Table 3.10**) showed that no inconsistency existed between direct and indirect evidence. In the certainty assessment of NMA estimates of the 90 paired comparisons, 53.3% (48/90) warranted low and 46.7% (42/90) warranted moderate certainties (**Table 3.11**). All the low certainty results of NMA estimates were due to imprecision, inconsistency, and indirectness. The point estimates and credible intervals of comparisons between minimally invasive discectomy surgeries (PELD, MED, PLDD and tubular discectomy) and OD/MD showed no significant differences in the overall

complication rates, complication rates by general classification and MCDC, and reoperation rates (**Table 3.12 and Figure 3.4**). The funnel plot showed no significant publication bias (**Figure 3.5**).

Table 3.9 Surface under cumulative ranking curve (SUCRA) results for the complication rates by different classification schemes reported for different discectomy procedures

	MD/discectomy	**MED**	**PELD**	**PLDD**	**Tubular discectomy**
Overall complication	0.316	0.351	0.856	0.470	0.506
Durotomy	0.626	0.317	0.672	0.526	0.359
Reherniation	0.625	0.324	0.278	0.696	0.578
General classification					
Intra-op complication	0.599	0.302	0.500	0.524	0.574
Post-op complication	0.352	0.525	0.939	0.514	0.170
Modified Clavien-Dindo classification					
Type I	0.477	0.230	0.803	0.481	0.510
Type II	0.321	0.730	0.612	0.417	0.420
Type III	0.482	0.509	0.367	0.605	0.537
Reoperation	0.637	0.643	0.358	0.163	0.699

Table 3.10 Node-splitting results of the network meta-analysis for all dichotomous outcomes. Odds ratio (OR) with 95% confidence intervals (CI) and p values were used to determine the difference between direct and indirect evidence

		Log$_e$ OR (95% CI)			*P* (Direct vs. indirect)
		Direct	**Indirect**	**Network**	
Overall complication	MD vs MED	0.07 (-0.56, 0.69)	-0.58 (-2.18 – 1.01)	0.65 (-1.07, 2.36)	0.516
	MD vs PELD	-0.79 (-1.65, 0.07)	-0.14 (-1.63, 1.34)	-0.65 (-2.36, 1.07)	0.516
	MED vs PELD	-0.21 (-1.56, 1.14)	-0.86 (-1.92, 0.20)	0.65 (-1.07, 2.36)	0.516
Durotomy	MD vs MED	0.36 (-0.31, 1.04)	-0.23 (-3.36, 2.91)	0.59 (-2.62, 3.80)	0.718
	MD vs PELD	-0.32 (-1.75, 1.11)	0.27 (-2.60, 3.14)	-0.59 (-3.80, 2.62)	0.718
	MED vs PELD	-0.09 (-2.88, 2.70)	-0.68 -2.27, 0.90）	0.59 (-2.62, 3.80)	0.718
Reherniation	MD vs MED	0.45 (-0.50, 1.40)	-0.19 (-2.14, 1.76)	0.64 (-1.54, 2.82)	0.565
	MD vs PELD	0.25 (-0.84, 1.34)	0.89 (-0.99, 2.77)	-0.64 (-2.82, 1.54)	0.565
	MED vs PELD	0.44 (-1.18, 2.06)	-0.20 (-1.65, 1.26)	0.64 (-1.54, 2.82)	0.565
Intra-op complication	MD vs MED	0.52 (-0.17, 1.22)	-1.91 (-4.61, 0.79)	2.43 (-0.36, 5.21)	0.088
	MD vs PELD	0.57 (-2.06, 0.91)	1.85 (-0.50, 4.21)	-2.43 (-5.21, 0.36)	0.088
	MED vs PELD	1.33 (-0.92, 3.58)	-1.10 (-2.74, 0.55)	2.43 (-0.36, 5.21)	0.088
Post-op complication	MD vs MED	-0.14 (-0.63, 0.36)	-0.14 (-1.40, 1.13)	-0.002 (-1.36, 1.36)	0.997
	MD vs PELD	-0.64 (-1.27, -0.07)	-0.64 (-1.84, 0.56)	-0.002 (-1.36, 1.36)	0.997
	MED vs PELD	-0.50 (-1.60, 0.59)	-0.50 (-1.31, 0.30)	-0.002 (-1.36, 1.36)	0.997
Type I	MD vs MED	0.53 (-0.24, 1.30)	-0.83 (-2.76, 1.11)	1.36 (-0.71, 3.43)	0.198
	MD vs PELD	-0.93 (-2.00, 0.14)	0.43 (-1.35, 2.22)	-1.36 (-3.43, 0.71)	0.198
	MED vs PELD	-0.10 (-1.71, 1.51)	-1.46 (-2.76, -0.16)	1.36 (-0.71, 3.43)	0.198
Type II	MD vs MED	-0.81 (-1.71, 0.10)	0.98 (-2.56, 4.52)	-1.78 (-5.43, 1.87)	0.339
	MD vs PELD	-0.23 (-1.70, 1.25)	-2.01 (-5.35, 1.33)	1.78 (-1.87, 5.43)	0.339
	MED vs PELD	-1.20 (-4.42, 2.01)	0.58 (-1.15, 2.31)	-1.78 (-5.43, 1.87)	0.339
Type III	MD vs MED	0.03 (-0.70, 0.77)	-0.43 (-2.36, 1.49)	0.47 (-1.59, 2.52)	0.656
	MD vs PELD	0.01 (-1.04, 1.06)	0.48 (-1.30, 2.25)	-0.47 (-2.52, 1.59)	0.656
	MED vs PELD	0.44 (-1.17, 2.05)	-0.03 (-1.31, 1.25)	0.47 (-1.59, 2.52)	0.656
Reoperation	MD vs MED	-0.01 (-0.88, 0.86)	-0.12 (-2.34, 2.11)	-0.10 (-2.28, 2.49)	0.933
	MD vs PELD	0.33 (-0.82, 1.47)	0.43 (-1.66, 2.52)	-0.10 (-2.49, 2.28)	0.933
	MED vs PELD	0.44 (-1.46, 2.34)	0.34 (-1.10, 1.78)	0.10 (-2.28, 2.49)	0.933

Table 3.11 Network meta-analysis (NMA) results including certainty assessments. It presents a more detailed summary of the evidence, including the number of direct comparisons, the direct, indirect and network estimates and their associated confidence intervals (CI) and credible intervals (CrI), and the certainty of the evidence

	Comparison	No.	Direct estimate (95% CI)	Indirect estimate (95% CrI)	Network estimate (95% CrI)
Overall complication	MED vs MD/discectomy	6	1.07 (0.64, 1.79) M[1]	0.99 (0.61, 1.38) L[1,2]	0.98 (0.61, 1.57) M
	PELD vs MD/discectomy	6	0.48 (0.26, 1.02) H[1,4]	0.73 (0.09, 1.37) L[1,2]	0.58 (0.30, 1.09) M
	PLDD vs MD/discectomy	2	0.88 (0.41, 1.92) M[1]	0.95 (0.17, 1.72) L[1,2]	0.88 (0.35, 2.19) M
	Tubular vs MD/discectomy	3	0.75 (0.29, 1.96) M[1]	1.05 (0.64, 1.47) L[1,2]	0.85 (0.41, 1.78) M
	PELD vs MED	1	0.84 (0.35, 2.01) L[1,3]	1.36 (0.65, 2.87) VL[1,2,3]	0.59 (0.29, 1.18) M
	PLDD vs MED	0	-	0.90 (0.32, 2.51) L[1,2]	0.90 (0.32, 2.51) L
	Tubular vs MED	0	-	0.87 (0.36, 2.08) L[1,2]	0.87 (0.36, 2.08) L
	PLDD vs PELD	0	-	1.53 (0.50, 4.66) L[1,2]	1.53 (0.50, 4.66) L
	Tubular vs PELD	0	-	1.48 (0.56, 3.91) L[1,2]	1.48 (0.56, 3.91) L
	Tubular vs PLDD	0	-	0.97 (0.30, 3.12) L[1,2]	0.97 (0.30, 3.12) L
Durotomy	MED vs MD/discectomy	6	0.71 (0.35, 1.40) M[1]	0.86 (0.17, 1.55) L[1,2]	1.40 (0.72, 2.72) M
	PELD vs MD/discectomy	6	1.66 (0.26, 10.44) M[1]	1.25 (0.59, 3.08) L[1,2]	0.82 (0.23, 2.94) M
	PLDD vs MD/discectomy	2	-	1.02 (0.06, 16.43) L[1,2]	1.02 (0.06, 16.43) L
	Tubular vs MD/discectomy	3	0.93 (0.30, 2.82) M[1]	0.89 (0.08, 1.69) L[1,2]	1.35 (0.60, 3.02) M
	PELD vs MED	1	1.10 (0.07, 17.84) L[1,3]	0.75 (0.22, 24.83) VL[1,2,3]	0.58 (0.15, 2.31) M
	PLDD vs MED	0		0.73 (0.04, 12.66) L[1,2]	0.73 (0.04, 12.66) L
	Tubular vs MED	0		0.96 (0.34, 2.73) L[1,2]	0.96 (0.34, 2.73) L
	PLDD vs PELD	0		1.25 (0.06, 26.63) L[1,2]	1.25 (0.06, 26.63) L
	Tubular vs PELD	0		1.65 (0.36, 7.50) L[1,2]	1.65 (0.36, 7.50) L
	Tubular vs PLDD	0		1.33 (0.07, 23.99) L[1,2]	1.33 (0.07, 23.99) L
Reherniation	MED vs MD/discectomy	6	0.61 (0.26, 1.39) M[1]	0.81 (0.03, 1.64) L[1,2]	1.41 (0.61, 3.27) M
	PELD vs MD/discectomy	6	0.74 (0.24, 2.33) M[1]	0.88 (0.26, 2.03) L[1,2]	1.52 (0.60, 3.84) M
	PLDD vs MD/discectomy	2	1.14 (0.52, 2.47) M[1]	1.06 (0.28, 1.83) L[1,2]	0.87 (0.35, 2.14) M
	Tubular vs MD/discectomy	3	1.40 (0.35, 5.65) M[1]	0.94 (0.19, 1.69) L[1,2]	1.02 (0.34, 3.10) M
	PELD vs MED	1	0.66 (0.15, 2.85) M[1]	0.92 (0.22, 3.76) L[1,2]	1.07 (0.37, 3.12) L
	PLDD vs MED	0		0.62 (0.18, 2.11) L[1,2]	0.62 (0.18, 2.11) L
	Tubular vs MED	0		0.72 (0.20, 2.58) L[1,2]	0.72 (0.20, 2.58) L
	PLDD vs PELD	0		0.57 (0.16, 2.09) L[1,2]	0.57 (0.16, 2.09) L
	Tubular vs PELD	0		0.67 (0.16, 2.78) L[1,2]	0.67 (0.16, 2.78) L
	Tubular vs PLDD	0		1.17 (0.28, 4.90) L[1,2]	1.17 (0.28, 4.90) L
Intra-op complication	MED vs MD/discectomy	6	0.61 (0.32, 1.19) M[1]	0.49 (0.17, 1.16) M[1,2,4]	1.43 (0.69, 2.95) M
	PELD vs MD/discectomy	6	3.56 (0.38, 32.92) H[1,4]	1.06 (1.16, 3.19) L[1,2]	1.11 (0.30, 4.01) M
	PLDD vs MD/discectomy	2	-	1.02 (0.06, 17.09) L[1,2]	1.02 (0.06, 17.09) L
	Tubular vs MD/discectomy	3	0.93 (0.49, 1.77) M[1]	0.59 (0.05, 1.23) L[1,2]	0.99 (0.38, 2.61) M
	PELD vs MED	1	0.27 (0.03, 2.51) H[1,4]	2.26 (0.09, 59.54) M[1,2,4]	0.78 (0.20, 3.02) M

	PLDD vs MED	0		0.71 (0.04, 13.15) L[1,2]	0.71 (0.04, 13.15) L
	Tubular vs MED	0		0.69 (0.22, 2.21) L[1,2]	0.69 (0.22, 2.21) L
	PLDD vs PELD	0		0.92 (0.04, 20.46) L[1,2]	0.92 (0.04, 20.46) L
	Tubular vs PELD	0		0.90 (0.19, 4.28) L[1,2]	0.90 (0.19, 4.28) L
	Tubular vs PLDD	0		0.97 (0.05, 19.21) L[1,2]	0.97 (0.05, 19.21) L
Post-op complication	MED vs MD/discectomy	6	1.11 (0.71, 1.73) M[1]	1.05 (0.60, 1.49) L[1,2]	0.87 (0.57, 1.35) M
	PELD vs MD/discectomy	6	1.17 (0.34, 4.01) M[1]	1.24 (0.67, 1.90) L[1,2]	0.53 (0.31, 0.90) M
	PLDD vs MD/discectomy	2	1.14 (0.52, 2.47) M[1]	1.06 (0.28, 1.83) L[1,2]	0.87 (0.39, 1.92) M
	Tubular vs MD/discectomy	3	0.99 (0.45, 2.21) M[1]	0.92 (0.41, 1.42) L[1,2]	1.27 (0.64, 2.51) M
	PELD vs MED	1	1.57 (0.57, 4.33) L[1,3]	1.22 (0.20, 2.23) VL[1,2,3]	0.60 (0.32, 1.11) M
	PLDD vs MED	0		1.00 (0.40, 2.46) L[1,2]	1.00 (0.40, 2.46) L
	Tubular vs MED	0		1.45 (0.65, 3.22) L[1,2]	1.45 (0.65, 3.22) L
	PLDD vs PELD	0		1.65 (0.64, 4.31) L[1,2]	1.65 (0.64, 4.31) L
	Tubular vs PELD	0		2.41 (1.00, 5.82) M[1,2,4]	2.41 (1.00, 5.82) M
	Tubular vs PLDD	0		1.46 (0.51, 4.16) L[1,2]	1.46 (0.51, 4.16) L
Type I	MED vs MD/discectomy	6	0.60 (0.26, 1.38) M[1]	0.83 (0.29, 1.38) L[1,2]	1.43 (0.66, 3.08) M
	PELD vs MD/discectomy	6	3.04 (0.25, 7.40) M[1]	1.62 (0.73, 2.51) L[1,2]	0.57 (0.22, 1.47) M
	PLDD vs MD/discectomy	2	-	1.02 (0.05, 18.92) L[1,2]	1.02 (0.05, 18.92) L
	Tubular vs MD/discectomy	3	0.83 (0.51, 1.35) M[1]	0.92 (0.43, 1.41) L[1,2]	0.94 (0.29, 2.98) M
	PELD vs MED	1	1.10 (0.34, 3.55) L[1,3]	0.51 (0.18, 1.46) VL[1,2,3]	0.40 (0.14, 1.16) L
	PLDD vs MED	0		0.71 (0.03, 14.61) L[1,2]	0.71 (0.03, 14.61) L
	Tubular vs MED	0		0.65 (0.16, 2.69) L[1,2]	0.65 (0.16, 2.69) L
	PLDD vs PELD	0		1.80 (0.08, 38.85) L[1,2]	1.80 (0.08, 38.85) L
	Tubular vs PELD	0		1.65 (0.36, 7.67) L[1,2]	1.65 (0.36, 7.67) L
	Tubular vs PLDD	0		0.92 (0.04, 21.32) L[1,2]	0.92 (0.04, 21.32) L
Type II	MED vs MD/discectomy	6	2.17 (0.88, 5.34) H[1,4]	1.4 (0.50, 2.30) L[1,2]	0.50 (0.21, 1.19) M
	PELD vs MD/discectomy	6	1.67 (0.08, 33.21) M[1]	1.29 (0.93, 3.50) L[1,2]	0.60 (0.15, 2.30) M
	PLDD vs MD/discectomy	2	-	1.02 (0.06, 16.43) L[1,2]	1.02 (0.06, 16.43) L
	Tubular vs MD/discectomy	3	-	0.96 (0.10, 9.33) L[1,2]	0.96 (0.10, 9.33) L
	PELD vs MED	1	3.29 (0.13, 81.92) M[1,3,4]	1.09 (0.10, 11.94) V[1,2,3]	1.20 (0.26, 5.49) M
	PLDD vs MED	0		2.04 (0.11, 37.69) M[1,2,4]	2.04 (0.11, 37.69) M
	Tubular vs MED	0		1.93 (0.17, 22.01) L[1,2]	1.93 (0.17, 22.01) L
	PLDD vs PELD	0		1.71 (0.08, 37.55) L[1,2]	1.71 (0.08, 37.55) L
	Tubular vs PELD	0		1.61 (0.11, 22.65) L[1,2]	1.61 (0.11, 22.65) L
	Tubular vs PLDD	0		0.94 (0.03, 34.27) L[1,2]	0.94 (0.03, 34.27) L
Type III	MED vs MD/discectomy	6	0.97 (0.45, 2.08) M[1]	0.98 (0.32, 1.63) L[1,2]	0.98 (0.50, 1.92) M
	PELD vs MD/discectomy	6	0.98 (0.34, 2.82) M[1]	1.00 (0.06, 2.06) L[1,2]	1.15 (0.47, 2.78) M
	PLDD vs MD/discectomy	2	1.14 (0.52, 2.47) M[1]	1.06 (0.28, 1.83) L[1,2]	0.87 (0.36, 2.09) M
	Tubular vs MD/discectomy	3	1.16 (0.45, 2.98) M[1]	0.99 (0.31, 2.67) L[1,2]	0.95 (0.40, 2.26) M
	PELD vs MED	1	0.66 (0.15, 2.85) M[1]	0.98 (0.28, 3.39) L[1,2]	1.17 (0.44, 3.10) M
	PLDD vs MED	0		0.89 (0.29, 2.67) L[1,2]	0.89 (0.29, 2.67) L
	Tubular vs MED	0		0.96 (0.33, 2.81) L[1,2]	0.96 (0.33, 2.81) L
	PLDD vs PELD	0		0.76 (0.22, 2.64) L[1,2]	0.76 (0.22, 2.64) L
	Tubular vs PELD	0		0.83 (0.24, 2.78) L[1,2]	0.83 (0.24, 2.78) L

	Tubular vs PLDD	0		1.09 (0.32, 3.74) L[1,2]	1.09 (0.32, 3.74) L
Reoperation	MED vs MD/discectomy	6	1.00 (0.48, 2.10) M[1]	1.00 (0.38, 1.62) L[1,2]	0.97 (0.44, 2.13) M
	PELD vs MD/discectomy	6	0.72 (0.26, 1.98) M[1]	0.87 (0.14, 1.88) L[1,2]	1.42 (0.53, 3.78) M
	PLDD vs MD/discectomy	2	0.63 (0.23, 1.76) M[1]	1.15 (0.35, 3.76) L[1,2]	2.06 (0.73, 5.80) M
	Tubular vs MD/discectomy	3	1.14 (0.43, 3.04) M[1]	0.79 (0.16, 1.41) L[1,2]	0.87 (0.32, 2.41) M
	PELD vs MED	1	0.66 (0.15, 2.85) M[1]	0.95 (0.33, 1.55) L[1,2]	1.46 (0.48, 4.45) M
	PLDD vs MED	0		2.11 (0.58, 7.76) M[1,2,4]	2.11 (0.58, 7.76) M
	Tubular vs MED	0		0.90 (0.25, 3.24) L[1,2]	0.90 (0.25, 3.24) L
	PLDD vs PELD	0		1.45 (0.35, 6.05) L[1,2]	1.45 (0.35, 6.05) L
	Tubular vs PELD	0		0.62 (0.15, 2.53) L[1,2]	0.62 (0.15, 2.53) L
	Tubular vs PLDD	0		0.42 (0.10, 1.79) M[1,2,4]	0.42 (0.10, 1.79) M

Quality of evidence: H high, M moderate, L low, VL very low; [1]-rated down for imprecision, [2]-rated down for indirectness, [3]-rated down for inconsistency, [4]-rated up for large effect

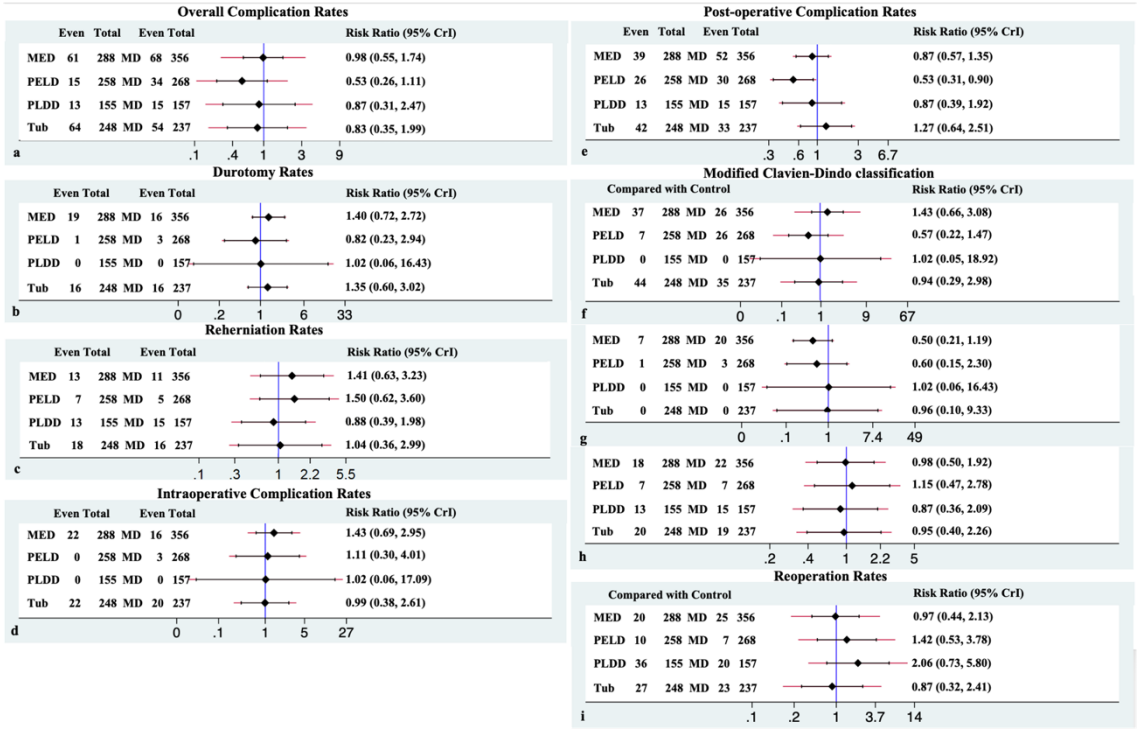

Figure 3.4 Odds ratio with 95% credible intervals (CrI) of comparisons between the four minimally invasive discectomy techniques (PELD, PLDD, MED, and tubular discectomy) and microdiscectomy were used to measure relative efficacy. The results of comparisons were shown as follows: the overall complication rate (Fig 4a), durotomy rates (Fig 4b), reherniation rates (Fig 4c), intraoperative complication rates (Fig 4d), post-operative complication rates (Fig 4e), the complication rates by modified Clavien-Dindo classification scheme (Fig 4f shows Type 1 complication rates, Fig 4g shows Type II complication rates, Fig 4h shows Type III complication rates, and Fig 4i shows reoperation rates)

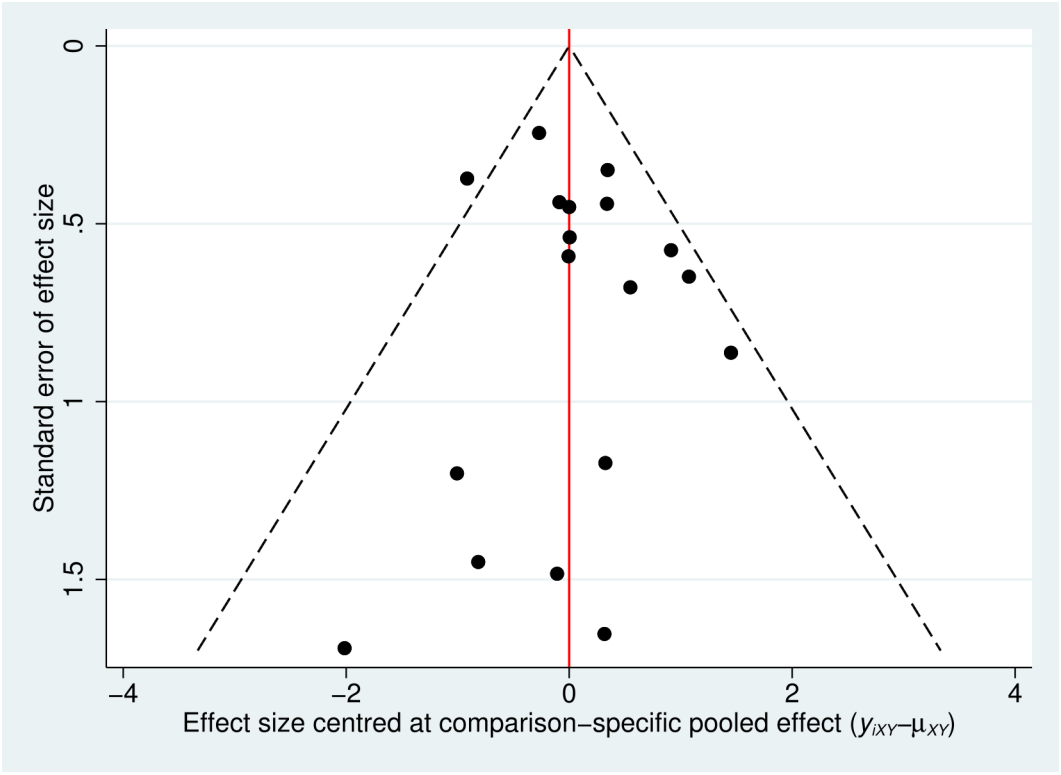

Figure 3.5 Comparison-adjusted funnel plot for different discectomy procedures network. Publication bias of included studies. The red line represents the null hypothesis that the study-specific effect sizes don't differ from the respective comparison-specific pooled effect estimates. Each node corresponds to different comparisons. The comparison-adjusted funnel plot appears symmetric, implying the absence of small-study effects in the network.

3.4 Discussion

In this study, we conducted a NMA of complication rates associated with various discectomy techniques for the surgical treatment of LDH. Complication rates in different classification schemes and reoperation data were extracted from 18 RCTs and analysed. There were no obvious inconsistencies between indirect and direct evidence.

Our results showed that PELD had the lowest overall complication rates of the procedures analysed. PELD and PLDD had the lowest rates of durotomy and reherniation. However, there is no significant difference between each discectomy technique concerning clinically significant complication and reoperation through direct evidence, which is consistent with the findings of prior meta-analyses [11, 13, 15, 16, 20, 22]. The SUCRA rankings in the present study provide a clear ranking of different discectomy techniques for the complication rates by different classification schemes (**Table 3.2**). The procedures from lowest to highest incidence were ordered according to their SUCRA score of overall complication rates as follows: PELD, tubular discectomy, PLDD, MED and OD/MD. An advantage with PELD compared to the other techniques is the coexisting of two major features of minimally invasive discectomy techniques: lesser trauma to soft tissues and better visualization of the operative field. We posit this to be the main cause of PELD ranking the lowest for overall complication rates. These findings are inconsistent with previously reported data [62], which may partly be due to the different definition of surgical technique and complications in the present study.

Although quality assessment has been widely used in clinical research, there is still no consensus on formulating a standard to define and classify surgical complications. The general classification scheme categorizes complications into intraoperative and post-

operative complications, according to the time when they become apparent [12]. It may be useful for the management of complications to have clear guidelines for symptoms. Our results showed that discectomy/microdiscectomy had the lowest intraoperative complication rates, whereas MED had the highest. Regarding post-operative complication rates, PELD showed the lowest complication rates and tubular discectomy had the highest. The risk for complications of lumbar microdiscectomy surgery can be minimized if certain requisites are considered, and also by meticulous attention to preoperative, intraoperative and post-operative details. A good visualization of discectomy technique has low incidence of intraoperative complications and percutaneous discectomy technique has low incidence of post-operative complications.

Therapeutic consequences have been recommended as a way of classifying complications in spine surgery [58, 60]. MCDC for complications is based on the management required for each complication, which can guide the surgeons in deciding the most suitable surgical strategy according to the severity of surgical complications. We first used the MCDC to evaluate the complications following different discectomy surgeries for symptomatic LDH. We found that PELD had the lowest complications that required conservative treatment. MED was associated with complications that usually did not require pharmacological intervention. PLDD was associated with complications that usually did not require a surgical intervention.

SUCRA scores were used to rank the effectiveness of each treatment. However, most comparisons were in low to very low certainty range, which may have resulted in misleading inferences of SUCRA rankings. Grading the evidence from a NMA can enable clinicians, policy makers, and patients to make informed decisions. Our results showed that 53.3% (48 in 90 paired comparisons) low certainty of NMA estimates was

due to indirectness and imprecision (**Table 3.10**). Therefore, despite the high rates of low certainty, low risk of bias, no inconsistency and no publication bias support the SUCRA ranking of our NMA results.

Although the results of our NMA are comprehensive, there are still limitations that may affect our findings. First, the missing of unpublished studies and gray literature (e.g., conference abstract, dissertations, policy documents, book chapters) due to multiple characteristics and potential confounders is likely to impact descriptive results of NMA. Second, the small size of direct comparisons and the small sample size in each treatment arm may have reduced the statistical robustness of the results. Third, there was substantial heterogeneity due to the inconsistency regarding the duration of follow-up. Finally, this NMA solely investigated the relative rank of each discectomy technique under different complication outcomes.

3.5 Conclusion

This study is the first NMA to compare the complication rates of different discectomy techniques using two classification schemes (general classification and MCDC) for the surgical treatment of symptomatic LDH. Our results show that PELD is the safest discectomy technique in the five discectomy techniques (e.g., OD/MD, PELD, MED, PLDD, and tubular discectomy) for the surgical treatment of symptomatic LDH in terms of minimal rates for overall complications, post-operative complications, and complications necessitating conservative treatment. OD/MD, MED and PLDD are the safest procedure for LDH with minimal intraoperative complication rates, complications requiring pharmacological and surgical treatment respectively. Tubular discectomy is the safest discectomy technique for LDH with minimal reoperation rates. Due to the

inherent limitations of this study, further research should be performed to explore complication rates of these discectomy techniques using a standardized complication scheme.

Despite the frequent usage of different discectomy techniques, there are variations in the technique used and the complications encountered when performing lumbar discectomy for LDH. There is a lack of clarity as to why there is variation and, even more, no consensus on what the best way is to manage LDH.

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Chapter 4. The Complication Cascade: Surgeons' Perceptions Around Discectomy Surgery for Lumbar Disc Herniation Based on an Online Survey of Orthopaedic and Neurosurgeons in Australia and New Zealand

While the complication outcomes vary between techniques as reported in the previous chapters, variations may be attributed to a variety of factors including the "surgical learning curve", surgeon's experience, level of training, and the frequency of use. Despite the availability of various evidence-based guidelines, substantial variability still exists in the surgical practice for the management of lumbar disc herniation. It is still unknown why there is variation in lumbar disc herniation management and no consensus on the best approach to management. A study on the surgeons' perceptions around discectomy surgery for lumbar disc herniation is required. Understanding practice-based differences in treatment of lumbar disc herniation is vital for reducing unwarranted variation in the delivery of spine surgical health care. Identifying factors that influence surgeons' decision-making will offer useful insights for developing the most cost-effective and safest surgical strategy as well as developing surgeon education materials for common lumbar pathologies.

4.1 Introduction

Since the first publication on discectomy for ruptured intervertebral disc by Mixter and Barr in 1934 [1], a variety of surgical techniques have been developed, including the more recent introduction of different minimally invasive and innovative surgical procedures [2-7]. While the clinical outcomes vary between techniques, the variations may be

attributed to a variety of factors including the surgical learning curve, surgeon's experience, level of training, and the frequency of use.

Despite the availability of various evidence-based guidelines, there is a lack of consensus amongst orthopaedic surgeons and neurosurgeons on the clinical management of spinal disorders, particularly around the choice of surgical procedure and/or instrumentation [8-10]. Some factors responsible for this variation include the volume of spine surgery case exposure during speciality training [11], number of surgeries performed per year and number of years in practice (practice length) [12], practice cultures based on geographical region and practice setting (e.g., academic, private) [10, 13], complication rates associated with different surgical techniques [14, 15], and variability in costs [16]. In the United States, the surgical management of lumbar disc herniation (LDH) and recurrent LDH (rLDH) is under increased scrutiny, mainly due to wide variations in surgery costs based on geographical region, speciality, operative volume, and practice duration of the treating surgeon [12, 13]. In Australia, over 12000 discectomy procedures are performed annually for primary LDH and rLDH patients (2018 unpublished data from Australia Institute Health and Welfare). Various discectomy procedures give excellent short-term clinical outcomes [17, 18]. Yet, there is a lack of clarity as to why there is variation and, even more, no consensus on what the best way is to manage primary LDH or rLDH.

We conducted an online, anonymous survey of orthopaedic surgeons and neurosurgeons in Australia and New Zealand to capture variations in the surgical management of LDH (and rLDH) patients. The main objective of the survey was: (1) to capture variation in techniques used for the surgical treatment of primary LDH and rLDH (first and second rLDH); (2) to capture perceived complications of the various surgical procedures for primary LDH and rLDH; and (3) to capture any variation in the choice of surgical

procedures based on individual factors. The survey results will be useful in identifying factors that influence a surgeons' decision-making for the surgical management of LDH patients in the Australia and New Zealand region, and for further developing surgeon education and training materials.

4.2 Methods

4.2.1 Study design

After obtaining ethics approval from the University of New South Wales - Human Research Ethics Committee (HC 180800), a 33-question online survey was created on the online platform Survey Monkey (www.surveymonkey.com), with questions specific to the surgical techniques for primary and recurrent LDHs and the potential complications associated with both procedures. The survey included three sections: Section I included seven questions on details of the surgeons' practice; Section II included eighteen questions on lumbar discectomy for primary LDH; and Section III included eight questions on revision lumbar surgery for rLDH. For all frequency-based questions, we captured the surgeon's opinion using the 5-point Likert scale with options: "never", "seldom", "sometimes", "often", and "always". The questionnaire is available in the **Appendix 1**.

The survey uses an overlapping panel design involving 3 rounds of interviews by three centers (include 6 panels from St George Private Hospital in Australia, 3 panels from Spine Society of Australia, and 3 panels from Harvard Medical School in United States) over a half year period. All questions in this survey are based on treatment and rehabilitation guidelines for symptomatic LDH, previously published studies, surgeons opinoin, and patients' need.

4.2.2 Participants

The survey was sent to clinicians who met the following inclusion criteria: (1) an orthopaedic surgeon or a neurosurgeon who routinely performs spinal surgery; (2) practice based in Australia and New Zealand; (3) in clinical practice at the time of participating in the survey.

4.2.3 Conducting the survey

With support from the Spine Society of Australia, Australian Orthopaedic Association, Neurosurgical Society of Australasia, New Zealand Orthopaedic Association, Neurological Association of New Zealand, and International Society for the Study of the Lumbar Spine, the online link to the survey was emailed to all surgeons affiliated with the societies. The email explained the purpose in detail, and the anonymous survey was entirely voluntary.

To increase response rate, the survey was sent 3 times via email. Because surveys were returned anonymously, all recipients received 3 emails in 6 weeks (the interval between each email is 2 weeks), and the second and third emails included the statement, “If you responded to this survey previously, please disregard this email.”

4.2.4 Statistical analysis

Data was summarized in contingency tables using counts and percentages. Chi-squared test of independence was used to test for differences among different surgical procedures and differences in perceptions around surgical complications. The percentage data in the table and figure is the surgeons’ perceptions around surgical complications rather than actual complication rates. The threshold for statistical

significance was set at 2-sided $P<0.05$. Statistical tests were conducted using the commercially available software package SPSS (v24.0, IBM Corporation, Armonk, USA).

4.3 Results

4.3.1 Participants and general details of surgeons' work

Invitations were sent to 150 surgeons in total in the Australia and New Zealand region. Ninety-six completed the survey (response rate = 64%). The majority of respondents were from Australia (65 [68%]), orthopaedic surgeons (62 [65%]), hybrid practitioners (58 [61%]), had more than five years of practicing experience as an orthopaedic or neurosurgeon (87 [90%]), performed more than 50% spine surgeries in their practice (86 [90%]), performed more than 150 spine surgeries per year (63 [66%]), and performed more than 25 discectomies per year (68 [70%]) (**Figure 4.1**).

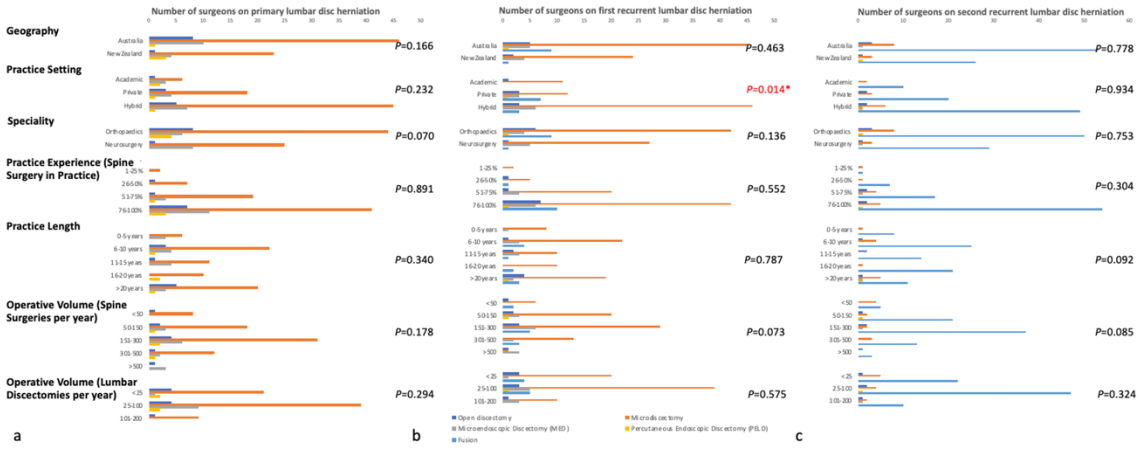

Figure 4.1 The choice of surgical procedures for primary lumbar disc herniation (LDH) and recurrent LDH (rLDH). The association between individual surgeon factors (Geography, practice setting, speciality, practice experience, practice length, and operative volume) and the choice of surgical procedures for the primary LDH and rLDH

(a: primary LDH, b: first rLDH, and c: second rLDH). Chi-squared test of independence was used for examining between-group differences. * Statistically significant difference, $P<0.05$.

4.3.2 Perception on discectomy for primary LDH

4.3.2.1 Variations in surgical procedures

In the absence of a neurological deficit (e.g., lower extremity weakness, bowel or bladder incontinence), most of the participating surgeons reported that they would consider a period of either 4 to 8 weeks (66% (63)) or 8 to 12 weeks (27% (26)) as the minimum duration of symptoms before offering surgery. The remaining 7% (7) deemed more than 12 weeks as an acceptable period of radicular pain after which surgery could be offered. Respondents reported using various discectomy techniques for primary LDH: 73% (69) of the surgeons performed microdiscectomy, 14% (14) performed microendoscopic discectomy, 9% (9) performed open discectomy, and 4% (4) of the surgeons did percutaneous endoscopic discectomy. There was no significant difference in the choice of surgical procedure for primary LDH when comparing different individual factors for the responding surgeons (e.g., geography, practice setting, speciality, practice experience (the percentage of spine surgery in practice), practice length, and operative volume (the annual of spine surgeries performed and the annual of lumbar discectomies performed)) (**Figure 4.1**).

4.3.2.2 Intraoperative and post-operative complications following discectomy

Surgeons ranked durotomy as the most common intraoperative complication and reherniation as the most common post-operative complication when performing

discectomy surgery for primary LDH (97% (93) and 95% (91) respectively) (**Table 4.1**). Nearly 97% (93) of respondents estimated the incidence of intraoperative complications to be less than 5% in their practice and 75% (72) estimated post-operative complications in less than 5% of their patients when performing discectomy for primary LDH. No significant differences were identified in the perceived intraoperative and post-operative complication rates following primary discectomy surgery when comparing individual surgeon factors or type of surgical procedure performed (**Figure 4.2**, **Table 4.2, and Table 4.3).**

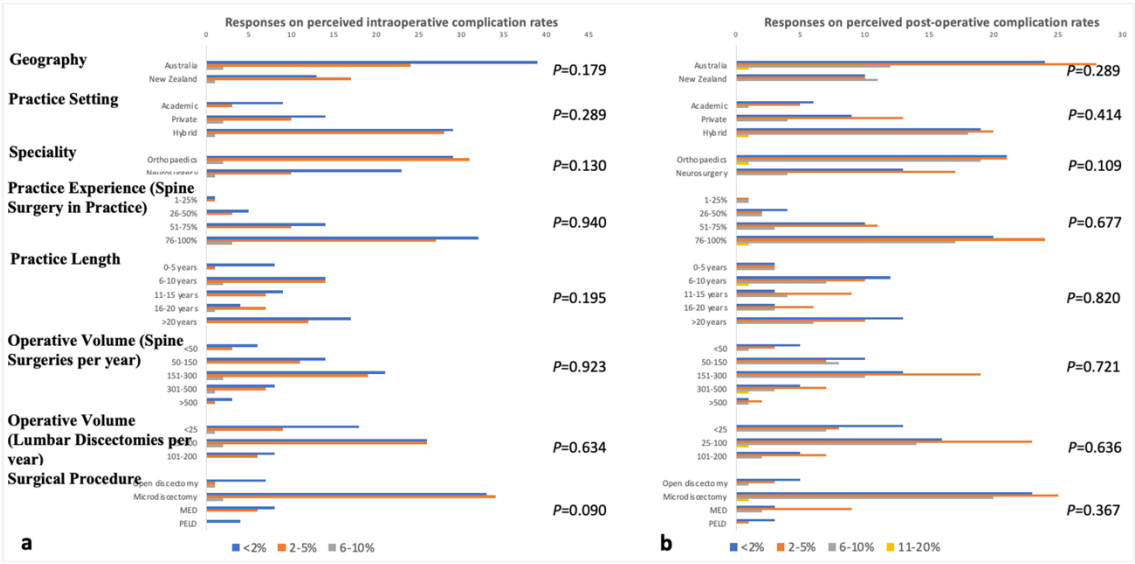

Figure 4.2 Perceived complications rates following discectomy for primary lumbar disc herniation (LDH). The association between surgeon demographic factors (geography, practice setting, speciality, practice experience, practice length, and operative volume) and perceived intraoperative complication rates (Figure 2a) and post-operative complication rates (Figure 2b) following discectomy for primary LDH. Chi-squared test of independence was used for examining between-group differences.

Table 4.1 Surgeon's perceptions around surgical complications following discectomy for primary lumbar disc herniation

Characteristic	Open discectomy	Microdiscectomy	Tubular Discectomy	Microendoscopic Discectomy (MED)	Percutaneous Endoscopic Discectomy (PELD)	Fusion	*P* value [a]
Intraoperative complication							
Durotomy							
Yes	9 (100%)	66 (96%)	0	14 (100%)	4 (100%)	0	1.000
No	0	3 (4%)	0	0	0	0	
Nerve root injury							
Yes	1 (11%)	36 (52%)	0	7 (50%)	1 (25%)	0	0.096
No	8 (89%)	33 (48%)	0	7 (50%)	3 (75%)	0	
Wrong surgery level							
Yes	3 (33%)	13 (19%)	0	4 (29%)	0	0	0.545
No	6 (66.7%)	56 (81%)	0	10 (71%)	4 (100%)	0	
Haemorrhage							
Yes	1 (11%)	17 (14%)	0	4 (29%)	1 (25%)	0	0.825
No	8 (89%)	52 (86%)	0	10 (71%)	3 (75%)	0	
Post-operative complication							
Superficial infection							
Yes	7 (78%)	59 (86%)	0	10 (71%)	4 (100%)	0	0.442
No	2 (22%)	10 (14%)	0	4 (29%)	0	0	
Deep infection							
Yes	4 (44%)	30 (43%)	0	5 (36%)	0	0	0.453
No	5 (56%)	39 (57%)	0	9 (64%)	4 (100%)	0	
Hematoma							
Yes	1 (11%)	29 (42%)	0	7 (50%)	3 (75%)	0	0.128
No	8 (89%)	40 (58%)	0	7 (50%)	1 (25%)	0	
Reherniation							
Yes	7 (78%)	66 (96%)	0	14 (100%)	4 (100%)	0	0.169
No	2 (22%)	3 (4%)	0	0	0	0	
Post-operative segment instability							
Yes	1 (11%)	22 (32%)	0	3 (25%)	1 (25%)	0	0.671
No	8 (89%)	47 (68%)	0	9 (75%)	3 (75%)	0	

[a] Chi-squared test of independence was used for between-group differences. The percentage data in the table is the surgeons' perceptions around surgical complications rather than actual complication rates following discectomy for primary lumbar disc herniation.

Table 4.2 Perceived intraoperative complications rates following discectomy for primary lumbar disc herniation (LDH)

Characteristic	<2%	2-5%	6-10%	11-20%	>20%	*P* value [a]
Geography						
Australia	39 (41%)	24 (25%)	2 (2%)	0	0	0.179
New Zealand	13 (13%)	17 (18%)	1 (1%)	0	0	
Practice Setting						
Academic	9 (9%)	3 (3%)	0	0	0	0.289
Private	14 (15%)	10 (10%)	2 (2%)	0	0	
Hybrid	29 (30%)	28 (29%)	1 (1%)	0	0	
Speciality						
Orthopaedics	29 (30%)	31 (32%)	2 (2%)	0	0	0.130
Neurosurgery	23 (24%)	10 (10%)	1 (1%)	0	0	
Practice experience (Spine Surgery in Practice)						
1-25%	1 (1%)	1 (1%)	0	0	0	0.940
26-50%	5 (5%)	3 (3%)	0	0	0	
51-75%	14 (15%)	10 (10%)	0	0	0	
76-100%	32 (33%)	27 (28%)	3 (3%)	0	0	
Practice length						
0-5 years	8 (8%)	1 (1%)	0	0	0	0.195
6-10 years	14 (15%)	14 (15%)	2 (2%)	0	0	
11-15 years	9 (9%)	7 (7%)	0	0	0	
16-20 years	4 (4%)	7 (7%)	1 (1%)	0	0	
>20 years	17 (18%)	12 (12%)	0	0	0	
Operative Volume (Spine Surgeries per year)						
<50	6 (6%)	3 (3%)	0	0	0	0.923
50-150	14 (15%)	11 (11%)	0	0	0	
151-300	21 (22%)	19 (20%)	2 (2%)	0	0	
301-500	8 (8%)	7 (7%)	1 (1%)	0	0	
>500	3 (3%)	1 (1%)	0	0	0	
Operative Volume (Lumbar Discectomies per year)						
<25	18 (19%)	9 (9%)	1 (1%)	0	0	0.634
25-100	26 (27%)	26 (27%)	2 (2%)	0	0	
101-200	8 (8%)	6 (6%)	0	0	0	
Surgical interventions						
Open discectomy	7 (7%)	1 (1%)	1 (1%)	0	0	0.090
Microdiscectomy	33 (34%)	34 (35%)	2 (2%)	0	0	
MED	8 (8%)	6 (6%)	0	0	0	
PELD	4 (4%)	0	0	0	0	

P<0.05. [a] Fisher's exact test was used for between-group differences. The percentage data in the table is the surgeons' perceptions around surgical complications rather than actual complication rates.

Table 4.3 Perceived post-operative complications rates following discectomy for primary lumbar disc herniation (LDH)

Characteristic	<2%	2-5%	6-10%	11-20%	>20%	*P* value [a]
Geography						
Australia	24 (25%)	28 (30%)	12 (13%)	1 (1%)	0	0.289
New Zealand	10 (10%)	10 (10%)	11 (11%)	0	0	
Practice Setting						
Academic	6 (6%)	5 (5%)	1 (1%)	0	0	0.414
Private	9 (9%)	13 (14%)	4 (4%)	0	0	
Hybrid	19 (20%)	20 (21%)	18 (19%)	1 (1%)	0	
Speciality						
Orthopaedics	21 (22%)	21 (22%)	19 (20%)	1 (1%)	0	0.109
Neurosurgery	13 (14%)	17 (18%)	4 (4%)	0	0	
Practice experience (Spine Surgery in Practice)						
1-25%	0	1 (1%)	1 (1%)	0	0	0.677
26-50%	4 (4%)	2 (2%)	2 (2%)	0	0	
51-75%	10 (10%)	11 (11%)	3 (3%)	0	0	
76-100%	20 (21%)	24 (25%)	17 (18%)	1 (1%)	0	
Practice length						
0-5 years	3 (3%)	3 (3%)	3 (3%)	0	0	0.820
6-10 years	12 (13%)	10 (10%)	7 (7%)	1 (1%)	0	
11-15 years	3 (3%)	9 (9%)	4 (4%)	0	0	
16-20 years	3 (3%)	6 (6%)	3 (3%)	0	0	
>20 years	13 (14%)	10 (10%)	6 (6%)	0	0	
Operative Volume (Spine Surgeries per year)						
<50	5 (5%)	3 (3%)	1 (1%)	0	0	0.721
50-150	10 (10%)	7 (7%)	8 (8%)	0	0	
151-300	13 (14%)	19 (20%)	10 (10%)	0	0	
301-500	5 (5%)	7 (7%)	3 (3%)	1 (1%)	0	
>500	1 (1%)	2 (2%)	1 (1%)	0	0	
Operative Volume (Lumbar Discectomies per year)						
<25	13 (14%)	8 (8%)	7 (7%)	0	0	0.636
25-100	16 (16%)	23 (24%)	14 (15%)	1 (1%)	0	
101-200	5 (5%)	7 (7%)	2 (2%)	0	0	
Surgical interventions						
Open discectomy	5 (5%)	3 (3%)	1 (1%)	0	0	0.367
Microdiscectomy	23 (24%)	25 (26%)	20 (21%)	1 (1%)	0	
MED	3 (3%)	9 (9%)	2 (2%)	0	0	
PELD	3 (3%)	1 (1%)	0	0	0	

[a] Fisher's exact test was used for between-group differences. The percentage data in the table is the surgeons' perceptions around surgical complications rather than actual complication rates.

4.3.2.3 Risk factors for complications

Thirty-two percent of the respondents reported that a surgeon's experience is the most important factor in the risk for surgical complications (**Figure 4.3)**. No significant difference was identified in the perceived risk for durotomy and reherniation following primary discectomy for LDH when comparing individual surgeon factors (except for the annual volume of spine surgeries performed, and the annual volume of lumbar discectomies performed). Significant differences were observed, however, when categorizing the respondents based on operative volume: surgeons with a higher operative volume (>150 spine surgeries per year) perceived a higher risk for reherniation following primary discectomy than those with a lower operative volume (<150 spine surgeries per year) (90% of respondents with a high operative volume perceived reherniation vs 10% of respondents with a low operative volume perceived reherniation, *P*=0.013) and surgeons who performed more than 25 lumbar discectomies per year perceived a higher risk for durotomy in primary discectomies than those who performed less than 25 lumbar discectomies per year (73% of respondents with a high operative volume perceived durotomy vs 27% of respondents with a low operative volume perceived durotomy, *P*=0.023) (**Table 4.4**).

Table 4.5 presents surgeons' perceived complications at various stages of discectomy for primary LDH. The use of intraoperative imaging to mark/confirm the level of discectomy surgery was perceived to significantly reduce the incidence of wrong level surgery (*P*=0.030). Conversely, the use of a mix of instruments (burr and Kerrison punch) for laminectomy or laminotomy, limited removal of the intervertebral disc (free fragment and unilateral removal), wound irrigation, use of different methods for

hemostasis, annular closure after completion of the discectomy and use of anti-adhesive were not perceived to significantly reduce the incidence of complications.

4.3.2.4 Post-operative management

In terms of post-operative advice and restrictions, all surgeons expected patients to ambulate within 24 hours after surgery and almost 76% (73) reported prescribing physiotherapy during post-operative rehabilitation.

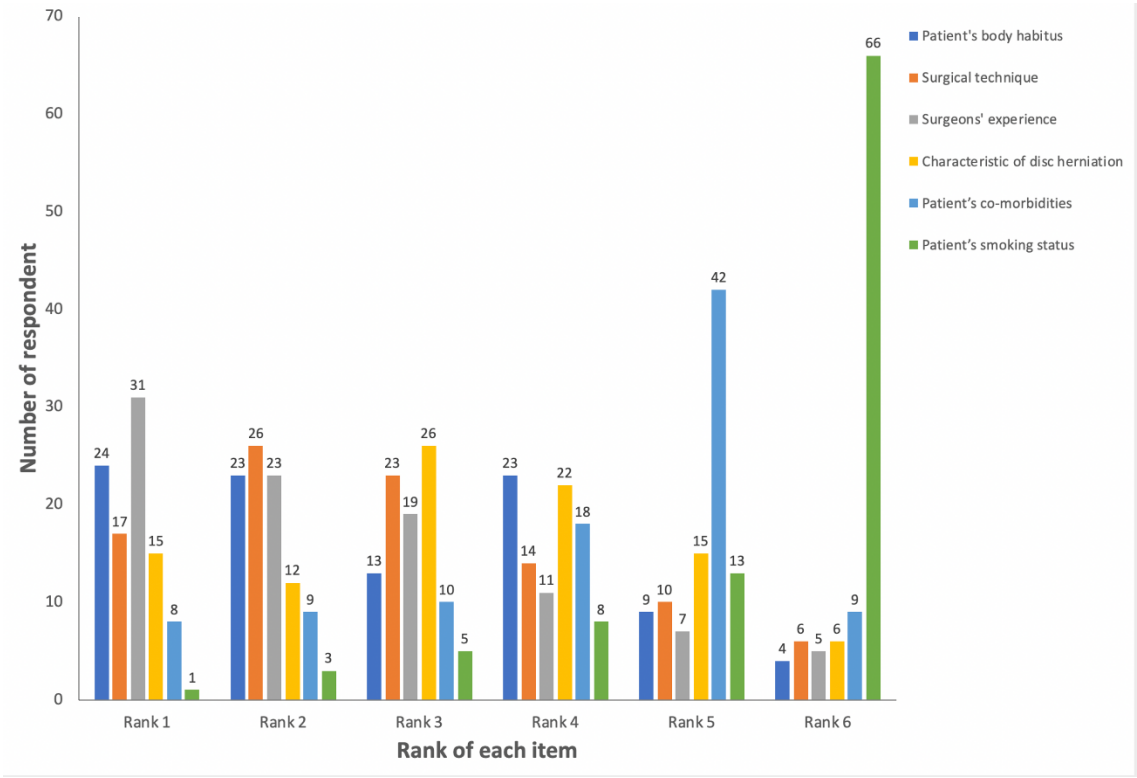

Figure 4.3 Surgeons' perceptions of the risk factor for complications. Survey participants were asked to rank several items which may increase the risk for a surgical complication to develop during lumbar discectomy, in the order of importance with 1 being the most important item and 6 being the least important item.

Table 4.4 The association between surgeon demographic factors and perceived occurrence of reherniation and durotomy

	Following Primary Discectomy			Following Revision Surgery			Following Primary Discectomy			Following Revision Surgery		
	Perceived reherniation (%)	**No perceived reherniation (%)**	***P* value [a]**	**Perceived reherniation (%)**	**No perceived reherniation (%)**	***P* value [a]**	**Perceived durotomy (%)**	**No perceived durotomy (%)**	***P* value [a]**	**Perceived durotomy (%)**	**No perceived durotomy (%)**	***P* value [a]**
Geography												
Australia	60 (66%)	5 (100%)	0.171	47 (69%)	18 (64%)	0.640	62 (67%)	3 (100%)	0.549	61 (67%)	4 (80%)	1.000
New Zealand	31 (34%)	0		21 (31%)	10 (36%)		31 (33%)	0		30 (33%)	1 (20%)	
Practice Setting												
Academic	11 (12%)	1 (20%)		7 (10%)	5 (18%)		56 (60%)	2 (67%)		12 (13%)	0	
Private	24 (26%)	2 (40%)	0.153	20 (29%)	6 (21%)	0.492	26 (28%)	0	0.483	24 (26%)	2 (40%)	0.82
Hybrid	56 (62%)	2 (40%)		41 (61%)	17 (61%)		11 (12%)	1 (33%)		55 (61%)	3 (60%)	
Speciality												
Neurosurgery	32 (35%)	2 (40%)	0.826	25 (37%)	9 (32%)	0.815	33 (35%)	1 (33%)	1.000	32 (35%)	2 (40%)	1.000
Orthopaedics	59 (65%)	3 (60%)		43 (63%)	19 (68%)		60 (65%)	2 (67%)		59 (65%)	3 (60%)	
Practicing Length												
0-5 y	9 (10%)	0	0.460	5 (7%)	4 (14%)	0.441	8 (9%)	1 (33%)	0.258	8 (9%)	1 (20%)	0.395
>5 y	82 (90%)	5 (100%)		63 (93%)	24 (86%)		85 (91%)	2 (67%)		83 (91%)	4 (80%)	
Practice Experience (Spine Surgery)												
<50%	8 (9%)	2 (40%)	0.083	4 (6%)	6 (21%)	0.059	10 (11%)	0	1.000	8 (9%)	2 (40%)	0.083
>50%	83 (91%)	3 (60%)		64 (94%)	22 (79%)		83 (89%)	3 (100%)		83 (91%)	3 (60%)	
Spine Surgery per year												
<150	9 (10%)	3 (60%)	0.013 [b]	3 (4%)	6 (21%)	0.017[b]	8 (9%)	1 (33%)	0.258	32 (35%)	2 (40%)	1.000
>150	82 (90%)	2 (40%)		65 (96%)	22 (79%)		85 (91%)	2 (67%)		59 (65%)	3 (60%)	
Lumbar Discectomies per year												
<25	25 (27%)	3 (60%)	0.118	13 (19%)	12 (43%)	0.022[b]	25 (27%)	3 (100%)	0.023[b]	26 (29%)	2 (40%)	0.627
>25	66 (73%)	2 (40%)		55 (81%)	16 (57%)		68 (73%)	0		65 (71%)	3 (60%)	

[a] Chi-squared test of independence was used for between-group differences.

[b] Statistically significant difference, P<0.05. Surgeon demographic factors include geography, practice setting, speciality, practice length, practice experience, and operative volume. The percentage data in the table is the surgeons' perceptions around surgical complications rather than actual complication rates.

Table 4.5 The association between surgical techniques for primary lumbar disc herniation and perceived complications at different stages of the procedure

Surgical techniques	Perceived complication (%)	No complication (%)	*P* value
Mark/confirm surgical level	**Wrong level**	**None**	
Before incision	0	7 (9%)	
Before incision and after reaching bone	12 (60%)	59 (78%)	
After reaching bone	7 (35%)	9 (12%)	0.030[b]
Review imaging and anatomy	1 (5%)	1 (3%)	
Technique for laminectomy/laminotomy	**Durotomy**	**No durotomy**	
Burr	13 (14%)	1 (33%)	
Hand-held Kerrison punch	16 (17%)	0	
Bone scalpel	2 (2%)	0	0.812
Mixture (burr and Kerrison punch)	62 (67%)	2 (67%)	
Removal of disc	**Instability**	**No instability**	
Free fragment	6 (22%)	26 (38%)	
With small extent unilateral	8 (30%)	28 (41%)	
With large extent unilateral	11 (41%)	12 (17%)	0.079
With large extent bilateral	2 (7%)	3 (4%)	
Complete	0	0	
"Flush out"/irrigate	**Deep infection**	**No deep infection**	
Never (0%)	8 (21%)	8 (14%)	
Seldom (1-25%)	7 (18%)	13 (23%)	
Sometimes (26-50%)	6 (15%)	3 (5%)	0.205
Often (51-75%)	5 (13%)	16 (28%)	
Always (100%)	13 (33%)	17 (30%)	
Annular closure	**Reherniation**	**No reherniation**	
Do not	83 (91%)	5 (100%)	
Suture	0	0	
Device	8 (9%)	0	0.641
Glue	0	0	
Haemostasis	**Hematoma**	**No hematoma**	
Electrocautery	33 (34%)	48 (50%)	
Direct pressure	31 (32%)	32 (33%)	
Sponge	25 (26%)	35 (36%)	0.840
Bone wax	27 (28%)	32 (33%)	
Fibrin sealant	23 (24%)	33 (34%)	
Anti-adhesive	**Back failure syndrome**	**None**	
No	5 (83%)	72 (80%)	
Yes	1 (17%)	18 (20%)	1.000

Chi-squared test of independence was used for between-group differences.

[b] Statistically significant difference, P<0.05. The percentage data in the table is the surgeons' perceptions around surgical complications rather than actual complication rates.

4.3.3 Perception on various surgical procedures for rLDH

4.3.3.1 Variation in surgical procedures

Almost 90% (86) of the surgeons would perform a repeat discectomy surgery, and 10% (10) would perform fusion surgery for treating the first rLDH in their patients. Eighty-two percent (78) of the surgeons would perform fusion surgery, and 18% (18) would perform a discectomy surgery for treating the second rLDH. No significant difference was identified in the choice of surgical procedure for treating the first and the second rLDH when comparing individual surgeon factors except practice setting: surgeons in private practice had greater odds of selecting fusion surgery compared with surgeons in other practice settings (academic practice, 0%; private practice, 70%; hybrid practice, 30%; *P*=0.014) (**Figure 4.1**).

4.3.3.2 Intraoperative and post-operative complications in revision surgery/ies

Nearly 60% (57) of surgeons perceived a less than 5% intraoperative complication rate and 55% (53) of surgeons perceived a less than 5% post-operative complications rate when performing revision surgery/ies for rLDH. Specifically, surgeons perceived durotomy and superficial infection as the most common intraoperative and post-operative complications following revision surgeries for rLDH (95% (91) and 85% (82), respectively) (**Table 4.6**). A significant difference was identified in the perceived intraoperative complication rates when comparing operative volume (Annual volume of

spine surgeries performed: *P*=0.016 and Annual volume of lumbar discectomies performed: *P*=0.036) (**Figure 4.4, Table 4.7, and Table 4.8**).

4.3.3.3 Risk factors for complications

No significant differences were identified in the perceived reherniation and durotomy rates following revision surgeries for rLDH when comparing individual surgeon factors (except the annual volume of spine surgeries performed, and the annual volume of lumbar discectomies performed). Surgeons with a higher operative volume (>150 spine surgeries per year) perceived a higher risk for reherniation following revision surgeries than those with a lower operative volume (<150 spine surgeries per year) (96% of respondents with a high operative volume perceived reherniation vs 4% of respondents with a low operative volume perceived reherniation, *P*=0.017) and surgeons with a higher operative volume (>25 lumbar discectomies per year) perceived a higher risk for reherniation following revision surgeries than those with a lower operative volume (<25 lumbar discectomies per year) (81% of respondents with a high operative volume perceived reherniation vs 19% of respondents with a low operative volume perceived reherniation, *P*=0.022) (**Table 4.4**).

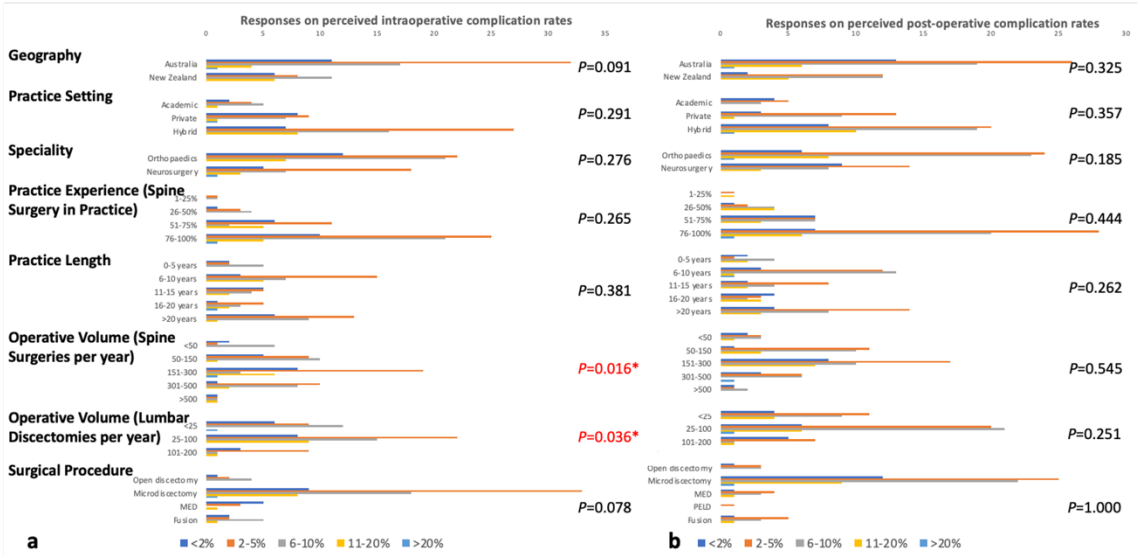

Figure 4.4 Perceived complications rates following revision surgery/ies for recurrent lumbar disc herniation (rLDH). The association between surgeon demographic factors (geography, practice setting, speciality, practice experience, practice length, and operative volume) and perceived intraoperative complication rates (Figure 4a) and post-operative complication rates (Figure 4b) following revision surgery/ies for rLDH. Chi-squared test of independence was used for examining between-group differences.

Table 4.6 Surgeon's perceptions around surgical complications following revision surgeries for recurrent lumbar disc herniation

Characteristic	Open discectomy	Microdiscectomy	Tubular Discectomy	Microendoscopic Discectomy (MED)	Percutaneous Endoscopic Discectomy (PELD)	Fusion	*P* value [a]
Intraoperative complication							
Durotomy							
Yes	7 (88%)	65 (97%)	0	9 (90%)	1 (100%)	9 (90%)	0.217
No	1 (12%)	2 (3%)	0	1 (10%)	0	1 (10%)	
Nerve root injury							
Yes	2 (25%)	38 (57%)	0	5 (50%)	0	5 (50%)	0.389
No	6 (75%)	29 (43%)	0	5 (50%)	1 (100%)	5 (50%)	
Wrong surgery level							
Yes	0	6 (9%)	0	1 (10%)	0	0	1.000
No	8 (100%)	61 (91%)	0	9 (90%)	1 (100%)	10 (100%)	
Haemorrhage							
Yes	2 (25%)	19 (28%)	0	5 (50%)	0	3 (30%)	0.702
No	6 (75%)	48 (72%)	0	5 (50%)	1 (100%)	7 (70%)	
Post-operative complication							
Superficial infection							
Yes	6 (75%)	60 (90%)	0	7 (70%)	0	9 (90%)	0.053
No	2 (25%)	7 (10%)	0	3 (30%)	1 (100%)	1 (10%)	
Deep infection							
Yes	4 (50%)	29 (43%)	0	3 (30%)	0	7 (70%)	0.353
No	4 (50%)	38 (57%)	0	7 (70%)	1 (100%)	3 (30%)	
Hematoma							
Yes	2 (25%)	29 (43%)	0	5 (50%)	0	1 (10%)	0.186
No	6 (75%)	38 (57%)	0	5 (50%)	1 (100%)	9 (90%)	
Reherniation							
Yes	4 (50%)	50 (75%)	0	9 (90%)	1 (100%)	4 (40%)	0.052
No	4 (50%)	17 (25%)	0	1 (10%)	0	6 (60%)	
Post-operative segment instability							
Yes	1 (13%)	27 (40%)	0	6 (60%)	0	3 (30%)	0.270
No	7 (87%)	40 (60%)	0	4 (40%)	1 (100%)	7 (70%)	

[a] Chi-squared test of independence was used for between-group differences. The percentage data in the table is the surgeons' perceptions around surgical complications rather than actual complication rates.

Table 4.7 Perceived intraoperative complications rates following revision surgery/ies for recurrent lumbar disc herniation (rLDH)

Characteristic	<2%	2-5%	6-10%	11-20%	>20%	*P* value [a]
Geography						
Australia	11 (11%)	32 (33%)	17 (18%)	4 (4%)	1 (1%)	0.091
New Zealand	6 (6%)	8 (8%)	11 (11%)	6 (6%)	0	
Practice Setting						
Academic	2 (2%)	4 (4%)	5 (5%)	1 (1%)	0	0.291
Private	8 (8%)	9 (9%)	7 (7%)	1 (1%)	1 (1%)	
Hybrid	7 (7%)	27 (28%)	16 (17%)	8 (8%)	0	
Speciality						
Orthopaedics	12 (12%)	22 (23%)	21 (22%)	7 (7%)	0	0.276
Neurosurgery	5 (5%)	18 (19%)	7 (7%)	3 (3%)	1 (1%)	
Practice experience (Spine Surgery in Practice)						
1-25%	0	1 (1%)	1 (1%)	0	0	0.265
26-50%	1 (1%)	3 (3%)	4 (4%)	0	0	
51-75%	6 (6%)	11 (11%)	2 (2%)	5 (5%)	0	
76-100%	10 (10%)	25 (26%)	21 (22%)	5 (5%)	1 (1%)	
Practice length						
0-5 years	2 (2%)	2 (2%)	5 (5%)	0	0	0.381
6-10 years	3 (3%)	15 (16%)	7 (7%)	5 (5%)	0	
11-15 years	5 (5%)	5 (5%)	4 (4%)	2 (2%)	0	
16-20 years	1 (1%)	5 (5%)	3 (3%)	2 (2%)	1 (1%)	
>20 years	6 (6%)	13 (14%)	9 (9%)	1 (1%)	0	
Operative Volume (Spine Surgeries per year)						
<50	2 (2%)	1 (1%)	6 (6%)	0	0	0.016*
50-150	5 (5%)	9 (9%)	10 (10%)	1 (1%)	0	
151-300	8 (8%)	19 (20%)	3 (3%)	6 (6%)	1 (1%)	
301-500	1 (1%)	10 (10%)	8 (8%)	2 (2%)	0	
>500	1 (1%)	1 (1%)	1 (1%)	1 (1%)	0	
Operative Volume (Lumbar Discectomies per year)						
<25	6 (6%)	9 (9%)	12 (13%)	0	1 (1%)	0.036*
25-100	8 (8%)	22 (23%)	15 (16%)	9 (9%)	0	
101-200	3 (3%)	9 (9%)	1 (1%)	1 (1%)	0	
Surgical interventions						
Open discectomy	1 (1%)	2 (2%)	4 (4%)	0	0	0.078
Microdiscectomy	9 (9%)	33 (34%)	18 (19%)	8 (8%)	1 (1%)	
MED	5(5%)	3 (3%)	0	1 (1%)	0	
Fusion	2 (2%)	2 (2%)	5 (5%)	1 (1%)	0	

* Statistically significant difference, $P<0.05$. [a] Fisher's exact test was used for between-group differences. The percentage data in the table is the surgeons' perceptions around surgical complications rather than actual complication rates.

Table 4.8 Perceived post-operative complications rates following revision surgery/ies for recurrent lumbar disc herniation (rLDH)

Characteristic	<2%	2-5%	6-10%	11-20%	>20%	*P* value [a]
Geography						
Australia	13 (14%)	26 (27%)	19 (20%)	6 (6%)	1 (1%)	0.325
New Zealand	2 (2%)	12 (13%)	12 (13%)	5 (5%)	0	
Practice Setting						
Academic	4 (4%)	5 (5%)	3 (3%)	0	0	0.357
Private	3 (3%)	13 (14%)	9 (9%)	1 (1%)	0	
Hybrid	8 (8%)	20 (21%)	19 (20%)	10 (10%)	1 (1%)	
Speciality						
Orthopaedics	6 (6%)	24 (25%)	23 (24%)	8 (8%)	1 (1%)	0.185
Neurosurgery	9 (9%)	14 (15%)	8 (8%)	3 (3%)	0	
Practice experience (Spine Surgery in Practice)						
1-25%	0	1 (1%)	0	1 (1%)	0	0.444
26-50%	1 (1%)	2 (2%)	4(4%)	1 (1%)	0	
51-75%	7 (7%)	7 (7%)	7 (7%)	3 (3%)	0	
76-100%	7 (7%)	28 (29%)	20 (21%)	6 (6%)	1 (1%)	
Practice length						
0-5 years	2 (2%)	1 (1%)	4 (4%)	2 (2%)	0	0.262
6-10 years	3 (3%)	12 (13%)	13 (14%)	1 (1%)	1 (1%)	
11-15 years	2 (2%)	8 (8%)	4 (4%)	2 (2%)	0	
16-20 years	4 (4%)	3 (3%)	2 (2%)	3 (3%)	0	
>20 years	4 (4%)	14 (15%)	8 (8%)	3 (3%)	0	
Operative Volume (Spine Surgeries per year)						
<50	2 (2%)	3 (3%)	3 (3%)	1 (1%)	0	0.545
50-150	1 (1%)	11 (11%)	10 (10%)	3 (3%)	0	
151-300	8 (8%)	17 (18%)	10 (10%)	7 (7%)	0	
301-500	3 (3%)	6 (6%)	6 (6%)	0	1 (1%)	
>500	1 (1%)	1 (1%)	2 (2%)	0	0	
Operative Volume (Lumbar Discectomies per year)						
<25	4 (4%)	11 (11%)	9 (9%)	4	0	0.251
25-100	6 (6%)	20 (21%)	21 (22%)	6 (6%)	1 (1%)	
101-200	5 (5%)	7 (7%)	1 (1%)	1 (1%)	0	
Surgical interventions						
Open discectomy	1 (1%)	3 (3%)	3 (3%)	0	0	1.000
Microdiscectomy	12 (12%)	25 (26%)	22 (23%)	9 (9%)	1 (1%)	
MED	1 (1%)	4 (4%)	3 (3%)	1 (1%)	0	
PELD	0	1 (1%)	0	0	0	
Fusion	1 (1%)	5 (5%)	3 (3%)	1 (1%)	0	

[a] Fisher's exact test was used for between-group differences. The percentage data in the table is the surgeon's perceptions around surgical complications rather than actual complication rates.

4.4 Discussion

The main objective of this survey was to capture the perception of orthopaedic surgeons and neurosurgeons in the Australia and New Zealand region about the surgical management of primary LDH and rLDH, and compare the findings based on individual surgeon factors. A majority of respondents reported performing a discectomy surgery for both primary LDH and the first rLDH, while greater than 80% of the surgeons reported the use of fusion surgery for treating the second rLDH in their patients. A surgeons' perception around the choice of surgical procedure for rLDH was affected by their practice setting (academic/private/hybrid). Nearly a third of surgeons reported that surgical experience was the most important factor that influences the risk for surgical complications. Contrary to our expectations, surgeons with higher operative volume (>150 spine surgeries per year) perceived a greater risk for reherniation and durotomy than those with lower operative volume. Similarly, surgeons with higher operative volume perceived complication rates to be higher following revision surgeries for rLDH.

4.4.1 Variations in the surgical procedures

Most surgeons reported microdiscectomy to be their surgical technique of choice for a primary LDH (73%) and the first rLDH (72%), while 82% opted for a fusion procedure for the second rLDH. Compared with other minimally invasive discectomy approaches, microdiscectomy offers a broader visualization of the surgical field via a small exposure and is also associated with a smaller surgical learning curve [19, 20]. This could be the reason why most surgeons reported using microdiscectomy for a primary LDH.

Alternatively, endoscopic surgery is a relatively newer technique and thus may need more time for broader adoption.

Due to the absence of evidence-based guidelines, there remains controversy on the choice of repeat discectomy or fusion surgery for rLDH [21]. Many surgeons advocate repeat discectomy for the first rLDH in the absence of deformity, LBP or instability [22-24]. This correlates with the findings in our study. A repeat discectomy for the second rLDH may require more aggressive disc removal and laminectomy, all of which may increase the risk for segmental instability and recurrent pain. As such, fusion is often the favored procedure for the second rLDH to maintain stability and decrease the risk of recurrent herniation [12, 25]. This again is in line with the findings of this survey.

Geographical location of a surgeons' practice impacts the availability of resources (e.g., specific surgical instruments) and the formation of practice cultures, which has been reported to influence a surgeons' decision-making process for surgical management of spinal pathologies [10, 13, 26]. However, in our survey, different geographical regions (Australia versus New Zealand) did not have a significant effect on a surgeons' preference for managing primary LDH and rLDH. This finding is inconsistent with previously reported data [10, 13, 27], which may partly be due to the different definitions of geographical region (first report on ANZ region data) in the present study.

Surgeons in different practice settings (academic/private/hybrid) had different perceptions around the choice of surgical procedures for the first rLDH in their patients (more surgeons choose fusion surgery for the first rLDH in private practice). A possible explanation for this variation could be the differences in financial incentives and access to resources for surgical management. In the current era of value-based health care, patients will choose the most cost-effective surgical strategy with a lower risk of

reoperation and less additional expenditures for further treatment, which may potentially increase a surgeons' choice of fusion surgery for first rLDH patients in private practice. Another possible explanation is that the choice of treatment may be related to the potential medical disputes regarding inequality in the costs of health service and clinical efficacy in private practice.

We found that there was no difference in management for primary LDH and rLDH based on whether the surgeon was orthopaedic, or neurosurgery trained. This is in contrast to prior studies that have evaluated speciality variations in surgical decision making between orthopaedic and neurosurgeons for spinal pathologies [9, 11, 13]. These studies have shown that there is substantial variability in residency training among different specialities in the United States, which leads to differences in practice patterns for surgeons when they start their practices. Why this difference exists in the United States and not in Australia and New Zealand would require further investigation into the respective residency curriculums.

Our survey results showed no significant difference in the choice of surgical procedure based on the number of years in practice. A previous study reported that surgeons in the United States practicing for more than five years were less likely to choose fusion over discectomy for a rLDH, compared with surgeons with less than five years of experience [12]. This contrasts with our study's findings, and thus further supports the notion that surgeons' preferences are developed as a result of both surgical training and experience in practice.

Prior studies have shown that higher operative volume is strongly associated with better clinical outcomes [28]. The operative volume influences surgeon's decision-making in

the choice of procedure for LDH patients. However, the present study did not find any difference in the surgical management of LDH for different operative volumes.

4.4.2 Perceived complications

Identification of complication profiles is important in choosing the optimal surgical procedure for a pathology. Our prior meta-analysis and network meta-analysis reported the variation in complication rates among different discectomy techniques and the hierarchy of these techniques regarding complication rates [14, 29]. By understanding the complications associated with various discectomy techniques, surgeons can determine individualized surgical treatment options for each patient. Although most of the surgeons perceived the incidence of complications to be less than 5% for primary LDH patients, the results of our survey suggest that surgeons should be alert to the possibility of durotomy during the procedure and reherniation post-operation. Recurrent LDH after a primary lumbar discectomy is the most common negative sequela with a reported prevalence of 5-15% [24, 30-32]. Although different revision surgeries have been successfully employed in the treatment of rLDH, these procedures still carry a higher risk of complications due to epidural scar formation along with soft tissue damage following repeated exposure [33, 34]. We found that the surgeons perceived durotomy and superficial infection as the most common complications following revision surgeries for rLDH. Herein surgeons recommended using a meticulous surgical technique to protect soft tissues and dural sac [35].

The association between various stages of discectomy and surgeon perceived complications showed that surgeons are most wary of incorrectly marking/confirming the discectomy level before incision or/and after reaching bone to reduce the occurrence of wrong surgery level. All the stages of discectomy surgery must be fully mastered;

otherwise, it will be apt to mislead both doctors and patients about the safety and efficacy of the various discectomy techniques. While technical proficiency is essential, the final option of surgical procedure depends on strict compliance with a prerequisite for surgical indication [36].

This study examined the potential factors that may influence a surgeons' perception around complications following different surgical procedures for LDH. Surgeon demographic factors did not appear to affect the surgeons' perception of complication rates. The only variable that did was the surgeons' operative volume, and this was true for perceived reherniation and durotomy following primary discectomy as well as revision surgery for rLDH. Our data indicated that the more experienced surgeons who had higher operative volumes also reported a higher possibility of recurrent herniation and durotomy. Knowing these commonly perceived complications will help surgeons to design the detailed surgical plan to on how to minimize the occurrence of these potential complications and address these complications when they occur. Therefore, surgeons' annual operative volume has important implications for choosing the optimal procedure for LDH patients (primary LDH and rLDH) concerning surgical complications [28].

4.4.3 Limitations

Our study has a number of limitations. First, although we are unable to obtain the exact number of orthopaedic surgeons and neurosurgeons currently practicing in Australia and New Zealand region, we can calculate the number from previously reported data (Royal Australasian College of Surgeons. 2018 Surgical Workforce Census Summary Report. The number of orthopaedic surgeons and neurosurgeons is approximately 1502 ((6761/9) *2). According to different classification of sub-specialties (spine, joint, trauma, oncology, sports medicine, and pediatric in orthopedic; pediatric, trauma,

functional neurosurgery, neurovascular surgery, traumatology, skull-based surgery and spinal surgery in neurosurgery), the total number of spine surgeons in neurosurgeons and orthopaedic surgeons is around 232 (1502/ (2*6) +1502/ (2*7)). The invitation rate of the practicing surgeon in Australia and New Zealand is 64.7% (150/232) and the response rate of the practicing surgeon in Australia and New Zealand is 41.4% (96/232). Our response rate was not markedly different from, and in some cases better than, other surveys conducted online [12, 13]. Meanwhile, we sent out a pre-notification email, and a personalized and customized invite to take the survey to increase the response rate. However, the nonresponse bias still exists due to the inability to assess the impact of the nonrespondents' anonymous data. Second, the difference among different regional backgrounds in Australia and New Zealand (such as states in Australia, and provinces in New Zealand) are not covered in the survey. Third, in order to be consistent with previously published studies, we did not include nucleotomy and sequestrectomy as treatment options, both of which could impact the recurrence rate for LDH patients. Fourth, the case scenarios of the choice of surgical procedure for the first and second rLDH did not include factors that would potentially affect the decision-making process, such as smoking, body mass index, spondylolisthesis, and segment stability. Although there is a detailed description of the intraoperative and post-operative surgical complication following revision surgery/ies for rLDH, these do not distinguish the complications for first rLDH and the second rLDH. Fifth, the multivariate analyses (e.g., age, geography, practice setting, speciality, practice experience, practice length, and operative volume) haven't been performed in our study due to lack of enough participants. Finally, this survey was to capture the surgeons' perceptions around discectomy surgery for lumbar disc herniation based on their experience and opinions. All the perceived complications and related occurrence rates would be largely subjected

to performance and recall bias. The survey design may also have a degree of experimenters' bias. All of these potentially limit the generalizability of conclusions drawn.

4.5 Conclusions

This survey of orthopaedic and neurosurgeons in the Australia and New Zealand region is a preliminary attempt to capture the variability in surgical decision-making for LDH and rLDH based on surgeon characteristics and perceived complications. Our findings show discrepancies in the surgical procedures offered to patients and surgeon perceived complications. Microdiscectomy is the most popular surgical choice for primary LDH and first rLDH patients, and fusion surgery is the most popular surgical choice for the second rLDH. We found that practice setting was the main factor that influences the surgical decision-making process for the first rLDH. A meticulous surgical technique is recommended to minimize the most perceived complications, such as durotomy, reherniation and superficial infection. Surgeons with a higher operative-volume perceived a higher likelihood of herniation and durotomy, which could provide more information to surgeons to reduce or avoid these complications.

Recognizing the substantial variations that exist in the surgical management of primary LDH and rLDH will help in standardizing the protocols for effective management of this spinal condition and improve outcomes.

It represents a survey of a fraction 41.4% of orthopaedic surgeons and neurosurgeons currently practicing in the Australia and New Zealand region; this potentially limits the generalizability of the conclusions. In order to capture the findings in different regions,

a further global survey to capture variations in the surgical management of patients with LDH (and rLDH) is needed.

Based on previous chapters, the resulting consequence of this is a cascade of complications initiated by the surgeons' choice on the different discectomy techniques, complications that can adversely affect the psychological state of patients and place a significant burden on the health care system. Previously published study showed that dissatisfaction (persistent low back pain and disability) following discectomy for LDH is about and revision surgery rate is 20% in a 7-year survivorship analysis [37, 38]. More than 80% dissatisfaction following discectomy is considered surgical complications as the main reason. Therefore, the investigation of additional factors that impact post-operative outcomes (complications/dissatisfaction) is required.

This chapter has been submitted to *Archives of Orthopaedic and Trauma Surgery* entitled "Clinicians' perceptions around discectomy surgery for lumbar disc herniation: a survey of orthopaedic and neurosurgeons in Australia and New Zealand (*Archives of Orthopaedic and Trauma Surgery*, 2021, doi: 10.1007/s00402-021-04019-3)".

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Chapter 5. Do Markers of Inflammation and/or Muscle Regeneration in Lumbar Multifidus Muscle and fat Differ Between Individuals with Good or Poor Outcome Following Microdiscectomy for Lumbar Disc Herniation?

Nealy up to 30% occurrence rate of dissatisfaction following discectomy affect the psychological state of patients and place a significant burden on the health care system. Therefore, it is important to find out the potential risk factors and identify lumbar disc herniation patients at an increased risk of dissatisfaction as well as the best practices regarding its management to decrease the cost and morbidity associated with this condition. Many etiological factors may explain this issue, especially the structural change of back muscle and the change of disc height.

Structural back muscle changes, including fat infiltration, muscle atrophy, and fiber changes, are ubiquitous with LBP and are thought to be regulated by inflammatory and regeneration processes. Muscle changes might be relevant for recovery after microdiscectomy, but a link between expression of inflammatory and muscle regeneration genes in paraspinal tissues and clinical outcome has not been tested.

5.1 Introduction

Microdiscectomy is the most common surgical procedure for lumbar disc herniation (LDH) [1]. However, persistent low back pain (LBP) following microdiscectomy is observed in almost 30% of patients and rates of revision surgery have been reported up to 20% [2, 3]. Many different etiological factors may explain persistent LBP after microdiscectomy, such as inappropriate patient selection/diagnosis, poor operative

technique, iatrogenic instability, and surgical complications. However, the understanding of persistent LBP after microdiscectomy remains incomplete. Therefore, the investigation of additional factors that impact post-operative outcomes is required.

Lumbar multifidus muscle (LMM) is a paraspinal muscle that is considered important for control of spine motion. Recent studies highlight changes in the LMM (reduced cross-sectional area (CSA) [4], fiber-type transformation [5], and fatty infiltration [6]) in association with LDH [7, 8] that may be relevant for symptoms. Additionally, a smaller LMM CSA is predictive of LBP over 12-month in men [4]. Furthermore, depending on the duration of LBP, specific exercise interventions have been found to restore LMM CSA, in association with improved LBP [9, 10]. Taken together, these factors indicate that individuals with healthier LMM (no fiber-type transformation, atrophy, fatty infiltration, or structural changes) might have a better chance for recovery after microdiscectomy than those whose muscle is already undergoing structural change. Therefore, investigation of the mechanisms that regulate LMM structural changes in association with LBP in LDH patients is required.

Three main mechanisms have been proposed for structural changes in LMM: disuse, denervation, and an active process mediated by a localized muscle inflammatory response. Denervation or disuse of LMM is a plausible explanation for remodeling of the tissue [11], such as the shift from slow to fast myosin isoforms muscle phenotypes [12], decreased CSA [4], and decreased force output and fatigue resistance [13]. However, data from animal models provide evidence of changes in muscle fat and connective tissue that would have a major impact on muscle function that is related to dysregulation of expression of inflammatory markers (e.g., pro-inflammatory cytokines tumor necrosis factor (TNF) and interleukin-1β (IL-1β) [12, 14]. The dysregulation of

the inflammatory state of LMM has been confirmed in humans with LDH and high levels of fatty infiltration [15]. It has been proposed that inflammatory processes mediate the balance between muscle degeneration/regeneration, by regulation the expression of the molecules that promote muscle regeneration, such as Insulin-like growth factor (IGF-1), Irisin and Brain derived neurotrophic factor (BDNF). It is interesting to wonder if impaired regenerative capacity of the LMM due to a dysregulated inflammatory state could contribute to poor outcomes following microdiscectomy. This proposal requires examination.

The aim of this study was to determine whether inflammatory and muscle regeneration marker(s) in LMM at the time of microdiscectomy surgery in LDH patients with radiculopathy differ between individuals with good and poor (persistent LBP) outcome after surgery.

5.2 Materials and Methods

5.2.1 Study design

This study analysed a series of participants with chronic LBP who underwent microdiscectomy for LDH with radiculopathy. Gene profiling was conducted on tissue that would normally be discarded during microdiscectomy across two institutions under Hospital IRB approval for research on the surgically discarded tissue. Subsequent IRB approval was obtained for the further analysis of post-operative outcome data that is routinely collected at our service from the University Human Research Ethics Committee.

5.2.2 Participants

A total of twenty-one patients with LDH who underwent lumbar microdiscectomy surgery from May 2015 to August 2017 consented to collection of discarded surgical tissue samples for research were included. All participants met the following inclusion criteria: (1) age ≥ 18 years old; (2) LDH on MRI; (3) lower extremity radiculopathy and LBP; (4) unsuccessful conservative treatment for more than 6 weeks; (5) no concomitant instrumentation, or instrumentation during follow-up; (6) surgery performed at the L4-L5 or/and L5-S1 level; and (7) treatment selected using a shared-decision making process. Patients with major spinal deformity, tumor, infection, spondylolisthesis, cauda equina syndrome, or history of lumbar spine surgery (fusion, laminectomy or discectomy) and who declined to participate were excluded.

5.2.3 Clinical assessment

Prior to and 6 months after microdiscectomy surgery patients reported the intensity of their LBP and leg pain on a 10-cm visual analogue scale (VAS; 0 - no pain; 10 - worst pain imaginable) and physical functioning scale (PFS) on 18-items. For the modified AAOS-Modems disability outcome tool spine-service version of the PFS, each item was manually rated with 5 points for one of three possible responses (not limited at all (0), little limitation (3), and limited quite a lot (5)) [16]. Patients were allocated into good and poor outcome groups based on their post-operative improvement rate which was consistent with their opinion on rating the outcomes as satisfactory and not satisfactory after surgery. Using a threshold of a 33% or greater reduction in VAS, participants were allocated to a good (VAS LBP+) or poor (VAS LBP-) outcome group [17]. A PFS of 25% or greater was used to allocate participants to a good (PFS+) or poor (PFS-) recovery group [18].

5.2.4 Imaging features

Fat infiltration of the LMM was visually graded on the MRI scans using the Kjaer method by two independent raters (Xiaolong Chen and Jose Vargas Castillo from Spine Service, Department of Orthopaedic Surgery, St. George Hospital Campus, New South Wales, Australia) [6]. Scores were allocated as "normal/mild" for estimates of 0–10% fat and fibrous tissue within the muscle, "slight" for 10–50% fat, and "severe" for >50% fat. Participants were divided into low (no or slight) or high (severe) fat infiltration. Controversial scores were resolved by the third rater (Ashish D. Diwan from Spine Service, Department of Orthopaedic Surgery, St. George Hospital Campus, New South Wales, Australia).

5.2.5 Sample collection

A standard surgical approach for microdiscectomy utilizing loupe magnification with head illumination and MLD-retractors (Aesculap, Tübingen, Germany) and Midas Rex (Medtronic, Minneapolis, MN) was used. As surgery proceeded and surgical tissues were removed, the locations of sample collection for each patient were according to **Figure 5.1**. Samples from the deep multifidus muscles, intramuscular fat, sub-cutaneous fat and epidural fat, adjacent to the surgical segment were harvested from the side ipsilateral to the disc herniation during microdiscectomy surgery.

5.2.6 Quantitative Polymerase Chain Reaction (qPCR) assay

Tissue samples were stored in RNA later at -20°C. RNA extraction from muscle and adipose tissues was performed using the RNeasy Fibrous Tissue Mini Kit (QIAGEN) and RNeasy Lipid Tissue Mini Kit (QIAGEN), respectively. cDNA was synthesized using SuperScript IV First-Strand Synthesis System (Thermo fisher) and purified using the Isolate II PCR and Gel Kit (Bioline). qPCR assays were performed using IQ SYBR

Green Mastermix (Bio-Rad) and the primer pairs in **Table 5.1**. All protocols were performed per manufacturers' instructions. The expression of each gene was converted to a percentage of the house keeping gene glyceraldehyde 3-phosphate dehydrogenase.

5.2.7 Inflammatory and muscle regeneration markers

The choice of inflammatory and muscle regeneration markers is based on previously published studies [6, 13]. All inflammatory and signalling molecule transcripts were examined using human specific oligos (**Table 5.1**) for quantitative PCR assays and normalised to GAPDH transcript, including inflammatory markers (TNF, IL-1β, IL-6, IL-15, Arginase 1 (Arg-1), Nitric oxide synthase 2 (Nos-2), and transforming growth factor beta 1 (TGF-β1)) and muscle regeneration markers (BDNF, IGF-1, and Irisin) in deep LMM and inflammatory markers (TNF, IL-1β, IL-6, Arg-1, and Nos-2) in intramuscular, epidural, and sub-cutaneous fat.

5.2.8 Statistical analysis

All data is presented as mean ± standard deviation (SD). Paired *t*-test was used to compare the clinical outcomes of PFS, VAS leg pain and LBP between preoperative and 6 months post-operative follow-up. T tests were used to compare the expression of individual clinical outcomes between the low- and high-fat infiltration groups. As data were not normally distributed, the non-parametric Mann-Whitney U test was performed to compare the expression of inflammatory and muscle regeneration markers and the demographic features between VAS LBP+ and VAS LBP- groups, and between PFS+ and PFS- groups.

Spearman's rank correlation coefficient was used to test the association between the expression of inflammatory and muscle regeneration markers in LMM at the time of

surgery and the clinical scores (VAS LBP) preoperatively and at 6 months post-operatively. Statistical analysis was undertaken using SPSS v24.0 (SPSS Inc., Chicago, IL., USA) with a $P<0.05$ considered to be statistically significant.

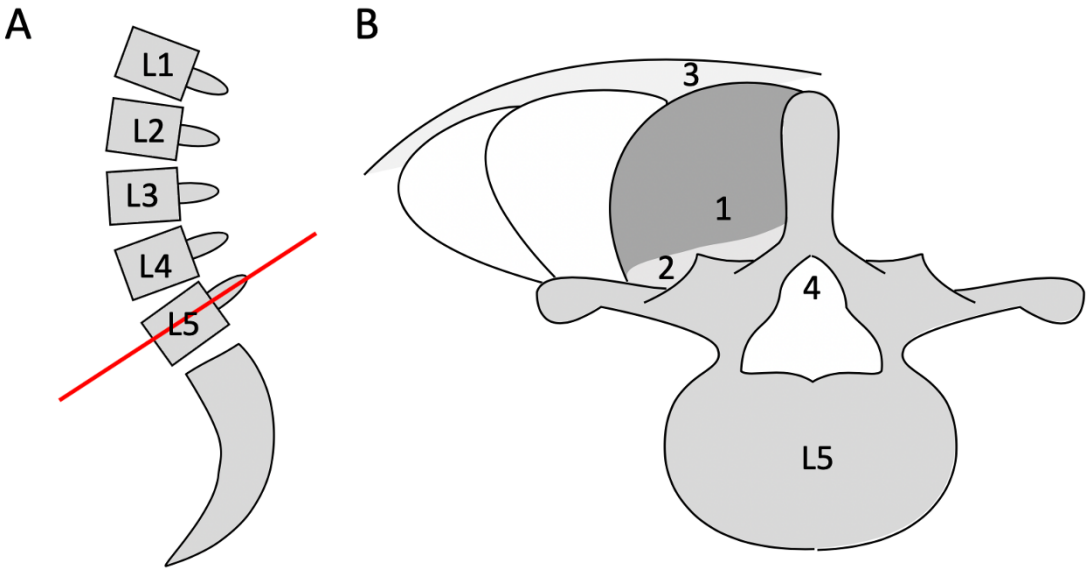

Figure 5.1 Sites for sample collection. (A) Sagittal view of the lumbar spine. (B). Axial view at the level of the of the L5 vertebrae to demonstrate the approximate sites for tissue samples; (1) Multifidus muscle; (2) Intramuscular adipose tissue, (3) Sub-cutaneous adipose tissue; and (4) Epidural adipose tissue.

Table 5.1 Cytokines and molecules involved in muscle/adipose and primer sequences used for quantitative polymerase chain reaction (qPCR) analysis.

Gene	Full name	Primer Sequences	Role	Function in muscle/adipose
Inflammatory markers				
TNF	Tumor Necrosis Factor	F: 5'-GAGGCCAAGCCCTGGTATG-3' R: 5'-CGGGCCGATTGATCTCAGC-3'	Pro-inflammatory cytokine	Chronically elevated humoral TNF regulates muscle atrophy via the ubiquitin pathway. Muscle-synthesized TNF promotes muscle adaptation and fast muscle fiber expression.
IL-1β	Interleukin 1 Beta	F: 5'-AGCTACGAATCTCCGACCAC-3' R: 5'-CGTTATCCCATGTGTCGAAGAA-3'	Pro-inflammatory cytokine	Role in early phases of myogenesis and reduction of fibrosis
IL-6	Interleukin 6	F: 5'-ACTCACCTCTTCAGAACGAATTG-3' R: 5'-CCATCTTTGGAAGGTTCAGGTTG-3'	Pro- and anti-inflammatory cytokine	Exercise produced IL-6 has anti-inflammatory properties but macrophage IL-6 is pro-inflammatory.
IL-15	Interleukin 15	F: 5'-GCCATAGCCAGCTCTTCTTCA-3' R: 5'-CTGCACTGAAACAGCCCAAA-3'	Pleiotropic cytokine	Downstream of other pro-inflammatory cytokines and promotes a pro-inflammatory environment in the muscle.
TGF-β1	Transforming Growth Factor Beta 1	F: 5'-GGCCAGATCCTGTCCAAGC-3' R: 5'-GTGGGTTTCCACCATTAGCAC-3'	Anti-inflammatory mediator	Promotes atrophy/slow-to-fast transformation and induces differentiation of myocytes into myofibroblasts
Arg-1	Arginase 1	F: 5' TGGACAGACTAGGAATTGGCA 3' R: 5' CCAGTCCGTCAACATCAAAACT 3'	Anti-inflammatory cytokine	M2 type macrophage marker
Nos-2	Nitric oxide synthase 2	F: 5' AGGGACAAGCCTACCCCTC 3' R: 5' CTCATCTCCCGTCAGTTGGT 3'	Pro-inflammatory cytokine	M1 type macrophages marker
Muscle Regeneration markers				
BDNF	Brain Derived Neurotrophic Factor	F: 5'-TAACGGCGGCAGACAAAAAGA-3' R: 5'-GAAGTATTGCTTCAGTTGGCCT-3'	Growth factor	Promotes hypertrophy/muscle regeneration
Irisin	Irisin	F: 5'-TGAGGCTGAGAAGATGGCCT-3' R: 5'-ACGCTTCAATGATGTCATACTGG-3'	Exercise induced myokine	Promotes hypertrophy/ muscle regeneration

IGF-1	Insulin-like Growth Factor 1	F: 5’-GCTCTTCAGTTCGTGTGTGGA-3’ R: 5’-GCCTCCTTAGATCACAGCTCC-3’	Growth factor	Regulates muscle growth/development/regeneration and promotes hypertrophy

F = forward primer, R = reverse primer.

5.3 Results

5.3.1 Demographics

Twenty-one patients with LDH (15 males and 6 females; mean ± SD age of 43 ± 12 years) who underwent microdiscectomy were included. Thirteen (62%) patients were observed to have *slight* fat infiltration and four (19%) patients had *severe* fat infiltration. There was no difference in age and BMI between the patients with good (VAS LBP+ and PFS+) and poor (VAS LBP- and PFS-) recovery (**Table 5.2**).

5.3.2 Clinical outcomes at 6 months post-operation

When all participants were considered, VAS LBP reduced by 45% from a preoperative value of 7.7 ± 2.1 to 4.2 ± 2.9 at 6 months post-operatively (t=5.444, P<0.001). VAS leg pain score decreased by 58% following microdiscectomy surgery (t=5.826, P<0.001).

Although the total PFS score at 6 months follow-up improved by 46% relative to the preoperative PFS score (t=6.156, P<0.001), there was no difference in three items of the PFS (limitation on vigorous activities (t=1.905, P=0.069), limitation on lifting or carrying groceries (t=1.855, P=0.077), and limitation on lying stomach (t=1.670, P=0.109)) (**Table 5.3**).

When data were considered for individual participants, 15 (72%) patients achieved good recovery in VAS LBP and 15 (72%) patients achieved good recovery in PFS at 6 months after microdiscectomy.

Higher preoperative levels of fat infiltration in the LMM displayed worse function and leg pain as measured by the PFS and VAS, respectively (**Table 5.4**).

5.3.3 Inflammatory and regeneration markers in paraspinal tissues between groups with good and poor recovery at 6 months post-operatively

There was no significant difference of expression of inflammatory markers in muscle tissue harvested from the deep LMM between VAS LBP+ and VAS LBP- groups. Expression of BDNF in LMM at the time of surgery was 91% (P=0.014) lower in the VAS LBP- group than the VAS LBP+ group. Expression of IL-1β in sub-cutaneous fat was 48% (P=0.026) higher in the VAS LBP- than VAS LBP+ group. No differences to any inflammatory or regenerative markers were detected in intramuscular or epidural fat (**Table 5.5**).

None of the investigated inflammatory and muscle regeneration markers in multifidus muscle or paraspinal fat tissues differed between groups based on the improvement of PFS (**Table 5.5**).

5.3.4 Association between inflammatory and muscle regeneration markers and preoperative and 6 months follow-up post-operative VAS LBP

There was no significant correlation between the molecular markers in intramuscular fat, epidural fat, and sub-cutaneous fat and VAS LBP at preoperatively. Expression of IL-1β (r=0.670, P<0.01) and TGF-1β (r=0.652, P<0.05) in the deep LMM were strongly correlated with LBP preoperative VAS LBP (**Table 5.6**).

There was no significant correlation between the molecular markers in deep LMM, intramuscular fat and epidural fat and VAS LBP at 6-month post-operation. Expression

of IL-1β (r=0.674, P<0.01) and TNF (r=0.678, P<0.01) in sub-cutaneous fat was strongly correlated with post-operative VAS LBP (**Table 5.6**).

Table 5.2 Baseline characteristics

	Numbers	***P*-value***
Male: Female	15:6	
Age (years)	43±12	
VAS LBP+ group	42±11	0.495
VAS LBP- group	46±17	
PFS+ group	42±13	0.470
PFS- group	46±8	
BMI (kg/m^2)	28±3	
VAS LBP+ group	28±3	0.905
VAS LBP- group	28±5	
PFS+ group	28±4	0.733
PFS- group	27±3	
Segment		
L4-L5	11	
L5-S1	6	
L4-L5+L5-S1	4	
Fat Infiltration		
Grade 0	4	
Grade 1	13	
Grade 2	4	

VAS = visual analogue scale, LBP = low back pain, PFS = physical functioning scale, BMI = body mass index; Data are presented as mean ± standard deviation.

* - between group comparison with Mann-Whitney U test

Table 5.3 Clinical status at baseline and at 6-month following microdiscectomy

	Pre-op	Post-op	*t*	*P*-value
VAS of low back pain	7.7±2.1	4.2±2.9	5.444	0.000***
VAS of leg pain	7.1±3.1	2.6±2.7	5.826	0.000***
Physical functioning: Limitation on	58.7±17.7	31.8±19.4	7.069	0.000***
Vigorous activities	4.7±1.1	2.25±1.51	1.905	0.069
Moderate activities	4.1±1.5	3.5±1.6	2.611	0.016*
Lifting or carrying groceries	3.3±1.4	2.7±1.8	1.855	0.077
Climbing several flights of stairs	3.8±1.5	1.8±2.0	5.389	0.000***
Climbing one flight of stairs	2.5±1.8	0.6±1.4	5.854	0.000***
Bending, kneeling, stooping	4.3±1.0	2.7±1.6	6.407	0.000***
Walking more than 1.5 km	4.0±1.3	2.1±1.9	4.878	0.000***
Walking several blocks	3.4±1.8	1.4±1.9	4.727	0.000***
Walking one block	2.3±1.8	0.8±1.6	4.212	0.000***
Sitting	4.0±1.3	2.4±2.0	4.143	0.000***
Standing erect	3.4±2.0	1.6±1.9	3.842	0.001**
Lying on back	2.7±2.1	1.1±1.9	3.106	0.005**
Lying on stomach	2.7±2.1	1.7±2.1	1.670	0.109
Lying on sides	2.4±1.5	0.8±1.5	3.686	0.001**
Grooming or bathing self	2.9±1.7	1.1±1.5	4.701	0.000***
Sexual activities	3.4±2.0	2.0±1.7	3.936	0.001**
Initiating gait	2.9±2.1	1.0±1.7	4.237	0.000***
Crossing streetlights	1.4±1.8	0.3±0.9	3.558	0.002**

Data are presented as mean ± standard deviation.

Significant difference * $P<0.05$, ** $P<0.01$, *** $P<0.001$ (paired *t*-test).

Table 5.4 Clinical features of participants between low-fat and high-fat infiltration groups

	Low-fat infiltration	**High-fat infiltration**	**P value**
VAS of low back pain	7.8±1.8	7.6±2.1	0.81
VAS of leg pain	5.3±3.3	8.6±1.0	0.004**
Physical functioning Scale	21.6±10.0	33.4±10.9	0.002**

Significant difference * $P<0.05$, ** $P<0.01$, *** $P<0.001$

Table 5.5 Inflammatory and muscle regeneration markers in different recovery groups based on pain visual analogue scale (VAS) for low back pain (LBP) and physical functioning scale (PFS)

		VAS LBP+	VAS LBP-	*P*-value	PFS+	PFS-	*P*-value
Deep multifidus muscle	TNF	0.00009±0.00002	0.00012±0.00005	0.553	0.00009±0.00009	0.00011±0.00005	0.230
	IL-1β	0.00026±0.0001	0.00005±0.00002	0.445	0.00003±0.00002	0.00004±0.00005	0.612
	IL-15	0.00041±0.00013	0.00107±0.00046	0.145	0.00051±0.00050	0.00087±0.00102	0.485
	TGF-β1	0.10±0.02	0.15±0.06	0.721	0.11±0.05	0.13±0.15	0.383
	Arg-1	0.0030±0.009	0.0059±0.0031	0.225	0.0032±0.0029	0.0060±0.0084	1.000
	Nos-2	0.019±0.003	0.032±0.022	0.513	0.016±0.011	0.037±0.047	0.440
	BDNF	0.00097±0.00022	0.00009±0.00004	0.014*	0.00095±0.00074	0.00015±0.00008	0.112
	Irisin	0.0025±0.0006	0.0068±0.0033	0.343	0.0031±0.0025	0.005±0.0071	0.949
	IGF-1	0.28±0.04	0.34±0.15	0.953	0.28±0.13	0.33±0.30	0.954
Intramuscular fat	TNF	0.0035±0.0006	0.0077±0.0029	0.180	0.0051±0.0055	0.0045±0.0021	0.633
	IL-1β	0.009±0.002	0.011±0.004	0.733	0.010±0.007	0.009±0.009	0.799
	IL-6	0.0047±0.0011	0.0077±0.0020	0.180	0.0051±0.0044	0.0073±0.0037	0.336
	Arg-1	0.014±0.002	0.024±0.009	0.387	0.016±0.014	0.019±0.008	0.498
	Nos-2	0.18±0.07	0.17±0.06	0.953	0.13±0.07	0.32±0.34	0.571
	TNF	0.008±0.003	0.010±0.002	0.073	0.009±0.010	0.008±0.003	0.379

Sub-cutaneous fat	IL-1β	0.012±0.007	0.023±0.010	0.026*	0.019±0.026	0.011±0.003	0.412
	IL-6	0.013±0.003	0.017±0.005	0.220	0.014±0.009	0.018±0.017	0.521
	Arg-1	0.020±0.004	0.021±0.004	0.660	0.020±0.014	0.022±0.008	0.703
	Nos-2	0.23±0.05	0.22±0.05	0.875	0.24±0.12	0.19±0.09	0.727
Epidural fat	TNF	0.0071±0.0012	0.0069±0.0027	0.949	0.0062±0.0031	0.0094±0.0064	0.343
	IL-1β	0.022±0.007	0.021±0.011	0.851	0.020±0.023	0.028±0.021	0.575
	IL-6	0.017±0.005	0.009±0.003	0.412	0.016±0.016	0.011±0.008	0.949
	Arg-1	0.046±0.016	0.031±0.021	0.432	0.045±0.060	0.033±0.036	0.676
	Nos-2	0.21±0.05	0.13±0.04	0.240	0.16±0.12	0.25±0.21	0.635

Significant difference * $P<0.05$ (Mann-Whitney U test).

Table 5.6 Association between inflammatory and muscle regeneration markers in lumbar multifidus muscle with preoperative and post-operative pain visual analogue scale (VAS) for low back pain (LBP)

Tissue	**Marker**	**Preoperative VAS LBP**		**Post-operative VAS LBP**	
		Spearman's rank correlation coefficient (r)	***P*-value**	**Spearman's rank correlation coefficient (r)**	***P*-value**
Deep multifidus muscle	TNF	0.385	0.115	0.432	0.057
	IL-1β	0.670	0.008**	0.172	0.469
	IL-15	-0.013	0.972	0.280	0.379
	TGF-β1	0.652	0.037*	0.278	0.280
	Arg-1	0.227	0.445	0.254	0.402
	Nos-2	-0.239	0.433	0.294	0.307
	BDNF	0.285	0.396	-0.302	0.315
	Irisin	0.218	0.475	0.189	0.500
	IGF-1	0.514	0.060	0.188	0.485
Intramuscular fat	TNF	-0.037	0.889	0.302	0.223
	IL-1β	0.052	0.849	0.305	0.235
	IL-6	-0.001	0.996	0.387	0.113
	Arg-1	-0.359	0.157	0.028	0.915
	Nos-2	0.196	0.484	0.295	0.285
Sub-cutaneous fat	TNF	0.130	0.645	0.678	0.007**
	IL-1β	-0.071	0.809	0.684	0.005**
	IL-6	-0.150	0.594	0.375	0.152
	Arg-1	0.212	0.431	0.166	0.525
	Nos-2	0.229	0.473	0.354	0.235
Epidural fat	TNF	-0.354	0.214	0.207	0.460
	IL-1β	-0.015	0.959	0.126	0.655
	IL-6	-0.144	0.624	-0.246	0.376
	Arg-1	0.477	0.062	0.055	0.839
	Nos-2	0.054	0.855	0.334	0.243

Significant difference * $P<0.05$, ** $P<0.01$.

5.4 Discussion

This study aimed to identify whether markers of inflammation and muscle regeneration in LMM and overlying fat at the time of surgery were related to post-operative recovery from microdiscectomy for LDH with radiculopathy. There were two major findings. First, contrary to our hypothesis, those with poor outcome (persistent LBP) did not have worse inflammatory profile in LMM, however, they did have evidence of altered muscle regeneration. Second, pro-inflammatory cytokine expression was elevated in sub-cutaneous fat overlying the back muscles in those with poor outcome. These findings have potential implications for understanding recovery after surgery.

5.4.1 Multifidus muscle health and post-operative recovery

Animal studies have identified dysregulation of local inflammatory activity as a novel mechanism to explain fat and connective tissue accumulation in multifidus muscle after intervertebral disc injury [5, 19]. Based on the evidence of the association between pro-inflammatory markers in LMM and degeneration, we hypothesised that a more pro-inflammatory profile in the muscle might predict poor recovery. Our data did not support this hypothesis. Instead, the results showed that the 28% of patients who did not report a reduction of VAS LBP of at least 33% at 6 months post-operatively had a lower expression of BDNF in LMM in samples harvested during surgery than individuals with a reduction of VAS LBP of 33% or more. BDNF is a diffusible protein produced by both motoneurons and skeletal muscle. It is a bidirectional signalling molecule important for maintaining normal motor unit function. In adult skeletal muscles, BDNF is expressed in muscle satellite cells [20] and is upregulated in muscle injury followed by the activation and proliferation of satellite cells, suggesting that BDNF might play a

role in regulation of satellite cell differentiation and skeletal muscle regeneration in response to muscle injury [21]. BDNF also has emerged as an important modulator of axon regeneration, which could rescue the muscle atrophy and promote nerve remyelination if muscle changes are mediated by denervation [22]. Animal studies provide evidence for involvement of BDNF as a myokine in skeletal muscle regeneration following exercise [23]. A role in muscle regeneration [24] of LMM to restore CSA might be relevant for maintenance of improved LBP after surgery.

LMM denervation has been observed in individuals with poor outcome after laminectomy/disc surgery [25, 26]. In a retrospective study of 178 patients who had undergone laminectomies, radiologic, neurophysiologic, and muscle biopsy data provided the evidence that disturbed back muscle innervation was related to disability. This was interpreted to suggest reduced of muscular support might be contribute to the failed back syndrome [25]. This is supported by the observation that rehabilitation of LMM function after discectomy surgery improves post-operative recovery [27]. The observation of lower BDNF at baseline in individuals with poor outcome might indicate a lesser capacity to recover muscle health following microdiscectomy. Conversely, individuals with high BDNF might have better capacity to recover muscle and sustain a good outcome as a consequence of improved muscle control.

5.4.2 Pro-inflammatory cytokine expression in sub-cutaneous fat and surgical outcome

These data showed that expression of the pro-inflammatory cytokine IL-1β was elevated in sub-cutaneous fat overlying the back muscles in LDH patients with poor post-operative outcome (VAS LBP-), and expression of both IL-1β and TNF was

correlated with VAS LBP. Locally, pro-inflammatory cytokines can sensitise nociceptive neurons and contribute development of inflammatory and pathological pain [28]. Systemically, pro-inflammatory cytokine expression is increasingly recognised in chronic pain conditions, such as the elevation of TNF in chronic LBP [29] and IL-1β in complex regional pain syndrome [30]. A recent prospective longitudinal study showed that the elevation of TNF in blood was associated with poor recovery after acute episode of LBP [31]. Moreover, systemic pro-inflammatory cytokines expression has been implicated in the association between obesity and osteoarthritis [32, 33] and adipose is considered to be the source of the pro-inflammatory cytokines. Sub-cutaneous fat could be a source of systemic pro-inflammatory cytokines. In obesity, paraspinal adipose tissue has been shown to be in a pro-inflammatory state and a source of pro-inflammatory cytokines expression, which could drive the accumulation and/or polarization of adipose tissue macrophages to low grade chronic inflammation [34, 35]. Although our participants with good and bad outcome did not differ in terms of BMI, intervertebral disc injury may provide an alternative stimulus for the pro-inflammatory response in this tissue of our participant group. TNF as a pro-inflammatory mediator has been shown to play a central role in the pathophysiology of discogenic LBP and could initiate and coordinate inflammatory reactions to interfere with normal healing [36]. Both pro-inflammatory cytokines may be relevant for the poor outcome of LDH patients after microdiscectomy. Upregulation of TNF expression is associated with pain intensity, disability, and LBP chronicity [31]. IL-1β is a potent inflammatory cytokine involved in mechanism of allodynia, and possibly in the development of post-operative chronic pain [37]. Future studies should measure systemic inflammatory cytokines as a potential factor in predicting post-operative outcome.

5.4.3 Methodological issues

Several methodological issues require consideration. First, participants had reported use of anti-inflammatory drugs, age, BMI, body fat distribution, exercise history, smoking history, and diabetes, and these might have influenced our measures of inflammatory response. Second, tissue samples collected for this study were not harvested as controlled biopsies but were deemed discarded tissue taken during surgery. Despite all care in selecting areas to collect samples from, there is a possibility of tissue sampling error. Third, using a different threshold for pain assessment might have resulted in a different result [38]. Our threshold was based on a previous study that reported a 33% decrease in VAS as indicative of a clinically important change in pain intensity and patients' opinion on rating the outcomes as satisfactory and not satisfactory after surgery. [17]. Fourth, the extent of preoperative psychological features may affect clinical outcome and systemic cytokine response in LDH patients scheduled for lumbar microdiscectomy. However, the psychological features were not fully assessed in this study. Fifth, due to lack of high-quality images, the quantitative measurement (e.g., CSA) on LMM was not performed. As the increasing of participants enrolment, future study on evaluating the relationship between quantitative data on LMM and clinical outcomes in the patients with symptomatic LDH will be conducted. Finally, the present small sample study did not include a control group. The multivariate analyses haven't been performed in our study due to lack of enough participants.

5.5 Conclusion

The results supported that increased fatty infiltration of the multifidus muscle is associated with poor clinical outcome. On the other hand, composed muscle function

due to back pain result in disability and reduce the ability to carry out activities of daily life, which can lead to altered muscle structure.

This study provides novel observation of a relationship between inflammation in sub-cutaneous fat overlying the back region and poor outcome after microdiscectomy for LDH with radiculopathy. Contrary to our hypothesis, there was no evidence of a dysregulated inflammatory profile in LMM in individuals with poor outcome. However, reduced expression of molecules that promote muscle regeneration in LMM in individuals with poor outcomes have potential relevance for restoration of muscle control after surgery.

Due to several methodological issues, future long-term follow-up prospective randomized controlled study should explore the change of marker(s) in LMM using a larger sample size with more rigorous research designs (randomized controlled design).

Structural back muscle changes are ubiquitous with LBP and are confirmed to be regulated by inflammatory and regeneration processes in this chapter. However, there is no consensus on the other risk factors for the dissatisfaction following discectomy for symptomatic lumbar disc herniation, especially the loss of disc height.

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Chapter 6. Does Disc Height Change Associated with Pain Score Change Following Discectomy Surgery in Lumbar Disc Herniation Patients? A Systematic Review and Meta-Analysis

Intervertebral disc height has previously been found to be related to persistent low back pain following discectomy surgery for symptomatic lumbar disc herniation. In theory, removal of herniated nucleus material during discectomy procedure leads to immediate loss of disc height. The intervertebral disc space narrowing, and thinning has been associated with acute or chronic disabilities of the lumbar spine. However, there is a paucity of information regarding disc height change following discectomy and its clinical significance, especially using different methods to estimate the disc height. Therefore, this chapter presents a review to evaluate the impact of discectomy on disc height following discectomy surgery and the association of disc height and disc height index change with pain score.

6.1 Introduction

Many different etiological factors may explain persistent low back pain (LBP) after discectomy, such as inappropriate patient selection, unclear diagnosis, poor operative technique, iatrogenic instability, etc. However, the understanding of the 30% of lumbar disc herniation patients with persistent LBP after discectomy remains incomplete [1].

Intervertebral disc (IVD) height has previously been found to be related to lumbar disc herniation (LDH). Migration of the herniated disc influences the load-carrying capacity of that motion segment and consequently the spinal column, and studies have reported a correlation between the volume of disc material removed and the loss of disc height

(DH) [2, 3]. The IVD space narrowing, and thinning has been associated with acute or chronic disabilities of the lumbar spine [4]. Furthermore, there is evidence that DH reduction following lumbar discectomy is potentially a contributor to long-term back and leg pain [5, 6]. However, there is a paucity of information regarding DH change following discectomy and its clinical significance, especially using different methods to estimate the DH.

There is no agreement as to the ideal way to measure the DH. Clinicians often rely on their own subjective interpretation of lumbar spine radiographs, however, numerous techniques using different imaging methods published in the literature have been described as more accurate, albeit more time consuming [7-12]. This lack of consensus leads to great inter- and even intra- observer variability. A simple and reproducible technique to measure DH is required.

DH can be measured as an absolute value, although this may be influenced by the magnification and position of the patient on the scan. Simple values can be used in daily practice for quick comparisons. For more in-depth studies and more accurate readings, the disc height index (DHI) has been introduced. By normalising images, variations in the size of the vertebral column and position of the patient do not affect the final measurement and allow for a reliable analysis [9].

The field accepts generally that disc height decreases with time following discectomy, while there is no reason to challenge that view what remains unknown is the quantitative and temporal nature of this natural phenomenon and also whether there is a correlation with back pain.

In order to understand the clinical significance of the DH change after a discectomy the main objectives of the present review are (1) to evaluate the impact of discectomy surgery on the DH and DHI in LDH patients; (2) to identify the affection of different methods to estimate DH and DHI; and (3) to evaluate association of DH and DHI change with pain score (primary outcome) and disability score (secondary outcome) change at any follow-up time period.

6.2 Methods

6.2.1 Search strategy

Online databases MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials were searched in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines to identify all relevant studies published between January 1977 and October 2020 [13]. The search included the following terms: “lumbar spine”, “intervertebral disc”, “herniation”, “discectomy”, “microdiscectomy”, “minimally invasive surgery”, “endoscopic”, “laser”, and “percutaneous discectomy”, with appropriate combinations of operators “AND”, “OR”, and “NOT”. The reference lists of relevant studies were evaluated for the purposes of the present study. The language of the included studies was restricted to English. The review protocols are registered on PROSPERO (International Prospective Register of Systematic Reviews number, CRD42020220260).

6.2.2 Inclusion criteria

1) Randomized controlled trails (RCTs) and observational studies of any discectomy technique (microendoscopic discectomy (MED), percutaneous endoscopic lumbar

discectomy (PELD), tubular discectomy, or open discectomy or microdiscectomy (MD)) for symptomatic LDH patients.

2) Studies which reported DH and/or DHI after discectomy surgery.

3) Studies which reported the pain intensity change of the low back and/or leg and with Numeric Rating Pain Scale (NPS) or Visual Analogue Scale (VAS) before and after discectomy surgery.

6.2.3 Exclusion criteria

1) Studies which compared discectomy procedures with other spinal surgeries, such as chemical nucleolysis, intradiscal electrothermal annuloplasty, and surgeries involving the use of an implant.

2) Case reports, reviews, and conference reports.

3) *In vitro* biomechanical studies and computational modelling studies.

6.2.4 Types of outcomes measures

Primary outcome: The change in pain intensity score of LBP and/or leg pain before and after discectomy surgery, as measured in VAS or NPS and the change in the DH or DHI before and after discectomy surgery.

Secondary outcomes: The association between the back-specific disability questionnaires (Oswestry Disability Index (ODI)) and DH and/or DHI changes following discectomy surgery for LDH.

6.2.5 Selection of studies

Two reviewers (Xiaolong Chen and Jose Vargas Castillo from Spine Service, Department of Orthopaedic Surgery, St. George Hospital Campus, New South Wales, Australia) independently reviewed all titles and abstracts that were identified in the initial online search of databases. Full-text articles and reference lists were reviewed for the relevant abstracts. When consensus could not be reached between the reviewers, a third reviewer (Ashish D. Diwan) was consulted to resolve the disagreement.

6.2.6 Data extraction

Two reviewers (Xiaolong Chen and Jose Vargas Castillo) extracted data independently. The reviewers collected the following data: methods (first author's name, publication year, study design, sample size, mean duration of follow-up), participants (number of participants, age, gender), interventions (surgical procedure and level), and outcomes (primary outcome: pain intensity scores and DH and/or DHI and secondary outcome: back-specific disability scores).

6.2.7 Risk of bias within trials

The 13 criteria recommended in the Cochrane Back and Neck Group guidelines [14] were used to assess the risk of bias of RCTs that were included in this meta-analysis. "Low risk," "high risk," or "unclear risk," were used to score the risk of bias for individual criteria. Thereafter, for the overall risk of bias evaluation, a "low overall risk" of bias was attributed to the study when seven or more of the 13 criteria were considered low risk [14].

The Newcastle-Ottawa Scale (NOS) was used to assess the methodological quality of the included observational studies [15]. The “star system” of NOS ranges from 0 to 9. A study awarded seven or more stars was regarded as high-quality.

A sensitivity analysis was conducted to assess the impact of including studies with a high overall risk of bias. Controversial scores were resolved by the third reviewer (Ashish D. Diwan).

6.2.8 Statistical analysis

Estimates of effect sizes from each trial were used to compute Hedges’ d standardized mean differences (SMD) to standardize results of studies using different outcome measures to a uniform scale [16]. SMD and standard deviation (SD) were calculated. To calculate SMD, the mean change for the post-operative data was subtracted from the mean change for preoperative data, and the difference was divided by the pooled baseline SD. The SD were generated by dividing the standard deviations by the square root of the study population. Chi-squared (I^2) statistic was used to measure heterogeneity among the trials. $I^2 < 50\%$ implied homogeneity and the analysis followed a fixed-effects model by the Mantel-Haenszel method. $I^2 > 50\%$ indicated heterogeneity and, consequently, a random-effects model was used according to the DerSimonian-Laird method. We conducted subgroup analysis and sensitivity analysis to assess the impact of heterogeneity. SMD and 95% confidence intervals (CI) were reported. Meta-analyses results were also assessed using forest plots. Risk of publication bias was evaluated using the Begg-Mazumdar test. The statistical significance was set at 5% ($\alpha = 0.05$).

To calculate the association of mean pain change with DH and/or DHI change, we included DH and/or DHI change as a predictor in a meta-regression analysis.

Finally, this meta-analysis was performed according to the Quality of Reporting of Meta-analyses group and the Meta-analysis of Observational Studies in Epidemiology group recommendations for improving the quality of reporting of meta-analyses of clinical RCTs and observational studies, respectively [17, 18]. RevMan (Review Manager 5.3 version. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.) was used to evaluate the risk of bias in RCTs and STATA software (release 15, StataCorp LLC, TX) was used for the statistical analyses.

6.2.9 Evaluating the quality of evidence

The quality of the evidence informing this meta-analysis was assessed u Grading of Recommendations Assessment, Development and Evaluation (GRADE) scale, which rated evidence quality as high, moderate, low, or very low [19].

6.3 Results

6.3.1 Study selection

The literature search is illustrated in the PRISMA flow diagram (**Figure 6.1**). Eighteen studies met the selection criteria for the purposes of the present review, which included 2 RCTs [20, 21] and 16 observational studies [5, 22-36].

6.3.2 Study characteristics

Within the 893 patients in the eligible studies, the mean age was 40 years, of which 37.3% were female. The mean overall follow-up was 211 weeks (range from 3 to 797.8 weeks).

One RCT and 9 observational studies (a total of 527 patients with a mean follow-up duration of 135.6 weeks) [21-25, 29, 30, 34-36] used the following two methods to estimate the DH (method-1 group):

(1) DH method-1a on L3-L4 to L5-S1: average of anterior and posterior DH = (a+c)/2 [23, 30];

(2) DH method-1b on L1-L2 to L5-S1: average of anterior, middle, and posterior DH = (a+b+c)/3) to measure the DH [21, 22, 24, 25, 29, 34-36].

One RCT and 7 observational studies (a total of 366 patients with a mean follow-up duration of 305.3 weeks) [5, 20, 26-28, 31-33] used the following three methods to estimate the DHI (method-2 group):

(1) DHI method-2a L2-L3 to L5-S1: the ratio of DH to the sagittal diameter of the overlying vertebral body = [(a + b + c)/3]/d [20, 31, 32];

(2) DHI method-2b L2-L3 to L5-S1: the ratio of DH to the height of the overlying vertebral body = disc height/vertebral height [26, 28, 33];

(3) DHI method-2c L2-L3 to L5-S1: the ratio of preoperative DHI to the post-operative DHI = Preoperative DHI/post-operative DHI) [5, 27].

All the details of included measurements are presented in **Figure 6.2** and the study characteristics of all included studies are provided in **Table 6.1**.

6.3.3 Quality assessment

Two of the included RCTs had a low overall risk of bias [20, 21]. All observational studies were awarded more than seven stars, which demonstrated high-quality (**Table 6.2**).

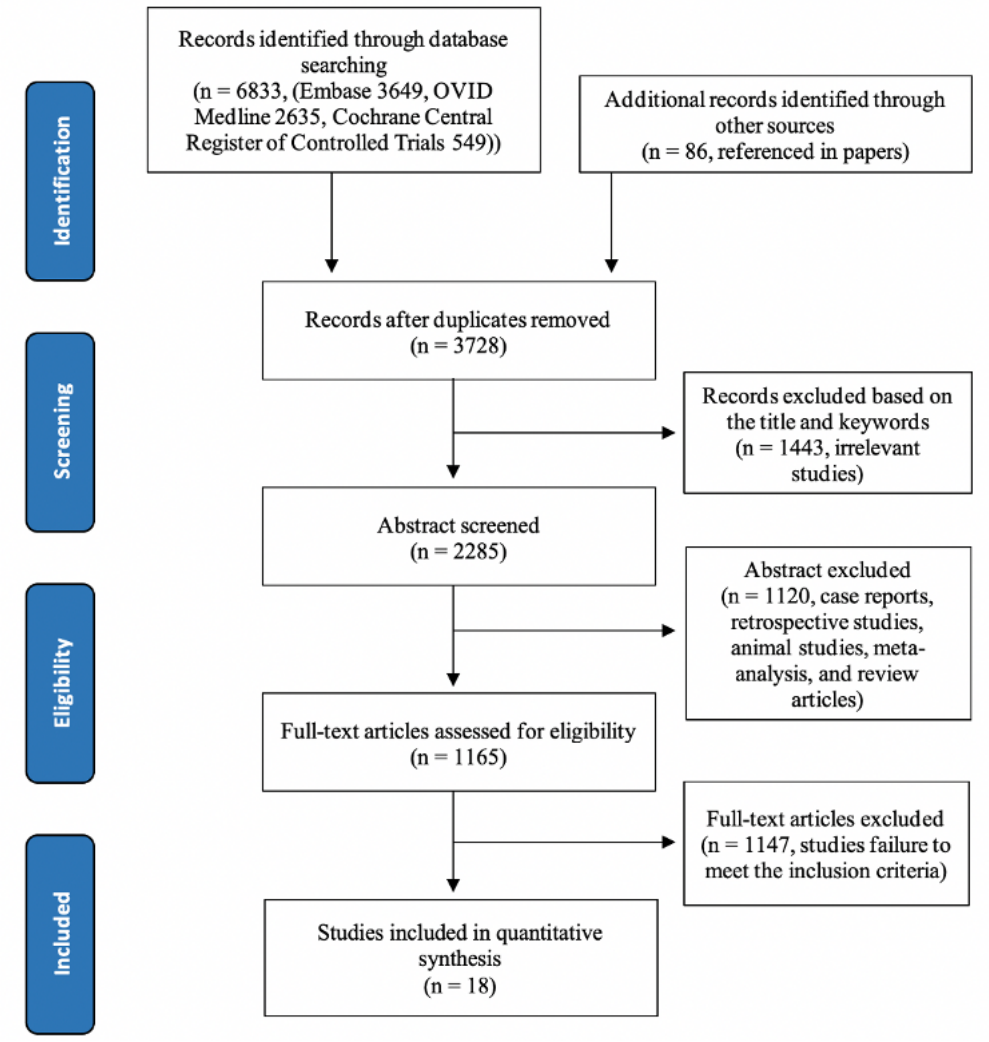

Figure 6.1 Flow chart showing the procedure and results of the literature search in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.

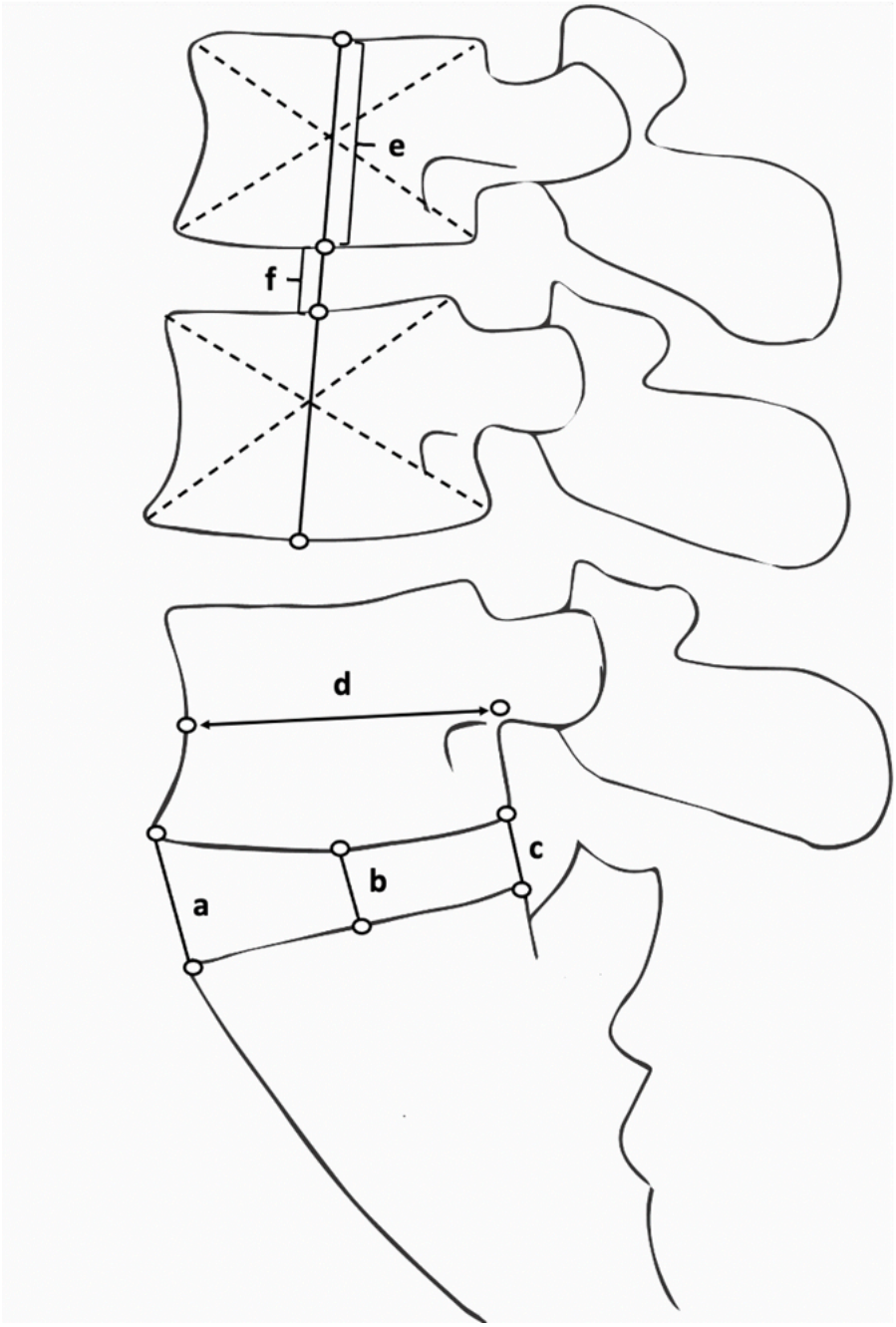

Figure 6.2 The details of measurements for disc height (DH) and disc height index (DHI) from the selected studies. Note: a = anterior DH, b = middle DH, c = posterior DH, d = sagittal diameter of the overlying vertebral body, e = the vertebral height, f = the middle DH, DH method-1a: average of anterior and posterior DH = (a+c)/2; DH method-1b: average of anterior, middle, and posterior DH = (a+b+c)/3; DHI method-2a: the ratio of DH to the sagittal diameter of the overlying vertebral body DHI = [(a + b +

c)/3]/d; DHI method-2b: the ratio of DH to the height of the overlying vertebral body DHI = f/e; DHI method-2c: the ratio of preoperative DHI to the post-operative DHI = Preoperative DHI/post-operative DHI (No specific measurement has been mentioned for DHI).

Table 6.1 Demographic data, surgical technique, surgery-related clinical outcomes, and disc height outcome for the selected studies

Author year	Population						Outcome							Adverse event	Re-op	Study design
	N total	Intervention	No female	Mean age	BMI	Surgical level	Back pain	leg pain	Disability	Disc height	DHI	ROM	Follow-up (week)			
Lee 2015	40	Discectomy	13	42.7		L3/4, L4/5, L5S1	Y	Y	Y		Y		52.2	3	1	RCT
Vodicar 2017	30	Discectomy	10	36.6		L4/5, L5S1	Y	Y	Y	Y			26.1	2	0	RCT
Saruhashi 2004	47	Discectomy	13	38.3		L3/4, L4/5, L5S1			Y	Y			521.4	4		Cohort study
Parker 2016	76	Discectomy		39.8		L3/4, L4/5, L5S1	Y	Y	Y	Y			104.4	0	0	Cohort study
Son 2018	48	Discectomy	21	57.1	23.7	L1/2, L2/3	Y	Y	Y	Y		Y	52.2	0	0	Cohort study
McGirt 2009	108	MD	36	41		L3/4, L4/5, L5S1	Y	Y	Y	Y			104.4	24	11	Cohort study
Lee 2009	54	PELD	16	45.1		L4/5	Y	Y	Y		Y		148.7	2	2	Cohort study
Eun 2016	38	PELD	14	53.74		L3/4, L4/5, L5S1	Y	Y	Y		Y		585			Cohort study
Choi 2016	43	PELD	16	36.1		L2/3, L3/4, L4/5, L5S1	Y	Y	Y	Y	Y		104.4	2	2	Cohort study
Qiao 2020	64	PELD	21	54.39	24.46	L4/5	Y	Y	Y	Y			104.4			Cohort study
Tsuji 1992	80	Discectomy	31	29		L3/4, L4/5, L5S1				Y			286.8	9	9	Case serials
Ishihara 1997	7	Discectomy	4	12.1		L4/5, L5S1	Y				Y		372.3			Case serials
Yorimitsu 2001	72	Discectomy	25	38		L2/3, L3/4, L4/5, L5S1	Y	Y			Y	Y	745.6		9	Case serials
Sayyahmelli 2012	33	Discectomy	14	39.42		L4/5, L5S1					Y		3			Case serials
Son 2015	79	Discectomy	39	37.6		L4/5, L5S1	Y	Y	Y		Y	Y	797.8		11	Case serials
Luo 2020	25	Discectomy	11	45.6	23.1	L3/4, L4/5, L5S1				Y			52.2	1	0	Case serials
Sharma 2019	18	PELD	7	35.1		L4/5, L5S1	Y	Y	Y				52.2	3	1	Case serials
Mahatthanatrakul 2019	31	PELD	8	38.3	52.2	L3/4, L4/5, L5S1	Y	Y	Y	Y			52.2			Case serials

N = number, BMI = body mass index, DHI = disc height index, ROM = range of motion, Re-op = re-operation, Y = yes, RCT = randomized controlled trials, MD = microdiscectomy, PELD = percutaneous endoscopic lumbar discectomy

Table 6.2 Assessment of the methodological quality of observational studies according to the Newcastle-Ottawa Scale (NOS)

Author	Year	Country	Surgical Procedures	Study type	Selection (/4)	Comparability (/2)	Outcome/ Exposure (/3)	Total Score (/9)
Saruhashi	2004	Japan	Discectomy	Cohort	4	2	3	9
Parker	2016	USA	Discectomy	Cohort	4	2	3	9
Son	2018	Korea	Discectomy	Cohort	4	2	3	9
McGirt	2009	Japan	MD	Cohort	4	2	3	9
Lee	2009	Korea	PELD	Cohort	4	2	3	9
Choi	2016	Korea	PELD and MD	Cohort	4	2	3	9
Eun	2016	Korea	PELD	Cohort	4	2	3	9
Qiao	2020	China	PELD	Cohort	4	2	3	9
Tsuji	1992	Japan	Discectomy	Case series	4	0	3	7
Ishihara	1997	Japan	Discectomy	Case series	4	0	3	7
Yorimitsu	2001	Japan	Discectomy	Case series	4	0	3	7
Sayyahmelli	2012	Iran	Discectomy	Case series	4	0	3	7
Son	2015	Korea	Discectomy	Case series	4	0	3	7
Luo	2020	China	Discectomy	Case series	4	0	3	7
Sharma	2019	Korea	PELD	Case series	4	0	3	7
Mahatthanatrakul	2019	Thailand	PELD	Case series	4	0	3	7

MD = microdiscectomy, PELD = percutaneous endoscopic lumbar discectomy, USA = United States of America; A study awarded seven or more stars was regarded as a high-quality study.

6.3.4 Outcomes for DH change

Based on all of the ten included studies, the change in DH after discectomy surgery showed 14.4% reduction (SMD = -0.74 (95% CI = -0.86 to -0.61), I^2 = 23.6%, P = 0.226) [21-25, 29, 30, 34-36]. There was a 17.3% reduction of DH in the method-1a group [23, 30] (SMD = -0.74 (95% CI = -0.97 to -0.51) and 12.6% reduction in the method-1b group [21, 22, 24, 25, 29, 34-36] (SMD = -0.73 (95% CI = -0.88 to -0.59)) after discectomy surgery by mixed effect model (**Figure 6.3**). For all studies we rated the level of evidence as low or very low-quality due to inconsistency of results and/or lack of blinding in estimates [21-25, 29, 30, 34-36].

Subgroup analysis, meta-regression and sensitivity analysis of the results are list in **Table 6.3**. It showed no effect on the results based on publication date, number of patients and follow-up period. A funnel plot of the results of included trials indicated no publication bias.

6.3.4.1 Temporal analysis

We obtained subgroup analysis based on follow-up period. In the method-1a group, the changes in DH after discectomy surgeries at 12 months follow-up period showed a significant change (SMD = -0.74 (95% CI = -0.97 to -0.51). In the method-2 group, the same occurred in the 12 months, 12 to 24 months and after 60 months follow-up (≤12 months: SMD = -0.72 (95% CI = -0.90 to -0.55); <12-24 months≤: SMD = -0.90 (95% CI = -1.12 to -0.68); >60 months: SMD = -0.93 (95% CI = -1.36 to -0.51)). We rated the quality of evidence as low-quality due to the lack of blinding in estimates.

6.3.4.2 The association of clinical scores with DH change

In the method-1a group, the mean initial DH was 9.4 mm and the reduction in DH ranged from 5.2% to 26%. As shown in **Table 6.3**, there was a significant relationship between the reduction in DH and decrease in back pain score (r = 0.68, (95%CI = 0.07-1.30), p = 0.034) after discectomy surgery [21, 24, 25, 29, 34-37]. The same statistically significant relationship occurred in the method-1b group (r = 0.74, (95%CI = 0.08-1.40), p = 0.033) [21, 24, 25, 29, 34-36]. Based on different follow-up period in each measurement group for subgroup analysis, no significant association was found between the change in DH and decrease in clinical scores (**Table 6.3**).

6.3.5 Outcomes for DHI change

In eight studies [5, 20, 26-28, 31-33], the DHI after discectomy surgeries showed 11.5% reduction (SMD = -0.81 (95% CI = -0.97 to -0.65), I^2 = 95.8%, P = 0.000). Based on all 3 DHI measuring methods, there was a significant reduction of DH after discectomy surgery by mixed effect model (DHI method-2a group [20, 31, 32] (SMD = -0.52 (95% CI = -0.84 to -0.21)), DHI method-2b group [26, 28, 33] (SMD = -0.42 (95% CI = -0.63 to -0.20)) and DHI method-2c [5, 27] (SMD = -2.56 (95% CI = -2.95 to -2.18))) (**Figure 6.4**). The large magnitude of effect upgraded the low-quality evidence to moderate quality.

A sensitivity analysis of the results for significant heterogeneity is list in **Table 6.3**. It showed no effect on the heterogeneity based on publication date, number of patients and follow-up period. A funnel plot of the results of included trials indicated no publication bias.

6.3.5.1 Temporal analysis in different measurement group

Subgroup analysis based on follow-up period was performed in **Figure 6.4**. In the method-2a group, the changes in DHI after discectomy surgeries in different follow-up periods showed a significant change (≤12 months: SMD = -0.47 (95% CI = -0.80 to -0.14); >60 months: SMD = -1.20 (95% CI = -2.35 to -0.05)). In the method-2b group, the changes in DHI after discectomy surgeries in different follow-up periods also showed a significant change (≤12 months: SMD = -0.73 (95% CI = -1.16 to -0.29); <12-24 months≤: SMD = -0.44 (95% CI = -0.82 to -0.06); >60 months: SMD = -0.24 (95% CI = -0.55 to -0.08)). In the method-2c group, the changes in DHI after discectomy surgeries only showed a significant change after the 60 months follow-up (SMD = -2.56 (95% CI = -2.95 to -2.18)) and the results affected the significant heterogeneity (I^2 = 98.5%, P = 0.000). We upgraded the quality of evidence to moderate due to the large magnitude of effect.

6.3.5.2 The association of clinical scores with DHI change

The method-2 group, with a total of 366 patients had a mean initial DHI of 0.56 and showed a reduction in DHI that ranged from 5.7% to 19%. As shown in **Table 6.3**, no significant relationship between DHI change and decrease in clinical scores could be established [20, 26-28, 33]. No significant relationship was found between the change in DHI and decrease in clinical scores at any of the follow-up periods.

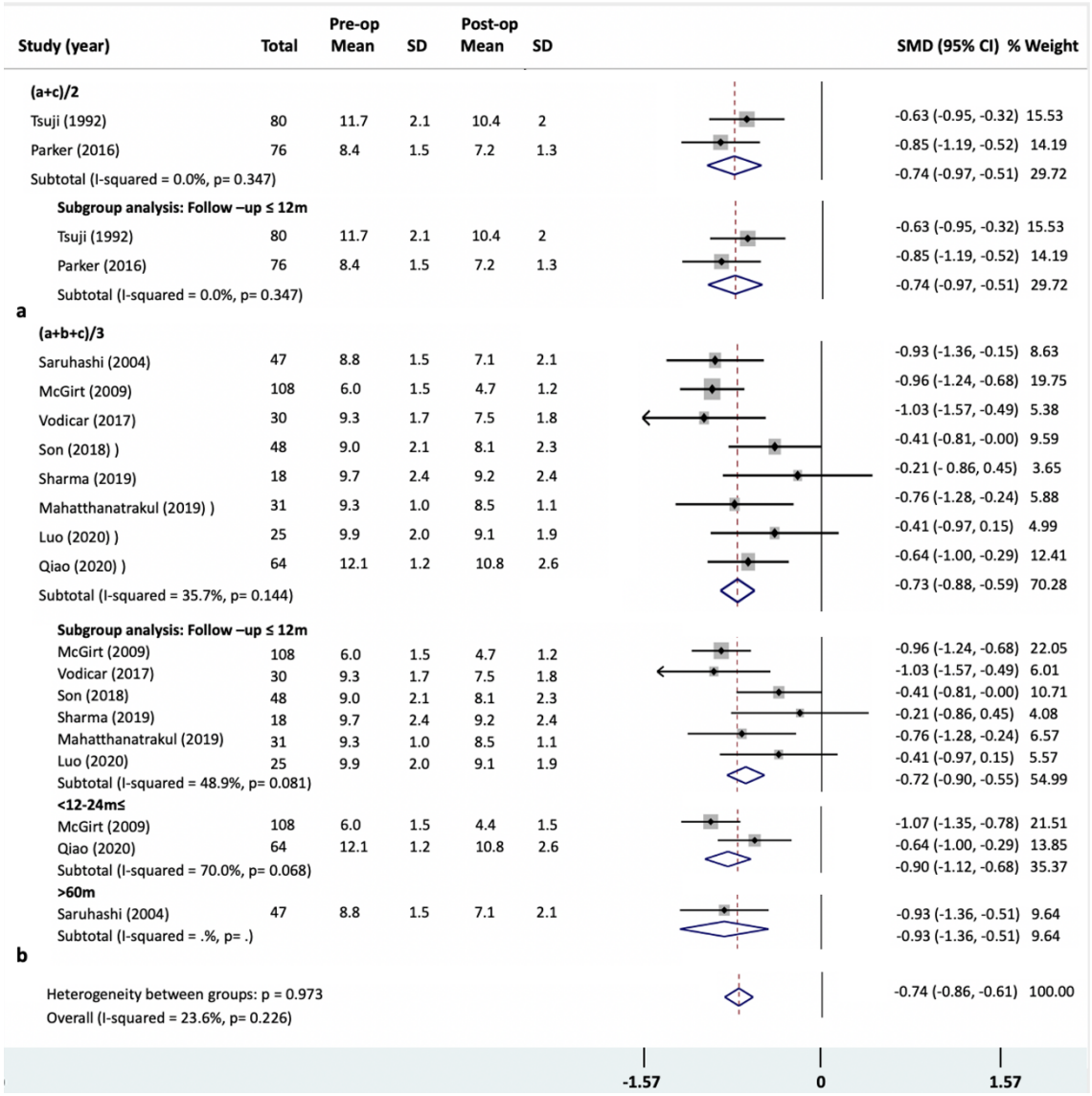

Figure 6.3 Disc height (DH) changes in different measurements following discectomy surgeries were reported as standardized mean difference (SMD) and 95% confidence intervals (CI). Temporal analysis based on follow-up period in each measurement group was performed. Note: Two methods were used to measure the disc height: method-1a (Figure 2a): average of anterior and posterior disc height = (a+c)/2; method-1b (Figure 2b): average of anterior, middle, and posterior disc height = (a+b+c)/3

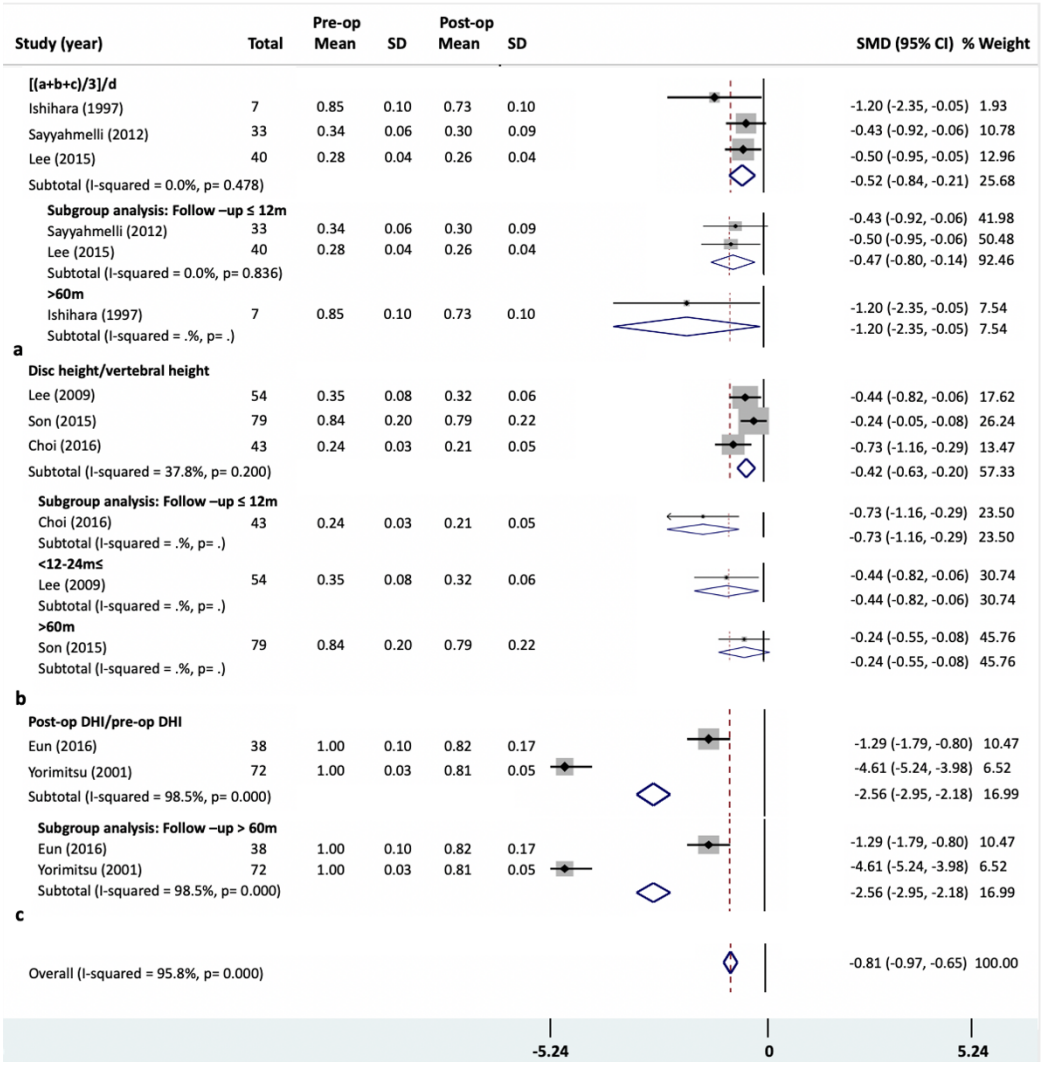

Figure 6.4 Disc height index (DHI) changes in different measurements following discectomy surgeries were reported as standardized mean difference (SMD) and 95% confidence intervals (CI). Temporal analysis based on follow-up period in each measurement group was performed. **Note:** Three methods were used to measure the DHI: method-2a (Figure 3a): the ratio of disc height to the sagittal diameter of the overlying vertebral body = [(a + b + c)/3]/d; method-2b (Figure 3b): the ratio of disc height to the hight of the overlying vertebral body = disc height/vertebral height; method-2c (Figure 3c): the ratio of preoperative DHI to the post-operative DHI = Preoperative DHI/post-operative DHI.

Table 6.3 Grading of Recommendations Assessment, Development and Evaluation (GRADE) level of quality assessment. The table presents a detailed summary of the evidence, including statistical model (effect size and associated confidence intervals (CI)), regression data, tests of homogeneity, publication bias (Begg's test), and the certainty of the evidence

Outcome	Test	Statistical model			Homogeneity		Begg's P	Level of quality
		ES/r	95% CI	P value	P value	I^2 (%)		
Disc height (DH)	**Random effect model Test**							
	All	-0.74	-0.86, -0.61[a]	-	0.226	23.6	0.421	L^2
	DH method-1a: (a+c)/2	-0.74	-0.97, -0.51[a]		0.347	0.0		L^2
	Follow-up ≤12 months	-0.74	-0.97, -0.51[a]		0.347	0.0		L^2
	DH method-1b: (a+b+c)/3	-0.73	-0.88, -0.59[a]		0.144	35.7		L^2
	Follow-up ≤12 months	-0.72	-0.90, -0.55[a]		0.081	48.9		L^2
	Follow-up <12-24 months≤	-0.90	-1.12, -0.68[a]		0.068	70.0[c]		$VL^{2,3}$
	Follow-up >60 months	-0.93	-1.36, -0.51[a]		-	-		-
	Sensitivity analysis				-			
	Publication date	0.01	-0.10, 0.02		0.576	30.2	-	
	Follow-up period	-0.01	-0.01, 0.01		0.447	27.3		
	Number of patients	-0.01	-0.01, 0.01		0.143	9.6		
	Meta-regression							
	Back pain with all DH data	0.68	0.07, 1.30	0.034*	-			
	Subgroup: DH method-1b: (a+b+c)/3	0.74	0.08, 1.40	0.033*				
	Leg pain with all DH data	-0.09	-1.57, 1.39	0.890				
	Subgroup: DH method-1b: (a+b+c)/3	-0.13	-1.86, 1.60	0.865				
	ODI with all DH data	-0.01	-0.05, 0.03	0.613				
	Subgroup: DH method-1b: (a+b+c)/3	0.01	-0.02, 0.03	0.637				
Disc height index (DHI)	**Random effect model Test**							
	All	-0.81	-0.97, -0.65[a]	-	0.000[b]	95.8[c]	0.138	$VL^{2,3}$
	DHI method-2a: [(a + b + c)/3]/d	-0.52	-0.84, -0.21[a]		0.478	0.0		L^2
	Follow-up ≤12 months	-0.47	-0.80, -0.14[a]		0.836	0.0		$M^{2,5}$
	Follow-up >60 months	-1.20	-2.35, -0.05[a]		-			L^2
	DHI method-2b: disc height/vertebral height	-0.42	-0.63, -0.20[a]		0.200	37.8		$M^{2,5}$
	Follow-up ≤12 months	-0.73	-1.16, -0.29[a]		-			L^2
	Follow-up <12-24 months≤	-0.44	-0.82, -0.06[a]					$M^{2,5}$

	Follow-up >60 months	-0.24	-0.55, -0.08[a]					M[2,5]
	DHI method-2c: Pre-op DHI/post-op DHI	-2.56	-2.95, -2.18[a]		0.000[b]	98.5[c]		M[2,5]
	Follow-up >60 months	-2.56	-2.95, -2.18[a]		0.000[b]	98.5[c]		M[2,5]
	Sensitivity analysis				-			-
	Publication date	0.12	-0.04, 0.28		0.125	93.9	-	
	Follow-up period	-0.01	-0.01, 0.01		0.195	96.1		
	Number of patients	0.02	-0.04, 0.08		0.491	96.4		
	Meta-regression							
	Back pain with all DHI data	0.03	-0.02, 0.07	0.144	-			
	Subgroup: DHI method-2b: disc height/vertebral height	0.01	-0.12, 0.14	0.601				
	Leg pain with all DHI data	-0.01	-0.52, 0.51	0.984				
	Subgroup: DHI method-2b: disc height/vertebral height	0.03	-0.72, 0.78	0.686				
	ODI with all DH data	-0.01	-0.05, 0.03	0.628				
	Subgroup: DHI method-2b: disc height/vertebral height	0.01	-0.04, 0.05	0.462				

Pre-op = preoperative, post-op = post-operative, CI = confidence intervals; ES = effect size, ODI = Oswestry Disability Index; Two methods were used to measure the disc height: method-1a: average of anterior and posterior disc height = (a+c)/2; method-1b: average of anterior, middle, and posterior disc height = (a+b+c)/3); Three methods were used to measure the DHI: method-2a: the ratio of disc height to the sagittal diameter of the overlying vertebral body = [(a + b + c)/3]/d; method-2b: the ratio of disc height to the hight of the overlying vertebral body = disc height/vertebral height; method-2c: the ratio of preoperative DHI to the post-operative DHI = Preoperative DHI/post-operative DHI.

[a] 95% CI including 0 means no statistical significance, while not including 1 means have statistical significance; [b] $P < 0.05$ indicated significance; [c] $I^2 > 50\%$ implied heterogeneity. Quality of evidence: H = high, M = moderate, L = low, VL = very low. Significant difference * $P<0.05$, ** $P<0.01$, *** $P<0.001$. [1]-rated down for imprecision, [2]-rated down for risk of bias, [3]-rated down for inconsistency, [4]-rated down for publication bias, [5]-rated up for large magnitude of effect (Strong evidence of association—significant relative risk or effect size of > 2 (< 0.5) based on consistent evidence

from two or more observational studies, with no plausible confounders (+1); Very strong evidence of association—significant relative risk or effect size of > 5 (< 0.2) based on direct evidence with no major threats to validity (+2)).

6.4 Discussion

This is the first meta-analysis and meta-regression addressing the impact of discectomy surgery on DH in LDH patients. We identified a total of 18 studies with 893 LDH patients who underwent open discectomy, MD, PELD surgery. All studies reported DH/DHI and pain scores for back/leg pain before and after discectomy procedure. In the studies that used the DH to assess the changes in IVD height, there is low or very low-quality evidence of DH change based on different follow-up periods, across both subgroups (DH method-1a and -1b group). Amongst the studies that assessed the DHI as a way to determine the change in the IVD height after a discectomy surgery, there is moderate quality evidence of DHI change. The results of this study suggest that there is a strong positive association between the reduction in DH and a decrease in back pain scores after discectomy surgery, especially when the method chosen to assess this change was that of the subgroup DH method-1b.

In theory, the removal of herniated disc results directly in a loss of DH post-operatively. Mechanical characterization change of the IVD after discectomy surgery accelerates the ageing and degeneration of disc, increasing the loss of DH as time follow-up. In order to understand the changes that the IVD height experiences after discectomy surgery, we have performed the first meta-analysis of the impact that discectomy surgeries have on DH. We demonstrate in this study that despite the use of various methods, there is a 11.2% decrease in the first 12 months and this loss of DH is further decreased to 16.6% at 60 months (**Table 6.4**). These findings are consistent with previously reported data [3, 25, 38]. An observational study reported the correlation between the volume of disc material removed and DH loss. The loss of DH started following discectomy, with significant decreases in DH noted at 12 months post-surgery and continued to decrease

even after the 60-month follow-up [39]. Loss of DH represents biomechanical deficits in the IVD that lead to osteochondrosis and neuroforaminal stenosis. These changes could affect pain scores and disability indexes, and ultimately, they could affect the overall quality of life for these patients.

The post-surgical changes to the IVD, represented with a reduction of its DH, are characterized by a cascade of cellular, structural, biochemical, and functional changes; and are strongly implicated as a cause of LBP [40, 41]. The decreased intradiscal pressure and the increased loads on facet joints noted following the DH loss after discectomy surgery could account for an increase in post-procedure pain scores [42]. Cadaveric and in-*vitro* studies have shown that the disruption of annular integrity led to significant alterations in both operative and proximal discal pressure after discectomy surgery [42], which also revealed the correlation of the decreased DH and increased radial disc bulge with the increased removal volume of IVD [43]. Our results show that there is a strong positive association between the change of DH and back pain score, especially in method- 1b group. A possible explanation for the relationship is that the loss of DH may result in lessened relative motion and therefore less motion related pain in the near term. In the longer term, the lessened motion may have untoward sequelae for the adjacent levels of the spine and longer-term follow-up would be necessary to understand the ultimate clinical implications for post-discectomy reduction in DH.

Although an association between the change of DH and the change of back pain score was found in our study, there still exists different conclusions on the association between different measurements. The lack of uniformity between the different studies analyzed makes the endeavor of drawing conclusions from this meta-analysis a difficult one.

Although the low-quality evidence on our results does not help support the accepted fact in the field that DH decreases post discectomy and the association with pain score change, we have learnt that one challenge is the numerous methods of estimating disc height following this study. It may hence be important to first find the most sensitive and valid tool for disc height measurement post discectomy.

Table 6.4 The percentage of reduction of disc height based on follow-up period after discectomy surgery for lumbar disc herniation

Follow-up period	Study (Author_Year)	Percentage of the reduction of disc height
≤12 months	Tsuji 1992	11.11%
	McGirt 2009	21.00%
	Parker 2016	14.49%
	Vodicar 2017	19.35%
	Son 2018	9.61%
	Sharma 2019	5.15%
	Mahatthanatrakul 2019	8.31%
	Luo 2020	8.05%
	Sayyahmelli 2012	9.52%
	Lee 2015	5.70%
	Choi 2016	11.00%
<12-24 months≤	McGirt 2009	26.00%
	Qiao 2020	10.83%
	Lee 2009	8.91%
<24-60 months≤	Tsuji 1992	17.09%
>60 months	Tsuji 1992	23.08%
	Saruhashi 2004	19.32%
	Ishihara 1997	14.12%
	Yorimitsu 2001	19.00%
	Son 2015	5.95%
	Eun 2016	18.00%

6.4.1 Limitations

Although the results of our analysis are comprehensive, there are certain limitations which must be noted. First, the small number of RCTs included in this study may have reduced the statistical robustness of the results. Second, meta-regression analysis describes observational associations across trials because comparisons of trial-level characteristics lack the benefit of randomization to support causal interpretation of findings. Consequently, associations between trial-level characteristics and effects of interventions are subject to the same limitations as findings from observational studies, such as ecological bias and bias by unmeasured confounding. Third, there is substantive heterogeneity in the studies due to wide variation in the duration of follow-up, different measurements for DH and DHI, and different surgical techniques. Fourth, there is lack of structured protocol to conduct the measurement in included studies. Finally, the primary literature is varied and does not routinely discuss age and surgical levels in reporting radiological results, which may increase heterogeneity and reveal inherent differences associated with pain scores. Guidelines for measurement and better standardization of spine imaging phenotypes are needed to allow study comparisons and pooling of data to facilitate interpretation of the collective body of related research.

6.5 Conclusion

The results of this study show moderate or very low-quality grade evidence of a decrease in DH after a discectomy procedure. While there seems to be a strong association between the reduction in DH and the decrease in LBP after discectomy, especially when the DH is assessed using the group 2b method, the limitations of the results found in this review do not offer a robust level evidence for practical

applications of this finding. Standardising DHI measurement reported in the literature will allow further analysis.

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Chapter 7. Which is the Most Sensitive and Valid Measurement Method for Lumbar Intervertebral Disc Height? An Intra and Inter-Rater Agreement and Reliability Study

In the previous chapter, a significantly change of disc height following discectomy surgery and an association between the change of disc height and the change of back pain score were found. There still exists different conclusions on the association between disc height index in different measurements and pain score change following discectomy surgery. The lack of uniformity between the different studies analyzed makes the endeavor of drawing conclusions from this result a difficult one. Therefore, an accurate, efficient, and reproducible measurement for intervertebral height is required.

7.1 Introduction

Low back pain (LBP) is the leading cause of disability worldwide with a lifetime prevalence that exceeds 90% [1]. Within the vast differential of LBP, the degeneration of intervertebral disc (IVD) is considered as a significant contributor [2]. Radiological examinations of the morphologic characteristic of lumbar IVD such as height has been found to be related to the degeneration [3]. The change of IVD height influences the load-carrying capacity of the spinal column, and morphologic abnormalities such as IVD space narrowing, and thinning have been potentially associated with acute or chronic disabilities of the lumbar spine [4]. However, there is a paucity of information

using different methods to estimate the DH and its clinical significance. Therefore, an accurate and efficient measurement for IVD height is required.

Compared with lying supine during MRI and CT scan, the standing X-ray of lumbar spine can better present the state of IVD under load. Therefore, X-ray is considered as the most frequently used technique despite known difficulties, both in interpretation and clinical significance of findings. Clinicians often rely on their own subjective interpretation of lumbar spine radiographs, however, numerous methods for DH using X-ray published in the literature have been described as more accurate, albeit, and more time consuming [5-10]. DH can be measured as an absolute value, although this may be influenced by the magnification and position of the patient on the scan. Simple values can be used in daily practice for quick comparisons. For more in-depth studies and more accurate readings, the DHI has been introduced. By normalising images, variations in the size of the vertebral column and position of the patient do not affect the final measurement and allow for a reliable analysis. Many DHI measurement methods of IVD has been discussed previously in the literature [5-10]. However, this lack of consensus leads to great inter- and even intra-rater variability. A simple and reproducible method to measure DHI is required.

Bland and Altman´s Limits of Agreement (LOA) is the most popular [11], and recommended statistical method for evaluation of agreement between different methods or observers [12, 13]. The standard error of measurement (SEM) is similarly regarded as a suitable parameter of agreement, but is, however, sensitive to variability in the population [14]. Although recent study reported use of LOA for evaluating agreement of measurements on intervertebral disc morphology using MRI images [15], it is rarely used when evaluating agreement in the different measurements of DHI using X-ray.

Therefore, we need to use LOA to evaluate intra- and inter-rater agreement and reliability of DHI using the previously reported methods [5-10].

The primary objective of this study is to evaluate intra- and inter-rater agreement and reliability of seven previously reported DHI measurement methods.

7.2 Materials and Methods

Ethical approval was obtained from the Human Research Ethics Committee of the University of New South Wales (NRR-HC180423) for the intra- and inter-rater agreement and reliability study using repeated measurement methods of individuals' X-rays.

7.2.1 Design and patients

The study is conducted as a retrospective review of radiological images, radiology reports, and demographic data of patients over the age of 18 years who had routine standing lateral X-ray of lumbar spine from St George MRI in Sydney (Australia) from March 2017 onwards. Only patients who signed the consent form to allow use of their de-identified data for research and auditing purposes were included in the present study. The patients who had a history of spine surgery were excluded from the study.

7.2.2 Measurements

The standard standing lateral X-ray images of lumbar spine were assessed. The patient is naturally standing up, looking horizontally, hands resting on a vertical support, upper limbs relaxed, elbows half bent [16]. The corresponding radiology reports were read by the first author (Xiaolong Chen). Seven methods were used to measure the DHI of each lumbar IVD level on standing later X-ray images (L1-L2, L2-L3, L3-L4, L4-L5, and

L5-S1) [5-10]. The details of DHI measurement methods are presented as follows and showed in **Figure 7.1**.

Method 1 of DHI is expressed as a ratio of the sum of anterior and posterior IVD height to disc diameter [5]. Method 2 of DHI is expressed as a ratio of the mid-disc height to mid-vertebral body height [6]. Method 3 of DHI is expressed as a ratio of the mid-disc height to disc diameter [6]. Method 4 of DHI is expressed as a ratio of the mean of anterior, middle, and posterior IVD height to the sagittal diameter of the proximal vertebral body [7]. Method 5 of DHI is expressed as a ratio of IVD height to vertebral height which cross the centre of adjacent vertebral bodies [8]. Method 6 of DHI is expressed as a ratio of the mean of anterior, middle, and posterior IVD height to the mean of proximal and distal vertebral body height [9]. Method 7 of DHI is expressed as a ratio of the sum of anterior and posterior IVD height to the sum of superior and inferior disc depth [10].

A quadrilateral was drawn to define the vertebral corners and minimize the affection of osteophytes. A line was drawn cross the potential points of each corner which was caused by the vertebral rotation for inexact body position during the scan and the anatomy deformity (such as scoliosis, vertebral rotation, and vertebral fracture). Mid-point of the line was identified as the real vertebral corner. Direct line was draw cross the two points which were located at the vertebral body. Indirect line was drawn cross the potential points which were location at direct lines.

If MRI scans already performed and presented in St Georgy MRI, the images were assessed the IVD degeneration. IVD degeneration is defined as the presence of at least one of the following: nucleus pulposus degeneration, IVD bulge or IVD herniation, annular tear, Modic changes of endplate, and Schmorl's node [17-21]. Nucleus pulposus

degeneration is defined as Pfirrmann grade ≥ 3 [22]. Participants were allocated into different groups (degeneration group and no degeneration group) based on the IVD degeneration status.

In order to reduce the potential bias due to difference of equipment and software, raters used Apple MacBook with integrated touchpads and the *InteleViewer*^{TM} diagnostic imaging software for measurement.

7.2.3 Training and blinding of raters

Two raters conducted the measurements: one is a medical student (Stone Sima: 3rd Year Student of Bachelor of Medical Studies/Doctor of Medicine at University of New South Wales, New South Wales, Australia) who has no prior training in the interpretation of radiological images (Rater 1); the other is an experienced spine surgeon and back pain researcher (Xiaolong Chen) with extensive experience in interpreting radiological images (Rater 2). Thirty participants from the final data collection period were randomly selected for training. Each rater reviewed the 30 cases independently, after which the cases were collectively reviewed, and consensus were reached on the measurement procedures. Once the raters reached an agreement on the measurement procedures, the data of these 30 cases was used to analysis the intra-rater reliability. The intra- and inter-rater agreement were tested between two out of seven measurements performed by each rater. The inter-rater reliability was tested between two raters who were purposely chosen to represent an inexperienced, and an experienced interpreter of radiological images.

To enhance the quality and applicability of the study, both raters were blinded in several aspects. Each rater was blinded to his own prior measurements and the findings of the

other ratter. The order of participants was randomly changed between the two intra-rater measurement sessions. There was a 2-week interval between the first and second measurement sessions to lessen the likelihood of recognition of participants.

7.2.4 Statistical analysis

Numeric variables are presented as mean ± standards deviation (SD). Categorical variables are summarized using counts (n) and percentages (%). The intra- and inter-rater agreement between two out of seven methods for DHI were analysed using Bland and Altman´s LOA. LOA is based on graphical techniques and provides a plot of mean differences (MDs) between the two methods of measurement (the bias), as well as the SD of the differences (**Figure 7.2**). The 95% confident intervals (95% CI) of MDs were reported to describe the precision of the bias. If the 95% CI doesn't include zero, it can be assumed that there is a bias. Furthermore, LOA was presented as a proportion of mean values for each method. The proportion will be calculated as follows: ((upper LOA +(−1*(lower LOA)))/(the mean)) *100%. Following previously published data, we consider percentages lower than 50% as an indicator of acceptable precision [15].

Intra-class correlation coefficient (ICC) estimates, and their 95% CI were calculated using SPSS statistical package version 24 (SPSS Inc, Chicago, IL) based on a single-rating, absolute-agreement, 2-way fixed-effects model for intra-rater reliability. Results of inter-rater reliability was evaluated with ICC based on a single-rating, consistency, 2-way random-effects model in all participants and different degeneration groups. Values of ICC less than 0.5, between 0.5 and 0.75, between 0.75 and 0.9, and greater than 0.90 are indicative of poor, moderate, good, and excellent reliability, respectively [23]. Subgroup analysis was performed based on different segmental level, the status of IVD degeneration, and different related lines (direct and indirect line).

7.2.5 Factors analysis on the Bland and Altman´s plot

Potential factors for the data that were far above or below the LOA on the graphs were assessed and reported in a narrative form.

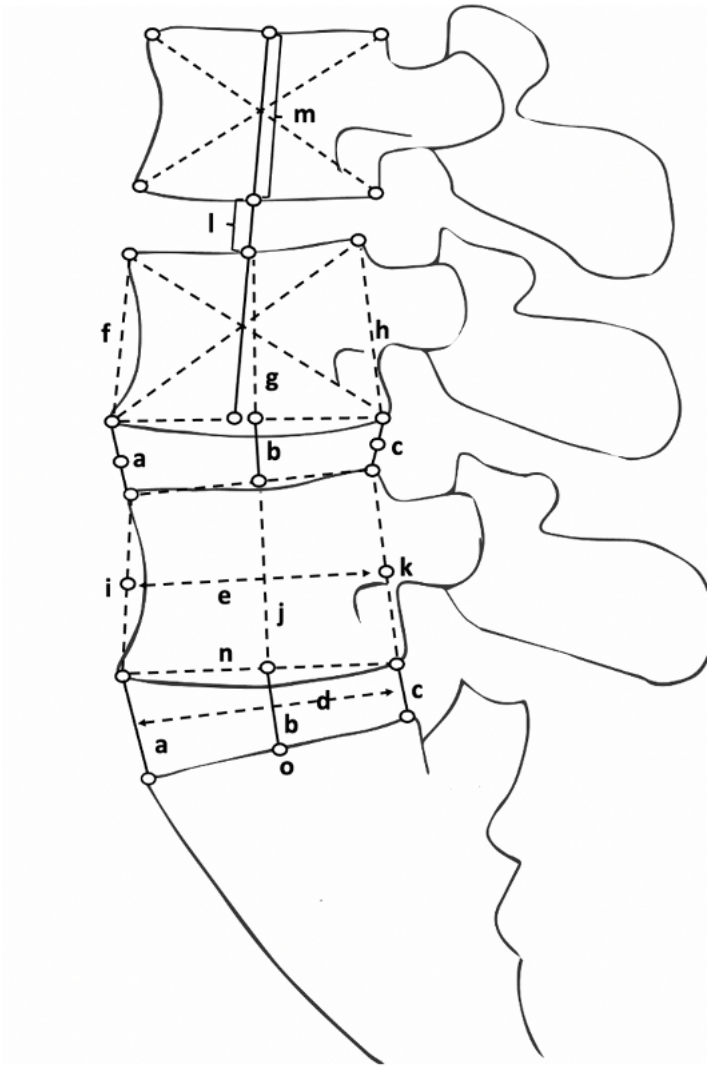

Figure 7.1 The details of disc height index (DHI) measurements. Note: a: The shortest distance between the anterior edges of the neighbouring endplate will be recorded as the anterior disc height; b: The mid-disc height between the upper and lower bisection points is measured at the midpoint of vertebrae; c: The shortest distance between the posterior edges of the neighbouring endplate will be recorded as the posterior disc height; d: The disc diameter will be measured between the midpoints of the lines drawn

from the endpoints of the superior vertebral endplate to the inferior; e: The sagittal diameter of the vertebral body from the anterior to posterior margin will be measured at the mid-vertebral level; f-h: The proximal vertebral body height will be measured from the anterior (f), middle (g), and posterior (h) portions of each respective disc level; i-k: The distal vertebral body height will be measured from the anterior (i), middle (j), and posterior (k) portions of each respective disc level; l, m: The mid-vertebral line is the line connecting the L3 and L4 centres. The centre of the vertebral body is a crossing point of 2 diagonal lines of each vertebral body (l is intervertebral disc height, m is intervertebral height); n: superior disc depth; o: inferior disc depth. According to the classification of related lines, line a, c, f, h, i, k, n and o are defined as direct lines and line b, d, e, g, j, l, and m are defined as indirect lines.

Method 1: DHI = [(a+c)/d] *100%

Method 2: DHI = (b/g) *100% or (b/j) *100%

Method 3: DHI = (b/d) *100%

Method 4: DHI = [(a+b+c)/3/e] *100%

Method 5: DHI = (l/m) *100%

Method 6: DHI = [2*(a+b+c)/((f+g+h)+(i+j+k))] *100%

Method 7: DHI = [(a+c)/(n+o)] *100%

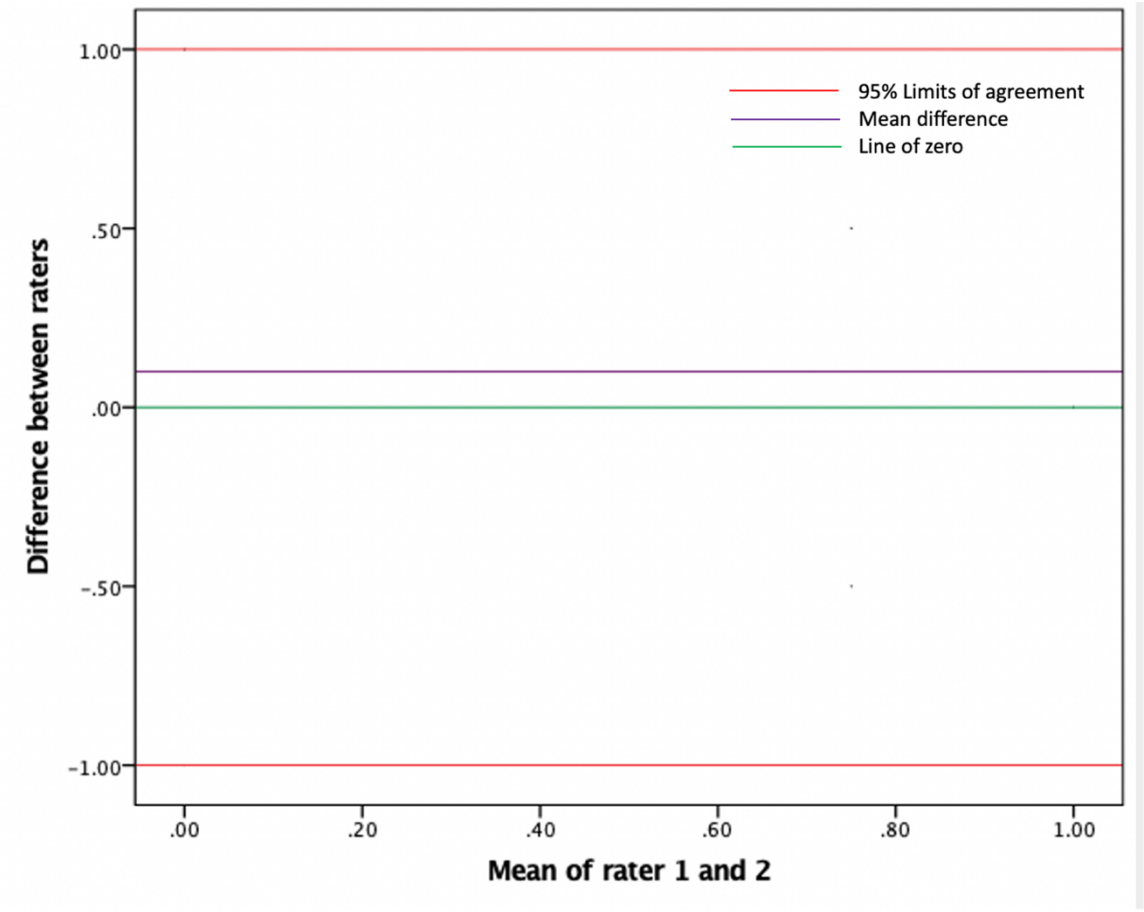

Figure 7.2 The Bland and Altman plot of Limits of Agreement (LOA) between two raters on the different measurements for disc height index (DHI). The y-axis shows the mean difference between raters' measurements, and the x-axis shows the mean value of both raters' measurements. The green line shows the range of mean difference includes zero. The purple line shows the mean difference between measurements. Red lines show the 95% LOA.

7.3 Results

In total, the standing lumbar X-ray from 288 participants were included in this study for evaluation of both intra- and inter-rater reliability and agreement. There were 122 females and 166 males, all aged between 19 and 89 years. Of 367 lumbar levels with IVD degeneration in 278 participants who performed MRI scans (**Table 7.1**).

7.3.1 Intra-rater reliability

The intra-rater reliability for DHI of all measurement methods, using ICC, was good-to-excellent from 0.807 (0.794, 0.812) to 0.922 (0.913, 0.946) by rater 1 and from 0.827 (0.802, 0.841) to 0.918 (0.806, 0.823) by rater 2, respectively (**Table 7.2**).

7.3.2 Inter-rater agreement

7.3.2.1 Method 1

The 95% CI of mean difference of DHI on segmental level L3-L4 ranged between -0.006 and 0.005, with LOA ranging between -0.10 and 0.10 (LOA as proportion of mean values is 33.9%). The 95% CI of mean difference of DHI on segmental level L5-S1 ranged between -0.014 and 0.002, with LOA ranging between -0.15 and 0.13 (LOA as proportion of mean values is 46.7%) (**Table 7.33** and **Figure 7.3A**).

7.3.2.2 Method 2, 3, and 5

The 95% CI of mean difference of DHI on all lumbar levels did not include zero or LOA as proportion of mean values is more than 50% (**Table 7.3**, **Figure 7.3B**, **Figure 7.3C**, and **Figure 7.3E**).

7.3.2.3 Method 4

The 95% CI of mean difference of DHI on segmental level L4-L5 ranged between -0.008 and 0.002, with LOA ranging between -0.06 and 0.06 (LOA as proportion of mean values is 38.7%) (**Table 7.3** and **Figure 7.3D**).

7.3.2.4 Method 6

The 95% CI of mean difference of DHI on segmental level L3-L4 ranged between -0.003 and 0.010, with LOA ranging between -0.12 and 0.12 (LOA as proportion of mean values is 17%). The 95% CI of mean difference of DHI on segmental level L4-L5 ranged between -0.009 and 0.001, with LOA ranging between -0.08 and 0.08 (LOA as proportion of mean values is 40%) (**Table 7.3** and **Figure 7.3F**).

7.3.2.5 Method 7

The 95% CI of mean difference of DHI on segmental level L3-L4 ranged between -0.003 and 0.003, with LOA ranging between -0.04 and 0.04 (LOA as proportion of mean values is 27.6%). The 95% CI of mean difference of DHI on segmental level L5-S1 ranged between -0.006 and 0.001, with LOA ranging between -0.06 and 0.06 (LOA as proportion of mean values is 40%) (**Table 7.3** and **Figure 7.3G**).

7.3.3 Inter-rater reliability

The inter-rater reliability for measurements of DHI was good-to-excellent in all but method 2 and 5 (ICCs ranged from 0.634 (0.598, 0.667) to 0.984 (0.982, 0.985); method 2: 0.736 (0.712, 0.759); method 5: 0.634 (0.598, 0.667)) (**Table 7.4**).

7.3.3.1 Temporal analysis

Based on different segmental levels, ICCs for DHI on segment level L1-L2 was moderate in method 2, 3, and 5 groups (ICC: 0.641 (0.568, 0.705), 0.718 (0.657, 0.770),

0.500 (0.409, 0.582)). ICCs for DHI on segment level L2-L3 was moderate in method 2 and 5 groups (ICC: 0.620 (0.543, 0.686), 0.726 (0.666, 0.776)). ICCs for DHI on segment level L3-L4 was moderate in method 2 and 5 groups (ICC: 0.693 (0.628, 0.749), 0.728 (0.669, 0.778)) (**Table 7.4**).

Based on the status of IVD degeneration, ICCs of DHI on all segmental levels in degeneration group and no degeneration group have a similar range based on the classification criterion for poor, moderate, good, and excellent reliability (**Table 7.5**).

ICCs of related lines to good-to-excellent reliability methods were excellent in all but only indirect line in method 1 and 4 (ICCs lie in the range from 0.8 to 0.9, **Table 7.6**).

7.3.3.2 Factors analysis on the Bland and Altman's plot

A total of 609 outliers in 9174 segmental levels' data includes 57 outliers in the method 1 group, 65 outliers in the method 2 group, 171 outliers in the method 3 group, 182 outliers in the method 4 group, 37 outliers in the method 5 group, 42 outliers in the method 6 group, and 55 outliers in the method 7 group (**Table 7.7**). The nucleus pulposus degeneration (394) and disc herniation (186) affected the raters to distinguish vertebral corners and structural boundaries.

Table 7.1 Patient demographic and clinic-radiological information

Parameter	Number of patients (%)
F:M	122:166
Age	47.67±16.79
Diagnosis	
Spondylolisthesis	32 (11.1%)
Disc herniation	57 (19.8%)
Spinal stenosis	174 (60.4%)
Scoliosis	11 (3.8%)
Normal	88 (30.6%)
MRI scans (number of patients)	278 (96.5%)
Intervertebral disc degeneration (number of patients)	231 (83.1%)
Lumbar levels with intervertebral disc degeneration (total)	367
L1-L2	2 (0.5%)
L2-L3	0
L3-L4	36 (9.8%)
L4-L5	160 (43.6%)
L5S1	169 (46%)

F: female; M: male; MRI: Magnetic resonance imaging

Table 7.2 Intra-rater measures' reliability results

Measurement method		N	Rater 1_ICC (95% CI)	Rater 2_ICC (95% CI)
Method 1	L1-L2	30	0.907 (0.902, 0.921)	0.917 (0.908, 0.924)
	L2-L3	30	0.867 (0.860, 0.882)	0.866 (0.854, 0.884)
	L3-L4	30	0.876 (0.861, 0.893)	0.888 (0.876, 0.893)
	L4-L5	30	0.822 (0.811, 0.843)	0.858 (0.836, 0.873)
	L5S1	30	0.855 (0.841, 0.873)	0.878 (0.856, 0.893)
	All	150	0.875 (0.872, 0.889)	0.907 (0.902, 0.928)
Method 2	L1-L2	30	0.821 (0.817, 0.842)	0.845 (0.822, 0.864)
	L2-L3	30	0.807 (0.794, 0.812)	0.827 (0.802, 0.841)
	L3-L4	30	0.922 (0.913, 0.946)	0.912 (0.895, 0.946)
	L4-L5	30	0.823 (0.812, 0.844)	0.834 (0.828, 0.862)
	L5S1	30	0.842 (0.817, 0.881)	0.868 (0.860, 0.890)
	All	150	0.848 (0.807, 0.855)	0.871 (0.869, 0.889)
Method 3	L1-L2	30	0.822 (0.810, 0.864)	0.842 (0.838, 0.876)
	L2-L3	30	0.843 (0.831, 0.861)	0.861 (0.849, 0.873)
	L3-L4	30	0.830 (0.815, 0.856)	0.833 (0.805, 0.856)
	L4-L5	30	0.853 (0.842, 0.883)	0.869 (0.857, 0.883)
	L5S1	30	0.851 (0.812, 0.865)	0.863 (0.841, 0.876)
	All	150	0.850 (0.832, 0.864)	0.865 (0.844, 0.875)
Method 4	L1-L2	30	0.882 (0.962, 0.896)	0.892 (0.882, 0.898)
	L2-L3	30	0.831 (0.822, 0.848)	0.842 (0.812, 0.855)
	L3-L4	30	0.877 (0.872, 0.882)	0.879 (0.868, 0.885)
	L4-L5	30	0.852 (0.834, 0.881)	0.872 (0.865, 0.889)
	L5S1	30	0.916 (0.901, 0.923)	0.918 (0.806, 0.823)
	All	150	0.879 (0.869, 0.912)	0.887 (0.875, 0.914)
Method 5	L1-L2	30	0.817 (0.801, 0.841)	0.841 (0.823, 0.866)
	L2-L3	30	0.854 (0.833, 0.867)	0.858 (0.843, 0.872)
	L3-L4	30	0.845 (0.840, 0.869)	0.876 (0.855, 0.883)
	L4-L5	30	0.861 (0.832, 0.877)	0.873 (0.847, 0.879)
	All	120	0.858 (0.836, 0.873)	0.871 (0.845, 0.881)
Method 6	L1-L2	30	0.878 (0.848, 0.881)	0.882 (0.878, 0.891)
	L2-L3	30	0.822 (0.817, 0.881)	0.871 (0.862, 0.889)
	L3-L4	30	0.852 (0.827, 0.881)	0.866 (0.854, 0.887)
	L4-L5	30	0.856 (0.843, 0.883)	0.884 (0.872, 0.894)
	All	120	0.859 (0.846, 0.879)	0.878 (0.873, 0.888)
Method 7	L1-L2	30	0.860 (0.842, 0.866)	0.869 (0.851, 0.878)
	L2-L3	30	0.851 (0.812, 0.865)	0.863 (0.841, 0.876)
	L3-L4	30	0.845 (0.814, 0.868)	0.871 (0.855, 0.886)
	L4-L5	30	0.855 (0.843, 0.865)	0.865 (0.844, 0.875)
	L5S1	30	0.912 (0.878, 0.922)	0.864 (0.848, 0.872)
	All	150	0.866 (0.844, 0.916)	0.868 (0.858, 0.876)

N: number of levels; ICC: Intraclass correlation coefficient; 95% CI: 95% confidence interval.

Table 7.3 Inter-rater measures agreement results

	Level	N	Mean	SD	Mean difference (95% CI)	95% LOA	Proportion of mean values (%)
Method 1	L1-L2	288	0.55	0.07	0.00 (-0.008, 0.008)	-0.14, 0.14	50.9
	L2-L3	288	0.55	0.05	0.01 (0.005, 0.016) *	-0.09, 0.11	36.4
	L3-L4	288	0.59	0.05	0.00 (-0.006, 0.005)	-0.10, 0.10	33.9
	L4-L5	288	0.61	0.09	0.01 (0.001, 0.022) *	-0.17, 0.19	59.0
	L5-S1	288	0.6	0.07	-0.01 (-0.014, 0.002)	-0.15, 0.13	46.7
	All	1440	0.58	0.07	0.00 (0.002, 0.007) *	-0.14, 0.14	48.3
Method 2	L1-L2	288	0.36	0.07	-0.03 (-0.034, -0.019) *	-0.17, 0.11	77.8
	L2-L3	288	0.38	0.07	-0.03 (-0.039, -0.021) *	-0.17, 0.11	73.7
	L3-L4	288	0.39	0.07	-0.03 (-0.036, -0.020) *	-0.17, 0.11	71.8
	L4-L5	288	0.39	0.06	-0.02 (-0.026, -0.014) *	-0.14, 0.10	61.5
	L5-S1	288	0.37	0.06	-0.02 (-0.024, -0.009) *	-0.14, 0.10	64.9
	All	1440	0.38	0.07	-0.02 (-0.033, -0.018) *	-0.16, 0.12	73.7
Method 3	L1-L2	288	0.29	0.04	-0.01 (-0.015, -0.006) *	-0.09, 0.07	55.2
	L2-L3	288	0.3	0.04	-0.01 (-0.019, -0.010) *	-0.09, 0.07	53.3
	L3-L4	288	0.32	0.04	-0.01 (-0.014, -0.005) *	-0.09, 0.07	50.0
	L4-L5	288	0.3	0.03	0.00 (-0.009, -0.001) *	-0.06, 0.06	40.0
	L5-S1	288	0.27	0.04	0.00 (-0.003, 0.006)	-0.08, 0.08	59.3
	All	1440	0.3	0.04	-0.01 (-0.021, -0.009) *	-0.09, 0.07	53.3
Method 4	L1-L2	288	0.29	0.03	-0.01 (-0.013, -0.005) *	-0.07, 0.05	41.4
	L2-L3	288	0.9	0.09	-0.02 (-0.033, -0.013) *	-0.20, 0.16	40.0
	L3-L4	288	0.31	0.03	-0.01 (-0.012, -0.006) *	-0.07, 0.05	38.7
	L4-L5	288	0.31	0.03	0.00 (-0.008, 0.002)	-0.06, 0.06	38.7
	L5-S1	288	0.3	0.04	-0.01 (-0.016, -0.008) *	-0.09, 0.07	53.3
	All	1440	0.42	0.05	-0.01 (-0.018, -0.008) *	-0.11, 0.09	47.6
Method 5	L1-L2	288	0.36	0.13	-0.02 (-0.037, -0.008) *	-0.27, 0.23	138.9
	L2-L3	288	0.37	0.08	-0.02 (-0.030, -0.012) *	-0.18, 0.14	86.5
	L3-L4	288	0.37	0.06	-0.01 (-0.021, -0.078) *	-0.13, 0.11	64.9
	L4-L5	288	0.36	0.05	-0.01 (-0.012, 0.003)	-0.11, 0.09	55.6
	All	1440	0.37	0.09	-0.02 (-0.021, -0.008) *	-0.20, 0.16	97.3
Method 6	L1-L2	288	0.34	0.04	-0.01 (-0.012, -0.003) *	-0.10, 0.06	47.1
	L2-L3	288	0.35	0.04	-0.01 (-0.013, -0.005) *	-0.10, 0.06	45.7
	L3-L4	288	1.41	0.06	0.00 (-0.003, 0.010)	-0.12, 0.12	17.0
	L4-L5	288	0.4	0.04	0.00 (-0.009, 0.001)	-0.08, 0.08	40.0
	All	1440	0.62	0.04	-0.00 (-0.010, 0.003)	-0.08, 0.08	25.8
Method 7	L1-L2	288	0.27	0.04	0.00 (-0.002, 0.006)	-0.08, 0.08	59.3
	L2-L3	288	0.28	0.02	0.01 (0.003, 0.008) *	-0.03, 0.05	28.6
	L3-L4	288	0.29	0.02	0.00 (-0.003, 0.003)	-0.04, 0.04	27.6
	L4-L5	288	0.31	0.05	0.00 (0.001, 0.010) *	-0.10, 0.10	64.5
	L5-S1	288	0.3	0.03	0.00 (-0.006, 0.001)	-0.06, 0.06	40.0

	All	1440	0.29	0.03	0.00 (0.002, 0.010) *	-0.06, 0.06	41.4

N: number of levels; SD: standard deviation; CI: confidential intervals; LOA: Limits of Agreement. * Bias was considered present if the 95% CI did not include zero.

Table 7.4 Inter-rater measures' reliability results

Measurement method		**N**	**Inter-rater_ICC (95% CI)**
Method 1	L1-L2	288	0.956 (0.945, 0.965)
	L2-L3	288	0.877 (0.847, 0.901)
	L3-L4	288	0.972 (0.964, 0.977)
	L4-L5	288	0.844 (0.807, 0.874)
	L5S1	288	0.852 (0.817, 0.881)
	All	1440	0.927 (0.919, 0.934)
Method 2	L1-L2	288	0.641 (0.568, 0.705)
	L2-L3	288	0.620 (0.543, 0.686)
	L3-L4	288	0.693 (0.628, 0.749)
	L4-L5	288	0.779 (0.729, 0.821)
	L5S1	288	0.849 (0.813, 0.878)
	All	1440	0.736 (0.712, 0.759)
Method 3	L1-L2	288	0.718 (0.657, 0.770)
	L2-L3	288	0.781 (0.731, 0.822)
	L3-L4	288	0.980 (0.975, 0.984)
	L4-L5	288	0.866 (0.834, 0.892)
	L5S1	288	0.888 (0.860, 0.910)
	All	1440	0.936 (0.930, 0.942)
Method 4	L1-L2	288	0.954 (0.942, 0.963)
	L2-L3	288	0.938 (0.922, 0.950)
	L3-L4	288	0.977 (0.972, 0.982)
	L4-L5	288	0.872 (0.841, 0.897)
	L5S1	288	0.824 (0.783, 0.858)
	All	1440	0.984 (0.982, 0.985)
Method 5	L1-L2	288	0.500 (0.409, 0.582)
	L2-L3	288	0.726 (0.666, 0.776)
	L3-L4	288	0.728 (0.669, 0.778)
	L4-L5	288	0.761 (0.708, 0.805)
	All	1152	0.634 (0.598, 0.667)
Method 6	L1-L2	288	0.951 (0.938, 0.961)
	L2-L3	288	0.847 (0.811, 0.877)
	L3-L4	288	0.862 (0.829, 0.889)
	L4-L5	288	0.886 (0.859, 0.909)
	All	1152	0.995 (0.995, 0.996)
Method 7	L1-L2	288	0.959 (0.949, 0.968)
	L2-L3	288	0.891 (0.864, 0.913)
	L3-L4	288	0.927 (0.909, 0.942)
	L4-L5	288	0.840 (0.802, 0.871)
	L5S1	288	0.867 (0.835, 0.893)
	All	1440	0.916 (0.908, 0.924)

N: number of levels; ICC: Intraclass correlation coefficient; 95% CI: 95% confidence interval.

Table 7.5 Inter-rater measures' reliability results of disc height index (DHI) on all segmental levels in degeneration and no degeneration group

Measurement method		Number of Levels	ICC (95% CI)
Method 1	L1-L2		
	Degeneration	2	-
	No degeneration	276	0.957 (0.946, 0.966)
	L2-L3		
	Degeneration	278	0.879 (0.849, 0.903)
	No degeneration	0	
	L3-L4		
	Degeneration	36	0.969 (0.940, 0.984)
	No degeneration	242	0.972 (0.965, 0.979)
	L4-L5		
	Degeneration	160	0.941 (0.920, 0.956)
	No degeneration	118	0.888 (0.843, 0.921)
	L5S1		
	Degeneration	169	0.877 (0.836, 0.907)
	No degeneration	109	0.789 (0.706, 0.851)
Method 2	L1-L2		
	Degeneration	2	-
	No degeneration	276	0.659 (0.586, 0.721)
	L2-L3		
	Degeneration	278	0.629 (0.552, 0.695)
	No degeneration	0	
	L3-L4		
	Degeneration	36	0.889 (0.794, 0.942)
	No degeneration	242	0.641 (0.560, 0.709)
	L4-L5		
	Degeneration	160	0.805 (0.743, 0.853)
	No degeneration	118	0.795 (0.718, 0.853)
	L5S1		
	Degeneration	169	0.859 (0.813, 0.894)
	No degeneration	109	0.830 (0.761, 0.881)
Method 3	L1-L2		
	Degeneration	2	-
	No degeneration	276	0.729 (0.669, 0.780)
	L2-L3		
	Degeneration	278	0.789 (0.740, 0.829)
	No degeneration	0	
	L3-L4		
	Degeneration	36	0.996 (0.992, 0.998)
	No degeneration	242	0.962 (0.951, 0.970)
	L4-L5		
	Degeneration	160	0.871 (0.828, 0.904)
	No degeneration	118	0.852 (0.793, 0.895)
	L5S1		

	Degeneration	169	0.896 (0.861, 0.922)
	No degeneration	109	0.875 (0.822, 0.913)
Method 4	L1-L2		
	Degeneration	2	-
	No degeneration	276	0.956 (0.945, 0.965)
	L2-L3		
	Degeneration	278	0.942 (0.927, 0.954)
	No degeneration	0	
	L3-L4		
	Degeneration	36	0.885 (0.786, 0.940)
	No degeneration	242	0.982 (0.977, 0.986)
	L4-L5		
	Degeneration	160	0.933 (0.910, 0.951)
	No degeneration	118	0.904 (0.864, 0.932)
	L5S1		
	Degeneration	169	0.867 (0.824, 0.900)
	No degeneration	109	0.766 (0.755, 0.824)
Method 5	L1-L2		
	Degeneration	2	-
	No degeneration	276	0.500 (0.409, 0.582)
	L2-L3		
	Degeneration	278	0.727 (0.666, 0.778)
	No degeneration	0	
	L3-L4		
	Degeneration	36	0.713 (0.505, 0.843)
	No degeneration	242	0.744 (0.682, 0.796)
	L4-L5		
	Degeneration	160	0.768 (0.695, 0.824)
	No degeneration	118	0.763 (0.715, 0.795)
Method 6	L1-L2		
	Degeneration	2	-
	No degeneration	276	0.854 (0.819, 0.883)
	L2-L3		
	Degeneration	278	0.727 (0.666, 0.778)
	No degeneration	0	
	L3-L4		
	Degeneration	36	0.857 (0.737, 0.924)
	No degeneration	242	0.863 (0.827, 0.892)
	L4-L5		
	Degeneration	160	0.941 (0.920, 0.956)
	No degeneration	118	0.930 (0.900, 0.951)
Method 7	L1-L2		
	Degeneration	2	-
	No degeneration	276	0.960 (0.950, 0.969)
	L2-L3		
	Degeneration	278	0.894 (0.867, 0.915)
	No degeneration	0	
	L3-L4		

	Degeneration	36	0.865 (0.751, 0.929)
	No degeneration	242	0.933 (0.915, 0.948)
	L4-L5		
	Degeneration	160	0.944 (0.924, 0.959)
	No degeneration	118	0.811 (0.793, 0.846)
	L5S1		
	Degeneration	169	0.892 (0.856, 0.919)
	No degeneration	109	0.803 (0.725, 0.861)

ICC: Intraclass correlation coefficient; 95% CI: 95% confidence interval.

Table 7.6 Inter-rater measures' reliability results of related lines to each measurement method (method could be used on all segment levels and ICCs are good-to-excellent) on disc height index (DHI) of all segmental levels

Measurement method		**Number of Levels**	**ICC (95% CI)**
Method 1	L1-L2		
	Anterior disc height	288	0.989 (0.986, 0.991)
	Posterior disc height	288	0.954 (0.943, 0.964)
	Disc diameter	288	0.864 (0.855, 0.871)
	L2-L3		
	Anterior disc height	288	0.967 (0.959, 0.974)
	Posterior disc height	288	0.954 (0.942, 0.963)
	Disc diameter	288	0.867 (0.859, 0.874)
	L3-L4		
	Anterior disc height	288	0.962 (0.952, 0.970)
	Posterior disc height	288	0.955 (0.944, 0.964)
	Disc diameter	288	0.866 (0.858, 0.873)
	L4-L5		
	Anterior disc height	288	0.958 (0.947, 0.966)
	Posterior disc height	288	0.939 (0.924, 0.952)
	Disc diameter	288	0.963 (0.853, 0.870)
	L5S1		
	Anterior disc height	288	0.956 (0.945, 0.965)
	Posterior disc height	288	0.852 (0.817, 0.881)
	Disc diameter	288	0.859 (0.848, 0.867)
Method 3	L1-L2		
	Mid-disc height	288	0.930 (0.912, 0.944)
	Disc diameter	288	0.964 (0.955, 0.971)
	L2-L3		
	Mid-disc height	288	0.913 (0.892, 0.931)
	Disc diameter	288	0.967 (0.959, 0.974)
	L3-L4		
	Mid-disc height	288	0.930 (0.912, 0.944)
	Disc diameter	288	0.966 (0.958, 0.973)
	L4-L5		
	Mid-disc height	288	0.949 (0.937, 0.960)
	Disc diameter	288	0.963 (0.953, 0.970)
	L5S1		
	Mid-disc height	288	0.942 (0.927, 0.953)
	Disc diameter	288	0.959 (0.948, 0.967)
Method 4	L1-L2		
	Anterior disc height	288	0.989 (0.986, 0.991)
	Mid-disc height	288	0.930 (0.912, 0.944)
	Posterior disc height	288	0.954 (0.943, 0.964)
	Sagittal vertebral	288	0.877 (0.870, 0.881)
	L2-L3		

		Anterior disc height	288	0.967 (0.959, 0.974)
		Mid-disc height	288	0.913 (0.892, 0.931)
		Posterior disc height	288	0.954 (0.942, 0.963)
		Sagittal vertebral	288	0.883 (0.866, 0.879)
	L3-L4			
		Anterior disc height	288	0.962 (0.952, 0.970)
		Mid-disc height	288	0.930 (0.912, 0.944)
		Posterior disc height	288	0.955 (0.944, 0.964)
		Sagittal vertebral	288	0.873 (0.866, 0.879)
	L4-L5			
		Anterior disc height	288	0.958 (0.947, 0.966)
		Mid-disc height	288	0.949 (0.937, 0.960)
		Posterior disc height	288	0.939 (0.924, 0.952)
		Sagittal vertebral	288	0.873 (0.866, 0.879)
	L5S1			
		Anterior disc height	288	0.956 (0.945, 0.965)
		Mid-disc height	288	0.942 (0.927, 0.953)
		Posterior disc height	288	0.852 (0.817, 0.881)
		Sagittal vertebral	288	0.869 (0.861, 0.876)
Method 7	L1-L2			
		Anterior disc height	288	0.989 (0.986, 0.991)
		Posterior disc height	288	0.954 (0.943, 0.964)
		Superior disc depth	288	0.967 (0.958, 0.974)
		Inferior disc depth	288	0.963 (0.954, 0.971)
	L2-L3			
		Anterior disc height	288	0.967 (0.959, 0.974)
		Posterior disc height	288	0.954 (0.942, 0.963)
		Superior disc depth	288	0.967 (0.958, 0.974)
		Inferior disc depth	288	0.994 (0.992, 0.995)
	L3-L4			
		Anterior disc height	288	0.962 (0.952, 0.970)
		Posterior disc height	288	0.955 (0.944, 0.964)
		Superior disc depth	288	0.965 (0.956, 0.972)
		Inferior disc depth	288	0.961 (0.951, 0.969)
	L4-L5			
		Anterior disc height	288	0.958 (0.947, 0.966)
		Posterior disc height	288	0.939 (0.924, 0.952)
		Superior disc depth	288	0.964 (0.955, 0.971)
		Inferior disc depth	288	0.959 (0.948, 0967)
	L5S1			
		Anterior disc height	288	0.956 (0.945, 0.965)
		Posterior disc height	288	0.852 (0.817, 0.881)
		Superior disc depth	288	0.965 (0.956, 0.972)
		Inferior disc depth	288	0.944 (0.930, 0955)

ICC: Intraclass correlation coefficient; 95% CI: 95% confidence interval.

Anterior disc height: The shortest distance between the anterior edges of the neighbouring endplate will be recorded as the anterior disc height; Mid-disc height: The mid-disc height between the upper and lower bisection points is measured at the midpoint of vertebrae; Posterior disc height: The shortest distance between the posterior edges of the neighbouring endplate will be recorded as the posterior disc height; Disc diameter: The disc diameter will be measured between the midpoints of the lines drawn from the endpoints of the superior vertebral endplate to the inferior. e: The sagittal diameter of the vertebral body from the anterior to posterior margin will be measured at the mid-vertebral level.

Table 7.7 Potential factors for the outliers (out of the 95% Limits of Agreement (LOA) on the Bland and Altman plot)

Method	Level	Number of outliers	Potential factor
Method 1	L1-L2	12	9 outliers of nucleus pulposus degeneration, 3 outliers of disc herniation
	L2-L3	19	15 outliers of nucleus pulposus degeneration, 4 outliers of disc herniation
	L3-L4	10	8 outliers of nucleus pulposus degeneration, 1 outlier of disc herniation, 1 normal
	L4-L5	2	2 outliers of nucleus pulposus degeneration
	L5-S1	14	7 outliers of nucleus pulposus degeneration, 6 outliers of disc herniation, 1 normal
	All	57	41 outliers of nucleus pulposus degeneration, 14 outliers of disc herniation, 2 normal
Method 2	L1-L2	15	9 outliers of nucleus pulposus degeneration, 5 outliers of disc herniation, 1 normal
	L2-L3	15	10 outliers of nucleus pulposus degeneration, 5 outliers of disc herniation
	L3-L4	13	10 outliers of nucleus pulposus degeneration, 3 outliers of disc herniation
	L4-L5	10	8 outliers of nucleus pulposus degeneration, 2 outliers of disc herniation
	L5-S1	12	6 outliers of nucleus pulposus degeneration, 5 outliers of disc herniation, 1 normal
	All	65	43 outliers of nucleus pulposus degeneration, 20 outliers of disc herniation, 2 normal
Method 3	L1-L2	37	21 outliers of nucleus pulposus degeneration, 15 outliers of disc herniation, 1 normal
	L2-L3	26	20 outliers of nucleus pulposus degeneration, 6 outliers of disc herniation
	L3-L4	21	16 outliers of nucleus pulposus degeneration, 3 outliers of disc herniation, 2 normal
	L4-L5	45	38 outliers of nucleus pulposus degeneration, 13 outliers of disc herniation, 4 normal
	L5-S1	42	24 outliers of nucleus pulposus degeneration, 17 outliers of disc herniation, 1 normal
	All	171	109 outliers of nucleus pulposus degeneration, 54 outliers of disc herniation, 8 normal
Method 4	L1-L2	57	34 outliers of nucleus pulposus degeneration, 17 outliers of disc herniation, 6 normal
	L2-L3	5	4 outliers of nucleus pulposus degeneration, 1 outlier of disc herniation
	L3-L4	42	31 outliers of nucleus pulposus degeneration, 7 outliers of disc herniation, 4 normal
	L4-L5	44	29 outliers of nucleus pulposus degeneration, 11 outliers of disc herniation, 4 normal
	L5-S1	34	18 outliers of nucleus pulposus degeneration, 15 outliers of disc herniation, 1 normal
	All	182	116 outliers of nucleus pulposus degeneration, 51 outliers of disc herniation, 15 normal
Method 5	L1-L2	1	1 outlier of nucleus pulposus degeneration

	L2-L3	12	6 outliers of nucleus pulposus degeneration, 6 outliers of disc herniation
	L3-L4	10	6 outliers of nucleus pulposus degeneration, 4 outliers of disc herniation
	L4-L5	14	8 outliers of nucleus pulposus degeneration, 6 outliers of disc herniation
	All	37	21 outliers of nucleus pulposus degeneration, 16 outliers of disc herniation
Method 6	L1-L2	11	5 outliers of nucleus pulposus degeneration, 6 outliers of disc herniation
	L2-L3	10	7 outliers of nucleus pulposus degeneration, 3 outliers of disc herniation
	L3-L4	13	9 outliers of nucleus pulposus degeneration, 4 outliers of disc herniation
	L4-L5	8	6 outliers of nucleus pulposus degeneration, 2 outliers of disc herniation
	All	42	27 outliers of nucleus pulposus degeneration, 15 outliers of disc herniation
Method 7	L1-L2	6	5 outliers of nucleus pulposus degeneration, 1 outlier of disc herniation
	L2-L3	17	14 outliers of nucleus pulposus degeneration, 3 outliers of disc herniation
	L3-L4	17	13 outliers of nucleus pulposus degeneration, 3 outliers of disc herniation, 1 normal
	L4-L5	1	1 outlier of nucleus pulposus degeneration
	L5-S1	14	4 outliers of nucleus pulposus degeneration, 9 outliers of disc herniation, 1 normal
	All	55	37 outliers of nucleus pulposus degeneration, 16 outliers of disc herniation, 2 normal

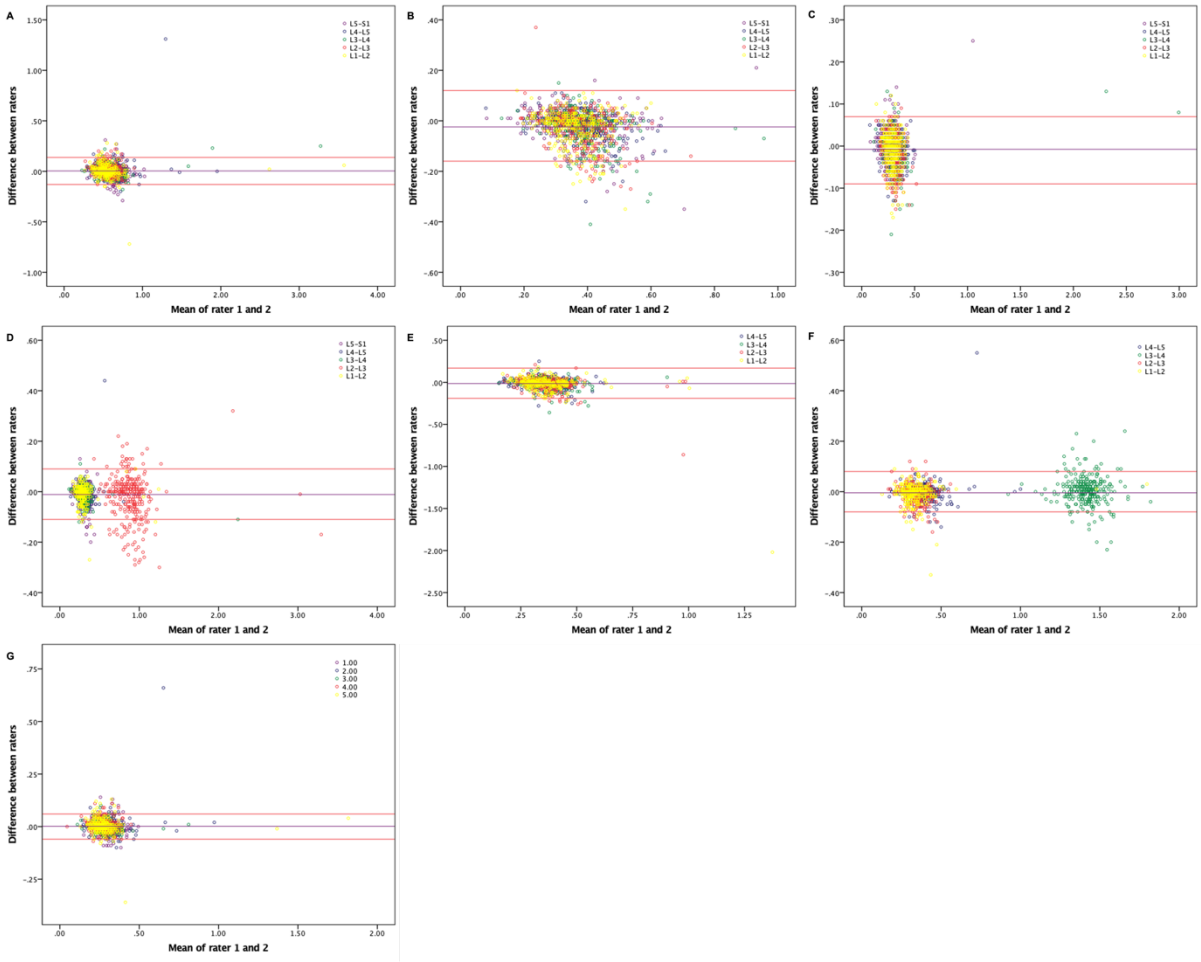

Figure 7.3 The Bland and Altman plot showing the relationship between mean values and differences between rater 1 and rater 2 on the measurements of DHI using two out of seven reported methods (A: method 1; B: method 2; C: method 3; D: method 4; E: method 5; F: method 6; G: method 7). Mean difference with 95% confidence intervals (CI) of the measurements between rater 1 and rater 2 was reported to describe the precision of the bias. The purple line shows the mean difference between measurements. Red lines show the 95% Limits of Agreement (LOA), between which 95% of all measurement differences are located.

7.4 Discussion

The reduction of IVD height is the key point in the pathological process of IVD degeneration, and the diseases of lumbar degeneration often demonstrate the reduction of IVD height in the radiographic images. Therefore, a reproducible method to measure IVD height is required. To be the best of our knowledge, this is the first study to investigate the intra- and inter-rater reliability and agreement of previously reported DHI methods to measure DH on the standing lateral lumbar X-ray images. We used a structured protocol including descriptions of testing positions, standard training session of measurements on images for raters, unified measurement platform and tools, and blinding of raters [24].

Although the measurements on X-ray images would be affected by body posture and vertebral position of the patient on the scan and the experience of raters [15, 25-28], our study still shown that intra-rater reliability was good-to-excellent for all the seven DHI assessment methods on X-ray images by both inexperienced and experienced raters. A possible explanation is the existence of division in the process of calculating the DHI, which can minimize the measurement bias by the inconsistent magnification and vertebral position on the X-ray scan. We posit the systematic training and structured protocol to conduct the measurement to be the other main cause of the good-to-excellent intra-rater reliability on DHI measurement methods on X-ray images. Therefore, the systematic training before measurement and a standard measurement process following structured protocol could provide a good-to-excellent intra-rater reliability for the DHI measurement on X-ray images.

Agreement is commonly used to evaluate how well the measurements produced by two raters, devices or systems agree with each other, while reliability is concerned with

measurement error plus the variability between study objects and the focus is distinction between persons [15, 29]. Previously published study recommended reporting inter-rater agreement parameters via LOA, and further, when reporting reliability using ICC, they should be reported together with error estimates such as the standard error of the mean [29]. Following the results of Bland and Altman´s LOA, we found that the DHI measurements in method 2, 3, and 5 on all segmental levels and method 1, 4, 6 and 7 on some special segmental levels had bias or/and out of the acceptable cut-off proportion. Due to different numbers of indirect lines in each method, it indicates a poor-to-moderate consensus regarding the anatomical delineation on the length measurements between the two raters. These were consistent with the status of ours' study that all indirect lines involved in method 2 and 5 and partial indirect lines involved in method 1, 3, and 4 with a poor-to-moderate agreement. Meanwhile, nucleus pulposus degeneration and disc herniation were showed to impact of the inter-rater agreement on distinguish vertebral corners and structural boundaries.

This study uses both LOA and reliability to express reproducibility. The inter-rater reliability was good-to-excellent in all but method 2 and 5. Although IVD degeneration can cause discs to lose height and might potentially affect the accuracy and agreement of DHI measurement [9], our findings denied the influence of IVD degeneration on the inter-rater reliability results in different measurement methods on DHI (ESM_1_Table 1). The potential risk factors for the moderate inter-rater reliability on DHI measurement in method 2 and 5 include measurement bias of indirect lines and other bias from anatomical structure. Due to use of multiple indirect lines in method 2 and 5, the potential secondary measurement bias following the first bias by the inexact positioning of vertebral corners and indistinguishable IVD boundaries between structures during drawing the direct line might cause the moderate inter-reliability. This

indicates that a complicated measurement method would cause a poor-to-moderate consensus between raters. Despite good-to-excellent inter-rater reliability on DHI measurement in method 1, 3, 4, 6, and 7, there still showed relatively poor results of inter-rater reliability on indirect lines in method 1 and 4 (ESM_1_Table 2). Therefore, the accurate and effective determination of vertebral corners for direct line can significantly reduce the measurement error. As for the positioning of vertebral corners, two possible interfering factors could be the presence of osteophytes and the rotation of vertebral body, hence, modifying the visual appearance of the vertebra [15, 25, 30]. While our structured protocol could minimize the influence of osteophytes on marking the corners, it can't provide a method to avoid the objective factor that leads to vertebral rotation. For instance, upper vertebral rotation by IVD no perpendicular to the projection might be the reason for moderate inter-rater reliability of DHI measurements on upper segmental level (L1-L2 and L2-L3). Meanwhile, the shorter DH of the upper IVD could induce cumulative error in the marking of vertebral corners, which was posited to be the other reason. We couldn't find studies that definitively discussed any of these factors regarding similar problems with measurement bias of indirect lines, vertebral rotation, or boundary distinction. However, we still thought that these could be the main reasons why some ICCs of inter-rater reliability were moderate. As it stands, our study potentially showed that there was a good-to-excellent intra- and inter-rater reliability and agreement on the DHI measurements in method 7 for all IVD segmental levels. For future use of these methods, specification in advance of measurements, and persistent implementation of detailed protocol for the location of projection, measurement of indirect lines, and dealing with vertebral rotation, should be conducted by all raters.

7.4.1 Study limitation and future study

Several methodological issues require consideration. First, the potential measurement error due to notably inexact definition of anatomic measurement points, the location of projection during the scan, definition of standard process to fix vertebral rotation, and intra- and inter-rater variation, despite a structural protocol being provided to raters. Future, a standardized protocol to assess DHI was required. Second, due to the difficulties in distinguishing the boundary of disc on X-ray, the raters can only use point-based measurement method instead of area-based method. Third, the acceptable precision of the range of LOA set at 50% following previously published data would affect the results [15]. Fourth, due to the different reference values of each DHI method, the direct comparison between two out of seven measurement methods can't be done. Finally, the aim of this study was to establish reproducibility and reliability, not to report prevalence or reference values for either a general or a clinical population.

7.5 Conclusion

The intra-rater and most inter-rater reliability for DHI measurement was good-to-excellent for different methods following a structured protocol. However, the inter-rater reliability was moderate in some DHI measurement methods, indicating difficulties in the performance of these methods. The complicated methods (more indirect lines) and IVD degeneration (nucleus pulposus degeneration and disc herniation) potentially affected the agreement on inter-rater measurements. Caution should be taken when measuring used complicated method and defining anatomical landmarks during vertebral rotation. Future multicenter study on the validity of different measurement methods following a standardized protocol is needed.

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7.6 References

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Chapter 8. Discussion, Conclusions and Recommendations

8.1 Discussion

The current work is amongst the first thesis dedicated solely to understanding failures related to the most common spinal operation, discectomy. Hence it lays the foundation of a strategy to understand failure using multiple methodological techniques. While not conclusive to the cause or solution of failed discectomy, the current work offers a foundation on which the problem can be addressed.

Discectomy is the main surgical treatment for symptomatic lumbar disc herniation recommended for patients who are non-responsive to at least six weeks of non-surgical treatment or/and had a progressive neurological impairment [1]. Various discectomy techniques for symptomatic lumbar disc herniation provide a good clinical outcome in short-term follow-up [2-5]. However, a high rate of complications or reoperation is observed [6][7][8]. The fewer incidence rate of complications following a discectomy surgery will have a superior clinical utility as it directly impacts efficacy and cost. A discectomy technique that has a higher rate of complications will significantly increase patients' suffering, healthcare system, and social-economic burdens. Therefore, mastering the epidemiological data, previous literature data, and related risk factors of complications can lead to adoption of relevant measures to prevent and reduce the incidence of complications following different discectomy surgeries.

Although previous studies have reported the incidence rate of various surgical complications in the treatment of symptomatic lumbar disc herniation following different discectomy surgeries [9-48], such as nerve root injury, durotomy, hematoma, neurological deficit, medical complications, surgical errors, wound complications, and

recurrent disc herniation, there is still some confusion due to inconsistent classification of complications. Formulating a standard to define and classify surgical complications is required. According to different standards, complications are routinely divided into major and minor. medical and surgical, intraoperative, and post-operative, and modified Clavien-Dindo classification [49-56]. Due to the lack of consistent definitions for the major and minor complications, the health care provider should be more careful when using this classification. The general classification (intraoperative and post-operative) [52] and modified Clavien-Dindo classification [49-56] for complications as the most suitable classifications because they are based on the management required for each complication, which can guide the surgeons to choose a suitable surgical strategy.

Therefore, understanding the resultant list of and hierarchy of complication rates using the general and modified Clavien-Dindo classifications following different discectomy techniques, exploring the factors like surgical technique variations, investigating the tissue molecular markers at discectomy, finding the association between disc height changes and back pain changes following discectomy, and evaluating the sensitive and valid measurement tool(s) for the disc height index will provide useful insights for developing guidelines for selecting the safest and most cost-effective procedure.

Previous studies reported that nerve root injury occurs in 1 to 2%, new or worsening neurologic deficits occur in 1 to 3%, incidental durotomy occurs in approximately 3%, wound complications occur in 1 to 2%, and reoperation occurs in about 6% at 1 year following discectomy and in almost 13% at 4 years follow-up [9, 47]. These inconsistent results are from different surgeons, different centres, and different studies (Randomised control study and observational study). To obtain more credible results, two separate meta-analyses (one for the Randomised controlled trials and the other for

the observational studies) was performed to examine the consistency of various studies with different potential biases. The meta-analysis for randomised controlled trials suggests that the overall complication rates following different discectomy surgeries are around 20%, the incidence of durotomy is nearly 5%, the re-herniation rate is about 10%, and the reoperation rate is as high as 10%. The resultant list of complication rates can provide a reasonable explanation for signing an informed consent form and a management expectation for the choice of an alternative surgical techniques. However, the hierarchy of different discectomy techniques regarding each complication rate is still unknown.

Network meta-analysis is the most useful technique for comparing three or more interventions or treatments for the same pathology by combining both direct and indirect evidence within a network of randomised controlled trials [57, 58]. Given the lack of substantial evidence regarding the hierarchy of different discectomy techniques regarding complication rates, our network meta-analysis performed a network meta-analysis of all complications reported in different discectomy studies to compare the complication rates of different discectomy techniques using two classification schemes (a general classification that includes intraoperative and post-operative complications and modified Clavien–Dindo classification). The results suggest that percutaneous endoscopic lumbar discectomy is the safest procedure for the surgical treatment of symptomatic lumbar disc herniation in terms of minimal rates for overall complications. Less paraspinal tissue trauma via the percutaneous procedure and a good operative field through an endoscope are posited as the primary reasons for the lower complication rates [59]. However, the percutaneous endoscopic lumbar discectomy learning curve is usually perceived to be steep. Also, the requirements of the appropriate disc height and foraminal dimension, surgeons' experience, and potentially increased number of

fluoroscopy shots will affect the surgeons' choice of the surgical technique [59]. Although microendoscopic discectomy is suggested as the safest procedure for symptomatic lumbar disc herniation in terms of minimal rates for complications necessitating pharmacological treatment, the poor perception of depth and the restricting surgical field with microendoscopic surgery should be taken into consideration.[12, 17]. Due to the less trauma on paraspinal tissues, percutaneous laser lumbar decompression is recommended as the safest procedure for lumbar disc herniation with minimal complications requiring surgical treatment. The strict indication should be taken seriously. Tubular combined with regular open discectomy/microdiscectomy could help a surgeon gain a better view of the operative field and result in less surgical trauma than the conventional open approach, all of which is expected to reduce complication and reoperation rates [60]. Therefore, the relative rank of different complications rates in this study can enable clinicians, policymakers, and patients to make informed decisions on using different discectomy techniques for symptomatic lumbar disc herniation.

While complication outcomes vary between different discectomy techniques, variations may be attributed to a variety of factors including the surgeon's experience, surgical learning curve, and level of training [61-66]. The findings of our online survey showed discrepancies in the surgical procedures offered to patients and surgeon perceived complications. Microdiscectomy is the most common surgical choice for primary lumbar disc herniation and first recurrent lumbar disc herniation patients. Fusion surgery is the most common surgical choice for the second recurrent lumbar disc herniation, which are consistent with most reported studies [67-70]. Microdiscectomy is the most used surgical treatment for symptomatic lumbar disc herniation and is the most cost-effective treatment, providing an excellent clinical outcome and producing fewer complication rates. There is still no consensus on the choice of surgical technique for

the recurrent lumbar disc herniation. Some surgeons advocate repeating discectomy for the first recurrent lumbar disc herniation in the absence of deformity, low back pain or instability [69-71]. However, a repeat discectomy for the second recurrent lumbar disc herniation may require more aggressive disc removal and laminectomy, all of which may increase the risk for segmental instability and recurrent pain. As such, fusion is often the preferred procedure for the second recurrent lumbar disc herniation to maintain stability and reduce the risk of recurrent herniation [64, 72]. Therefore, the online survey first captures the surgeons' perceptions on the choice of the different surgical techniques for the primary and recurrent lumbar disc herniation. Subsequently, surgeons in different practice settings(academic/private/hybrid) were found to affect the surgeons' perceptions around the choice of surgical procedures for the first recurrent lumbar disc herniation in their patients (many surgeons choose fusion surgery for the first recurrent lumbar disc herniation in private practice) due to the differences in financial incentives and access to resources for surgical management. Thereafter, the results of survey suggest that surgeons should be alert to the occurrence of durotomy and re-herniation following primary surgeries for primary lumbar disc herniation [70, 73-75], and surgeons recommended using a meticulous surgical technique to reduce the incidence of durotomy and superficial infection following revision surgeries for recurrent lumbar disc herniation[76]. In short, recognizing the substantial variations of individual factors of the responding surgeons that exist in the surgical management of primary lumbar disc herniation and recurrent lumbar disc herniation will help in standardizing the protocols for effective management of this spinal condition and improve outcomes [77].

Dissatisfaction following discectomy for symptomatic lumbar disc herniation is about 30% and revision surgery rate is 20% in a 7-year survivorship analysis [7, 8]. A

complication is considered the main reason for dissatisfaction following discectomy surgery. Therefore, investigating the potential risk factor(s) and formulating a treatment strategy based on the results of the investigation are required.

Multifidus muscles are important stabilizers of the lumbar neutral zone which account for more than two thirds of the stiffness of the spine [78]. Many prior investigations have reported that multifidus muscle atrophy and fat infiltration decrease the ability to control the neutral zone, a pathologic process that is closely correlated with low back pain [79-81]. Kjaer et al. reported that fat infiltration of the multifidus muscle was strongly associated with low back pain [79]. Barker et al. showed a positive correlation between the multifidus muscle atrophy of the affected side and the duration of low back pain, simultaneously, a positive correlation between the cross-sectional area of multifidus muscle on the affected side and the duration of symptoms [82]. Taken together, multifidus muscle remodeling, including the reduction in the cross-sectional area [83], fiber-type transformation [84], and fatty infiltration, contributes to poor outcomes after microdiscectomy for symptomatic lumbar disc herniation with radiculopathy [79, 83-88]. Disuse, denervation, and an active process mediated by a localized muscle inflammatory response have been reported as the three main mechanisms for the multifidus muscle changes, which observed in the animal models (such as dysregulation of expression of inflammatory markers (e.g., pro-inflammatory cytokines tumour necrosis factor (TNF) and interleukin-1b (IL-1b) and regulation the expression of muscle regeneration markers (e.g., Insulin-like growth factor (IGF-1), Irisin and Brain-derived neurotrophic factor (BDNF)) [83, 89-91]. BDNF as a skeletal muscle regeneration marker in response to muscle injury could rescue the muscle atrophy [92, 93], which might indicate the capacity to recover muscle health following microdiscectomy. IL-1b as proinflammatory cytokine contributes to the development of

inflammatory and post-operative chronic pain [94, 95], which is consistent with the results of this work. The results of this study firstly demonstrated an association between poor clinical outcome and impaired muscle regeneration profile in multifidus muscle (lower BDNF) and inflammatory dysregulation in subcutaneous fat overlying the back region (higher IL-1b), which supported mechanisms that regulate multifidus muscle structural changes in association with back pain in symptomatic lumbar disc herniation patients [96].

In theory, removal of the herniated intervertebral disc during the discectomy procedure leads to the loss of disc height immediately. Mechanical characterization change of the intervertebral disc after discectomy surgery accelerates the ageing and degeneration of the disc, increasing the loss of disc height as time follow-up. A meta-analysis firstly demonstrates that discectomy surgery produces significant and quantifiable reductions in disc height and disc height index, including an 11.2% decrease in the first 12 months and further decreased to 16.6% at 60 months, which are consistent with previously reported data [97-100]. Additionally, the intervertebral disc space narrowing and thinning after discectomy is characterized by a cascade of cellular, structural, biochemical, and functional changes; and are potentially associated with acute or chronic disabilities, back, and leg pain [101-103]. The decreased intradiscal pressure and the increased loads on facet joints noted following the disc height loss after discectomy surgery are posited as the primary reason for an increase in post-procedure pain scores [104, 105]. This work supports the hypothesis that the reduction in disc height is responsible for the decrease in back pain scores post discectomy, the limitations of the results found in this review do not offer robust level evidence for practical applications of this finding [100]. In regard to the lack of uniformity on the

measurement methods in disc height index, standardising measurement methods reported in the literature will allow further analysis.

Direct values of disc height can be used in daily practice for quick comparisons, while the disc height index could be used for more in-depth studies and more accurate readings [106-111]. Compared to the supine position during MRI and CT scans, the standing X-ray could better show the condition of the intervertebral disc under normal weight-bearing. The major errors arising in the mensuration process on X-ray include image un-sharpness (image quality), projection geometric distortion, inconsistency in patient positioning, imprecision in locating standard reference points, and observer error. Inherent errors in lumbar spine measurements are well recognized and must be minimized. This work first used a structured protocol including descriptions of testing positions, a standard training session of measurements on images for raters, a unified measurement platform and tools, and blinding of raters to measure disc height index on X-ray images [112]. By normalising images, variations in the size of the vertebral column and position of the patient do not affect the final measurement and allow for a reliable analysis. An intra- and inter-rater Bland and Altman´s Limits of Agreement and reliability of seven previously reported disc height index measurement methods were firstly reported [113]. Following the structured protocol, an intra- and inter-rater agreement and reliability study of seven previously reported disc height index measurement methods firstly reported the most sensitive and valid tool for disc height measurement post discectomy. However, caution should be taken when measuring used complicated methods and defining anatomical landmarks during vertebral rotation.

8.2 Main Findings

- First, the meta-analysis results suggest that the complication rates following different discectomy techniques are around 20%, the incidence of durotomy is nearly 5%, the re-herniation rate is about 8%, and the reoperation rate is as high as 10%. Compared to open discectomy/microdiscectomy, results of this thesis suggest that for the surgical treatment of symptomatic lumbar disc herniation, percutaneous endoscopic lumbar discectomy has the lowest risk of overall complications.
- Second, substantial evidence for the hierarchy of different discectomy techniques regarding complication rates was reported by the network meta-analysis. Percutaneous endoscopic lumbar discectomy is the safest procedure for symptomatic lumbar disc herniation with minimal overall complications rates due to the less damage to surrounding tissues and a good operative field through an endoscope. However, it has a learning curve. Open discectomy/microdiscectomy is the safest procedures for symptomatic lumbar disc herniation with minimal intraoperative complications, respectively. Percutaneous endoscopic lumbar discectomy, microendoscopic discectomy, and percutaneous laser disc decompression are the safest procedures for symptomatic lumbar disc herniation in terms of minimal rates for complications necessitating conservative, pharmacological, and surgical treatment, respectively. The relative rank can enable clinicians, policymakers, and patients to make informed decisions.
- Third, most orthopaedic surgeons and neurosurgeons who routinely performed spinal surgery in Australia and New Zealand reported that microdiscectomy is the most popular surgical choice for primary lumbar disc herniation and first recurrent lumbar disc herniation patients, and fusion surgery is the most popular surgical choice for the second recurrent lumbar disc herniation. Individual factors for the surgeons (e.g., geography, speciality, practice experience (the percentage of spine

surgery in practice), practice length, and operative volume (the annual of spine surgeries performed and the annual of lumbar discectomies performed)) didn't affect the choice of surgical procedure for primary and recurrent lumbar disc herniation except the practice setting. Surgeons in different practice settings (academic/private/hybrid) had different perceptions around the choice of surgical procedures for the first recurrent lumbar disc herniation patients. Surgeons perceived re-herniation and durotomy were reported as the most common complications following primary discectomy, and surgeons perceived durotomy and superficial infection were reported as the most common complications following revision surgeries for recurrent lumbar disc herniation. Surgeons with a higher operative volume (such as the annual of spine surgeries performed and the annual of lumbar discectomies performed) perceived a higher likelihood of herniation and durotomy.

- Fourth, the clinical study provides novel observation of a relationship between poor outcomes and inflammatory dysregulation in subcutaneous fat overlying the back region following microdiscectomy for symptomatic lumbar disc herniation. Individuals with poor outcomes had altered muscle regeneration genes (lower expression of brain-derived neurotrophic factor) in the deep multifidus muscle, but no difference in inflammatory profile.
- Fifth, removal of herniated disc material during the discectomy procedure leads to significant and quantifiable reductions in intervertebral disc height by different measurement methods in disc height and disc height index. Additionally, the reduction of disc height is responsible for the decrease in back pain scores post discectomy, while the numerous methods of estimating disc height index endeavor

concluding from this study a difficult one. Therefore, finding the most sensitive and valid tool for disc height index measurement post discectomy is required.

- Finally, following a structured protocol, intra- and inter-rater reliability was good-to-excellent for most disc height index measurement methods on X-ray. However, caution should be taken when measuring using complicated methods and defining anatomical landmarks during vertebral rotation. The complicated methods (more indirect lines) and intervertebral disc degeneration (nucleus pulposus degeneration and disc herniation) potentially affected the agreement on inter-rater measurements. A future multicenter study on the validity of different measurement methods following a standardized protocol is needed.

In short, here it has demonstrated that percutaneous endoscopic lumbar discectomy has the lowest complication rates, however, it has a learning curve, that surgeons in Australia and New Zealand do not have any variation in practice that may impact outcomes of primary discectomy, that the subcutaneous fat of patients with poorer outcomes has evidence of inflammation, that disc height diminishes after discectomy, and in case of disc height being used for a clinical trial evaluating annular closures or nucleus replacement then the method of reliable measurement was established with my current work.

8.3 Recommendations for Future Work

In future, predictive analytics for the management of symptomatic lumbar disc herniation, determining how to minimize the potential risk factor(s) for post-operative complications, and developing semi-automated software via a mathematical model will be performed. In the meanwhile, currently and in foreseeable future exciting times are anticipated for the evaluation of the safety and effectiveness of an elastomeric disc

spacer in maintaining disc height in patients undergoing single-level microdiscectomy for sciatica due to lumbar disc herniation.

- **Predictive analytics for the management of symptomatic lumbar disc herniation via multicentre**

This work will use presurgical data to predict which patients are likely to suffer from recurrent disc herniation following lumbar microdiscectomy surgery so alternative procedures can be recommended. Despite generally good clinical outcomes, re-herniation of disc material causing recurrent symptoms can occur in up to 5-10% of patients following a microdiscectomy. One way of handling this problem is to be able to predict whether patients are at high risk for re-herniation. In that case, the patient could be advised to choose an alternative treatment strategy including fusion, disc replacement, further conservative management, or utilization of implantable closures to make the microdiscectomy more secure. Many factors are known to be associated with a higher risk of re-herniation, but the extent of contribution of these factors either individually or in combination and the resultant overall patient-specific likelihood of re-herniation is not yet clear.

This project aims to investigate the inter-evaluator variability, determine how to minimize this variability, and adjust the mathematical model so that surgical complications might not only be reduced among the participating institutions, but the model's sensitivity and specificity are robust enough to make it employable in new institutes as well. This project hypothesizes that developing semi-automated software to calculate the input metrics for the model will create more consistency between institutions and improve the predictability of the model. Providing a framework to create a consistent measurement of inputs, regardless of institute or physician, will make it possible to provide a predictive tool capable of compiling all of the potential

risk factors for re-herniation and reporting a single unified likelihood so that care decisions are better informed. The protocol for this project has been developed and is under review by the panels from multicentre.

- **Preserve intervertebral disc height**

Although discectomy is widely perceived as a successful procedure for immediate pain relief, it has a high failure rate over time due to the ensuing reduction in mechanical stabilization and support of the spine. Clinical data have shown that nearly a third of discectomy patients are dissatisfied with their surgical outcomes at 12-month follow-up [114]. Furthermore, one in five patients will undergo repeat surgery within the first seven years of their microdiscectomy surgery [8, 115, 116]. Subsequent surgery may be required due to the following reasons: 1) pain as a result of decreased disc height following removal of nucleus pulposus; or 2) the residual nuclear material left within the cavity re-herniates; or 3) a combination of disc height loss and re-herniation. The post-surgical changes to the intervertebral disc, represented with a reduction of its disc height, are characterized by a cascade of cellular, structural, biochemical, and functional changes; and are strongly implicated as a cause of low back pain [117, 118]. The decreased intradiscal pressure and the increased loads on facet joints noted following the disc height loss after discectomy surgery could account for an increase in post-procedure pain scores [104]. Cadaveric and in-vitro studies have shown that the disruption of annular integrity led to significant alterations in both operative and proximal discal pressure after discectomy surgery [104], which also revealed the correlation of the decreased disc height and increased radial disc bulge with the increased removal volume of intervertebral disc [105]. Therefore, how to maintain or recover the disc height after discectomy surgery is required.

Annular tissue repair/closure system and nucleus replacement system as two main techniques are developed to preserve the intervertebral disc and reduce related complications. A previously published study supported that annular tissue repair/closure devices are beneficial for short-term outcomes, demonstrating the reduction in symptomatic disc re-herniation with low post-operative complication rates [119]. However, the loss of intervertebral disc height still occurs in the patients who underwent discectomy surgery with an annular tissue repair/closure device.

Hence the imperative, to perform a complete clearance of the fragmented nucleus, implant a self-assembling, in-situ curing elastomeric device, without further disrupting the annulus, and placing it within the confines of the apophyseal ring of the vertebral bodies, with a non-hygroscopic material that can closely mimic the stiffness of an innate nucleus; so that disc height is maintained.

During a discectomy, the elastomeric disc spacer will replace the removed nucleus tissues with a bespoke nucleus prosthesis made using an inert material to maintain the disc height of the motion segment. Based on a previous multi-center trial (Switzerland and Australia) on a soft and uncontained gel device [120], our lab designed a new elastomeric disc spacer. The material is contained within a silicone jacket that conforms to the shape of the nonlobotomized cavity when inflated and uses a proprietary system of sophisticated delivery instruments to fill the jacket with an inert in situ curing elastomeric filler material. A multi-center, randomized, blinded, long follow-up trial will be used to evaluate the safety and effectiveness of the new nucleus replacement device for the preservation of lumbar intervertebral disc height in patients undergoing microdiscectomy for sciatica due to lumbar disc herniation.

8.4 THESIS IMPACT STATEMENT: COVID-19

My ability to evaluate an elastomeric disc spacer biomechanically due to closure of mechanics laboratory and to conduct an early clinical trial due to pause on non-emergency surgery was curtailed due to the pandemic. However, I will pursue that as my post-doctoral work.

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Appendix 1: The Details of Online Survey

Variations in Primary Discectomy and Revision Surgery for Lumbar Disc Herniations: An Online Survey of Neuro- and Spine Surgeons in Australia and New Zealand

Part I: General Details

1. Is your practice academic, private, or a "hybrid" (i.e., a combination of academic and private)?

A. Academic
B. Private
C. Hybrid

2. Which best describes your training?

A. Orthopaedics
B. Neurosurgery

3. What percentage of your practice is spine surgery?

A. <10%
B. 11-25%
C. 26-50%
D. 51-75%
E. 76-100%

4. How many years have you been practicing as a spine surgeon?

A. 0-5 years
B. 6-10 years
C. 11-15 years
D. 16-20 years
E. >20 years

5. On average, how many spine surgeries of any type do you perform in a year?

A. <50
B. 50-150
C. 151-300
D. 301-500
E. >500

6. On average, how many lumbar discectomies do you perform in a year?

A. <25
B. 25-100
C. 101-200

D. 201-300
E. >300

7. Select which country you practice medicine in.
A. Australia
B. New Zealand

Part II: The Following Questions Pertain to Lumbar Discectomy for a *Primary* LDH

8. In the absence of a neurological deficit (e.g., lower extremity weakness, bowel or bladder incontinence), what is the minimum duration radicular pain must be present for you to offer surgery?

A. <2 weeks
B. 2-4 weeks
C. 4-8 weeks
D. 8-12 weeks
E. >12 weeks

9. When performing a lumbar discectomy, do you use intraoperative imaging to mark/confirm your level of surgery?

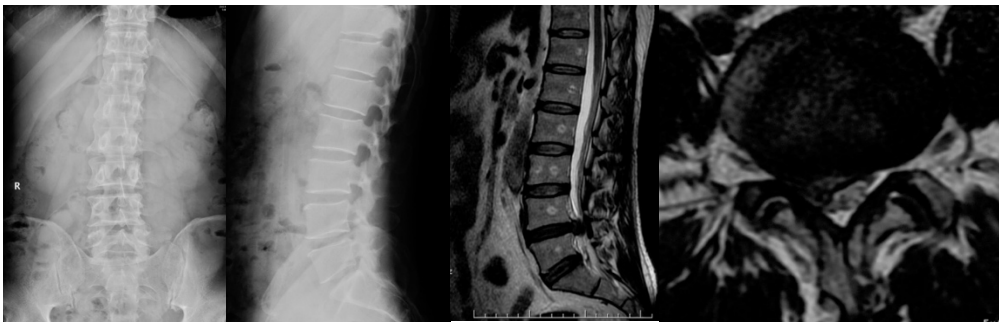
A. Yes, before making incision only
B. Yes, before making incision AND after reaching bone level
C. Yes, after reaching bone level only
D. No, I review pre-operative imaging and palpate for anatomy

10. Which of the following best describes your technique for a lumbar discectomy?

A. Conventional open discectomy (no magnification)
B. Open microdiscectomy (use of microscope and/or loupe magnification)
C. Tubular Discectomy without magnification
D. Tubular Discectomy with magnification (microscope and/or loupes)
E. Endoscopic Discectomy

11. How do you perform the laminectomy or laminotomy to enter the canal at L4-L5?

A. Burr
B. Hand held Kerrison punch
C. Bone scalpel
D. A mix of instruments (e.g., burr and Kerrison punch)
E. Others (please mention in the box below)



12. The images above demonstrate a disc herniation at the L4-L5 level on the right side, and the patient only has symptoms on the right side. Which of the following approaches would you use to perform a discectomy?

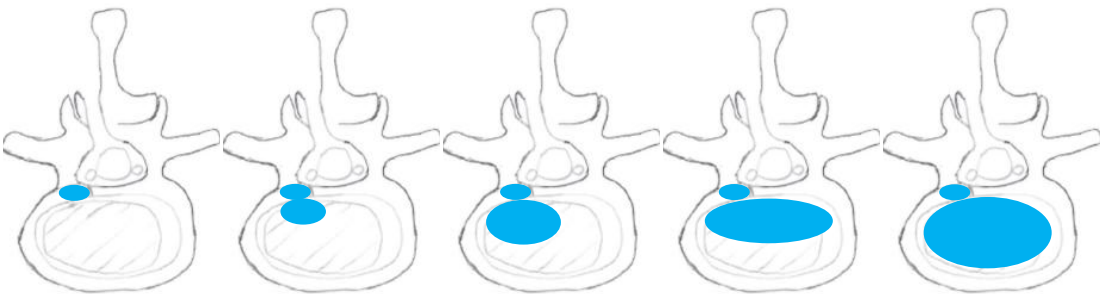
A. Midline approach
B. Posterior paramedian approach (Wiltse type)
C. Transforaminal approach
D. Extraforaminal approach
E. Interlaminar approach exposing both right and left sides
F. Others (please mention in the box below)

13. When performing a discectomy, which of the following best describes how you deal with the annular fibrosus?

A. If annular defect is present, I do not enlarge the existing annular tear, fish out the nucleus from the present annular defect.
B. Cruciate annulotomy if disc herniation is contained
C. Box cut annulotomy if disc herniation is contained
D. Linear annulotomy if disc herniation is contained

14. When performing a discectomy, which of the following illustrations best represents the amount of intervertebral disc you typically remove?

A. Only the free fragment disc (in case of sequestrated disc)
B. The free fragment with small extent of the disc unilaterally (only annulus)
C. The free fragment with large extent of the disc unilaterally (to nucleus pulposus)
D. The free fragment with large extent of the disc bilaterally
E. The free fragment with complete disc (mostly nucleus) bilaterally



15. During the discectomy, how often do you "flush out"/irrigate the disc space for purposes of clearing out more disc material?

A. Never (0%)
B. Seldom (1-25%)
C. Sometimes (26-50%)
D. Often (51-75%)
E. Always (100%)

16. The following question pertains to the closure of the annulus after completion of the discectomy. If you do not perform annular closure, please select A. If you routinely perform annular closure, please select the technique that you most commonly use (B-D).

A. I don't perform annular closure
B. Sutures
C. Devices (e.g., Barricade)
D. Glue

17. Which method/s do you use to achieve hemostasis during surgery? (select all that apply)

A. None
B. Irrigation
C. Bone wax
D. Epinephrine injected locally
E. Direct pressure with neuro patty or strip
F. Electrocautery
G. Hemostatic sponges (e.g., Gelfoam/Surgifoam)
H. Oxidized cellulose polymer (e.g., Surgicel)
I. Fibrin sealant (e.g., FloSeal)
J. Self-made hemostatic agent
K. Others (please mention in the box below)

18. Following the discectomy, do you place an anti-adhesive over the dura?

A. No
B. Yes

If yes, please mention in the box below.

19. How frequently does an *intraoperative* complication occur when performing primary lumbar discectomy?

A. <2%
B. 2-5%
C. 6-10%
D. 11-20%
E. >20%

20. In your experience, which of the following *intraoperative* surgical complication/s have occurred when performing lumbar discectomy? (select all that apply)

A. Durotomy
B. Nerve root injury
C. Wrong surgery level

D. Bowel injury
E. Urological injury
F. Hemorrhage
G. None of the above
H. Others (please mention in the box below)

21. The following is a list of factors that may increase the risk for a surgical complication in lumbar discectomies. Please rank each of the following items in order of importance with #1 being the most important factor and #6 being the least important factor.

A. Patient's body habitus and/or BMI
B. Surgical technique
C. Surgeon's experience
D. Characteristic of disc herniation (e.g., size, location, etc.)
E. Patient's co-morbidities (e.g., diabetes, coagulopathies)
F. Patient's smoking status

22. How soon after a lumbar discectomy do you permit patients to ambulate?

A. Immediately after surgery
B. 8 hours after surgery
C. 24 hours after surgery
D. 48 hours after surgery
E. ≥72 hours after surgery

23. How many weeks after discectomy do you prescribe physiotherapy?

A. I don't prescribe physiotherapy post-operation
B. Within two weeks post-operation
C. Between 2 to 4 weeks post-operation
D. Between 4 to 6 weeks post-operation
E. ≥ Six weeks post-operation

24. How frequently does a *post-operative* complication occur after performing lumbar discectomy?

A. <2%
B. 2-5%
C. 6-10%
D. 11-20%
E. >20%

25. In your experience, which of the following *post-operative* surgical complication/s have occurred after performing a lumbar discectomy? (select all that apply)

A. Wound complications or superficial infection
B. Deep infection
C. Hematoma
D. Reherniation
E. Post-operative segment instability
F. None of the above
G. Others (please mention in the box below)

Part III: The Following Questions Pertain to Revision Surgeries for a Recurrent LDH or Failed LDH

26. How often do you assess dynamic instability in the segment with a recurrent LDH?

A. Never (0%)
B. Seldom (1-25%)
C. Sometimes (26-50%)
D. Often (51-75%)
E. Always (76-100%)

27. A patient with a history of discectomy for an L4-L5 disc herniation, reherniates at the same level and is indicated for surgery. Which of the following best describes the surgical technique that you would choose?

A. Conventional open discectomy (no magnification)
B. Open microdiscectomy (use of microscope and/or loupe magnification)
C. Tubular Discectomy without magnification
D. Tubular Discectomy with magnification (microscope and/or loupes)
E. Endoscopic Discectomy
F. Total disc replacement or lumbar fusion (any type, interbody or posterolateral)

28. The above patient is treated with a revision discectomy but then reherniates again and is indicated for a third surgery. Which of the following best describes the surgical technique that you would choose?

A. Conventional open discectomy (no magnification)
B. Open microdiscectomy (use of microscope and/or loupe magnification)
C. Tubular Discectomy without magnification
D. Tubular Discectomy with magnification (microscope and/or loupes)
E. Endoscopic Discectomy
F. Total disc replacement or lumbar fusion (any type, interbody or posterolateral)

29. How frequently does an *intraoperative* complication occur when performing revision surgery/ies for recurrent LDHs?

A. <2%
B. 2-5%
C. 6-10%
D. 11-20%
E. >20%

30. In your experience, which of the following *intraoperative* surgical complication/s have occurred when performing revision surgery/ies for recurrent LDHs? (select all that apply)

A. Durotomy
B. Nerve root injury
C. Wrong surgery level
D. Bowel injury
E. Urological injury
F. Hemorrhage
G. None of the above
H. Others (please mention in the box below)

31. How frequently does a *post-operative* complication occur after performing revision surgery/ies for recurrent LDHs?

A. <2%
B. 2-5%
C. 6-10%
D. 11-20%
E. >20%

32. In your experience, which of the following *post-operative* surgical complication/s have occurred after performing revision surgery/ies for recurrent LDHs? (Select all that apply)

A. Wound complications or superficial infection
B. Deep infection
C. Hematoma
D. Reherniation
E. Post-operative segment instability
F. None of the above
G. Others (please mention in the box below)

33. In the event a technically feasible and well performing product is available, in your opinion is there a role for the following in some patients?

A. Annular repair
B. Biologic replacement or augmentation of the nucleus
C. Both of the above
D. Neither of the above