



Comparison of pure lateral and oblique lateral inter-body fusion for treatment of lumbar degenerative disk disease: a multicentric cohort study

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Abstract

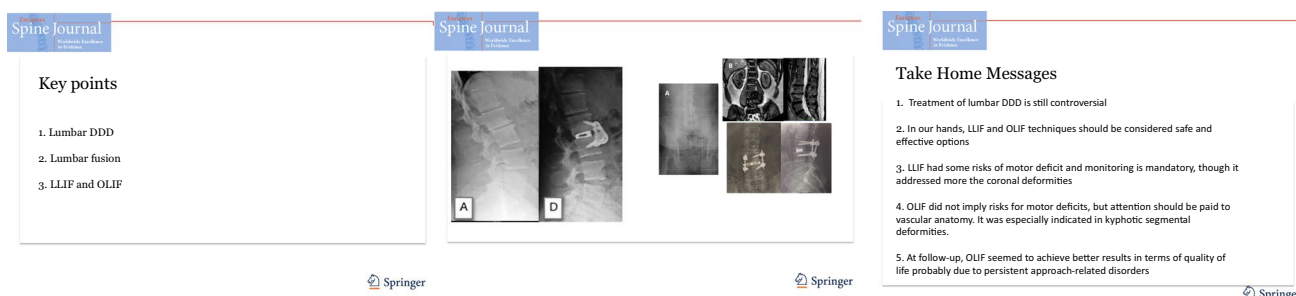
Purpose The most effective interbody fusion technique for degenerative disk disease (DDD) is still controversial. The purpose of our study is to compare pure lateral (LLIF) and oblique lateral (OLIF) approaches for the treatment of lumbar DDD from L1–L2 to L4–L5, in terms of clinical and radiological outcomes.

Materials and methods 45 patients underwent lumbar interbody fusion for pure lumbar DDD from L1–L2 to L4–L5 through LLIF ($n=31$, mean age 62.1 years, range 45–78 years) or OLIF ($n=14$, mean age 57.4 years, range 47–77 years). Clinical evaluations were performed with ODI and SF-36 tests. Radiological assessment was based on the modification of coronal segmental Cobb angles and segmental lumbar lordosis (L1–S1).

Results On ODI and SF-36, all patients presented good results at follow-up, with 26% the difference between the LIF and OLIF groups on ODI scale in the post-operative period, and 3.9 and 8.8 points difference on physical and mental SF-36 in favor of OLIF. Radiological parameters improved significantly in both groups. The mean correction was 6.25° for cCobb (11.3° in LIF and 1.9° in OLIF), 2.5° for sLL (2° in LLIF and 4° in OLIF).

Conclusions LLIF and OLIF represent safe and effective MIS procedures for the treatment of lumbar DDD. LLIF had some risks of motor deficit and monitoring is mandatory, though it addressed more the coronal deformities. OLIF did not imply risks for motor deficits, but attention should be paid to vascular anatomy. It was more effective in kyphotic segmental deformities.

Graphical abstract These slides can be retrieved under Electronic Supplementary material.



Keywords Lumbar spine · Degenerative disc disease · OLIF · LLIF · Lumbar fusion

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Extended author information available on the last page of the article

Introduction

Degenerative disk disease (DDD) is a common condition for which the treatment algorithm is still controversial, particularly about the technical indications and timing for intersomatic arthrodesis [1–4]. Many non-surgical physicians are, to date, still convinced that surgery is an overly aggressive treatment for such a condition [5].

The emerging diffusion of minimally invasive spine (MIS) techniques, such as lateral lumbar inter-body fusion (LLIF) and oblique lumbar inter-body fusion (OLIF), is progressively changing the treatment of patients suffering from lumbar DDD, as they are thought to achieve mono or pluri-segmental interbody fusion with a faster recovery, shorter hospital stay, reduced operative time and a lower rate of complications and lesser postoperative pain compared to standard posterior procedures [6, 7].

Considering the emerging interest for these techniques, the aim of our paper is to analyze experiences with LLIF and OLIF and compare clinical and radiological outcomes of such techniques in the management of pure mono or pluri-segmental DDD, evaluating the specific indications and risks for any procedure.

Materials and methods

A cohort of 45 patients (15 males and 30 females, mean age 60.7 years), consecutively enrolled in our institutes from January 2010 to December 2016, underwent a lumbar inter-body fusion for pure lumbar DDD from L1–L2 to L4–L5. Lordotic titanium or peek cages were used in all patients. Thirty-one patients were treated by a pure lateral trans-psoas approach (LLIF group) and 14 patients were treated by an oblique lateral retroperitoneal approach (OLIF group). All details concerning LLIF and OLIF surgical techniques are included in supplementary materials. For intervertebral fusion, we used different type of bone substitutes (bovine mineralized bone plus collagen; calcium phosphate granules or paste; paste of demineralized bone matrix). Spine stabilization was achieved by anterior plate or posterior percutaneous screws.

Inclusion criteria were: chronic axial low back pain exacerbated by prolonged standing and trunk mobility; previous failed conservative treatment for a minimum period of 6 months; Pfirrmann score 3 or more than 3; pre-operative bilateral fluoroscopy-assisted discography and facet joint injection that confirmed disk as pain generator. Exclusion criteria were: more than two segments of DDD; spine deformity with relevant global sagittal imbalance; radicular pain due to severe lumbar stenosis or herniated

disk; osteoporotic fractures; L5–S1 DDD for inability to compare at that level surgical procedures discussed in this topic; psycho-social issues.

Preoperative radiological evaluation including lumbar standing and dynamic X-rays, to evaluate spino-pelvic parameters and spinal stability, MRI and CT to detect also the course of great vessels. Patients with at least 6 months of follow-up were included in the analysis. No patient enrolled in the present cohort who underwent surgery was lost (mean FU 38 months; range 24–60). General and neurological conditions, as well as the quality of life, were evaluated at admittance (baseline parameters), 30 days after surgery, at 6 months and final follow-up, using the visual analog scale (VAS), Oswestry Disability Index (ODI), and SF-36 tests. The radiological evaluation was based on modifications of the coronal Cobb angle (cCobb) and segmental lumbar lordosis (sLL), compared to the baseline.

The potential source of biases is the dimension of the final cohort itself; nevertheless, on the post hoc estimated power tests, the size of the sample was found to be excellent ($1 - \beta = 0.83$ (for $\alpha 0.05$, effect size 0.8)). The entire cohort was analysed with SPSS v.18. ANOVA analysis was used to compare means of the scores between the subgroups. It is important to note that functional status related to variations between preoperative and follow-up, as expressed by ODI scores, was statistically rendered as fully ordinal three steps variables (Better-Stable-Worse). Oneway and Multivariate ANOVA were used to compare means between the two subgroups and between first evaluation and follow-up, while Chi-square tests were employed for nominal variables.

All the patients expressed written consent to the surgical procedure after appropriate information. All the patients explicitly consented to undergo the clinical-radiological follow-up, explaining the purpose of this study. MRI, CT and plain X-ray dynamic studies imply minimal or no harm towards the individuals included in the final cohort and are comprised among the radiological worldwide gold standards for the diagnosis and follow up of DDD cases. Data reported have been completely anonymized. So, this study is perfectly consistent, in any of its aspect, with WMA Helsinki declaration of Human Rights.

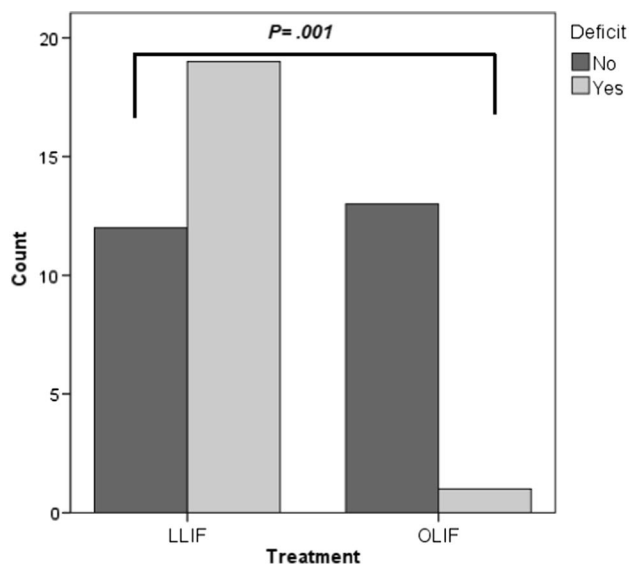
Results

45 patients were 45–78 years of age (mean 60.7 years), 15 males and 30 females. A total of 67 levels were treated: 6 L1–L2 (9%), all LLIF; 24 L2–L3(36%), 21 LLIF (87%) and 3 OLIF (13%); 23 L3–L4 (34%), 17 LLIF (73%) and 6 OLIF (27%); 14 L4–L5 (21%), 5 LLIF (36%) and 9 OLIF (64%) (Table 1).

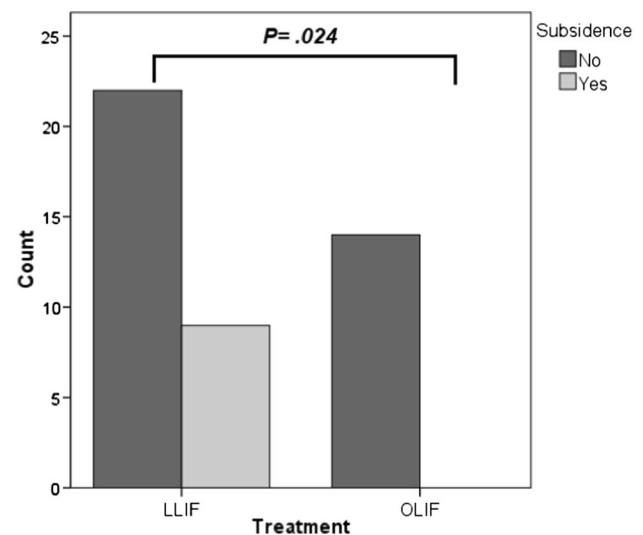
Two intraoperative complications occurred without further events: 1 patient in the LLIF group (2.2% of all patients,

Table 1 Demographic data and levels operated

Group	OLIF	LIF	Total
Demographic data			
Patients	14	31	45
Sex ratio (M/F)	08:06	07:24	15:30
Mean age	57.4	62.07692308	60.77777778
<i>n.</i> levels			
Single level	10	18	28
Two or more levels	4	13	17
Levels treated			
	18	49	67
L1–L2	–	6	6 (9%)
L2–L3	3	21	24 (36%)
L3–L4	6	17	23 (34%)
L4–L5	9	5	14 (21%)

**Fig. 1** Bar charts disclosing the Chi² analysis concerning the treatment and the incidence of postoperative motor deficit

3.2% of the LLIF group) presented with a peritoneal laceration and another patient in the OLIF group (2.2% of all patients and 7.1% of the OLIF group) experienced a rupture of the left iliac vein, intraoperatively repaired. In the post-operative period, a 70-year-old female treated with two-levels LLIF (2.2% of all patients, 3.2% of the LLIF group) suffered a myocardial infarction. Clinically, we observed 20 cases (44.4% of patients, 19 LLIF (95%) and 1 (5%) OLIF) of minor transient motor deficit (4 or 4+/5 motor) in ankle dorsal flexion associated with L3 or L4 dyesthesia; such symptoms had progressive and complete resolution within 1–4 weeks, except 1 who presented an L4 palsy with partial improvement at 1-year FU. These features presented strong statistical differences between the two subgroups ($p = 0.001$) (Fig. 1).

**Fig. 2** Bar charts disclosing the Chi² analysis concerning the treatment and the incidence of radiological signs of cage subsidence

Moreover, five patients in the LLIF group (11% of all patients, 16.1% of the LLIF group) presented with psoas hematomas, which required 4 days of bedrest. In the OLIF group, seven patients (15.5% of all patients, 50% of the OLIF group) presented with fluid retroperitoneal collection, which did not require any treatment.

Radiological signs of cage subsidence were noted in nine levels treated by LLIF, with one severe settling, while no case was recorded in the OLIF group. This feature also presented a statistically significant difference between the two subgroups ($p = 0.024$) (Fig. 2).

We recorded one plate mobilization (one OLIF) in the retroperitoneal space because of pulling out of screws, that required revision surgery. Overall reoperation rate for the total number of levels treated was about 1.5%.

Overall complication rate, including medical and surgical findings, calculated on 67 patients, amounted to 9% (4/45 patients, one myocardial infarction, one severe cage subsidence, one plate displacement and one partial improvement of L4 palsy), with no statistically significant difference between the two subgroups ($p = 0.102$).

Results on ODI and SF-36 are summarized in Tables 2, 3. The ODI scale differed 26% between the LLIF and OLIF groups in the post-operative period. Regarding the SF-36 tests, the physical scale differed 3.9 points and the mental scale 8.8 points in favor of the OLIF group.

Radiological parameters improved significantly in both groups (Figs. 3, 4). The mean correction was 6.3° for cCobb (11.5° in the LLIF group, 2.5° in the OLIF group; $p = 0.001$) (Fig. 5), 2.5° for sLL (2° in the LLIF group, 4° in the OLIF group; $p = 0.3$).

Discussion

Lumbar DDD is a common cause of chronic axial pain associated with pathological motion, misalignment, progressive deformity, and spinal stenosis. Although the relationship between instability and degeneration is not clear, the severity of disk degeneration seems to be related to the deterioration of segmental motion [8, 9]. Several conservative or surgical approaches have been attempted, according to the degree of degeneration, trying to decrease abnormal segmental motion and low back pain, but none was the panacea. Lumbar fusion techniques were proposed to achieve these

Table 3 SF-36 scores

	OLIF	LLIF	Tot
Mental scale			
Pre-op	38.2%	37.50%	37.85%
Post-op	55.90%	56.35%	56.12%
Follow-up	70.00%	60.22%	65.11%
<i>p</i> value		0.0012	0.03
Physical scale			
Pre-op	27.85%	29.72%	28.78%
Post-op	48.80%	39.58%	43.69%
Follow-up	55.00%	51.15%	53.7%
<i>p</i> value		0.009	0.006

aims, but interbody fusion, obtained through posterior or anterior approaches, with open standard or minimally invasive surgical techniques (MIS), seemed to show the highest fusion rate compared to posterolateral procedures [10]. MIS, such as LLIF or OLIF, can preserve lumbar muscles and soft tissues, allowing to apply larger symmetrical intervertebral cages, granting fusion and correction [11, 12].

The LLIF approaches the lumbar disc space via a lateral retroperitoneal, transpsoas corridor. This technique is suitable for all lumbar levels, but L5/S1 due to the overlap of

Table 2 ODI scores

	OLIF	LLIF	TOT	<i>p</i> value
Pre-op	14	31	45	
20%	0 (0%)	0 (0%)	0 (0%)	
40%	0 (0%)	0 (0%)	0 (0%)	
60%	2 (14.2%)	6 (19.4%)	8 (17.8%)	
80%	8 (57.1%)	15 (48.3%)	23 (51.1%)	
100%	4 (28.5%)	10 (32.3%)	14 (31.1%)	
Mean	79%	84%	82,6%	
Post-op				
Better	10 (71.4%)	7 (22.6%)	17 (37.8%)	
Stable	3 (21.5%)	19 (61.2%)	22 (48.8%)	
Worse	1 (7.1%)	5 (16.2%)	6 (13.4%)	
Mean	31%	57%	47%	
Follow-up				
Better	14 (100%)	29 (93.6%)	28 (100%)	
Stable	0 (0%)	2 (6.4%)	0 (0%)	
Worse	0 (0%)	0 (0%)	0 (0%)	
Mean	9%	17%	14%	
<i>p</i> value			0.001	0.574

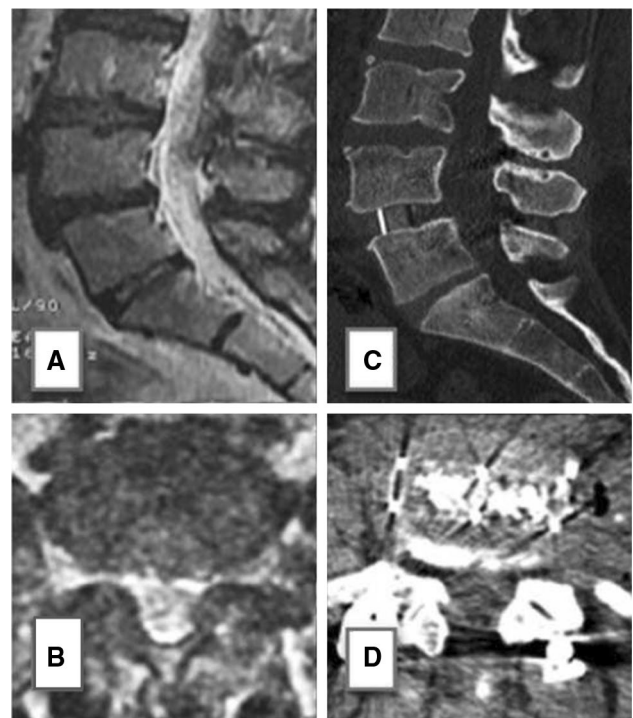


Fig. 3 **a, b** T2-weighted MRI scans revealed DDD at L4–L5, without signs of instability. **c, d** Postoperative CT scan at 2 years follow-up showing the interbody fusion obtained by LLIF cage and completed by a posterior percutaneous pedicular screws insertion

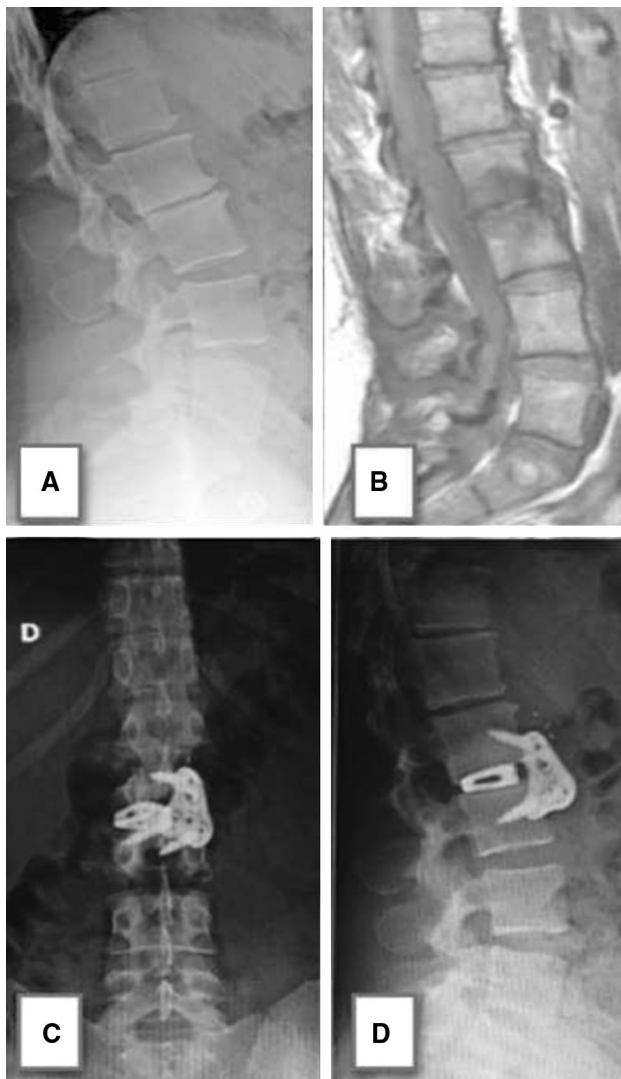


Fig. 4 **a, b** X-ray lateral view and sagittal T1-weighted MRI scan showing L2–L3 DDD with loss of segmental lordosis. **c, d** Postoperative X-rays in AP and lateral position demonstrating the L2–L3 cage insertion through OLIF approach and stabilization by plate. Restoration of segmental lordosis was 5°

the iliac crest that obstructs the lateral access. Neuromonitoring is essential in creating a transpsoas corridor because the lumbar plexus courses inside the psoas itself [12–14]. Lateral approach is contraindicated in patients with prior retroperitoneal surgery, retroperitoneal abscess, or abnormal vascular anatomy [15, 16]. Muscle-splitting allows the rapid postoperative mobilization. Disadvantages include potential risks for lumbar plexus, psoas muscle and bowel, particularly in L4/L5 [17]. Vascular injury may be difficult to control and it could represent another potential risk [12, 18, 19].

The OLIF approaches the disc space via a corridor between the peritoneum and psoas muscle [20]. In contrast to LLIF, the OLIF technique does not dissect or traverse the psoas muscle. Patient's position is always lateral, either left

or right side up depending on the surgeon's preference. Neuromonitoring is not requested. OLIF is suitable for L1–S1 levels [7]. It is contraindicated in patients with severe central canal stenosis, and it may be technically difficult in cases of high grade spondylolisthesis and in prior abdominal surgeries [21]. Fast postoperative mobilization due to the complete respect of paraspinal and psoas muscles can be achieved. Lumbar plexus and psoas injuries are unlikely, as dissection is performed anterior to the psoas. However, potential risks involved with OLIF surgery include sympathetic dysfunction and vascular injury [22].

Though LLIF established its place as a robust technique for deformity correction and interbody fusion, minimizing surgical-related morbidity and complications, OLIF requires further studies and data to establish its role [12, 23, 24]. The present study is the first comparing miniminvasive LLIF and OLIF techniques in treating mono or bi-segmental symptomatic DDD between L1 and L5.

Due to the growing diffusion of such techniques, there is a debate on their specific indications and limits [12, 18, 24–26].

On the radiological point of view, LLIF appeared superior to OLIF in segmental coronal deformity correction, whereas OLIF was two times more able than LLIF to correct kyphosis. This difference is probably related to the feasible resection of the anterior longitudinal ligament, obtainable by OLIF. Conversely, LLIF seemed to ensure better results in terms of the cCobb improvement. In all cases, approaching the segmental deformity, before inserting the definitive cage, it was particularly important to obtain the rupture of the contralateral osteophytes to mobilize the segment. In this way, as the cage progressed to its final lodgment, the coronal deformity was progressively reduced.

Interestingly, in the LLIF group, we recorded at follow-up the higher incidence of cage subsidence compared to OLIF. But, this findings did not seem significantly associated with less improvement of the segmental deformity or persistence of pain. In LLIF, this mechanical complication, in the absence of osteoporotic disorders, could be explained by more aggressive surgical maneuvers on end-plates and osteophytes during the cage insertion. In fact, no cases of cage subsidence were detected in the OLIF group, probably because, in our hands, the positioning of the cage was more gentle, less traumatic.

LLIF was always performed with the aid of intraoperative monitoring, as requested. Nevertheless, we had several cases of radicular irritation and one case of persistent motor deficit in patients undergoing the L4–L5 approach. The lumbar plexus generally lies beneath the posterior half of the lateral aspect of the L4–L5 disk, and this exposes the patient to a tremendous risk of nerve injury at this level [27]. In view of these observations, we are progressively abandoning LLIF and preferentially used the OLIF approach to treat



Fig. 5 **a, b** Standing X-ray films and MRI demonstrated L3–L4 DDD with segmental coronal deformity. 3-years follow-up standing X-rays showed the results of surgical procedures: LLIF plus posterior percutaneous stabilization. Coronal deformity was improved (8°)

L4–L5 DDD. On the contrary, we may decide for LLIF if the patient has bilateral osteophytes localized under the psoas muscles, which fix the spine and prevent a proper segmental correction.

OLIF demands a careful preoperative planning to detect the vascular anatomy, particularly the course of the left iliac vein, which represents the real limit of such approach. Sometimes, the vein, which can overlap L4–L5, is attached to anterior osteophytes, partially collapsed and fixed to the bone. In this condition, it is particularly difficult to dissect: in such cases, according to our experience of one intraoperative rupture of iliac vein, the surgeon is more likely to confront an intraoperative complication. Therefore, we actually suggest aborting the OLIF approach in this anatomical condition, because the vein dissection in a very narrow corridor can result in a vessel damage. The vein suture, through the mini approach used for OLIF can be very demanding, even for an expert vascular surgeon. The resulting hemorrhage could be impossible to control and potentially fatal. The careful pre-operative radiological vessel's study must avoid this circumstance, modifying the decision-making process towards the LLIF approach.

Most patients in the present series presented good clinical outcomes at follow-up, with significant improvement of VAS, ODI, and SF-36 scores. Interestingly, the score

measuring the quality of life seemed to be better in the OLIF group, probably due to persistent numbness in the thighs and frequent pain related to psoas contracture in the LLIF group. The approach-related symptoms and patient compliance represent other important factors that should be considered choosing the surgical procedure.

Conclusions

LLIF and OLIF techniques should be considered safe and effective options for the treatment of pure lumbar DDD. LLIF had some risks of motor deficit and monitoring is mandatory, though it addressed more the coronal deformities. OLIF did not imply risks for motor deficits, but attention should be paid to vascular anatomy. It was especially indicated in kyphotic segmental deformities. At follow-up, OLIF seemed to achieve better results in terms of quality of life probably due to persistent approach-related disorders detected after LLIF procedures.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

- Chou R, Baisden J, Carragee EJ et al (2009) Surgery for low back pain: a review of the evidence for an American Pain Society Clinical Practice Guideline. *Spine* 34(10):1094–1109
- Rao PJ, Loganathan A, Yeung V, Mobbs RJ (2015) Outcomes of anterior lumbar interbody fusion surgery based on indication: a prospective study. *Neurosurgery* 76:7–23
- Nakai S, Yoshizawa H, Kobayashi S (1999) Long-term follow-up study of posterior lumbar interbody fusion. *J Spinal Disord* 12:293–299
- Chen BL, Wei FX, Ueyama K et al (2011) Adjacent segment degeneration after single-segment PLLIF: the risk factor for degeneration and its impact on clinical outcomes. *Eur Spine J* 20:1946–1950
- Carreon LY, Glassman SD, Howard J (2008) Fusion and nonsurgical treatment for symptomatic lumbar degenerative disease: a systematic review of Oswestry Disability Index and MOS Short Form-36 outcomes. *Spine J* 8:747–755
- Berjano P, Lamartina C, Smith W, Aebi M (2015) Lateral access surgery: a decade of innovation. *Eur Spine J* 24(Suppl 3):285–286
- Ohtori S, Orita S, Yamauchi K et al (2015) Mini-open anterior retroperitoneal lumbar interbody fusion: oblique lateral interbody fusion for lumbar spinal degeneration disease. *Yonsei Med J* 56:1051–1059
- Fujiwara A, Lim TH, An HS et al (2000) The effect of disc degeneration and facet joint osteoarthritis on the segmental flexibility of the lumbar spine. *Spine* 25:3036–3044
- Inoue N, Espinoza Orías AA (2011) Biomechanics of intervertebral disk degeneration. *Orthop Clin N Am* 42:487–499
- Resnick DK, Choudhri TF, Dailey AT et al (2005) Guidelines for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 11: interbody techniques for lumbar fusion. *J Neurosurg Spine* 2:692–699
- Ozgur BM, Aryan HE, Pimenta L, Taylor WR (2006) Extreme lateral interbody fusion (XLIF): a novel surgical technique for anterior lumbar interbody fusion. *Spine J* 6:435–443
- Arnold PM, Anderson KK, McGuire RA Jr (2012) The lateral transposas approach to the lumbar and thoracic spine: a review. *Surg Neurol Int* 3(Suppl 3):S198–S215
- Phan K, Rao PJ, Scherman DB et al (2015) Lateral lumbar interbody fusion for sagittal balance correction and spinal deformity. *J Clin Neurosci* 22:1714–1721
- Marchi L, Abdala N, Oliveira L et al (2013) Radiographic and clinical evaluation of cage subsidence after stand-alone lateral interbody fusion. *J Neurosurg Spine* 19:110–118
- Malham GM, Parker RM, Goss B, Blecher CM (2015) Clinical results and limitations of indirect decompression in spinal stenosis with laterally implanted interbody cages: results from a prospective cohort study. *Eur Spine J* 24(Suppl 3):339–345
- Malham GM, Ellis NJ, Parker R et al (2017) Maintenance of segmental lordosis and disk height in stand-alone and instrumented extreme lateral interbody fusion (XLIF). *Clin Spine Surg* 30:E90–E98
- Malham GM, Ellis NJ, Parker RM, Seex KA (2012) Clinical outcome and fusion rates after the first 30 extreme lateral interbody fusions. *Sci World J*. <https://doi.org/10.1100/2012/246989>
- Barbagallo GM, Albanese V, Raich AL et al (2014) Lumbar lateral interbody fusion (LLIF): comparative effectiveness and safety versus PLIF/TLIF and predictive factors affecting LLIF outcome. *Evid Based Spine Care J* 5:28–37
- Lee YS, Park SW, Kim YB (2014) Direct lateral lumbar interbody fusion: clinical and radiological outcomes. *J Korean Neurosurg Soc* 55:248–254
- Liu L, Liang Y, Zhang H et al (2016) Imaging anatomical research on the operative windows of oblique lumbar interbody fusion. *PLoS One* 11(9):e0163452
- Phan K, Mobbs RJ (2015) Oblique lumbar interbody fusion for revision of non-union following prior posterior surgery: a case report. *Orthop Surg* 7:364–367
- Silvestre C, Mac-Thiong JM, Hilmi R, Roussouly P (2012) Complications and morbidities of mini-open anterior retroperitoneal lumbar interbody fusion: oblique lumbar interbody fusion in 179 patients. *Asian Spine J* 6:89–97
- Raco A, Miscusi M (2016) The extreme lateral minimally invasive approach to pure degenerative disk disease. In: Wang MY, Sama AA, Uribe JS (eds) *Lateral access minimally invasive spine surgery*. Springer, Switzerland, pp 143–154
- Mobbs RJ, Phan K, Malham G et al (2015) Lumbar interbody fusion: techniques, indications and comparison of interbody fusion options including PLIF, TLIF, MI-TLIF, OLIF/ATP, LLIF and ALIF. *J Spine Surg* 1:2–18
- Winder MJ, Gambhir S (2016) Comparison of ALIF vs. XLIF for L4/5 interbody fusion: pros, cons, and literature review. *J Spine Surg* 2:2–8
- Epstein NE (2016) Extreme lateral lumbar interbody fusion: do the cons outweigh the pros? *Surg Neurol Int* 7:S692–S700
- Uribe JS, Arredondo N, Dakwar E, Vale FL (2010) Defining the safe working zones using the minimally invasive lateral retroperitoneal transposas approach: an anatomical study. *J Neurosurg Spine* 13(2):260–266

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