KU LEUVEN

FACULTY OF MEDICINE

# Lumbar fusion surgery: are fusion success and clinical outcome associated?

Master Thesis proposed to achieve the degree of master in medicine by

**Vincent VAN GRINSVEN**

Unit: Faculty of Medicine, KULeuven

Department: Neurosurgery

Promotor: Prof. dr. Bart DEPREITERE

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# COVER LETTER

Dear Editor,

Lumbar fusion surgery has become a 'hot topic' with numerous publications on a variety of techniques and modifications to these techniques. These articles, however, often hold small sample sizes, are of minor quality and are often company funded giving a high risk for bias. They also don't investigate whether patients with successful fusion are clinically superior to those in whom solid bone fusion was not obtained. We questioned this because successful fusion does not always lead to a satisfactory clinical outcome.

Our goal was to systematically search the literature to provide an answer to this question. There is an expansion in the application of these techniques, but the evidence is questionable. Furthermore, they are invasive and come with the risk of severe complications.

Our inclusion criteria were broad, but strong and evidence-based. We gathered data on a total of 5340 patients, which undeniably gives a strong sample size. We succeeded in showing clinical improvement of clinical relevance after fusion surgery in this amount of subjects. We also found high successful fusion rates. Presence of association between these two variables could not be shown. This was because successful and failed fusion groups were never clinically compared. Studies were heterogeneous and reported inconsistently. We did formulate theories for a possible absence of association.

We did not only focus on the results of the included articles, but we also critically reviewed other aspects. We then were able to give advise for future investigation, based on the most frequent pitfalls in this published literature.

In our opinion, this paper can give four contributions to the medical scientific world. First, this study is one of the largest on scale to suggest clinically relevant benefit of fusion surgery and describe high fusion rates with all techniques. Second, this was one of the first large reviews with the primary goal to investigate the association between these two parameters and additionally mention the missing data to fully assess this subject. Third, we describe and summarize interesting insights, trends and concerns in lumbar fusion surgery. Fourth, it offers a summary of endlessly growing literature, based on a systematic selection protocol with strong, evidence-based inclusion criteria.

## ABSTRACT

**Background:** Lumbar arthrodesis is globally used as treatment for degenerative lumbar pathology when conservative management fails. Research articles on new techniques are rising exponentially. However, evidence on the association between successful fusion and clinical outcome is limited.

**Objective:** To evaluate the association between fusion success and clinical improvement.

**Methods:** We performed a literature review using PUBMED according to PRISMA guidelines. Study characteristics, Oswestry Disability Index (ODI) scores and radiographic outcome were extracted for analysis. We created six groups: Anterior and lateral lumbar interbody fusion (ALIF and LLIF) +/- Bone Morphogenetic Protein-2 (BMP-2), posterolateral and transforaminal lumbar interbody fusion (PLIF and TLIF) +/- BMP-2, posterolateral lumbar fusion (PLF) +/- BMP-2. Weighted averages were computed. Bivariate analysis was performed to evaluate the proposed association.

**Results:** We identified 56 articles. PRIMARY OUTCOMES: Mean follow-up was 29.1 months overall. Mean ODI improvement was >15 in all groups, which is clinically relevant. ODI improvement was highest in PLIF/TLIF with BMP-2 (35.1). ALIF/LLIF with BMP-2 had the highest fusion rate, (96.5%). PLF had the lowest mean ODI improvement (21.2) and fusion rate (84.9%). Association of solid fusion with clinical improvement could not be shown. SECONDARY OUTCOMES: There was no dose-related effect of BMP-2 on fusion rates. Fusion rates for titanium cages versus PEEK cages (91.7% vs 91.0% respectively) were similar.

**Conclusion:** ODI improvement after lumbar arthrodesis is clinically relevant in all groups. Fusion rates are high. However, we could not show an association mainly because of heterogeneity and inconsistency in studies. Further good-quality research is needed.

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**Achtergrond:** Lumbale artrodese is een wijd gebruikte behandeling van degeneratieve lumbale pathologie wanneer conservatieve aanpak faalt. Er is een enorme expansie aan onderzoeksartikels omtrent nieuwe technieken. Echter, het bewijs dat er een verband is tussen beenderige fusie en klinisch succes, is beperkt.

**Doel:** Zoeken naar de associatie tussen succesvolle fusie en klinische verbetering.

**Methoden:** We voerden een literatuurstudie uit in PUBMED, gebruik makende van de PRISMA richtlijnen. Studie-eigenschappen, de Oswestry Disability Index (ODI) en en radiologische uitkomst werden geëxtraheerd voor analyse. We hebben zes groepen gemaakt: Anterolaterale en laterale lumbale interbody fusie (ALIF en LLIF) met/zonder Bone Morphogenetic Protein-2 (BMP-2), posterolaterale en transforaminale lumbale interbody fusie (PLIF/TLIF) met/zonder BMP-2, posterolaterale lumbale fusie (PLF) met/zonder BMP-2. We hebben gewogen gemiddeldes berekend. We voerden een bivariaat analyse uit ter evaluatie van de hoger beschreven associatie.

**Resultaten:** We includeerden 56 artikels. PRIMAIRE RESULTATEN: Gemiddelde opvolging was 29,1 maanden voor alle groepen samen. Gemiddelde ODI verbetering was in alle groepen >15 punten, wat klinisch relevant is. ODI verbetering was het hoogste in PLIF/TLIF met BMP-2 (35.1). ALIF/LLIF met BMP-2 had de hoogste fusie ratio (96,5%). PLF had de laagste gemiddelde ODI verbetering (21,2) en fusie ratio (84,9%). We konden geen associatie tussen beenderige fusie en klinische verbetering aantonen. SECUNDAIRE RESULTATEN: Er was geen dosisgerelateerd effect van BMP-2 op fusie. Titanium en PEEK fusieprothesen hadden gelijke fusie ratio's (91.7% vs 91.0% respectievelijk).

**Conclusie:** ODI verbetering na lumbale artrodese is klinisch relevant voor alle technieken. Fusie ratio's zijn hoog. We konden echter geen associatie aantonen, vooral omdat er veel heterogeniteit was en inconsistente weergave van data in de studies. Er is nood aan verder onderzoek van goede kwaliteit.

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**What was already known on the topic**

- Present techniques for lumbar arthrodesis have moderate to high fusion rates.
- Lumbar arthrodesis can lead to a significant better postoperative status when compared to preoperative.
- Multiple theories try to explain why solid fusion does not predict superior clinical outcome.

**What this study adds**

- Evidence of clinically relevant improvement after fusion surgery in a large sample for different techniques.
- A descriptive bivariate analysis which could not show association between fusion success and clinical outcome.
- A summary of data, insights, trends and concerns in lumbar fusion surgery.

# INTRODUCTION

Low back pain caused by degenerative pathology is an important global issue, with a lifetime prevalence of 50% to over 80%. It is the main cause of YLD and therefore has a great medical and economic impact, with often long treatment trajectories and a disability allowance. Recurrence occurs in over 50% of patients. (1)

When considering a patient with low back pain, red flags should primarily be excluded, as these urgencies need immediate treatment. Secondly, radiculopathy should be evaluated. Entangled radiculopathy (significant or progressive paresis or untenable pain) requires urgent imaging followed by decompression. Yet, more than 20% of patients are not treated within the appropriate time range. In unentangled radiculopathy, a wait-and-see approach is advised. Patients in this category who haven't recovered after 6 weeks, should be reconsidered for intervention.(2-4)

Red flags and radiculopathy are excluded in 85% of patients. Back pain is then categorised as non-specific. In this group, 90% will recover within 6 weeks and a wait-and-see approach with active revalidation and pain relief is advised for at least 12 weeks. Detection of yellow flags should be considered. Only after a period of 12 weeks, intervention can be indicated.(5)

Spinal fusion procedures were first described in 1911 by Hibbs and Albee. At that time, spinal deformity and dysfunction caused by Pott disease was an important health issue. They used autologous bone from laminae, the iliac crest or ribs to form bony bridges between adjacent vertebrae, stabilizing deformity and subsequently improving patients' symptoms. However the procedure was promising, many patients developed pseudarthrosis.. In the years to come, surgeons were challenged to combine bone grafts with instrumentation, improving the rate of solid fusions.(6)

There are three main techniques in spinal fusion surgery.

Anterior lumbar interbody fusion (ALIF) involves an incision through the abdominal muscles and fascia, to reach the vertebrae retroperitoneally. This provides a very good exposure, making it possible to insert a large interbody cage. It also avoids manipulating posterior bone structures, muscles and ligaments that are involved in the pathophysiology of low back pain. Possible complications of this procedure are typically retrograde ejaculation, vascular, sympathetic and visceral injuries. A restriction of this approach is that it only gives access to L4-L5 and L5-S1, because of the anatomical course of the main vessels. It is the preferred approach in cervical fusion, because of the risk of cord manipulation associated with a posterior approach.

In posterior lumbar interbody fusion (PLIF) the incision is via the back musculature, which is much more familiar to the spine surgeon. After bilateral dissection, neural structures are spread to the sides, and cage is inserted on both sides of the intervertebral space. The main restriction is the manipulation of neural structures, with possible durotomy or nerve injuries

as complications. Additionally the painful low back structures are manipulated. PLIF can also be performed without interbody fusion (PLF).

Transforaminal lumbar interbody fusion (TLIF) is performed trough a unilateral posterior or posterolateral approach on the side of the patient's symptoms, which avoids retraction of neural structures. Only one cage is inserted in the midline. The main advantage is that no neural retraction is needed. However, this is a difficult technique with a long learning curve and a narrow surgical space.

Lateral lumbar interbody fusion (LLIF) is a relatively new technique, equivalent to ALIF but without a paramedian incision. The anterior longitudinal ligament is retained, adding stability. Its main restriction is that the iliac wing makes visibility of L5–S1 almost impossible.(7)

A wide range of tools such as cages, screws, bone grafts and osteoinductive proteins are used to increase the likelihood of obtaining solid bone fusion. Despite that fusion rates are often higher than 80%, patients with successful fusion do not always benefit from their intervention.

The research articles on the topic of lumbar fusion surgery are mainly small, supported by instrument developing companies or of minor quality. Therefore, there is a lack of class 1 evidence demonstrating the clinical relevance of these procedures, as well as association between successful fusion and an improved clinical outcome when compared to failed fusion. Clinicians often need to conduct by their own experience due to this lack of good evidence-based guidelines. We will search the literature to evaluate whether in lumbar arthrodesis it is necessary to obtain solid fusion to improve clinical outcomes in patients with degenerative pathology of the lumbar spine. This implicates a continued search for improving the existing fusion strategies.

## METHODS

### Search strategy

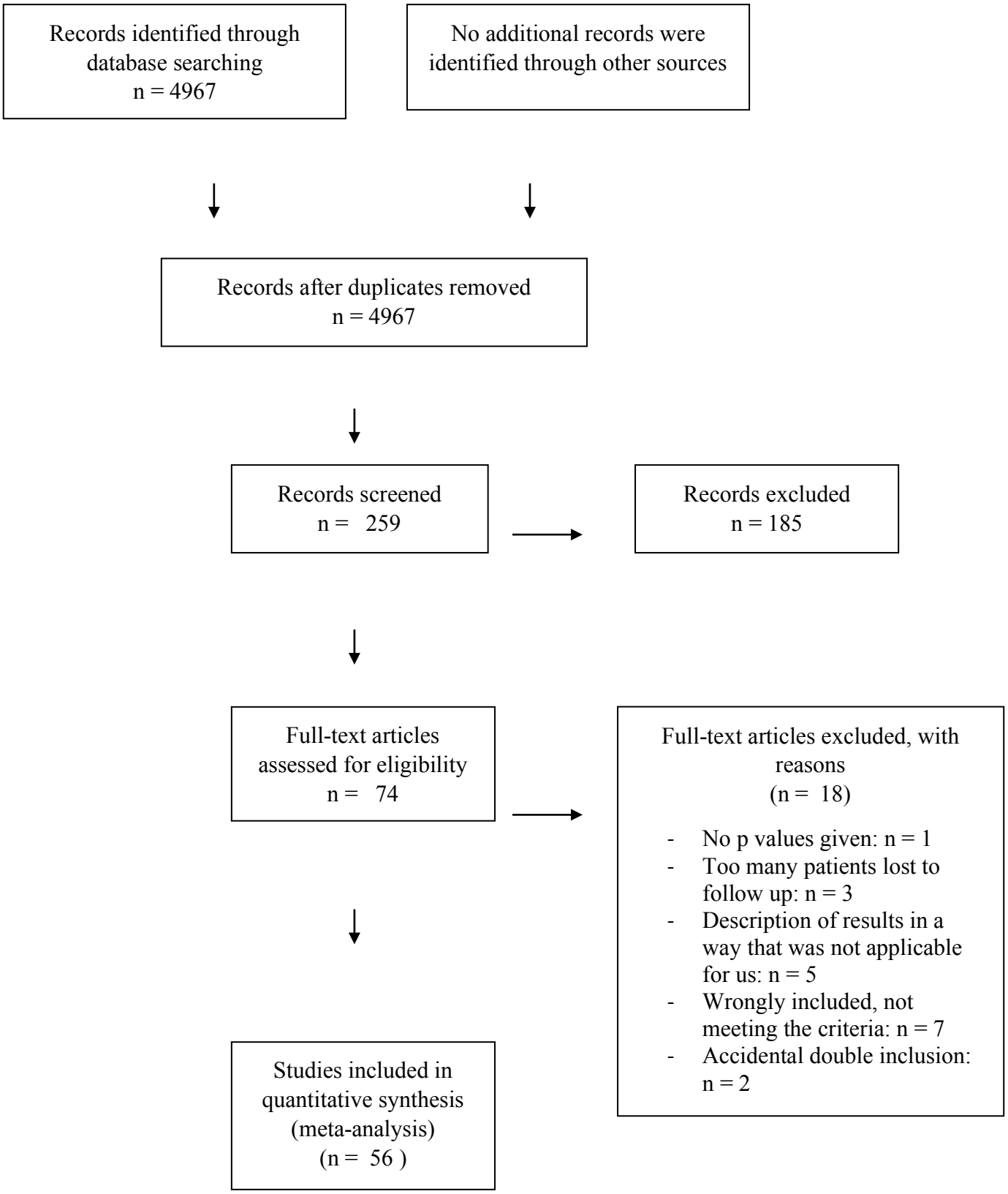
We performed a literature review guided by PRISMA guidelines, searching PUBMED, MEDLINE and COCHRANE LIBRARY. This review was conducted up to November 2017.

Following search strategy was used: (Lumbar spinal fusion and clinical outcome OR lumbar spinal fusion and functional improvement OR lumbar fusion rate and clinical outcome OR anterior lumbar interbody fusion OR posterolateral lumbar fusion OR PLF arthrodesis OR LLIF).

A description of our search is given in Table 1.

We used EndNote to manage our references.

Table 1. PRISMA



**Inclusion criteria**

Articles needed to study lumbar degenerative pathologies and describe clinical AND radiological assessment:

- Lumbar degenerative pathology: degenerative disc disease (DDD), spondylosis, spondylolisthesis, spinal stenosis, foraminal stenosis, lumbar disc herniation, revision surgery.
- Clinical assessment: Oswestry Disability Index.
- Assessment of fusion status: computed tomography as standard or when radiography was inconclusive.
- Randomized controlled trials, prospective trials, case-control studies and cohorts were included. Case reports, cadaveric, non-human, and biomechanical studies were excluded.
- Articles in English, published in a peer-reviewed journal.

**Evaluation of evidence quality**

Assessment of the evidence class of included articles was performed with the Oxford Centre for Evidence-based Medicine-Levels of Evidence. Good quality randomized controlled trials (RCTs) were considered Class I evidence. Moderate or poor quality RCT or company funded RCT and good quality cohort studies were considered Class II evidence. Moderate or poor quality cohort studies and case–control studies were considered Class III evidence. Case series studies were considered Class IV evidence.(8)

**Data extraction**

We extracted following data: (1)lead author and year of publication, (2)study design, (3)surgical procedure, bone graft and cage (4)indication for surgery, (5)mean age, (6)number of patients studied in each group, (7)average period of follow up, (8)ODI scores preoperative, postoperative and average improvement. Standard deviations were also extracted when reported. The selected ODI score was the one at last follow up. (8)Radiological fusion rate with 95% confidence interval and time of last fusion assessment (9)quality of the evidence of each study.

We divided all techniques into 6 groups:

*Group A* consisted of an anterior approach with interbody fusion (ALIF, LLIF, XLIF) and without BMP-2/BMP-7. *Group B* consisted of an anterior approach with interbody fusion and BMP-2/BMP-7. *Group C* consisted of a posterior approach with interbody fusion (PLIF, TLIF) and without BMP-2/BMP-7. *Group D* consisted of a posterior approach with interbody fusion and BMP-2/BMP-7. *Group E* consisted of a posterior approach without interbody fusion (PLF) and without BMP-2/BMP-7. *Group F* consisted of a posterior approach without interbody fusion and with BMP-2/BMP-7.

### Statistical analysis

Due to large heterogeneity (aberrant chi square test, extreme heterogeneity on one-way ANOVA) and poor reporting of standard deviations, a correct meta-analysis using the random-effects model was not feasible at student level at this time. Creating confidence levels around the average of averages without considering their own variance, would lead to false conclusions. Therefore, only weighted averages were calculated for age, follow-up, sample size, assessment of fusion and BMP dosage. We also calculated weighted average for pre- and postoperative ODI, as well as the improvement and fusion rate. Fusion rates were represented with a 95% confidence interval, calculated using the Clopper-Pearson binomial exact test.

For descriptive means, mean ODI improvement and fusion rate were plotted in a bivariate analysis using linear regression. ODI scores were also shown in box plots.

A $p < 0.05$ was considered statistically significant.

## Results

### Selected studies and characteristics

We identified 56 articles meeting our inclusion criteria out of 259 articles screened at our initial search. Of these articles there are 27 randomized controlled trials, 15 prospective cohort studies and 14 retrospective studies.

Fifteen studies included cohorts with an anterior approach with interbody fusion, of which 10 also used BMP-2/BMP-7 (table 2,3).

Twenty-eight studies included cohorts with a posterior approach with interbody fusion, of which 5 also used BMP-2/BMP-7 (table 4,5).

Seventeen studies included cohorts with a posterior approach without interbody fusion, of which 9 also used BMP-2/BMP-7 (table 6,7).

Eighteen studies were excluded after full analysis (table 1).

### Primary outcomes

A detailed description of the included articles is given in table 2-7.

The average age was 53.64 years old. The three most common diagnoses for surgery were degenerative/isthmic spondylolisthesis, central stenosis and degenerative disc disease. The total number of subjects was 5340. The average number of patients per study group was 50. The median was 40 patients. From *group A to F*, the number of patients were 585, 748, 2178, 303, 989 and 537, respectively. The smallest study contained 14 patients (9), while the largest existed of 463 (10) patients. Average follow-up time in all studies was 29.1 months, ranging from 6 (11) to 60 months (12). *Group D* had the longest mean follow up, being 36.3 months, while *group B* had the shortest mean follow up of 21.2 months.

Weighted average results for each group are described in table 8.

## Table 2: Anterior approach with interbody fusion and without BMP-2/BMP-7

| Study | Design | Surgical procedure | Graft | Cage | Indication | N° | F/U | ODI preop +/- SD | ODI postop +/- SD | ODI improvement | F/A | Fusion rate | CEBM |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Burkus JK et al. 2002 (13) | RCT | ALIF | ICBG | Titanium | DDD L4-L5 or L5-S1 | 22 | 24 m | 55,3 +/- 13,5 | 32,8 +/- 22,7 | 22,5 | 24 m | 68,4% (78,9-99,9%) | 2 |
| Kim JS et al 2009(14) | Retrospective analysis | MIS-ALIF with PPSF | / | | Isthmic spondylolisthesis (single level) | 48 | 30 m | 51,4 +/- 22,1 | 23,2 +/- 18,1 | 28,2 | NR | 93,8% (92,9-100%) | 3 |
| Burkus JK et al 2002 (15) | RCT | ALIF | ICBG | Titanium | DDD (single level) | 136 | 24 m | 55,1 +/- NR | 23,8 +/- NR | 31,3 | 24 m | 88,7% (83,1-99,4%) | 2 |
| Burkus JK et al 2005 (16) | RCT | ALIF | ICBG | Titanium | DDD (single level) | 52 | 24 m | 56,6 +/- NR | 28,9 +/- NR | 27,7 | 24 m | 76,1% (89,3-97,6%) | 2 |
| Strube P et al 2012(17) | Retrospective analysis | ALIF | Freeze-died allogenous bone | PEEK | Single-level DDD and facet joint arthritis L4/L5 or L5/S1 (single level) | 40 | 41 m | 62,9 +/- NR | 23 +/- NR | 39,9 | 12 m | 70,6% (93,1-100%) | 3 |
| Strube P et al 2012(17) | Prospective cohort study | APLF | Freeze-died allogenous bone | PEEK | Single-level DDD and facet joint arthritis L4-L5 or L5-S1 (single level) | 40 | 41 m | 62,4 +/- NR | 27 +/- NR | 35,4 | 12 m | 68,7% (75,7-99,1%) | 2 |
| Ohtori S et al 2011(18) | Prospective cohort study | ALIF | ICBG | No cage | Single level degenerative spondylolisthesis L4-L5 | 22 | 24 m | 47 +/- 13 | 15 +/- 5 | 32 | 24 m | 90,9% (95,9-99,9%) | 2 |
| Kim JS et al 2010(19) | Retrospective analysis | CIF | ICBG | PEEK | Single-level low-grade isthmic spondylolisthesis | 32 | 33 m | 60 +/- NR | 6,8 +/- NR | 53,2 | 41 m | 100% (71,5-100%) | 3 |
| Kim JS et al 2010 (19) | Retrospective analysis | ALIF with PPSF | Allograft bone chips | Titanium or PEEK | Single-level low-grade isthmic spondylolisthesis | 43 | 42 m | 49,3 +/- NR | 13,7 +/- NR | 35,6 | 33 m | 97,7% (92,1-100%) | 3 |
| Boden SD et al 2000 (9) | RCT | ALIF | ICBG | Titanium | DDD +/- spondylolisthesis (single level) | 3 | 24 m | 34,7 +/- 7,7 | 20 +/- 12,9 | 14,7 | 24 m | 66,7% (91,3-98,7%) | 1 |
| Slosar PJ et al 2007 (20) | Prospective cohort study | ALIF | Femoral ring (allograft) | No cage | DDD L3–S1, Grade I–II spondylolisthesis, or degenerative scoliosis | 30 | 24 m | 58,6 +/- NR | 29 +/- NR | 29,6 | 24 m | 89% (65,1-95,6%) | 2 |
| Korovessis P et al 2012(21) | Prospective cohort study | CIF | Local bone + DBM | Titanium | Single level DDD, degenerative olisthesis and/or lateral stenosis | 73 | 36 m | NR +/- NR | NR +/- NR | 50 | 36 m | 94,50% (78,9-99,9%) | 2 |
| Rodgers BW et al 2012(22) | Prospective cohort study | XLIF | b-TCP and bone marrow aspirate | PEEK | SD, DDD, ASD, stenosis, lateral listhesis, degenerative scoliosis, disc herniation and post-laminectomy instability | 44 | 17,3 m | 50,9 +/- 15,2 | 33,1 +/- 19,1 | 17,8 | 12 m | 92,3% (92,9-100%) | 2 |

Table 3. Group B: Anterior approach with interbody fusion and BMP-2/BMP-7

| Study | Design | Surgical procedure | Graft | Cage | Indication | N° | F/U | ODI preop +/- SD | ODI postop +/- SD | ODI improvement | F/A | Fusion rate | CEBM |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Burkus JK et al. 2002 (13) | RCT | ALIF | BMP-2 (12-18mg) | Titanium | DDDL4-L5 or L5-S1 | 24 | 24 m | 52,4 +/- 13,1 | 18,9 +/- 14,5 | 33,5 | 24 m | 95,80% (78,9-99,9%) | 2 |
| Malham GM et al 2016(23) | Retrospective analysis | ALIF | BMP-2 (3,8mg) | PEEK | DDD, spondylolisthesis L4-L5 or L5-S1 (single level) | 50 | 24 m | 49,9 +/- 16 | 20,2 +/- 18,7 | 29,7 | 24 m | 100% (92,9-100%) | 3 |
| Malham GM et al 2016(23) | Retrospective analysis | LLIF | BMP-2 (4,8mg) | PEEK | DDD, spondylolistheses (single level) | 40 | 24 m | 53 +/- 13,2 | 25,6 +/- 17,6 | 27,4 | 24 m | 95% (83,1-99,4%) | 3 |
| Burkus JK et al 2002 (15) | RCT | ALIF | BMP-2 (4,2 – 8,4 mg) | Titanium | DDD (single level) | 143 | 24 m | 53,7 +/- NR | 23,9 +/- NR | 29,8 | 24 m | 94,5% (89,3-97,6%) | 2 |
| Burkus JK et al 2005 (16) | RCT | ALIF | BMP-2 (8,4 – 12 mg) | Titanium | DDD (single level) | 79 | 24 m | 53,7 +/- NR | 20,4 +/- NR | 33,3 | 24 m | 98,5% (93,1-100%) | 2 |
| Rao PJ et al 2015(24) | Prospective cohort study | ALIF | BMP-2 / BMP-7 | PEEK | Degenerative spondylolisthesis | 27 | 17 m | 56,9 +/- 21,7 | 17,8 +/- 16,2 | 39,1 | 17 m | 91% (75,7-99,1%) | 2 |
| Gornet M et al 2011(25) | RCT | ALIF | BMP-2 | Titanium | DDD | 172 | 24 m | 54,5 +/- 12,6 | 25,3 +/- 19,6 | 29,2 | 24 m | 98,8% (95,9-99,9%) | 2 |
| Boden SD et al 2000(9) | RCT | ALIF | BMP-2 (1,95 – 3,9 mg) | Titanium | DDD +/- spondylolisthesis (single level) | 11 | 24 m | 38,9 +/- 3,5 | 13,5 +/- 5,1 | 25,4 | 24 m | 100% (71,5-100%) | 1 |
| Slosar PJ et al 2007(20) | Prospective cohort study | ALIF | Femoral ring (allograft) + BMP-2 (3 mg) | No cage | DDD L3–S1, Grade I–II spondylolisthesis, or degenerative scoliosis | 45 | 24 m | 61,1 +/- NR | 28,5 +/- NR | 32,6 | 24 m | 100% (92,1-100%) | 2 |
| Malham GM et al 2014(26) | Prospective cohort study | ALIF with hybrid construct | BMP-2 (2,52-4,56 mg) | PEEK | Severe discogenic pain, radiculopathy and Grade 1 and 2 degenerative and isthmic spondylolisthesis L4-L5 and/or L5-S1 | 45 | 12 m | 54,9 +/- 13,6 | 28,9 +/- 16,3 | 26 | 12 m | 97,8% (91,3-98,7%) | 2 |
| Malham GM et al 2014(26) | Prospective cohort study | ALIF | BMP-2 (2,52 – 4,56 mg) | PEEK | Severe discogenic pain, radiculopathy and Grade 1 and 2 degenerative and isthmic spondylolisthesis L4-L5 and/or L5-S1 | 86 | 12 m | 49,7 +/- 16 | 23,1 +/- 19,7 | 26,6 | 12 m | 96,5% (65,1-95,6%) | 2 |
| Malham GM et al 2012(27) | Retrospective analysis | XLIF | BMP-2 (4,2 mg) | PEEK | DDD, disc herniation, spondylolisthesis, degenerative scoliosis | 26 | 11,5 m | 56,9 +/- NR | 33,5 +/- NR | 23,4 | 12 m | 84,6% (78,9-99,9%) | 3 |

Table 4. Group C: Posterior approach with interbody fusion and without BMP-2/BMP-7

| Study | Design | Surgical procedure | Graft | Cage | Indication | N° | F/U | ODI preop +/- SD | ODI postop +/- SD | ODI improvement | F/A | Fusion rate | CEBM |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Lee GW et al. 2015(28) | RCT | PLIF | DBM | PEEK | LSS, isthmic/degenerative spondylolisthesis L4-L5 or L5-S1 (single level) | 39 | 12 m | 36,5 +/- 10,1 | 11 +/- 2,5 | 25,5 | 12 m | 87,20% (72,6-95,7%) | 1 |
| Lee GW et al. 2015(28) | RCT | PLIF + CS | DBM | PEEK | LSS, isthmic/degenerative spondylolisthesis L4-L5 or L5-S1 (single level) | 38 | 12 m | 35,1 +/- 9,7 | 10,5 +/- 2,8 | 24,6 | 12 m | 92,10% (79,6-98,4%) | 1 |
| Xue H et al 2012(29) | RCT | TLIF + UPS | Local bone | PEEK + carbon fiber | Spinal stenosis with spondylolisthesis, spondylolisthesis, lumbar disc herniation, lumbar discogenic back pain L3-S1 | 37 | 18 m | 43,4 +/- 2 | 15,4 +/- 1,7 | 28 | 24 m | 91,90% (78,1-98,3%) | 1 |
| Xue H et al 2012(29) | RCT | TLIF | Local bone | PEEK | Spinal stenosis with spondylolisthesis, spondylolisthesis, lumbar disc herniation, lumbar discogenic back pain L3-S1 | 43 | 18 m | 45,1 +/- 2,6 | 15,8 +/- 0,9 | 29,3 | 24 m | 93% (80,9-98,5%) | 1 |
| Müslüman AM et al 2011(30) | RCT | PLIF | Local bone | Titanium | LBP +/- sciatica, neurogenic claudicatio | 25 | 40 m | 30,2 +/- 5,7 | 13,4 +/- 1,95 | 16,8 | 25 m | 100% (86,3-100%) | 2 |
| vonderHoeh NH et al 2017(31) | RCT | TLIF | ICBG | PEEK | DDD, spondylolisthesis L3-S1 | 25 | 12 m | 55.91 +/- NR | 34 +/- NR | 21,91 | 12 m | 95.3% (79,6-99,9%) | 2 |
| vonderHoeh NH et al 2017(31) | RCT | TLIF | Local bone + HA | PEEK | DDD, spondylolisthesis L3-S1 | 25 | 12 m | 57.04 +/- NR | 25.78 +/- NR | 31,26 | 12 m | 91.7% (74,0-99,0%) | 2 |
| Huang WM et al 2017 (32) | RCT | PLIF | Local bone | PEEK | Lumbar disc herniation, lumbar spinal stenosis, or lumbar degenerative spondylolisthesis L3-L4 or L4-L5 (single level) | 21 | 24 m | 43.3 +/- 8,2 | 21.4 +/- 3,5 | 21,9 | 24 m | 68.2% (43,0-85,4%) | 1 |
| Huang WM et al 2017 (32) | RCT | PLIF + ISF | Local bone | PEEK | Lumbar disc herniation, lumbar spinal stenosis, or lumbar degenerative spondylolisthesis L3-L4 or L4-L5 (single level) | 22 | 24 m | 42.9 +/- 7,9 | 22.5 +/- 3,8 | 20,4 | 24 m | 76.2% (54,6-92,2%) | 1 |
| Choi WS et al 2017 (33) | RCT | MIS-TLIF | Local bone | NR (Straight shapened) | Isthmic/degenerative spondylolisthesis, foraminal stenosis with central stenosis, DDD, recurred disc herniation | 40 | 12 m | 50,9 +/- NR | 16,6 +/- NR | 34,3 | 12 m | 96,6% (86,8-99,4%) | 2 |
| Choi WS et al 2017 (33) | RCT | MIS-TLIF | Local bone | NR (Banana-shaped) | Isthmic/degenerative spondylolisthesis, foraminal stenosis with central stenosis, DDD, recurred disc herniation | 44 | 12 m | 48,2 +/- NR | 16,5 +/- NR | 31,7 | 12 m | 95,2% (84,5-99,4%) | 2 |
| Liu F et al 2017 (34) | Retrospective analysis | TLIF + UPS | Local bone | PEEK | Spinal stenosis, degenerative spondylolisthesis, disc herniation and discogenic low back pain | 109 | 52 m | 48 +/- 16,2 | 5 +/- 3,8 | 43 | 12 m | 89,5% (82,7-94,9%) | 3 |
| Liu F et al 2017 (34) | Retrospective analysis | TLIF | Local bone | PEEK | Spinal stenosis, degenerative spondylolisthesis, disc herniation and discogenic low back pain | 106 | 52 m | 46,8 +/- 18,2 | 5,6 +/- 3 | 41,2 | 12 m | 93,1% (86,9-97,3%) | 3 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Deng QX et al 2016(35) | Retrospective analysis | TLIF | ICBG | PEEK | Degenerative/ isthmic spondylolisthesis, DDD, lumbar stenosis, lumbar disc herniation | 124 | 24 m | 51 +/- 6,47 | 14,61 +/- 4,08 | 36,39 | 24 m | 91,57% (85,7-96,1%) | 3 |
| Deng QX et al 2016(35) | Retrospective analysis | TLIF | ICBG | n-HA/ PA66 | Degenerative/ isthmic spondylolisthesis, DDD, lumbar stenosis, lumbar disc herniation | 142 | 24 m | 50,56 +/- 6,41 | 14,69 +/- 4,13 | 35,87 | 24 m | 92,45% (86,6-98,1%) | 3 |
| Liu F et al 2016(36) | Retrospective analysis | TLIF + UPS | NR (autologous) | PEEK | Severe spinal stenosis with or degenerative spondylolisthesis (two level) Spondylolisthesis with spinal stenosis or recurrent lumbar disc herniation (single level) | 22 | 46 m | 46,5 +/- 15,2 | 6,5 +/- 2,8 | 40 | 46 m | 81,8% (59,7-94,8%) | 3 |
| Liu F et al 2016(36) | Retrospective analysis | TLIF + UPS and CTFS | NR | PEEK | Severe spinal stenosis or degenerative spondylolisthesis (two level) Spondylolisthesis with spinal stenosis or recurrent lumbar disc herniation (single level) | 28 | 46 m | 48 +/- 18,1 | 5,2 +/- 3,1 | 42,8 | 46 m | 89,3% (71,8-97,7%) | 3 |
| Liu F et al 2016(36) | Retrospective analysis | TLIF | NR | PEEK | Severe spinal stenosis or degenerative spondylolisthesis (two level) Spondylolisthesis with spinal stenosis or recurrent lumbar disc herniation (single level) | 34 | 46 m | 47,3 +/- 17,4 | 5,6 +/- 3 | 41,7 | 46 m | 94,1% (80,3-99,3%) | 3 |
| Lv C et al 2015(37) | Retrospective analysis | TLIF | Local bone | PEEK | Lumbar spinal stenosis L4-L5 or L5-S1 (single level) | 84 | 43 m | 42 +/- NR | 21 +/- NR | 21 | 35 m | 94,05% (86,7-98,0%) | 3 |
| Lv C et al 2015(37) | Retrospective analysis | TLIF | Local bone (morselized) | No cage | Lumbar spinal stenosis L4-L5 or L5-S1 (single level) | 96 | 30 m | 45 +/- NR | 19 +/- NR | 26 | 35 m | 94,79% (88,3-98,3%) | 3 |
| Gu G et al 2015(38) | Prospective cohort study | MIS-TLIF + UPS | Local bone | PEEK | Two-level lumbar stenosis and one-level spondylolisthesis with spinal stenosis | 35 | 32 m | 44,51 +/- 5,03 | 17,10 +/- 1,48 | 27,41 | 32 m | 94,3% (80,8-99,3%) | 2 |
| Gu G et al 2015(38) | Prospective cohort study | MIS-TLIF | Local bone | PEEK | Two-level lumbar stenosis and one-level spondylolisthesis with spinal stenosis | 39 | 32 m | 45,13 +/- 4,42 | 16,92 +/- 1,11 | 28,21 | 32 m | 94,9% (82,7-99,4%) | 2 |
| Lee GW et al 2014(39) | Prospective cohort study | PLIF | Local bone + DBM | PEEK | Spondylolisthesis (single level) | 42 | 24 m | 38,9 +/- 9,1 | 9,0 +/- 1,6 | 29,9 | 24 m | 90,4% (86,8-99,9%) | 2 |
| Seng C et al 2013(12) | Retrospective analysis | TLIF | Local bone or ICBG | NR | DDD, spondylolisthesis (single level) | 40 | 60 m | 42,1 +/- 16,3 | 12,3 +/- 1,9 | 29,8 | 60 m | 97,5% (86,8-99,9%) | 3 |
| Seng C et al 2013(12) | Retrospective analysis | MIS-TLIF | Local bone +/- DBM or ICBG | NR | DDD, spondylolisthesis (single level) | 40 | 60 m | 41,3 +/- 20,1 | 13,6 +/- 1,8 | 27,7 | 60 m | 97,5% (75,7-98,1%) | 3 |
| Zhang K et al 2014 (40) | RCT | TLIF + unilateral pedicle screw | Local bone | PEEK | Severe spinal stenosis with DDD, spondylolisthesis with spinal stenosis or revision surgery | 33 | 24 m | 42,4 +/- 16 | 18,8 +/- 3,2 | 23,6 | 24 m | 90,91% (80,8-99,3%) | 1 |
| Zhang K et al 2014(40) | RCT | TLIF | ICBG | PEEK | Severe spinal stenosis with DDD, spondylolisthesis with spinal stenosis or revision surgery | 35 | 24 m | 44,3 +/- 18,4 | 17,9 +/- 7,6 | 26,4 | 24 m | 94,29% (86,8-99,9%) | 1 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Zairi F et al 2013(41) | Retrospective analysis | MIS-TLIF | / | / | DDD or degenerative spondylolisthesis | 40 | 24 m | 60 +/- NR | 30 +/- 2,8 | 30 | 12 m | 97,5% (91,1-100%) | 3 |
| Zairi F et al 2013(41) | Retrospective analysis | TLIF | / | / | DDD or degenerative spondylolisthesis | 60 | 24 m | 60 +/- NR | 33 +/- 1,9 | 27 | 12 m | 98,3% (81,7-99,9%) | 3 |
| Kim JS et al 2009(14) | Retrospective analysis | MIS-TLIF | / | / | Isthmic spondylolisthesis (single level) | 46 | 30 m | 52,0 +/- 22 | 14,4 +/- 15,9 | 37,6 | NR | 97,8% (88,5-99,9%) | 3 |
| Michielsen et al 2013 (42) | RCT | PLIF | ICBG | PEEK | Lytic/degenrative spondylolisthesis, DDD, disc herniation | 19 | 24 m | 35 +/- 10,5 | 7,1 +/- 10,5 | 27,9 | 12 m | 100% (82,4-100%) | 1 |
| Wang J et al 2014(43) | Prospective cohort study | MIS-TLIF | Local bone | PEEK | Spinal canal stenosis, spondylolisthesis, postlaminectomy instability L3-L4, L4-L5 or L5-S1 (single level) | 42 | 36,1 m | 41,1 +/- 10,3 | 18,2 +/- 5,9 | 22,9 | 12 m | 97,6% (86,5-99,9%) | 2 |
| Wang J et al 2014(43) | Prospective cohort study | TLIF | Local bone | PEEK | Spinal canal stenosis, spondylolisthesis, postlaminectomy instability L3-L4, L4-L5 or L5-S1 (single level) | 39 | 36,1 m | 40,2 +/- 9,6 | 17,4 +/- 7,1 | 22,8 | 12 m | 97,4% (86,7-96,1%) | 2 |
| Wong AP et al 2014(44) | Prospective cohort study | MIS-TLIF | Local bone + BMA | PEEK | Spondylolisthesis with stenosis, postlaminectomy instability with stenosis and DDD with stenosis | 144 | 45 m | 52,8 +/- NR | 26 +/- NR | 26,8 | 19,2 m | 92,5% (82,1-97,9%) | 2 |
| Wong AP et al 2014(44) | Prospective cohort study | TLIF | Local bone + BMA | PEEK | Spondylolisthesis with stenosis, postlaminectomy instability with stenosis and DDD with stenosis | 54 | 46 m | 51,2 +/- NR | 33 +/- NR | 18,2 | 19,2 m | 93,5% (81,3-98,6%) | 2 |
| Gu G et al 2014 (45) | Prospective cohort study | MIS-TLIF | Local bone | PEEK | Lumbar disc herniation with ASD, two-level lumbar stenosis , DDD | 44 | 24 m | 43,7 +/- 4,3 | 16,5 +/- 2 | 27,2 | 12 m | 93,2% (78,6-98,3%) | 2 |
| Gu G et al 2014 (45) | Prospective cohort study | TLIF | Local bone | PEEK | Lumbar disc herniation with ASD, two-level lumbar stenosis , DDD | 38 | 24 m | 44,3 +/- 5,2 | 15,9 +/- 1,9 | 28,4 | 12 m | 92,1% (65,1-95,6%) | 2 |
| Choi UY et al 2013 (46) | RCT | MIS-TLIF + UPS | / | / | Lumbar disc herniation, spinal stenosis, degenerative spondylolisthesis, | 26 | 24 m | 27,8 +/- NR | 6,6 +/- NR | 21,2 | 24 m | 84,6% (81,7-99,9%) | 2 |
| Choi UY et al 2013 (46) | RCT | MIS-TLIF | / | / | Lumbar disc herniation, spinal stenosis, degenerative spondylolisthesis, | 28 | 24 m | 27,9 +/- NR | 9,5 +/- NR | 18,4 | 24 m | 96,3% (61,1-91,0%) | 2 |
| Haid RW et al 2004 (47) | RCT | PLIF | ICBG | Titanium | Single level DDD | 33 | 24 m | NR | NR | 24,9 | 24 m | 78,80% (75,1-99,9%) | 2 |
| Cao Y et al 2015 (48) | RCT | TLIF + UPS and CTFS | Local bone | NR | DDD, spinal stenosis | 20 | 12 m | 29,5 +/- NR | 1,8 +/- NR | 27,7 | 12 m | 95% (83,2-100%) | 2 |
| Cao Y et al 2015 (48) | RCT | TLIF | Local bone | NR | DDD, spinal stenosis | 20 | 12 m | 24,8 +/- NR | 2,1 +/- NR | 22,7 | 12 m | 100% (75,1-99,9%) | 2 |
| Lee CK et al 2010 (49) | Retrospective analysis | MIS-TLIF | Local bone alone or + HA or + allograft | PEEK | Grade 1 spondylolisthesis, DDD | 20 | 12 m | 30,32 +/- NR | 15.44 +/- NR | 14,88 | 12 m | 92,8% (82,8-96,4%) | 3 |
| Wu Y et al 2011 (50) | RCT | PLIF | Local bone + ICBG | PEEK | Degenerative/isthmic spondylolisthesis, spinal stenosis | 80 | 43,2 m | 36,4 +/- NR | 16,2 +/- NR | 20,2 | NR | 91% (85,4-98,9%) | 2 |
| Kim KT et al 2006 (51) | RCT | PLIF | Local bone | Titanium | Degenerative/isthmic spondylolisthesis, spinal stenosis | 57 | 36 m | 59,4 +/- 8,7 | 22,6 +/- 11,2 | 36,8 | 36 m | 95% (77,4-97,3%) | 1 |

Table 5. Group D: Posterior approach with interbody fusion and BMP-2/BMP-7

| Study | Design | Surgical procedure | Graft | Cage | Indication | N° | F/U | ODI preop +/- SD | ODI postop +/- SD | ODI improvement | F/A | Fusion rate | CEBM |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dahdaleh NS et al 2013 (52) | RCT | MIS-TLIF + UPS | BMP-2 | / | Degenerative spondylosis or spondylolisthesis (single level) | 20 | 12 m | 37,4 +/- 9,2 | 22,7 +/- 17,3 | 14,7 | 12 m | 93,8% (75,1-99,9%) | 1 |
| Dahdaleh NS et al 2013 (52) | RCT | MIS-TLIF | BMP-2 | / | Degenerative spondylosis or spondylolisthesis (single level) | 21 | 12 m | 39,2 +/- 12 | 17,9 +/- 18,7 | 21,3 | 12 m | 95% (76,2-99,9%) | 1 |
| Michielsen et al 2013 (42) | RCT | PLIF | BMP-2 (8mg) | PEEK | Lytic/degenrative spondylolisthesis, DDD, disc herniation | 19 | 24 m | 34,5 +/- 10 | 7 +/- 6,1 | 27,5 | 12 m | 100% (82,4-100%) | 1 |
| Haid RW et al 2004 (47) | RCT | PLIF | BMP-2 (4-8 mg) | Titanium | Single level DDD | 34 | 24 m | NR | NR | 29,6 | 24 m | 92,30% (76,3-98,1%) | 2 |
| Rouben D et al 2011 (53) | Retrospective analysis | MIS-TLIF | BMP-2 + local bone | / | Lumbar disc herniation, foraminal/lateral/central stenosis, DDD, degenerative spondylolisthesis 2-level fusion | 45 | 49 m | 73 +/- 12 | 29 +/- 19 | 44 | 49 m | 96% (91,7-98,3%) | 3 |
| Rouben D et al 2011 (53) | Retrospective analysis | MIS-TLIF | BMP-2 + local bone | / | Lumbar disc herniation, foraminal/lateral/central stenosis, DDD, degenerative spondylolisthesis 1-level fusion | 124 | 49 m | 68 +/- 14 | 30 +/- 21 | 38 | 49 m | 96% (91,2-100%) | 3 |
| Park P et al 2008 (54) | Retrospective analysis | MIS-TLIF | BMP-2 + local bone | PEEK | Isthmic/degenerative spondylolisthesis | 40 | 24 m | 55 +/- NR | 16 +/- NR | 39 | 24 m | 100% (75,1-100%) | 3 |

Table 6. Group E: Posterior approach without interbody fusion and without BMP-2/BMP-7

| Study | Design | Surgical procedure | Graft | Indication | N° | F/U | ODI preop +/- SD | ODI postop +/- SD | ODI improvement | F/A | Fusion rate | CEBM |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dimar JR et al 2006 (55) | RCT | PLF | ICBG | DDD L2-S1 (single level) | 45 | 24 m | 52,4 +/- NR | 31 +/- NR | 21,4 | 24 m | 73% (58,1-85,4%) | 2 |
| Kang J et al 2012 (56) | RCT | PLF | ICBG | Spinal stenosis with degenerative spondylolisthesis (single level) | 13 | 24 m | 36 +/- NR | 22,7 +/- NR | 13,3 | 12 m | 92% (64,0-99,8%) | 2 |
| Kang J et al 2012 (56) | RCT | PLF | DBM | Spinal stenosis with degenerative spondylolisthesis (single level) | 28 | 24 m | 39 +/- NR | 16,2 +/- NR | 22,8 | 12 m | 86% (67,3-96,0%) | 2 |
| Müslüman AM et al 2011 (30) | RCT | PLF | ICBG | LBP +/- sciatica, neurogenic claudicatio | 25 | 40 m | 29,2 +/- 6,42 | 14,12 +/- 2,42 | 15,08 | 25 m | 84% (63,9-95,5%) | 2 |
| Dimar JR et al 2009 (10) | RCT | PLF | ICBG | Degenerative disease from L2-L3 to L5-S1 (single level) | 224 | 24 m | 15,8 +/- NR | 8 +/- 0,95 | 7,8 | 24 m | 96% (92,5-98,1%) | 2 |
| Ohtori S et al 2011(57) | Prospective cohort study | PLF | Local bone | Lumbar spondylolisthesis L4-S1 | 30 | 24 m | 30 +/- 11 | 16 +/- 6 | 14 | 24 m | 60% (40,6-77,3%) | 2 |
| Ohtori S et al 2011 (57) | Prospective cohort study | PLF | Unilateral local bone | Lumbar spondylolisthesis L4-S1 | 32 | 24 m | 39 +/- 19 | 13 +/- 4 | 26 | 24 m | 89% (71,0-96,5%) | 2 |
| Lee GW et al 2014 (39) | Prospective cohort study | PLF | Local bone + DBM | Spondylolisthesis (single level) | 39 | 24 m | 37,5 +/- 9,4 | 8,6 +/- 1,3 | 28,9 | 24 m | 89,7% (75,8-97,1%) | 2 |
| Kanayama M et al 2006(58) | RCT | PLF | ICBG | Degenerative spondylolisthesis L3-L4 or L4-L5 (single level) | 10 | 12 m | 39,1 +/- NR | 15 +/- NR | 24,1 | 12 m | 90% (84,2-99,4%) | 2 |
| Glassman SD et al 2008 (59) | RCT | PLF | ICBG | Spinal stenosis, spondylolisthesis, and adjacent level degeneration | 52 | 24 m | 47 +/- 16,8 | 34,2 +/- 15,5 | 12,8 | 24 m | 70,8% (55,5-99,7%) | 2 |
| Delawi et al 2010 (60) | RCT | PLF | ICBG | Degenerative or isthmic spondylolisthesis with central or foraminal stenosis | 16 | 12 m | 53 +/- 13 | 27 +/- NR | 26 | 12 m | 67% (41,3-89,0%) | 2 |
| Boden SD et al 2002 (61) | RCT | PLF | ICBG | Single-level DDD with G1 or less spondylolisthesis | 5 | 17 m | 54 +/- NR | 31 +/- NR | 23 | 24 m | 40% (5,3-85,3%) | 2 |
| Ohtori S et al 2011 (18) | Prospective cohort study | PLF | Local bone | Single level degenerative spondylolisthesis L4-L5 | 24 | 24 m | 54 +/- 10 | 20 +/- 7 | 34 | 24 m | 62,5% (40,6-81,2%) | 2 |
| Cho JH et al 2017 (11) | RCT | PLF | ICBG | Spinal stenosis, grade 1 spondylolisthesis, or spondylolysis | 51 | 6 m | 44,95 +/- NR | 24,52 +/- NR | 20,43 | 6 m | 94,10% (83,8-98,8%) | 2 |
| Hurlbert JR et al 2013 (62) | RCT | PLF | ICBG | DDD | 99 | 48 m | 52 +/- NR | 26 +/- NR | 26 | 24 m | 69% (58,6-77,6%) | 2 |
| Korovessis P et al 2012(21) | Prospective cohort study | PLF | Local bone + DBM | Single level DDD, degenerative olisthesis and/or lateral stenosis | 72 | 36 m | NR | NR | 39 | 36 m | 87,50% (77,6-94,1%) | 2 |
| Kotani Y et al 2012(63) | Prospective cohort study | MIS-PLF | ICBG | Single level lumbar degenerative spondylolisthesis with spinal stenosis | 43 | 24 m | 52 +/- 13,2 | 12 +/- NR | 40 | 24 m | 98% (87,7-99,9%) | 2 |
| Kotani Y et al 2012 (63) | Prospective cohort study | PLF | ICBG | Single level lumbar degenerative spondylolisthesis with spinal stenosis | 37 | 24 m | 48,9 +/- 10,8 | 38 +/- NR | 9,9 | 24 m | 100% (90,5-100,0%) | 2 |
| Wu Y et al 2011(50) | RCT | PLF | ICBG | Degenerative/isthmic spondylolisthesis, spinal stenosis | 82 | 41 m | 34,5 +/- NR | 14,2 +/- NR | 20,3 | NR | 88% (78,7-94,0%) | 2 |
| Kim KT et al 2006 (51) | RCT | PLF | Local bone + ICBG | Degenerative/isthmic spondylolisthesis, spinal stenosis | 62 | 36 m | 59,8 +/- 7,8 | 27,6 +/- 11,1 | 32,2 | 36 m | 92% (82,2-97,3%) | 1 |

Table 7. Group F: Posterior approach without interbody fusion and with BMP-2/BMP-7

| Study | Design | Surgical procedure | Graft | Indication | N° | F/U | ODI preop +/- SD | ODI postop +/- SD | ODI improvement | F/A | Fusion rate | CEBM |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dimar JR et al 2006 (55) | RCT | PLF | BMP-2 (20mg) | DDD L2-S1 (single level) | 53 | 24 m | 54,5 +/- NR | 30 +/- NR | 24,5 | 24 m | 88% (77,0-95,7%) | 2 |
| Dimar JR et al 2009 (10) | RCT | PLF | BMP-2 (40mg) | Degenerative disease from L2-L3 to L5-S1 (single level) | 239 | 24 m | 15,6 +/- NR | 8,5 +/- 0,9 | 7,1 | 24 m | 89% (84,5-92,8%) | 2 |
| Kanayama M et al 2006 (58) | RCT | PLF | BMP-7 | Degenerative spondylolisthesis L3-L4 or L4-L5 (single level) | 9 | 12 m | 36,1 +/- NR | 18,5 +/- NR | 17,6 | 12 m | 77,8% (40,0-97,2%) | 2 |
| Glassman SD et al 2008 (59) | RCT | PLF | BMP-2 | Spinal stenosis, spondylolisthesis, and adjacent level degeneration | 50 | 24 m | 49,9 +/- 12,9 | 34,6 +/- 17,7 | 15,3 | 24 m | 86,3% (73,3-94,2%) | 2 |
| Delawi et al 2010 (60) | RCT | PLF | BMP-7 | Degenerative or isthmic spondylolisthesis with central or foraminal stenosis | 18 | 12 m | 44 +/- 15 | 12 +/- NR | 32 | 12 m | 63% (35,7-82,7%) | 2 |
| Boden SD et al 2002 (61) | RCT | PLF | BMP-2 (40 mg) | Single-level DDD with G1 or less spondylolisthesis | 11 | 17 m | 48 +/- NR | 36,5 +/- NR | 11,5 | 24 m | 100% (71,5-100,0%) | 2 |
| Boden SD et al 2002 (61) | RCT | PLF | BMP-2 (40 mg) | Single-level DDD with G1 or less spondylolisthesis | 9 | 17 m | 39,7 +/- NR | 11 +/- NR | 28,7 | 24 m | 100% (66,4-100,0%) | 2 |
| Cho JH et al 2017 (11) | RCT | PLF | BMP-2 (6 mg) | Spinal stenosis, grade 1 spondylolisthesis, or spondylolysis | 41 | 6 m | 44,25 +/- NR | 26,31 +/- NR | 17,94 | 6 m | 100% (91,4-100,0%) | 2 |
| Hurlbert JR et al 2013 (62) | RCT | PLF | BMP-2 (42 or 63 mg) | DDD | 71 | 48 m | 52 +/- NR | 22 +/- NR | 30 | 24 m | 94% (86,2-98,4%) | 2 |
| Stambough J et al 2010 (64) | Prospective cohort study | PLF | BMP-2 (12 mg) + local bone | DDD, degenerative spondylolisthesis, or degenerative scoliosis | 36 | 28 m | 54 +/- NR | 14 +/- NR | 40 | 26,4 m | 97,20% (86,5-99,9%) | 2 |

*The average ODI score in each study group is given with standard deviation when reported. Fusion rates are given with their 95% confidence interval. CEBM = Oxford Centre for Evidence-Based Medicine quality score. ICBG = Iliac crest bone graft, DBM = dense bone matrix, HA = hydroxyappatite, BMA = bone marrow aspirate, UPS = unilateral pedicle screw, MIS = minimally invasive, ISF = interspinous fastener, CTFS = contralateral translaminar facet joint screw, CS = cortical screws, PEEK = polyetheretherketone, n-HA/PA66 = nano-hydroxyapatite/polyamide 66, RCT = randomized controlled trial, F/U = follow-up in months, F/A = fusion assessment in months, DDD = degenerative disc disease, LSS = lumbar spinal stenosis, NR = not reported, SD = standard deviation.*

Table 8. Weighted average results

| Group | Age (years) | N° of subjects | Follow up (months) | ODI preop | ODI postop | ODI improvement | Fusion assessment (months) | Fusion rate |
|---|---|---|---|---|---|---|---|---|
| A | 49,14 | 45 | 29,6 m | 48,4 | 20,7 | 33,9 | 24,6 m | 86,9% |
| B | 45,75 | 62 | 21,2 m | 53,6 | 23,9 | 29,6 | 21,2 m | 96,5% |
| C | 56,08 | 48 | 31,9 m | 45,3 | 16,2 | 28,9 | 22,9 m | 92,6% |
| D | 48,53 | 43 | 36,3 m | 60,0 | 24,3 | 35,1 | 35,6 m | 96,2% |
| E | 56,93 | 49 | 28,5 m | 38,9 | 18,9 | 21,2 | 23,9 m | 84,9% |
| F | 56,55 | 54 | 25,2 m | 34,6 | 17,5 | 21,4 | 22,2 m | 89,4% |

Oswestry Disability Index

At an average of 29.6 months, average ODI improvement in *group A* was 33.9. In *group B* this improvement was found to be 29.6 at an average of 21.2 months.

In *group C* the mean improvement was 28.9 points at a mean follow up of 31.9 months. Subjects in *group D* had the largest mean improvement of 35.1 points average at a 36.3 months follow up. *Group E and F* had the lowest clinical improvement, being 21.2 and 21.4 points at 28.5 and 25.2 months follow up, respectively.

*Group D* had the highest preoperative and postoperative ODI score (60.0 and 24.3). *Group C* had the lowest postoperative score (16.2). *Group F* had the lowest preoperative ODI score (34.6).

The highest reported preoperative ODI in individual studies was 73 (53), the lowest was 15.6 (10).

Of all 56 studies, 26 did not report standard deviations from the mean ODI score.

No study reported the ODI scores in 'successful fusion' groups versus 'failed fusion' groups.

See Appendix A for box plots on the ODI scores in each group.

Radiological fusion rate

Evaluation of fusion was performed at an average of 23.7 months. The studies that used CT scan to confirm fusion, defined it as the presence of bridging bony trabeculae on CT scan. In 12 studies, CT was used when radiography was inconclusive. Radiographic criteria for fusion were: Lenke criteria in 2 studies (30, 51). Bridwell's posterior fusion grades in 1 study.(45) Christensen classification in 1 study. (50) Bony trabecular continuity and <4° of mobility between the segments on flexion–extension radiographs in 5 studies (14, 19, 34, 36, 50). Absence of angulation on dynamic flexion-extension radiographs, evidence of bridging bone, and absence of hardware lucency or migration in 1 study.(52) Bony bridge in the anterior part of the cage, or less than 5° movement on lateral flexion and extension views, and the absence of radiolucencies around the cage and cage migration in 2 studies.(30, 51) The presence of trabeculation and bone bridging between cages and adjacent endplates, the absence of greater than 3 mm translational motion and more than 5° angular motion upon flexion/extension radiographs in the fused segments and the absence of a radiolucent gap between the cages and endplates in 1 study. (35) Formation of trabecular bony bridges between contiguous vertebral bodies at the instrumented levels in 1 study.(38)

In *group A* the mean fusion rate was 86.9%, assessed at an average of 24.6 months. The lowest fusion rate was 66.7% (9.4% - 99.2%)(9), the highest was 100% (89.1% - 100%)(19) (table 2,8).

In *group B* the mean fusion rate was the highest, being 96.5% assessed at an average of 21.2 months. The lowest fusion rate was 84.6% (65.1% – 95.6%)(27) and three studies (9, 20, 23) reported a fusion rate of 100% in a study group, with a lower confidence interval value of 92.9% ; 71.5% and 92.1%, respectively (table 3,8).

In *group C* the mean fusion rate was 92.6%, assessed at an average of 22.9 months. The lowest fusion rate was 68.2% (43.0%-85.4%)(32), and three studies reported a fusion rate of 100% in a study group, with a lower confidence interval value of 86.3% ; 82.4% ; 83.2% respectively(30, 42, 48) (Table 4,8).

In *group D* the mean fusion rate was 96.2%, assessed at the highest average of 35.6 months. The lowest fusion rate was 92.3% (76.3%-98.1%)(47) and two studies (42, 54) reported a fusion rate of 100% in a study group, with a lower confidence interval value of 82.4% and 91.2% respectively (table 5,8).

In *group E* the mean fusion rate was the lowest: 84.9%, assessed at an average of 23.9 months. The lowest fusion rate was 40.0% (5.3% - 85.3%) (61) although this group only held 5 subjects. One study(63) reported a fusion rate of 100% with a lower confidence interval value of 90.5% (table 6,8).

In *group F* the mean fusion rate was 89.4%, assessed at an average of 22.2 months. The lowest fusion rate was 61.1% (35.7% - 82.7%)(60) and two studies (11, 61) reported fusion rates of 100% in a study group with a lower confidence value of 91,4% and 71,5% respectively (table 7,8).

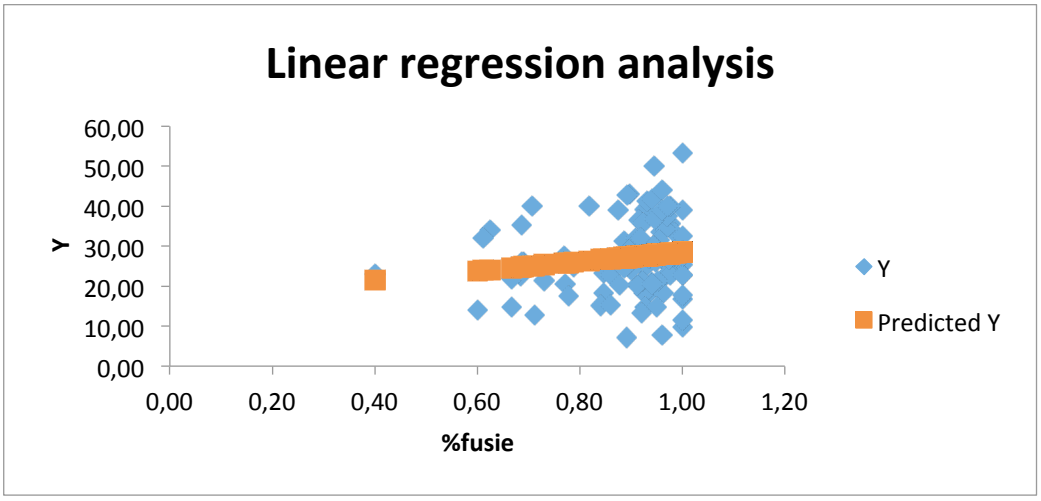
There were significant differences in fusion rates between studies within all groups, except for *group D* ($p < 0.05$).

Association of fusion rate with clinical improvement

We performed a bivariate linear regression analysis of ODI improvement with fusion rates for all groups combined (Figure 1) .

The null hypothesis is that successful fusion and clinical improvement do not show linear correlation. In other definitions: studies reporting higher fusion rates should report higher mean clinical improvement if association exists.

Figure 1. Bivariate linear regression analysis of mean ODI improvement and fusion rate.




*Y = Average ODI improvement for each study, Predicted Y value = Average ODI improvement when there is no fusion, X = fusion rate for each study.*

Predicted Y-value was 16,8. We found the slope to be 11,66, but p = 0,135. This means that when the null hypothesis is accepted, there is a chance of 13,5% that this value of slope can be found. This value is > 5%. Hence we cannot reject the null hypothesis.

**Secondary outcomes**

BMP-2

The used concentration of BMP-2 was reported in all studies but 8. (24, 25, 52-54, 58-60) The weighted average dose of BMP-2 was 18.05 mg. The highest used dosage was 63 mg (62), the lowest was 1.95 mg. (9) Regarding fusion rates for studies reporting their used dosage, we found a significant better fusion rate for two studies reporting doses of 3.8 mg and 1.95 – 3.9 mg, with fusion rates of 100% (92.9%-100%) and 97.8% (93.5%-100%) respectively(9, 23), compared to Dimar JR et al using 40 mg and reporting a fusion rate of 89.1% (84.5%-92.8%)(10) ($p<0.05$). Yet these studies used different techniques.

Cages

Fourteen studies used titanium cages, one used femoral ring allograft and one used n-HA/PA66. Forty-two studies used PEEK cages.

For the studies using titanium cages, we found a mean fusion rate of 91,7%. The studies using PEEK cages had a mean fusion rate of 91,0%.

Evidence quality

Most studies received score ’2’ when evidence quality was assessed. Only 7 studies were scored as evidence level ‘1’.

## DISCUSSION

Our goal was to search the literature to evaluate whether in lumbar arthrodesis it is necessary to obtain solid bone fusion to improve clinical outcomes in patients with degenerative pathology of the lumbar spine. The implanted hardware immobilizes the treated segments on short term. Solid bone bridging between the segments then ensures this fusion on long term.

Our review holds several strong elements.

We did not have to deal with heterogeneous clinical evaluation in patients because we only selected studies using the Oswestry Disability Index. The ODI is widely accepted as being an excellent tool for clinical use in low back pain. We did not only focus on improvement, but also on postoperative status to assess patient satisfaction. We did not distinguish between males and females in the various groups. It has been reported in studies that ODI scores are consistently higher in females, but other studies have not found this assumption.(65) Therefore, we did not make the difference.

We selected studies that used computed tomography as standard or as second opinion following radiography in case of uncertainty to evaluate fusion status. We did this because radiography alone tends to overestimate fusion and is therefore less reliable.(66)

Most individual studies consisted of small sample sizes. This often led to non-significant results because of a lack of power. Studies should exist of larger groups if they want to prove significant results. Our study involved a total of 5340 patients, which is undeniably a strong number that gives more reliable results.

We also critically reviewed and described the clinical and radiological assessment periods. It is, to our opinion, essential to provide a long follow up for more reliable results.

The mean ODI improvement was highest in *group D* with 35.1 points. The lowest was in *group E*, in which this was only 21.2 points. All six groups had an improvement of > 15 points, which was the minimum proposed by the FDA to be clinically relevant. (65) Groups using no interbody fusion tended to have lower mean clinical improvement.

The mean preoperative ODI scores had a remarkable difference, when considering the highest mean value (60.0) and the lowest mean value (34.6). These scores implicate that the included patients had a moderate to severe disability. Therefore, we can give no recommendations for crippled (score 61-80) or bed-bound (score 81-100) patients.

An important consideration is when a patient can be classified as a ‘responder’, meaning that after surgery he is satisfied and has a normal function. Recently, van Hooff et al suggested in their cross-sectional study of 1288 patients that a fair postoperative ODI score cut-off for patient true satisfaction is < 22. Similar results were reported in previous studies.(67) When considering our data, *group B and D* did not reach this value with their average postoperative scores. The other groups’ mean postoperative scores were below this cut-off, but statistical significance is to be shown.

We concluded that in each group, a clinically relevant ODI improvement was obtained. But we questioned true satisfaction in all groups. However, we acknowledge that satisfaction is subjective and very individual, with many confounders. It is impossible to generalize the cut-off for all included patients.

There were large differences in fusion rates between groups, but all groups had high fusion rates ranging from 84.9% (*group E*) to 96.5% (*group B*). There were significant differences in fusion rates between individual studies at a 95% confidence level. When compared to their control groups, groups using BMP-2 instead of other bone grafts tended to have higher fusion rates. There was no dose-related effect on fusion rates.

Earlier fusion with BMP-2 was reported by Slosar PJ et al at 6 months and clinical improvement was larger as well at this time.(20) Earlier fusion is important, especially in osteoporosis where implanted material can loosen more easily. (11) Secondly, when association between fusion and clinical improvement is shown, this could lead to a quicker alleviation of pain and therefore a quicker activation.

When comparing titanium cages with PEEK cages, we found similar fusion rates of 91,7% and 91,0%, respectively. Seaman S et al also reported similar fusion rates between these two cages as well, but fusion rates were lower. They also showed increased subsidence with titanium cages.(68)

We concluded that overall, fusion success is relatively high for all techniques. But we find it questionable that there is a direct association of solid fusion with a better clinical improvement. This is also shown in our bivariate analysis (Figure 1). Clinical results can be less than expected or unpredictable. But why are successful fusions not always clinically superior to failed fusions?

First, follow-up can be too short, which means that it is hard to clinically distinguish failed fusions because pseudarthrosis is often asymptomatic in early stages. On the other hand, successfully fused patients can still have painful back structures in early and prolonged stages because of surgical dissection and manipulation. The indication that led to surgery could have been an incidental finding that was expected to be the cause of pain, but was not in reality. Or there could have been more factors causing the patients' symptoms. It could also be that imaging of fusion is too strict, and patients suspected of failed fusion are actually to be considered as successfully fused.(62) Last, we should not forget the effect of yellow flags in a subdivision of patients.

Average follow-up was 29.1 months. It has been stated that ODI evaluation should be performed up until 24 months with a possibility of re-evaluation at 5 years. (65) This limit of 24 months was not reached by *group B*. In some studies, there were also large differences in follow-up duration between patients. The difference in follow-up duration of patients in the same study group could go up to 2 years. This can give a false representation of the clinical function, given that the last ODI score in the follow-up is included in the weighted average of these studies, but also in ours. To our opinion, clinical follow-up should be continued as long

as possible. However, we acknowledge that a re-evaluation at 5 years is not easy to accomplish, with high risk of drop-outs and high financial costs.

Undeniably, a short follow-up period has two important pitfalls.

Adjacent segment degeneration and disease is a disappointing long-term outcome that is known to be associated with invasive surgery of the spine. It is caused by a change in spine biomechanics. When 2 lumbar vertebrae are fused, there will only be 4 moving segments, so intradiscal pressure adjacent to the fusion level will rise. This pressure increases when even more segments are fused. Secondly, after fusion there is a disruption in stabilizing soft tissue anatomy adjacent to the fusion site. Postoperative sagittal malalignment and increased pelvic incidence are major stress factors.(69) Studies have reported 10-year prevalence of 14% to 36.1% in developing adjacent segment disease, with an estimated incidence of 2 to 4% on a year's basis.(70, 71)

Pseudarthrosis, an important cause of revision surgery, is often asymptomatic in early stages. The site of non-union is covered in fibrous tissue, stabilizing the area and preventing this site from being symptomatic.(72) However, in later stages it can become symptomatic. One proposed theory by Hegeness et al(73) is that in time the adjacent areas will become sclerotic with poor quality bone structure, pre-existing for microtrabecular fractures, causing pain. Another theory, stated by Hurlbert et al, is that the implanted hardware actually inhibits painful movement in the pseudartrotic site.(62) The economical and psychological costs of revision surgery for pseudartrosis should not be forgotten.

As these processes occur over time, the clinical status would be a more reliable representation of the reality when follow-up is prolonged.

Indications for surgery differed between studies, but in most studies there were also several possible diagnoses for surgery. Different threshold for surgery is reflected in the fact that the highest mean preoperative ODI was 73 (53), compared to the lowest being 15.6 (10).

Conversely, there was an important difference in contra-indications for inclusion. The most frequent contra-indications proposed for inclusion, relevant to our inclusion criteria, were osteoporosis, revision surgery, smoking, diabetes and the need for multilevel fusion. This causes an important heterogeneity in the proposed indications for surgery and in possible postoperative outcomes. Smoking, osteoporosis and diabetes are known to affect bone healing and thus negatively affect fusion. Multilevel fusion, as previously described, is at higher risk for adjacent segment disease and thus lower clinical improvement at long term. Revision surgery for pseudarthrosis has reported fusion successes of 40 to 100%, but clinical results were disappointing for both patients and surgeons.(74-77) In the retrospective analysis of Owens RK et al, the mean ODI improvement after revision for pseudarthrosis was only 9.71 points. Unfortunately fusion rate was not described (78).

Our review was one of the first to search the association between higher fusion rates and an improved clinical outcome. However, previous studies have already reported their findings concerning this subject.

Burkus JK et al(16) found a significantly higher fusion rate in the intervention group undergoing ALIF with BMP-2 than the control group receiving ICBG, but a significantly better improvement in ODI could not be shown.

This was also found by Slosar PJ et al, but they used allograft femoral rings instead of titanium cages.(20)

In their RCT with 197 subjects and an average follow up of 4 years, Hurlbert JR (62) et al found significant higher fusion rates in a PLIF procedure with BMP-2 compared to the control group that received ICBG. However, the two groups had similar clinical improvement.

Conversely, in the RCT of Dimar JR et al (55), the group receiving ICBG had significant higher fusion grades at 24 months follow up, but there was again no significant difference in clinical function compared to the BMP-2 group. Three years later, the new RCT of Dimar JR et al (10) with 463 subjects found significantly higher fusion rates for the BMP-2 group, with again no significant difference in clinical outcome.

In their meta-analysis of 19 RCT's, Zhang H et al found a significantly higher fusion rate in techniques using BMP-2 than those using BMP-7 or ICBG.(79) Clinical outcome did not differ significantly.

Umeta RS et al found a significant higher fusion rate in techniques using interbody fusion (ALIF, PLIF) when compared to PLF. Yet, there was no significant difference in ODI scores. (80)

Xie L et al found that in the minimally invasive TLIF group, postoperative ODI score was significantly lower than the open TLIF group with no differences in preoperative scores. But the two groups showed similar fusion rates.(8)

In contrast, Burkus JK et al showed in their study in 2002 that an ALIF with BMP-2 yielded a significant better fusion rate and clinical improvement when compared to ALIF with ICBG.(13)

We conclude that most studies cannot find association between fusion success and clinical improvement.

This review has limitations.

Because heterogeneity was large and standard deviations were often not reported , meta-analysis of the results was not performed and conclusions were drawn solely from weighted averages and a descriptive bivariate analysis. Future studies should focus on reporting more than only the mean scores, as this gives no representation of the spread of outcomes.

We did not distinguish for bias in the included studies.

We did not differentiate studies within groups for modified techniques. We did not differentiate for exact indication and contraindication. We acknowledge that they all influence the final outcome. However, extreme selection criteria are not feasible in this subject.

We studied the effect of fusion, but we did not study other important radiological characteristics that are important to assess after fusion, such as disc height, facet angle, sagittal balance or pelvic incidence angle.

The most important limitation is that we could not distinguish the ODI scores from failed fusions versus successful fusions. These subjects are always held in one group according to technique, and their clinical scores are described in the same means. If clinicians would want to study the true effect of solid fusion on clinical improvement, large multi-centre studies should be conducted with more homogenous indications. Reporting of results should be more than only weighted means. Successful versus failed fusions should be described in separate cohorts.

## CONCLUSION

In all groups we found a mean ODI improvement of clinical relevance, with the greatest improvement seen in posterior approaches with interbody fusion and BMP-2 or BMP-7. We confirm that when indications are correct, lumbar arthrodesis can offer satisfying clinical benefit.

We also found that fusion rates were high with all techniques, but differences were large. Use of BMP-2 tended to result in higher fusion rates. Although no superiority of one technique could be shown.

However, studies were often small, heterogeneous, lacked important data and did not distinguish successful and failed fusions in their reporting. Beside this, there are many factors influencing fusion success and clinical outcome. Therefore, we could not show association of solid fusion with higher clinical improvement. Future studies should focus on quality, consistent follow up, larger sample sizes and adequate reporting of results. Most importantly they should clinically distinguish patients in whom solid fusion is reached versus subjects in whom fusion failed.

## FUNDING

None

## CONFLICT OF INTEREST

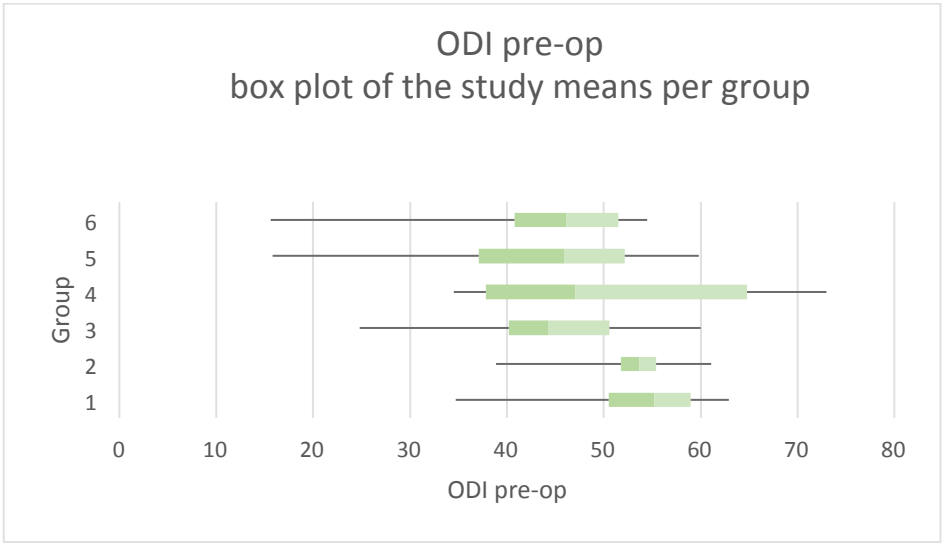
None

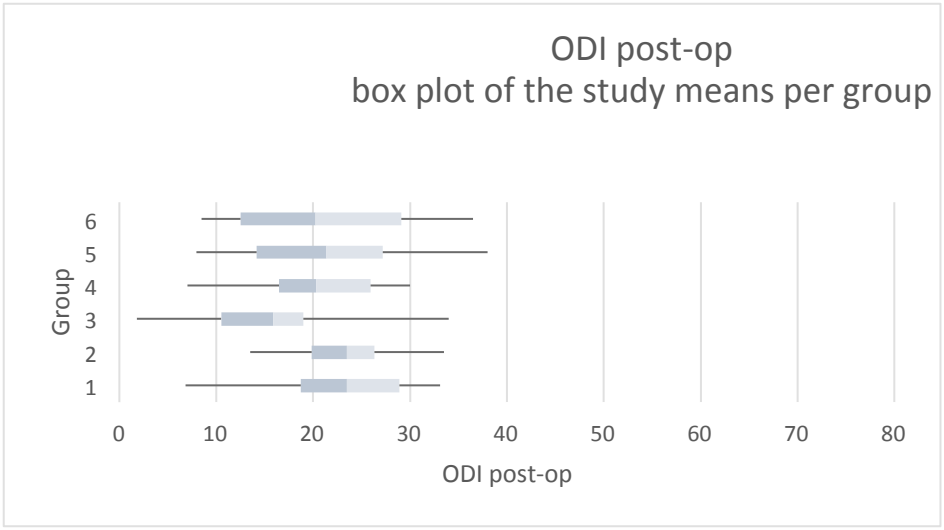
## FINANCIAL DISCLOSURE

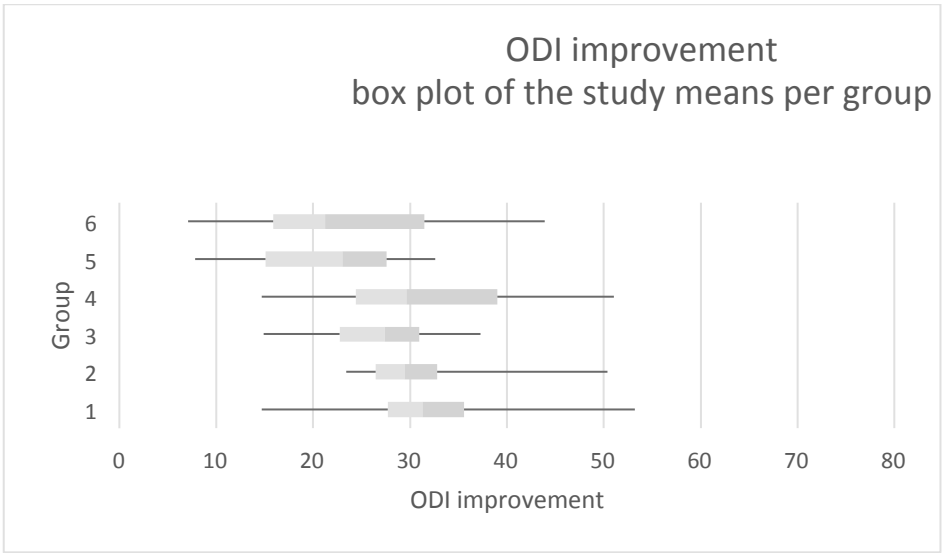
None

# APPENDICES

## Appendix A




*Group 1 to 6 = Group A-F in the same order.*

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