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Systematic Review

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Poor Bone Quality, Multilevel Surgery, and Narrow and Tall Cages Are Associated with Intraoperative Endplate Injuries and Late-onset Cage Subsidence in Lateral Lumbar Interbody Fusion: A Systematic Review

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Abstract

Background A major complication of lateral lumbar interbody fusion (LLIF) is cage subsidence, which may lead to clinical problems, including loss of disc height correction, altered spinal alignment, recurrent pain, and vertebral body fracture. A thorough review of the current knowledge about the risk factors for the two types of cage subsidence after LLIF—intraoperative endplate injury and late-onset cage subsidence—could bring attention to well-established risk factors for clinical consideration while identifying any incompletely characterized factors that require further research to clarify.

Questions/purposes We performed a systematic review to answer the following questions: (1) Are bone quality and surrogates for bone quality, such as patient age and sex, associated with an increased likelihood of cage subsidence? (2) Are implant-related factors associated with an increased likelihood of cage subsidence?

Methods Two independent reviewers comprehensively searched Medline, Embase, Cochrane Library, PubMed, and Web of Science from 1997 to 2020 to identify all potential risk factors for cage subsidence after LLIF. Discrepancies were settled through discussion during full-text screening. Search terms included "lateral" AND "interbody fusion" AND "subsidence" OR "settling" OR "endplate injury" OR "endplate violation" WITHOUT "cervical" OR "transforaminal" OR "biomechanical." Eligible studies were retrospective or prospective comparative studies, randomized controlled trials, and case series with sample sizes of 10 patients or more reporting risk factors for cage subsidence or endplate injury after LLIF. Studies that involved cervical interbody fusions and biomechanical and cadaveric experiments were excluded. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to assess the studies' quality of evidence. The initial database review found 400 articles. Thirty-four articles with moderate- to very-low-quality evidence met the inclusion criteria for analysis. A total of 3233 patients (58% [1860] of whom were female) were included in this review.

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Two types of cage subsidence were reviewed: late-onset cage subsidence, which occurs gradually postoperatively, and intraoperative endplate injury, which is derived from iatrogenic endplate violation during endplate preparation or cage insertion. Among 20 studies with moderate quality of evidence according to the GRADE criteria, eight studies reported risk factors for cage subsidence related to bone mineral density and its surrogates and 12 studies focused on risk factors regarding implant factors, including cage dimension, cage material, construct length, and supplementary instrumentation.

Results Patients with a dual x-ray absorptiometry T-score of -1.0 or less, age older than 65 years, and female sex were considered to have a high risk of both types of cage subsidence. Regarding cage size, cage width ≥ 22 mm helped to avoid late-onset cage subsidence, and cage height ≤ 11 mm was recommended by some studies to avoid intraoperative endplate injuries. Studies recommended that multilevel LLIF should be conducted with extra caution because of a high risk of losing the effect of indirect decompression. Studies found that standalone LLIF might be sufficient for patients without osteoporosis or obesity, and supplementary instrumentation should be considered to maintain the postoperative disc height and prevent subsidence progression in patients with multiple risk factors. The effect of the bone graft, cage material, endplate condition, and supplementary instrumentation on cage subsidence remained vague or controversial.

Conclusion Patients with poor bone density, patients who are older than 65 years, and female patients should be counseled about their high risk of developing cage subsidence. Surgeons should avoid narrow cages when performing LLIF to minimize the risk of late-onset cage subsidence, while being cautious of an aggressive attempt to restore disc height with a tall cage as it may lead to intraoperative endplate injury. For multilevel constructs, direct decompression approaches, such as posterior and transforaminal LIF, should be considered before LLIF, since the effect of indirect decompression may be difficult to maintain in multilevel LLIF because of high risks of cage subsidence. The effect of the cage material and supplementary instrumentation require stronger evidence from prospectively designed studies with larger sample size that randomly assign patients to polyetheretherketone (PEEK) or titanium cages and different fixation types. Future research on intraoperative endplate injuries should focus on the specific timing of when endplate violation occurs with the help of intraoperative imaging so that attempts can be made to minimize its occurrence.

Level of Evidence Level IV, therapeutic study.

Introduction

Lumbar interbody fusion (LIF) is an established surgical procedure that treats various spinal pathologic conditions, including degenerative disc disease, spinal deformities, trauma, infections, and neoplasia [14, 28]. LIF involves the insertion of a rigid intervertebral fusion cage in the intervertebral space after discectomy and endplate preparation to restore disc height and motion segment stability. The general microsurgical approach to lateral LIF (LLIF) was first described in 1997 [26]. Since then, variants of the LLIF procedure, including direct, extreme, and oblique LIF, have been reported [17, 32, 39]. LLIF is seeing wider use, with proposed advantages, including indirect neurologic decompression with less tissue trauma, minimal blood loss, and shorter operation times [20]. The lateral approach preserves the stabilizing ligaments and places them under tension, which may lead to improved biomechanical stability of the spinal segment [24]. In addition, in LLIF, an implant with a large footprint can be placed laterally to span the lateral borders of the ring apophysis, maximizing its contact with the cortical endplate and aiding in correcting the disc height for effective indirect decompression [25].

Cage subsidence is a major complication of LLIF. It may lead to compromised clinical results, such as a loss of disc height correction, alterations in spinal alignment, recurrent pain, and vertebral body fracture [34, 40, 41]. Subsequent progressive deformity and compression of the neural elements can lead to a reduced chance of successful fusion and possible revision surgery [20]. Subsidence is particularly concerning after LLIF because this technique relies on indirect decompression of the neural elements [24]. Two types of cage subsidence have been reported: late-onset cage subsidence, which occurs gradually postoperatively, and intraoperative endplate injury, which is derived from iatrogenic endplate violation during endplate preparation or cage insertion [37]. However, only a few studies have separately analyzed these two types of cage subsidence [15, 24, 36, 42]. A thorough review of the current knowledge about cage subsidence after LLIF could bring attention to any well-established risk factors for clinical consideration while identifying any incompletely characterized factors that need further research. Understanding the potential risk factors for these complications allows surgeons to better plan their surgeries. Preoperative planning of lumbar deformity correction using interbody cages can maximize outcomes and reduce complications [8, 47].

In this systematic review, we therefore asked: (1) Are bone quality and surrogates for bone quality, such as patient age and sex, associated with an increased likelihood of cage subsidence? (2) Are implant-related factors associated with an increased likelihood of cage subsidence?

Materials and Methods

Search Strategy

This systematic review followed the principles outlined in the Preferred Reporting Items for Systematic reviews and Meta-analyses guidelines. The databases included Medline, Embase, Cochrane Library, PubMed, and Web of Science. All databases were accessed through the University of Hong Kong libraries. Eligible articles were published from 1997 to 2020. In these databases, we searched for titles, abstracts, and keywords using key search items including "lateral" AND "interbody fusion" AND "subsidence" OR "settling" OR "endplate injury" OR "endplate violation" WITHOUT "cervical" OR "transforaminal" OR "biomechanical." The results of each database search were cross-checked by two independent investigators (HW, ZS). The abstracts of potentially relevant articles were screened based on the inclusion criteria, and full-text articles were obtained for eligible studies. Two researchers (HW, ZS) discussed any disagreements regarding accepting full-text articles until consensus was achieved. The references of each included article were reviewed for any other pertinent articles. Disagreements over inclusion were discussed and, where possible, resolved by consensus after referring to the inclusion and exclusion criteria and relevant theoretical and empirical issues.

Inclusion Criteria

Eligible studies were retrospective or prospective comparative studies, randomized controlled trials, nonrandomized trials, and case series with sample sizes of 10 patients or more reporting risk factors for cage subsidence or endplate injury after LLIF. Studies must have targeted conditions such as degenerative disc disorders, adjacent segment disease, Grade 1 or 2 spondylolisthesis, and degenerative scoliosis using anterolateral approaches such as LLIF and direct, extreme, and oblique LIF.

Exclusion Criteria

Studies that involved cervical interbody fusions, biomechanical or cadaveric studies, non-English-language studies, case reports, studies that involved tumor or trauma, and studies that involved spine fractures and corpectomy were excluded.

Search Results

The initial search yielded 400 articles: 110 from PubMed, six from Cochrane library, 58 from Medline, 126 from Embase, and 100 from Web of Science (Fig. 1). After duplicate records were removed, 183 studies were available for title and abstract screening. After the abstract screening, we excluded studies that were nonhuman or cadaveric studies, case reports, and studies examining intervertebral devices for corpectomy. Eighty-eight full-text articles that did not mention risk factors for cage subsidence were excluded. Thirty-four articles met the inclusion criteria and were included. There were 28 retrospective studies, five prospective studies, and one randomized controlled trial. A total of 3233 patients (of whom 58% [1860] were women) were included in this review. In all, 1617 patients underwent an LLIF procedure, 550 patients underwent an extreme LIF procedure, 376 patients underwent a direct LIF procedure, and 690 patients underwent an oblique LIF procedure. Two types of cage subsidence were recorded in this review: late-onset cage subsidence, which occurs gradually postoperatively, and intraoperative endplate injury, which is derived from iatrogenic endplate violation during endplate preparation or cage insertion.

Subsidence Criteria and Definition

We identified four main classifications for cage subsidence. (1) Sixteen studies applied the criteria reported by Marchi et al. [1, 2, 5-7, 22, 23, 25, 30, 31, 33, 34, 40, 41, 43, 45], who classified cage subsidence into four grades based on the amount of cage subsidence in the vertebral endplates on radiographs: Grade 0, 0% to 24% collapse of the level; Grade I, 25% to 49%; Grade II, 50% to 74%; and Grade III, 75% to 100%. According to Marchi's criteria [25], Grades 0 and I were considered low-grade and mild subsidence, respectively, while Grades II and III were considered high-grade and severe subsidence, respectively. (2) Ten studies defined cage subsidence as disc space loss more than a specific distance on a postoperative radiograph or CT image [4, 9, 10, 12, 13, 15, 21, 36, 37, 42]. Disc space loss of 1 mm, 2 mm, 3 mm, and 4 mm was applied to evaluate cage subsidence in a specific cohort. (3) Five studies defined cage subsidence as any compromise or discontinuity of either endplate at the index level on postoperative radiographs [16, 20, 24, 38, 44]. (4) Three studies directly reported the quantitative difference between postoperative and follow-up disc height on radiographs as the distance of cage subsidence [18, 19, 35].

Data Extraction and Quality Assessment

The main operative parameters extracted from the studies included the type of surgery (LLIF or direct, extreme, or oblique LIF), instrumentation, cage size and material, and

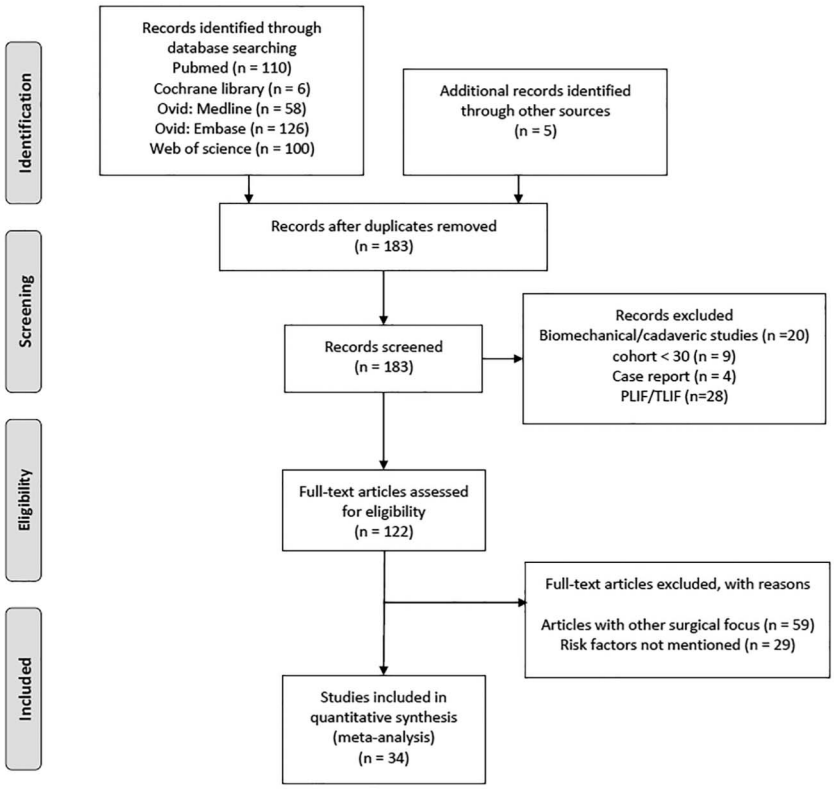

Fig. 1 Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) flowchart shows the selection process of studies included in the systematic review.

whether a bone graft was applied. The main outcomes extracted from the studies included the type of cage subsidence (intraoperative endplate injury or late-onset cage subsidence), the incidence and risk of cage subsidence, and reoperation rate. Details regarding each study's sample size, mean age of the participants, radiologic definition of cage subsidence, years of follow-up, indication for reoperation, and surgical outcomes and their complications were recorded, if the studies reported them. The risk factors identified in studies were classified into one of two categories: bone quality and its surrogates or implant factors, including cage size, construct length, cage material, cage position, and supplementary instrumentation.

The quality of included studies was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach [3, 11]. Randomized controlled trials were given a high quality of evidence, and observational studies and case series were given a low and very low quality of evidence, respectively. The quality of evidence was downgraded by one level according to the following criteria: inconsistency of results, imprecision of data, high probability of reporting bias, and limitation to study design. The quality of evidence was upgraded by one level if there was strong evidence of an association between independent variables and outcomes and evidence of a dose-response gradient.

Primary and Secondary Study Outcomes

Our primary study goal was to evaluate the role of bone quality and its surrogates in cage subsidence after LLIF surgery. To achieve this, we first summarized the findings from six studies that reported low bone quality as a risk factor for intraoperative endplate injury or late-onset cage subsidence. Secondly, we reviewed 10 studies that reported female sex, advanced age, smoking, and BMI as risk factors for cage subsidence as well as three studies that examined preoperative endplate conditions.

Our secondary study goal was to review implant-related risk factors for intraoperative endplate injury or late-onset cage subsidence after LLIF. To evaluate the impact of cage size, we summarized the findings from seven studies that focused on cage width and five studies that reported cage height as a risk factor for cage subsidence. Three studies that reported the association between construct length and cage subsidence were then discussed. In addition, the findings from three studies that discussed cage material and two studies that compared cage position were reviewed. Lastly, we included eight studies that compared different types of supplementary instrumentation in LLIF surgery.

There is some overlap between the primary and secondary outcomes because many included studies reported

on multiple risk factors, some of which were included in the primary outcome and some of which were included in the secondary outcome.

Results

Association of Bone Quality and its Surrogates with Cage Subsidence

Poor bone quality was one of the most frequently reported risk factors for cage subsidence (Table 1). Six studies reported that reduced bone quality or osteoporosis measured by dual-energy x-ray absorptiometry (DEXA) facilitates cage subsidence [1, 13, 31, 35, 37, 40]. In two studies, a lower mean DEXA T-score correlated with a higher incidence of late-onset cage subsidence (mean ± SD not reported, $p = 0.006$; and -1.65 ± 1.04 versus -0.45 ± -0.97; $p < 0.01$) [1, 40], and other authors [36] noted a lower T-score in patients with endplate injuries (-1.7 ± 0.2 versus -0.8 ± 0.1; $p = 0.02$). Based on a receiver operating characteristic curve analysis, Tempel et al. [40] reported that the sensitivity and specificity of a DEXA T-score of -1.0 or less for predicting late-onset graft subsidence were 78.3% and 63.2%, respectively, with an area under the curve of 80.1%. On the other hand, Satake et al. [36] reported a sensitivity of 83.9% and specificity of 58.3% in a receiver operating characteristic curve analysis using -1.0 SD of the T-score as a cutoff value of bone mineral density to predict intraoperative endplate injuries. In addition, two studies assessed bone quality using tools related to CT and reported an association between bone quality and late-onset cage subsidence [31, 45]. Okano et al. [31] used quantitative CT to measure endplate volumetric bone mineral density and reported that endplate-volumetric bone mineral density was lower in the group with severe subsidence than in the nonsevere subsidence group (median [interquartile range] 233.5 mg/cm^3 (193.4 to 273.3) versus 257.4 mg/cm^3 (216.3 to 299.4); $p = 0.026$). In addition, Xi et al. [45] reported that low segmental Hounsfield units (HUs) values of the lumbar spine were associated with late-onset cage subsidence (OR 15.694 [95% confidence interval 1.621 to 151.961]; $p = 0.017$). These authors reported a threshold of 135.02 HUs, with sensitivity of 60%, specificity of 92.3%, and area under the curve of 0.81 (95% CI 0.684 to 0.936), after using a receiver operating characteristic curve to establish criteria to separate mild (Grades 0 and I) and severe subsidence (Grades II and III) [45].

Surrogate measures of bone quality such as demographic factors and the preoperative condition of the endplate were examined as potential risk factors for cage subsidence (Table 1). Advanced age (older than 65 years) was a risk factor for late-onset cage subsidence in six studies because of its strong correlation with low bone quality and compromised endplate strength [5, 6, 9, 18, 25, 34]. Based on their findings, age older than 65 years may be associated with elevated risk of cage subsidence. Female sex seemed to be another risk factor for intraoperative endplate injury and late-onset cage subsidence [7, 25, 37]. Based on three studies that reported female sex as a risk factor, the risk of cage subsidence of female patients reached 32% (64 of 200), and male patients had a subsidence risk of 5.9% (8 of 134) [7, 25, 37]. Additionally, smoking and high BMI were potential risk factors for cage subsidence [7, 9, 24]. The endplate's preoperative condition was examined in three studies as potential risk factors for late-onset cage subsidence [9, 22, 30]. Some authors found that vertebral endplate lesions might lessen the mechanical strength or biological properties of the subchondral trabecular bone and subsequently affect the radiologic outcome of LIF [9]. However, these authors reported that most of the radiologic parameters at the last follow-up examination and the cage subsidence risks were not different, regardless of vertebral endplate lesions. By contrast, one study examined the influence of endplate sclerosis associated with Modic changes on late-onset cage subsidence and found that the cage subsidence risk in the nonsclerotic group was higher than that in the sclerotic group (11.1% [7 of 63] of levels versus 0% [0 of 15] of levels; $p < 0.01$) [22]. Similarly, another study reported that the presence of Type 2 Modic changes was associated with a lower risk of severe subsidence (OR 0.28 [95% CI 0.09 to 0.88]; $p = 0.029$) [30].

Association of Implant-Related Factors with Cage Subsidence

Cage size was the most mentioned implant-related risk factor for cage subsidence (Table 2). Low cage width seemed to be a crucial risk factor for cage subsidence, especially late-onset subsidence that occurred during the follow-up period. Seven studies compared the subsidence risk between patients in whom cages with different widths were used, and most authors reported less subsidence in groups with wider cages [1, 15, 18-20, 25, 42]. Specifically, 22-mm- and 26-mm-wide cages showed less cage subsidence than 18-mm cages, a standard width used in LLIF [1, 15, 19, 20, 25, 42]. In addition to cage width, implant height could play a role in intraoperative endplate injuries because aggressive cage insertion could result in perioperative complications [44]. Five studies reported that taller cages were more likely to have cage subsidence [16, 18, 37, 38, 42]. One study [37] found there were taller cages in the injury group than in the no-injury group (10.3 ± 0.3 mm versus 9.7 ± 0.1; $p = 0.03$), with the incidence of endplate injury increasing linearly as cage height

Table 1. Summary of studies that reported patients' bone quality and its surrogates as risk factors for cage subsidence

References	Study population	Study design	Evidence quality (as assessed by GRADE)	Type of subsidence	Risk of subsidence	Subsidence definition	Risk factors for cage subsidence reported in the study	Other findings related to subsidence	Bone graft used in the surgery	Percentage of fusion	Percentage of patients undergoing reoperation
Marchi et al. [25]	46 patients (61 lumbar levels) underwent LLIF with 18-mm interbody cages; 28 patients (37 lumbar levels) underwent treatment with 22-mm-wide cages	Retrospective comparative study	Low	Late-onset cage subsidence	At 1 year postoperatively, 22% (22 of 98) total levels; 30% (18 of 61) of standard and 11% (4 of 37) of wide cages had subsidence	Marchi's criteria on radiograph	Age older than 65 years and female sex Narrow cage	Wider cages decreased the risk of subsidence and better restored segmental lordosis	Calcium phosphate bone graft material	Percentage of fusion was 91% (89 of 98 levels) treated at final follow-up; a relationship between subsidence severity and fusion was not found	None reported
Malham et al. [24]	128 consecutive patients (178 treated levels) underwent LLIF	Prospective comparative study	Moderate	Both intraoperative endplate injury and late-onset cage subsidence	3% (4 of 128) of patients and 2% (4 of 178) of levels had intraoperative endplate injuries; at 24 months postoperatively, 10% (13 of 128) of patients and 8% (14 of 178) of levels had late-onset cage subsidence	Any compromise of either endplate	Smoking	None reported	Either of the following: (1) AttraX, an osteoinductive synthetic bone putty composed of 95% β- TCP and 5% hydroxyapatite, or (2) a combination of rhBMP-2 and Mastergraft β-TCP granules	Percentage of fusion for the late-onset subsidence group progressed from 0% (0 of 13 patients) to 90% (9 of 10 patients) at 24 months; for the no-subsidence group, percentage of fusion progressed from 30% (33 of 111 patients) at 6 months to 93% (68 of 73 patients) at 24 months; percentage of fusion is lower in the subsidence than no-subsidence group at 6 months (0%, 0 of 13 patients versus 30%, 33 of 111 patients; p = 0.0195)	None reported

Table 1. continued

References	Study population	Study design	Evidence quality (as assessed by GRADE)	Type of subsidence	Risk of subsidence	Subsidence definition	Risk factors for cage subsidence reported in the study	Other findings related to subsidence	Bone graft used in the surgery	Percentage of fusion	Percentage of patients undergoing reoperation
Tempel et al. [40]	335 patients (712 levels) underwent LLIF, 80 patients with DEXA available were studied	Retrospective comparative study	Moderate	Late-onset cage subsidence	8.7% (29 of 335) of patients had late-onset cage subsidence[a]	Marchi's criteria on radiographs	Osteopenia (DEXA T scores less than -1.0)	None reported	None reported	None reported	48% (14 of 29) of patients with subsidence underwent revision surgery with open posterior decompression and instrumentation
Satake et al. [37]	102 patients (201 levels) underwent XLIF	Retrospective comparative study	Moderate	Intraoperative endplate injury	Immediate postoperatively, 10.4% (21 of 201) of levels had intraoperative endplate injuries	Disc space loss more than 2 mm on radiographs	Higher ratio of female patients Low BMD	None reported	The last 8 patients (18 levels) received hydroxyapatite and collagen soaked in autologous bone marrow aspirate, the others received allograft bone	None reported	None reported

Table 1. continued

References	Study population	Study design	Evidence quality (as assessed by GRADE)	Type of subsidence	Risk of subsidence	Subsidence definition	Risk factors for cage subsidence reported in the study	Other findings related to subsidence	Bone graft used in the surgery	Percentage of fusion	Percentage of patients undergoing reoperation
Satake et al. [36]	93 patients underwent LLIF with bilateral pedicle screw fixation	Prospective comparative study	Moderate	Both intraoperative endplate injury and late-onset cage subsidence	16.8% (31 of 184) of segments had intraoperative endplate injuries; 11.4% (21 of 184) of segments had late-onset cage subsidence	A cage sinking more than 2 mm into the adjacent vertebral endplate on CT	Low BMD in segments with intraoperative endplate injuries	None reported	The last six patients (14 segments) received hydroxyapatite and collagen soaked in autologous bone marrow aspirate; the other patients (n = 87, 170 segments) received allograft bone harvested from the femoral head	The percentage of fusion confirmed by CT-MPR at postoperative 1 year was 35.5% (11 of 31) in segments with intraoperative endplate injury, 23.8% (5 of 21) in segments with late-onset cage subsidence, and 54.5% (72 of 132) in normal segments; segments with late-onset cage subsidence had lower percentage of fusion than those in the other two groups (23.8%, 5 of 21 segments versus 35.5%, 11 of 31 segments and 54.5%, 72 of 132 segments; p = 0.01)	None reported
Agarwal et al. [1]	55 patients with a median (range) age of 74 years (70-87 years) underwent LLIF alone	Retrospective comparative study	Low	Late-onset cage subsidence	At 1 year postoperatively, 9% (5 of 55) of patients had cage subsidence	Marchi's criteria on radiographs	A lower BMD (femoral neck T-score < -1.0)	None reported	None reported	None reported	9% (5 of 55) of patients had symptomatic graft subsidence

Table 1. continued

References	Study population	Study design	Evidence quality (as assessed by GRADE)	Type of subsidence	Risk of subsidence	Subsidence definition	Risk factors for cage subsidence reported in the study	Other findings related to subsidence	Bone graft used in the surgery	Percentage of fusion	Percentage of patients undergoing reoperation
Chen et al. [7]	126 vertebrae in 107 patients were treated by XLIF	Retrospective comparative study	Low	Late-onset cage subsidence	At 2 years postoperatively, 26.9% (29 of 107)[a] patients had high-grade subsidence	Marchi's criteria on radiographs	Age over 65 years and female sex High BMI Low BMD	The type of supplementary fixation did not influence the risk of cage subsidence	Allograft bone mixed with autologous bone marrow	Percentage of fusion was 85.71% (108 of 126 levels) at 2 years; at the last follow-up, solid fusion was considered to have occurred in 86.96% (20 of 23) of patients in the high-grade subsidence group and 75.73% (78 of 103) of patients in the low-grade subsidence group; no association between fusion and subsidence was found at the 2-year follow-up	None reported
Ko et al. [18]	213 patients underwent DLIF (n = 129) or OLIF (n = 84) performed by the same surgeon and met the inclusion criteria	Retrospective comparative study	Moderate	Late-onset cage subsidence	No risk of subsidence reported; the subsidence distance was 1.0 ± 1.5 mm in the DLIF group and 0.4 ± 1.1 mm in the OLIF group	Cage subsidence (in mm) was measured by adding the invasion depth of the lower endplate of the upper vertebral body and the invasion depth of the upper endplate of the lower vertebral body	Age older than 65 years	Cage subsidence at 1 year postoperatively was worse in the DLIF group than in the OLIF group (1.0 ± 1.5 mm versus 0.4 ± 1.1 mm; p = 0.001)	Demineralized bone matrix	Percentage of fusion 1 year after surgery was 89.7% (131 of 146 levels) and 91.6% (76 of 83 levels) in the DLIF and OLIF groups, respectively	None reported

Table 1. continued

References	Study population	Study design	Evidence quality (as assessed by GRADE)	Type of subsidence	Risk of subsidence	Subsidence definition	Risk factors for cage subsidence reported in the study	Other findings related to subsidence	Bone graft used in the surgery	Percentage of fusion	Percentage of patients undergoing reoperation
Jung et al. [13]	Eighty-four patients underwent DLIF: 41 in the osteopenia group (-2.5 < T < -1) and 43 in the normal BMD group	Retrospective comparative study	Low	Late-onset cage subsidence	At 2 years postoperatively, 17.1% (11 of 41)[a] of patients in the osteopenia group had subsidence; 9.3% (8 of 43)[a] of patients in the normal BMD group had subsidence	Interbody graft sinks into the adjacent vertebral bodies with any distance or for more than 3 mm on radiographs	Low BMD	None reported	Cancellous allograft bone chips mixed with bone marrow	At 24 months, 92.7% (38 of 41) of patients in the osteopenia group and 95.3% (41 of 43) of patients in the normal BMD group had fusion	None reported
Campbell et al. [5]	113 consecutive patients underwent LLIF. Patient groups receiving PEEK and titanium implants were closely matched (57 and 56 patients, respectively)	Prospective comparative study	Moderate	Late-onset cage subsidence	Titanium group: At 1 year postoperatively, Grade I subsidence was identified in 15.6% (9 of 57)[a] of patients; Grades II and III were noted in 2.2% (1 of 57)[a] of patients. PEEK: At 1 year of follow-up, Grade I subsidence was identified in 22.4% (12 of 56)[a] of patients, and Grades II and III were seen in 16.3% (9 of 56)[a] of patients and 4.1% (2 of 56)[â] (superscript a) of patients, respectively	Marchi's criteria on radiographs	Age over 65 years	None reported	Bone graft materials included in the cage were either demineralized allograft fibers, rhBMP-2, or both	None reported	10.6% of patients (12 of 113) underwent revision surgery

Table 1. continued

References	Study population	Study design	Evidence quality (as assessed by GRADE)	Type of subsidence	Risk of subsidence	Subsidence definition	Risk factors for cage subsidence reported in the study	Other findings related to subsidence	Bone graft used in the surgery	Percentage of fusion	Percentage of patients undergoing reoperation
Chung et al. [9]	86 consecutive patients (125 operated-on disc levels) underwent OLIF	Retrospective comparative study	Low	Late-onset cage subsidence	At 1 year, 7.2% (9 of 125) of levels had cage subsidence	A cage sinking into an adjacent vertebral body by > 2 mm on radiographs	Age over 65 years Higher BMI	Vertebral endplate lesions did not affect the overall radiological outcome in one- or two-level OLIF	Autologous iliac crest bone graft and demineralized bone matrix	Percentage of fusion was 98.4% (123 of 125 levels)	None reported
Rentenberger et al. [34]	133 patients (258 levels) underwent LLIF alone	Retrospective case series	Low	Late-onset cage subsidence	At 1 year postoperatively, 26.7% (69 of 258) of levels had cage subsidence	Marchi's criteria on radiographs	Age over 70 years	Lower volumetric BMD and an anteroposterior diameter > 21.7 mm of the implanted cage were potential risk factors for severe subsidence	None reported	None reported	15.8% (21 of 133) of eligible patients underwent revision surgery and 3.0% (4 of 133) were recommended for revision surgery
Liu et al. [22]	78 patients (92 levels) underwent OLIF alone	Retrospective comparative study	Low	Late-onset cage subsidence	At 1 year postoperatively, 7.6% (7 of 92) of levels had cage subsidence	Marchi's criteria on radiographs	None reported	Patients with MCs associated with endplate sclerosis had a lower risk of subsidence	None reported	None reported	None reported
Okano et al. [31]	96 patients (210 levels) underwent LLIF alone	Retrospective comparative study	Low	Late-onset cage subsidence	At 1 year postoperatively, 39.6% (38 of 96) of patients and 27.6% (58 of 210) of levels had severe subsidence	Marchi's criteria on radiographs	Low endplate volumetric BMD	None reported	None reported	None reported	One patient underwent posterior fusion because of sagittal imbalance due to severe cage subsidence
Okano et al. [30]	97 patients (206 levels) underwent LLIF alone	Retrospective comparative study	Moderate	Late-onset cage subsidence	At 1 year postoperatively, 32.0% (66 of 206) of levels had severe subsidence	Marchi's criteria on radiographs	Construct length	The presence of Type 2 MC was associated with a lower risk of severe subsidence	None reported	None reported	3% (2 of 66) of patients in the severe subsidence group had revision surgery directly related to subsidence

Table 1. continued

References	Study population	Study design	Evidence quality (as assessed by GRADE)	Type of subsidence	Risk of subsidence	Subsidence definition	Risk factors for cage subsidence reported in the study	Other findings related to subsidence	Bone graft used in the surgery	Percentage of fusion	Percentage of patients undergoing reoperation
Xi et al. [45]	68 patients underwent single-level LLIF	Retrospective comparative study	Low	Late-onset cage subsidence	At 1 year postoperatively, 19.1% (13 of 68) of patients had severe cage subsidence	Marchi's criteria on radiographs	Low segmental HU values of the lumbar spine	None reported	Morcellized allograft or bone morphogenetic protein	None reported	4.4% (3 of 68) of patients underwent revision surgery

Marchi's criteria: cage subsidence into four grades based on the amount of cage subsidence in the vertebral endplates on radiographs: Grade 0, 0% to 24% collapse of the level; Grade I, 25% to 49%; Grade II, 50% to 74%; and Grade III, 75% to 100%. Grades 0 and I were considered low-grade and mild subsidence, respectively, while Grades II and III were considered high-grade and severe subsidence, respectively.

[a]The percentages here are reported as they appeared in the original study; LLIF = lateral lumbar interbody fusion; XLIF = extreme lateral interbody fusion; DLIF = direct lateral interbody fusion; OLIF = oblique lateral interbody fusion; PEEK = polyetheretherketone; BMD = bone mineral density; MC = Modic changes; β-TCP = beta tricalcium phosphate; rh-BMP2 = recombinant human bone morphogenetic protein-2; DEXA = dual-energy x-ray absorptiometry; CT-MPR = computed tomography multiplanar reconstruction; GRADE = Grading of Recommendations Assessment, Development, and Evaluation approach; HU = Hounsfield unit.

increased. Shiga et al. [38] reported that cages with a 12-mm height were associated with more endplate injuries than 8-mm or 10-mm cages (46.7% versus 33.3% and 27.4%, patient number not reported). Another study reported that a greater proportion of patients with endplate injury had larger-sized cages than disc height in full extension lateral view (90% [18 of 20] of segments versus 5% [6 of 120] of segments; p < 0.001) [16]. In another study, patients with taller cages (≥ 14 mm) and those with narrower cages (OR 10.3 [95% CI 1.91 to 15.5]; p = 0.01) had an increased risk of cage settling of more than 4 mm [42]. In addition to implant size, the number of surgical levels has been reported to play a role in cage subsidence; three studies reported multilevel surgery as a risk factor for cage subsidence [16, 20, 30]. Kim et al. [16] suggested that multilevel fusion (> three levels) could lead to a high incidence of endplate injury. Okano et al. [30] reported that the number of fused levels was associated with severe late-onset cage subsidence (two levels: OR 14.56 [95% CI 2.03 to 327.30]; p = 0.025; three levels or more: OR 18.40 [95% CI 2.54 to 422.96]; p = 0.016). Other authors [20] found increasing risk of late-onset subsidence with longer construct length (one level: 10.3% [8 of 78] of patients; two levels: 9.4% [3 of 32] of patients; three levels: 25% [6 of 24] of patients; four levels: 50% [3 of 6] of patients; p < 0.01).

Intervertebral cages with different materials and positions could impose different risks on the endplate's integrity (Table 2); three studies compared the risk of cage subsidence of polyetheretherketone (PEEK) cage and titanium cage in LLIF patients [5, 36, 37]. Satake et al. [37] reported that using PEEK cages resulted in a higher incidence of endplate injury than titanium (12.4% [21 of 169] of segments versus 0% [0 of 32] of segments; p = 0.04). In another study, the same group [36] reported that levels with late-onset settling had a higher percentage of PEEK cages (100% [21 of 21] of segments versus 81.1% [107 of 132] of segments; p = 0.03). Other authors reported that the use of PEEK resulted in a higher late-onset subsidence risk at 12 months of follow-up compared with titanium cages (20.8% [10 of 48] of patients versus 4.5% [2 of 44] of patients; p = 0.012) [5].

In addition, cage position can influence the risk of late-onset cage subsidence after LLIF (Table 2); different definitions of cage position were used in two reports [18, 38]. Shiga et al. [38] defined the cage position by dividing the caudal endplate into five zones and reported that most late-onset cage subsidence occurred in the farthest anterior zone (50% [6 of 12] of segments). In another study, Ko et al. [18] defined the cage location as the distance from the anterior margin of the disc to the anterior metallic indicator of the cage on lateral images and reported that late-onset cage subsidence increased with a more posterior cage location (β = 0.293; p < 0.001). Regarding supplementary instrumentation, two studies compared patients who

Table 2. Summary of studies that reported implant-related factors as risk factors for cage subsidence

References	Study population	Study design	Evidence quality (as assessed by GRADE)	Type of subsidence	Risk of subsidence	Subsidence definition	Risk factors for cage subsidence reported in the study	Other findings related to subsidence	Bone graft used in the surgery	Percentage of fusion	Percentage of patients undergoing reoperation
Le et al. [20]	A total of 140 consecutive patients (238 levels) underwent XLIF	Retrospective comparative study	Moderate	Late-onset cage subsidence	At 2 years postoperatively, 14.3% (20 of 140) of patients had subsidence; 8.8% (21 of 238) of levels had subsidence	Any compromise of either endplate on postoperative radiographs	Supplemental lateral plates compared with bilateral pedicle screws Narrower cages Longer construct	Risk of subsidence decreased progressively with lower levels in the lumbar spine, but had a higher than expected risk at L4 to L5	Allograft (BMP-2, hydroxyapatite, and tricalcium phosphate) or cadaveric cancellous bone mixed with mesenchymal stem cells	None reported	None reported
Marchi et al. [25]	46 patients (61 lumbar levels) underwent treatment with 18-mm interbody cages; 28 patients (37 lumbar levels) underwent treatment with 22-mm-wide cages	Retrospective comparative study	Low	Late-onset cage subsidence	At 1 year postoperatively, 22% (22 of 98) of total levels; 30% (18 of 61) of standard and 11% (4 of 37) of wide cages had subsidence	Marchi criteria on radiographs	Narrow cage	Wider cages are associated with lower risk of subsidence and better restored segmental lordosis	Calcium phosphate bone graft material	Percentage of fusion was 91% (89 of 98 levels) treated at final follow-up; a relationship between subsidence severity and fusion was not found	None reported
Pimenta et al. [33]	30 patients with L4 to L5 DDD who underwent stand-alone LLIF were randomized into two groups with different bone grafts	Randomized controlled trial	Moderate	Late-onset cage subsidence	At 3 years postoperatively, 16.7% (5 of 30) of patients had subsidence: three in the SiCaP group and two in the bone morphogenic protein group	Marchi criteria on radiographs	None reported	SiCaP and rhBMP-2 bone graft substitutes resulted in similar risks of subsidence	Calcium phosphate ceramic was used on 15 patients; rh-BMP2 in collagen sponge was used in 15 patients	At 36 months, 100% (30 of 30) of patients undergoing XLIF achieved solid fusion	13% (4 of 30) of patients underwent additional minimally invasive direct decompression with the addition of pedicle screws

Table 2. continued

References	Study population	Study design	Evidence quality (as assessed by GRADE)	Type of subsidence	Risk of subsidence	Subsidence definition	Risk factors for cage subsidence reported in the study	Other findings related to subsidence	Bone graft used in the surgery	Percentage of fusion	Percentage of patients undergoing reoperation
Kim et al. [15]	125 patients were treated with standard DLIF cages (standard group) and 38 patients were treated with new cages with a larger lordosis (wide group)	Retrospective comparative study	Moderate	Both intraoperative endplate injury and late-onset cage subsidence	Intraoperative endplate injury: 24.8% (31 of 125) of patients with a standard cage; 42.1% (16 of 38) of patients with a wide cage Late-onset cage subsidence: 14.4% (18 of 125) of patients with a standard cage; 7.9% (3 of 38) of patients with a wide cage	Disc space loss more than 2 mm on radiographs	Narrower cages	Subsidence was less in the wide group (1.2 ± 0.5 mm) than in the standard group (4.4 ± 2.5 mm) ($p < 0.05$)	Demineralized bone matrix	None reported	None reported
Tohmeh et al. [42]	140 consecutive patients (223 levels) were treated with XLIF	Prospective comparative study	Moderate	Both intraoperative endplate injury and late-onset cage subsidence	Intraoperative endplate injury: 1 mm or more settling occurred in 20% (45 of 223) of cages and 4 mm or more occurred in 4.5% (10 of 223) of cages Late-onset cage subsidence: at 12 months postoperatively, 1 mm or more settling occurred in 62% (139 of 223) of cages and 4 mm or more occurred in 24% (53 of 223) of cages	Cage settling ≥ 1 mm and cage settling ≥ 4 mm on radiographs	Taller cage Narrower cage Shorter cage	Lateral plating led to a lower risk of cage subsidence but larger magnitude	Either rhBMP-2 or cellular matrix allograft	None reported	None reported

Table 2. continued

References	Study population	Study design	Evidence quality (as assessed by GRADE)	Type of subsidence	Risk of subsidence	Subsidence definition	Risk factors for cage subsidence reported in the study	Other findings related to subsidence	Bone graft used in the surgery	Percentage of fusion	Percentage of patients undergoing reoperation
Satake et al. [37]	102 patients (201 levels) underwent XLIF	Retrospective comparative study	Moderate	Intraoperative endplate injury	Immediately postoperatively, 10.4% (21 of 201) of levels had intraoperative endplate injuries	Disc space loss more than 2 mm on radiographs	PEEK as cage material compared with titanium Taller cage	None reported	The last 8 patients (18 levels) received hydroxyapatite and collagen soaked in autologous bone marrow aspirate; the others received allograft bone	None reported	None reported
Lang et al. [19]	21 patients (28 levels) underwent XLIF	Retrospective case series	Very low	Late-onset cage subsidence	No risk of subsidence reported. At 6 months postoperatively, the mean subsidence distance was 0.34 ± 0.26 mm	Difference between postoperative and follow-up disc height on radiographs	Narrow cages (18-mm-wide compared with 26-mm-wide)	None reported	Silicated calcium phosphate	None reported	None reported
Malham et al. [23]	40 patients (58 levels) were treated with XLIF with or without fixation	Prospective comparative study	Low	Late-onset cage subsidence	At 1 year postoperatively, 14.3% (3 of 21) of patients with standalone surgery had subsidence	Marchi criteria on CT	None reported	There was no difference in the risk of subsidence in patients with the standalone procedure and those with pedicle screw fixation	A combination of bone morphogenetic protein (rhBMP-2) and Mastergraft β-TCP granules	None reported	None reported

Table 2. continued

References	Study population	Study design	Evidence quality (as assessed by GRADE)	Type of subsidence	Risk of subsidence	Subsidence definition	Risk factors for cage subsidence reported in the study	Other findings related to subsidence	Bone graft used in the surgery	Percentage of fusion	Percentage of patients undergoing reoperation
Satake et al. [36]	93 patients underwent LLIF with bilateral pedicle screw fixation	Prospective comparative study	Moderate	Both intraoperative endplate injury and late-onset cage subsidence	16.8% (31 of 184) of segments had intraoperative endplate injuries; 11.4% (21 of 184) of segments had late-onset cage subsidence	A cage sinking more than 2 mm into the adjacent vertebral endplate on CT	PEEK as cage material compared with titanium in segments with late-onset cage subsidence	Most segments with intraoperative endplate injury; 90.3% (28 of 31) of segments had subsidence sites at the anterior corner in the superior endplate of the caudal vertebra Only 47.6% (10 of 21) of the segments with late-onset cage subsidence had subsidence at the same location	The last six patients (14 segments) received hydroxyapatite and collagen soaked in autologous bone marrow aspirate; the other patients (n = 87, 170 segments) received allograft bone harvested from the femoral head	The percentage of fusion confirmed by CT-MPR at postoperative 1 year was 35.5% (11 of 31) in segments with intraoperative endplate injury, 23.8% (5 of 21) in segments with late-onset cage subsidence, and 54.5% (72 of 132) in normal segments; segments with late-onset cage subsidence had lower percentage of fusion than those in the other two groups (23.8%, 5 of 21 segments versus 35.5%, 11 of 31 segments and 54.5%, 72 of 132 segments; p = 0.01)	None reported

Table 2. continued

References	Study population	Study design	Evidence quality (as assessed by GRADE)	Type of subsidence	Risk of subsidence	Subsidence definition	Risk factors for cage subsidence reported in the study	Other findings related to subsidence	Bone graft used in the surgery	Percentage of fusion	Percentage of patients undergoing reoperation
Shiga et al. [38]	80 patients (121 levels) underwent OLIF	Retrospective comparative study	Moderate	Late-onset cage subsidence	At 1 year postoperatively, 33.1% (40 of 121) of patients had cage subsidence	Postoperative discontinuity of the endplate contour affected by the cages on radiographs and CT	Cages with a 12-mm height compared with shorter cages (8 or 10 mm)	The largest sagittal correction and the most postoperative endplate injuries occurred in the farthest anterior zone (Zone I) Endplate injury occurred the most in Zone I (50.0% [6 of 12] of segments), whereas the fewest endplate injuries occurred in Zone II (21.1% [8 of 38] of segments)	None reported	The percentage of fusion with continuous bony fusion with both or either side of endplate amounted to 97.5% (118 of 121 levels)	None reported
Bocahut et al. [4]	69 patients underwent LLIF alone, 63 patients were assessed for subsidence	Retrospective comparative study	Low	Late-onset cage subsidence	At 1 year postoperatively, 32% (20 of 63) of patients had subsidence; the mean subsidence was 5.5 ± 1.5 mm	At least 4-mm loss of fused space height on CT	None reported	Subsidence was anterior in 50% (10 of 20) of patients	None reported	Fusion was achieved in 97% (67 of 69) of patients; the 2 patients with failed fusion had global subsidence	6% (4 of 63) of patients underwent revision surgery
Frisch et al. [10]	56 patients underwent LLIF	Retrospective comparative study	Very low	Late-onset cage subsidence	At 2 years postoperatively, 16.1% (5 of 31) of patients with static levels had subsidence; none with expandable levels had subsidence	A reduction in intervertebral disc height greater than 2 mm on radiographs	Static cages compared with expandable cages	Expandable group (120.2 ± 59.6 minutes) required longer operative time than static group (63.3 ± 37.8 minutes)	None reported	Solid fusion was observed in 100% (56 of 56) patients by 24-month follow-up	None reported

Table 2. continued

References	Study population	Study design	Evidence quality (as assessed by GRADE)	Type of subsidence	Risk of subsidence	Subsidence definition	Risk factors for cage subsidence reported in the study	Other findings related to subsidence	Bone graft used in the surgery	Percentage of fusion	Percentage of patients undergoing reoperation
Tempel et al. [41]	297 patients (623 levels) underwent LLIF alone	Prospective comparative study	Moderate	Late-onset cage subsidence	At 2 years postoperatively, 11.4% (34 of 297) of patients had cage subsidence	Marchi criteria on radiographs	Lateral plating	Cage subsidence is a predictor of revision surgery after stand-alone LLIF	None reported	The percentage of fusion was 93.9% (279 of 297 patients)	6.1% (18 of 297) of patients underwent revision surgery; 38.9% (7 of 18) of patients undergoing revision surgery suffered a vertebral body fracture
Chang et al. [6]	169 patients (262 operative levels) underwent OLIF	Prospective comparative study	Moderate	Late-onset cage subsidence	At 1 year postoperatively, cage subsidence was observed in 32.6% (85 of 261) of operated-on levels and in 36.9% (62 of 168) of patients	Marchi criteria on radiographs	Technical effort to achieve the greatest height possible	None reported	Allogeneic demineralized bone matrix mixed with cancellous bone	At 1 year postoperatively, 54.3% (51 of 94) of patients had all operated levels completely fused, while the other 46.7%[a] (43 of 94) of patients had at least 1 level with incomplete fusion For individual levels, complete interbody fusion was observed in 62.7% (84 of 134) of examined levels	1.8% (3 of 169) of patients did not have symptom relief with indirect decompression

Table 2. continued

References	Study population	Study design	Evidence quality (as assessed by GRADE)	Type of subsidence	Risk of subsidence	Subsidence definition	Risk factors for cage subsidence reported in the study	Other findings related to subsidence	Bone graft used in the surgery	Percentage of fusion	Percentage of patients undergoing reoperation
Kim et al. [16]	A total of 46 patients who underwent OLIF were included, with a total of 138 fusion segments	Retrospective comparative study	Low	Intraoperative endplate injury	At 1 week postoperatively, 30.4% (14 of 46) of patients and 23.9% (33 of 138) of segments demonstrated endplate injury-associated changes in cage placement	Changes in the cage placement indicate endplate injury	Multilevel fusion (> three levels) Greater cage height than disc height Larger lordosis correction angle	None reported	None reported	None reported	None reported
Ko et al. [18]	343 patients underwent DLIF (n = 201) or OLIF (n = 142) by the same surgeon	Retrospective comparative study	Moderate	Late-onset cage subsidence	No risk of subsidence reported; the subsidence distance was 1.0 ± 1.5 mm in the DLIF group and 0.4 ± 1.1 mm in the OLIF group	Cage subsidence (in mm) was measured by adding the invasion depth of the lower endplate of the upper vertebral body and the invasion depth of the upper endplate of the lower vertebral body	More-posterior cage location Narrow cage	Cage subsidence at 1 year postoperatively was worse in the DLIF group than in the OLIF group (1.0 ± 1.5 mm versus 0.4 ± 1.1 mm; p = 0.001)	Demineralized bone matrix	Percentage of fusion one year after surgery was 89.7% (131 of 146 levels) and 91.6% (76 of 83 levels) in the DLIF and OLIF groups, respectively	None reported
Samtani et al. [35]	48 patients underwent LLIF, 23 patients took alendronate, 25 patients were controls	Retrospective comparative study	Very low	Late-onset cage subsidence	No risk of subsidence reported	Distance of subsidence over four cage corners	None reported	Less subsidence at L4 to L5 in the alendronate group than in the control group	Allograft cellular bone matrix containing mesenchymal stem cells and osteoprogenitor cells combined with DBM alone or that in addition to a small rhBMP-2	None reported	12% (3 of 25) of patients in the control group had revision surgery

Table 2. continued

References	Study population	Study design	Evidence quality (as assessed by GRADE)	Type of subsidence	Risk of subsidence	Subsidence definition	Risk factors for cage subsidence reported in the study	Other findings related to subsidence	Bone graft used in the surgery	Percentage of fusion	Percentage of patients undergoing reoperation
Agarwal et al. [2]	297 patients (623 levels) underwent LLIF alone, 60 patients were analyzed	Prospective comparative study	Moderate	Late-onset cage subsidence	At 2 years postoperatively, 11.4% (34 of 297) of patients had cage subsidence	Marchi criteria on radiographs	18-mm implants compared with 22-mm	Endplate-implant area, width, and length mismatches were not risk factors	None reported	None reported	18-mm cage: 62.5% (5 of 8) of patients underwent a reoperation 22-mm cage: 59.1% (13 of 22) of patients underwent a reoperation
Campbell et al. [5]	113 consecutive patients underwent LLIF. Patient groups receiving PEEK and titanium implants were closely matched, at 57 and 56 patients, respectively	Prospective comparative study	Moderate	Late-onset cage subsidence	Titanium group: At 1 year postoperatively, Grade I subsidence was identified 15.6% (9 of 57)[a] of patients; Grades II and III were noted in 2.2% (1 of 57)[a] of patients PEEK: At 1 year of follow-up, Grade I subsidence was identified in 22.4% (12 of 56),[a] and Grades II and III were seen in 16.3% (9 of 56)[a] and 4.1% (2 of 56)[a] of patients, respectively	Marchi criteria on radiographs	rhBMP-2 use PEEK compared with titanium	None reported	Cancellous allograft bone chips mixed with bone marrow	At 24 months, 92.7% (38 of 41) of patients of the osteopenia group and 95.3% (41 of 43) of patients of the normal BMD group had fusion	10.6% (12 of 113) of patients underwent revision surgery

Table 2. continued

References	Study population	Study design	Evidence quality (as assessed by GRADE)	Type of subsidence	Risk of subsidence	Subsidence definition	Risk factors for cage subsidence reported in the study	Other findings related to subsidence	Bone graft used in the surgery	Percentage of fusion	Percentage of patients undergoing reoperation
He et al. [12]	32 patients underwent standalone OLIF and 41 underwent combined OLIF	Retrospective comparative study	Low	Late-onset cage subsidence	Combined OLIF group: At 2 years postoperatively, 7.3% (3 of 41) of patients had cage subsidence Standalone OLIF group: 15.6% (5 of 32) of patients had cage subsidence	A cage sinking into an adjacent vertebral body by > 2 mm on CT	None reported	No difference in the risk of cage subsidence between standalone group and combined OLIF group	Demineralized bone matrix	At 24 months, the fusion rate was 100% (41 of 41 patients) in the combined OLIF group and 93.8% (30 of 32 patients) in the standalone OLIF group	None reported
Li et al. [21]	69 patients (static, n = 32; expandable, n = 37) underwent minimally invasive LLIF at one to two contiguous levels	Retrospective comparative study	Low	Late-onset cage subsidence	At 1 year postoperatively, 2.2% (1 of 46) of levels in the expandable group had subsidence; 32.4% (12 of 37) of levels in the static group had subsidence	Measured reduction in disc height greater than 2 mm on radiographs	Static cage compared with expandable group	None reported	None reported	None reported	None reported
Okano et al. [30]	97 patients (206 levels) underwent LLIF alone	Retrospective case series	Low	Late-onset cage subsidence	At 1 year postoperatively, 32% (66 of 206) of levels had severe subsidence	Marchi criteria on radiographs	Longer construct	The presence of MC Type 2 was associated with a lower risk of severe subsidence	None reported	None reported	3% (2 of 66) of patients in the severe subsidence group had revision surgery directly related to subsidence
Wen et al. [43]	74 patients underwent single-level OLIF with BPS (n= 36) or UPS (n= 38)	Retrospective comparative study	Low	Late-onset cage subsidence	At 2 years postoperatively, 17.6% (13 of 74) of patients had high-grade subsidence	Marchi criteria on radiographs	None reported	Risk of cage subsidence did not differ between patients with UPS and patients with BPS	None reported	None reported	None reported

Table 2. continued

References	Study population	Study design	Evidence quality (as assessed by GRADE)	Type of subsidence	Risk of subsidence	Subsidence definition	Risk factors for cage subsidence reported in the study	Other findings related to subsidence	Bone graft used in the surgery	Percentage of fusion	Percentage of patients undergoing reoperation
Wewel et al. [44]	77 patients (134 levels) underwent LLIF	Retrospective comparative study	Low	Intraoperative endplate injury	Immediate postoperatively, 4% (3 of 77) of patients and 2.2% (3 of 134) of levels had intraoperative endplate injuries	Any violation of the superior or inferior endplate at the index level	None reported	All three cases of subsidence in this series occurred at the inferior endplate Endplate injury occurred during interbody placement	None reported	None reported	None reported

Marchi's criteria: cage subsidence into four grades based on the amount of cage subsidence in the vertebral endplates on radiographs: Grade 0, 0% to 24% collapse of the level; Grade I, 25% to 49%; Grade II, 50% to 74%; and Grade III, 75% to 100%. Grades 0 and I were considered low-grade and mild subsidence, respectively, while Grades II and III were considered high-grade and severe subsidence, respectively.

[a]The percentages are reported here as they appeared in the original study; LLIF= lateral lumbar interbody fusion; XLIF = extreme lateral interbody fusion; DDD = degenerative disc disease; β-TCP = beta tricalcium phosphate; rhBMP-2 = recombinant human bone morphogenetic protein-2; DLIF = direct lateral interbody fusion; PEEK = polyetheretherketone; OLIF = oblique lateral interbody fusion; UPS = unilateral posterior fixation; BPS = bilateral posterior fixation; SiCaP = silicated calcium phosphate; MC = Modic changes; CT-MPR = computed tomography multiplanar reconstruction; DBM = demineralized bone matrix; GRADE = Grading of Recommendations Assessment, Development, and Evaluation approach.

underwent standalone LIF and patients with bilateral pedicle screw fixation [12, 23]. These studies reported that no differences in subsidence risks between patients with standalone LIF and those with pedicle screws (15.6% [5 of 32] versus 7.3% [3 of 41]; p = 0.287; 14.3% [3 of 21] versus 0% [0 of 19]; p = 0.106). Furthermore, lateral plates and bilateral pedicle screws were compared in three studies [20, 41, 42]. In one study, no difference was found between the risk of cage subsidence between supplemental lateral plates and bilateral pedicle screws (24.5% [12 of 49] versus 8.6% [5 of 58]; p = 0.18) [20]. In another study, pedicle screw fixation was associated with a higher risk of late-onset cage subsidence of 1 mm or more compared with lateral plating (69.2% surgical levels versus 44.6% surgical levels, number of levels with subsidence not reported; p < 0.001), although the magnitude of settling at the anterior inferior endplate was greater for lateral plating (4.9 mm versus 3.5 mm; p = 0.03) [42]. Other authors [7, 43] compared cage subsidence risks between patients with unilateral screws and those with bilateral pedicle screws and reported no difference between them. The relationship between bone graft used, risk of subsidence, and fusion was inconclusive.

Discussion

Cage subsidence after LLIF can lead to compromised clinical results, such as the loss of indirect decompression and recurrence of neural compression [4-6, 33, 41]. A thorough review of the current knowledge about cage subsidence after LLIF could bring attention to any well-established risk factors while suggesting research needed to clarify any incompletely characterized preoperative concerns. Two types of cage subsidence exist—intraoperative endplate injury and late-onset cage subsidence—and these should be studied separately, since there are variations in risk factors associated with each one. In this systematic review, we found that patients with poorer bone quality, those older than 65 years, and women should be counseled about high risks of both types of cage subsidence. Regarding cage size, cage width at least 22 mm can help to avoid late-onset cage subsidence, and cage height no larger than 11 mm was recommended by some studies to avoid intraoperative endplate injuries. Studies recommended that multilevel LLIF should be conducted with extra caution because of a high risk of losing the effect of indirect decompression. The effect of preoperative endplate condition, bone graft, cage material, cage position, and supplementary instrumentation on cage subsidence remains incompletely characterized.

Limitations

This study has limitations. Because of the lack of uniform methods for assessing the extent of subsidence, four different criteria were used in the included studies, which can make it difficult to interpret and compare the results of such studies. However, we found that Marchi's criteria was only applied in studies of late-onset cage subsidence, which allows subsidence to be calculated as a percentage change in disc height. This assessment standard for subsidence was used in most of the articles we reviewed (16 of 26). On the other hand, all studies that measured intraoperative endplate injury defined cage subsidence as disc height loss more than 2 mm (4 of 7) or any discontinuity (3 of 7) of the endplate, mainly because a more precise criterion is needed to evaluate disc height changes immediately postoperatively that are more subtle than disc height loss during follow-up. Since one of the main goals of this review is to differentiate intraoperative endplate injury and late-onset cage subsidence, we decided to include studies with these different criteria for subsidence so that we could collect risk factors for both types of cage subsidence. In addition, most studies included in this review were retrospective studies, with a quality of evidence ranging from very low to moderate; only one randomized controlled trial was included. However, the evidence in the included studies showed consensus on the major risk factors for cage subsidence, such as bone quality, cage size, and construct length, while providing valuable insight on various minor risk factors, including age, sex, smoking, BMI, cage material, cage position, and supplementary instrumentation. Further, although all four surgical approaches reviewed in this study gain access to the intervertebral disc through the lateral side, there are minor differences in the shapes of the cages used for different approaches, which may lead to slight differences in the risk of cage subsidence.

Association of Bone Quality and its Surrogates with Cage Subsidence

Low bone quality was one of the most reported risk factors for cage subsidence. Six studies reported that reduced bone quality or osteoporosis measured by DEXA or CT was associated with an increased likelihood of cage subsidence [1, 13, 31, 35, 37, 40]. Based on previous studies [37, 40] with a moderate quality of evidence, patients with a DEXA T-score of -1.0 or less should be considered to have a high risk of late-onset cage subsidence. Patients with poor bone quality should be counseled about the possibility of increased surgical risk of developing cage subsidence. Posterior fixation and bone cement should be considered to increase the stability of the construct. For patients who do not need an emergency surgery or need to wait for an operation, medication for osteoporosis may be another way to manage the risk of cage subsidence. Parathyroid hormone treatment for more than 6 months should be considered preoperatively for eligible patients with osteoporosis [29].

Surrogate measures of bone quality also provide context for surgical planning and expectations. In two studies with a moderate quality of evidence, advanced age was a risk factor for late-onset cage subsidence because of its strong correlation with low bone quality and compromised endplate strength [25, 34]. Regarding female patients, one study noted a high ratio of females among all patients who suffered endplate injuries and suggested that postmenopausal women may be at an especially high risk of having cage subsidence [37]. Patients with preoperative characteristics such as age older than 65 years and female sex should be informed of the risk of cage subsidence during preoperative discussions, and close follow-up is necessary. The effect of smoking and BMI remain unclear because of a lack of studies with strong evidence. Among various preoperative endplate conditions, Modic changes have been suggested to be a favorable condition for patients who undergo LLIF. An endplate with Modic changes may have stronger mechanical properties, and an endplate with Modic changes or sclerosis may be suitable for standalone oblique LIF [22]. Additionally, microstructural changes associated with Type 2 Modic changes may help prevent cage subsidence [30]. Future studies with bone or endplate biopsies are needed to further evaluate the microstructural changes associated with Modic changes at the endplate.

Association of Implant-Related Factors with Cage Subsidence

Strong evidence suggests that cage size and construct length are risk factors for both types of cage subsidence. Narrower cages seem to be a crucial risk factor for late-onset subsidence that occurs during the follow-up period. Wider cages have more contact area with stronger and stiffer peripheral endplates, which provides more efficient axial load transfer and superior segmental stability to that of implants with smaller widths and cage-endplate interfaces [2, 20, 25]. Based on four studies with a moderate quality of evidence according to the GRADE criteria that reported narrow cages as a risk factor, cages wider than 22 mm can protect the surgical levels against late-onset cage subsidence, and 18-mm cages should be avoided if the disc space allows [2, 15, 18, 42]. One potential limitation of the studies mentioned was that they did not consider the size of the patients and their vertebrae; thus, future studies that adjust cage width based on individual vertebral size may be needed. In addition to narrow cages, taller cages were reported as a risk factor for cage subsidence, and many authors suggested caution against over-distraction of the disc space [16, 18, 36, 38, 42]. Le et al. [20] preferred to provide between 2 mm and 4 mm of distraction per affected level, which is accomplished with either an 8-mm or a 10-mm implant cage, while avoiding 12-mm implant cages. Another study observed that risk of intraoperative endplate injury increased markedly for a cage height of 10 mm to 12 mm, suggesting that surgeons should not use a cage height exceeding 11 mm, especially for patients with reduced bone mineral density [37]. Generally, aggressive distraction of the disc space should be avoided because it strongly correlates with intraoperative endplate injury, and special attention is required when implant cages taller than 12 mm are inserted into the disc space. Further, patients who underwent multilevel LLIF were reported to have a higher risk of endplate injury and late-onset cage subsidence than those undergoing single-level LLIF [16, 20, 24, 30]. This trend may be associated with the longer surgical time and increased technical complexity associated with placing a longer construct. Because the clinical effect of LLIF mainly relies on indirect decompression of the neural elements, for multilevel surgery, another approach with direct decompression, such as posterior and transforaminal LIF, should be considered before LLIF. This is because the effect of indirect decompression can be difficult to maintain because of the higher risk of severe cage subsidence.

Although some evidence from the included studies suggests that cage material, cage position, and supplementary instrumentation are associated with increased risk of cage subsidence, their roles in cage subsidence after LLIF may require further examination. Among synthetic cage materials, PEEK is favorable because it shares the same modulus of elasticity as bone does, avoiding stress shielding caused by the mismatch of stiffness [20]. However, several studies reported contradictory results and implied that PEEK implants may have inferior performance regarding subsidence prevention [5, 36, 37]. The poor performance of PEEK is likely because of its inferior osseoconductivity and bioactivity compared with titanium implants [5]. Although these three studies [5, 36, 37] reported that the inferior performance of PEEK cages had a moderate quality of evidence, more biomechanical evidence might be needed before the most favorable cage material is decided for LLIF because of the complex interaction between the cage and endplate. Besides cage material, cage position was evaluated as a potential risk factor for cage subsidence in two studies, but seemingly conflicting results were reported [18, 38]. Shiga et al. [38] defined the cage position by dividing the caudal endplate into five zones and reported that most late-onset cage subsidence occurred in the farthest anterior zone. To gain more lordosis correction with fewer endplate injuries, the authors suggested that surgeons should insert an oblique LIF cage with a height of up to 10 mm in this zone [38]. In another study, the cage location was defined as the distance from the anterior margin of the disc to the anterior metallic indicator of the cage on lateral images, and the authors reported that late-onset cage subsidence increased with a

more posterior cage location ($\beta = 0.293$; $p < 0.001$) [18]. Combining the findings from these two studies [18, 38], a cage position just anterior to the midline of the sagittal plane of the vertebral body seems to be a favorable position for preventing cage subsidence. Further, many variations of supplementary instrumentation have been reported, and most studies found no difference between them [7, 12, 20, 23, 41-43]. LLIF can be performed as a standalone surgery without posterior fixation, and good clinical results have been reported [27, 46, 48]. Generally, supplemental fixation increases stiffness, limits motion to aid in the fusion process, and protects indirect decompression [20]. Although the addition of screws stiffens the overall construct, the construct may not be resistant enough to axial compression once subsidence or fracture occurs in the presence of screw instrumentation [25]. Standalone LLIF may be sufficient for patients without osteoporosis or obesity, and supplementary instrumentation should be considered to maintain the postoperative disc height and prevent subsidence progression in patients with multiple risk factors.

Conclusion

Patients with poor bone density, who are older than 65 years, or who are female should be counseled about their high risk of developing cage subsidence. Surgeons should avoid narrow cages when performing LLIF to minimize the risk of late-onset cage subsidence, while being cautious of an aggressive attempt to restore disc height with a tall cage as it may lead to intraoperative endplate injury. For multilevel constructs, direct decompression approaches, such as posterior and transforaminal LIF, should be considered instead of LLIF, since the effect of indirect decompression may be difficult to maintain in multilevel LLIF because of the high risk of cage subsidence. The effect of the cage material and supplementary instrumentation require stronger evidence from prospectively designed studies with larger sample sizes that randomly assign patients to PEEK or titanium cages and different fixation types. Future research on intraoperative endplate injuries should focus on the specific timing of when endplate violation occurs, and these studies should use intraoperative imaging so that attempts can be made to minimize the frequency with which it occurs. The relationship between endplate injuries and clinical outcomes such as health-related quality of life scores should be studied in the future.

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