# Does Bone Morphogenetic Protein Use Reduce Pseudarthrosis Rates in Single-Level Transforaminal Lumbar Interbody Fusion Surgeries?

Jack Zhong, Jarid Tareen, Kimberly Ashayeri, Carlos Leon, Eaman Balouch, Nicholas O'Malley, Carolyn Stickley, Constance Maglaras, Brooke O'Connell, Ethan Ayres, Charla Fischer, Yong Kim, Themistocles Protopsaltis and Aaron J. Buckland

*Int J Spine Surg* published online 3 April 2024
http://ijssurgery.com/content/early/2024/04/03/8590



*The International Journal of Spine Surgery*
2397 Waterbury Circle, Suite 1,
Aurora, IL 60504, Phone: +1-630-375-1432

*International Journal of Spine Surgery*, Vol. 00, No. 0, 2024, pp. 1–10
https://doi.org/10.14444/8590


# Does Bone Morphogenetic Protein Use Reduce Pseudarthrosis Rates in Single-Level Transforaminal Lumbar Interbody Fusion Surgeries?

JACK ZHONG, MD[1]; JARID TAREEN, MD[1]; KIMBERLY ASHAYERI, MD[1]; CARLOS LEON, ME[1]; EAMAN BALOUCH, MD, PHD[1]; NICHOLAS O'MALLEY, BS[1]; CAROLYN STICKLEY, BS[1]; CONSTANCE MAGLARAS, PHD; BROOKE O'CONNELL, MS[1]; ETHAN AYRES, MD[1]; CHARLA FISCHER, MD[1]; YONG KIM, MD[1]; THEMISTOCLES PROTOPSALTIS, MD, FAAOS[1]; AND AARON J. BUCKLAND, MBBS, FRACS[1,2,3]

*[1]Department of Orthopedics, Division of Spine, NYU Langone Health, New York, NY, USA; [2]Melbourne Orthopedic Group, Melbourne, Australia; [3]Spine and Scoliosis Research Associates Australia, Windsor, Australia*

## ABSTRACT

**Background:** Recombinant human bone morphogenetic protein 2 (rhBMP-2, or BMP for short) is a popular biological product used in spine surgeries to promote fusion and avoid the morbidity associated with iliac crest autograft. BMP's effect on pseudarthrosis in transforaminal lumbar interbody fusion (TLIF) remains unknown.

**Objective:** To assess the rates of pseudarthrosis in single-level TLIF with and without concurrent use of BMP.

**Methods:** This was a retrospective cohort study conducted at a single academic institution. Adults undergoing primary single-level TLIF with a minimum of 1 year of clinical and radiographic follow-up were included. BMP use was determined by operative notes at index surgery. Non-BMP cases with iliac crest bone graft were excluded. Pseudarthrosis was determined using radiographic and clinical evaluation. Bivariate differences between groups were assessed by independent *t* test and $\chi^2$ analyses, and perioperative characteristics were analyzed by multiple logistic regression.

**Results:** One hundred forty-eight single-level TLIF patients were included. The mean age was 59.3 years, and 52.0% were women. There were no demographic differences between patients who received BMP and those who did not. Pseudarthrosis rates in patients treated with BMP were 6.2% vs 7.5% in the no BMP group ($P = 0.756$). There was no difference in reoperation for pseudarthrosis between patients who received BMP (3.7%) vs those who did not receive BMP (7.5%, $P = 0.314$). Patients who underwent revision surgery for pseudarthrosis more commonly had diabetes with end-organ damage (revised 37.5% vs not revised 1.4%, $P < 0.001$). Multiple logistic regression analysis demonstrated no reduction in reoperation for pseudarthrosis related to BMP use (OR 0.2, 95% CI 0.1–3.7, $P = 0.269$). Diabetes with end-organ damage (OR 112.6,95% CI 5.7–2225.8, $P = 0.002$) increased the risk of reoperation for pseudarthrosis.

**Conclusions:** BMP use did not reduce the rate of pseudarthrosis or the number of reoperations for pseudarthrosis in single-level TLIFs. Diabetes with end-organ damage was a significant risk factor for pseudarthrosis.

**Clinical Relevance:** BMP is frequently used "off-label" in transforaminal lumbar interbody fusion; however, little data exists to demonstrate its safety and efficacy in this procedure.

**Level of Evidence:** 3.

Biologics

Keywords: transforaminal interbody fusion, TLIF, bone morphogenetic protein, BMP, pseudarthrosis, fusion, diabetes mellitus, single-level, complications

## KEY POINTS

1. A total of 148 single-level adult TLIFs with a minimum of 1-year follow-up were included to compare the effects of BMP on rates of pseudarthrosis.
2. There was no difference in rates of pseudarthrosis or revision for pseudarthrosis among TLIFs with and without BMP use.
3. Diabetes with end-organ damage was shown to be a significant risk factor for pseudarthrosis on multivariate logistic regression.

## INTRODUCTION

Degenerative lumbar spine disease is a common cause of back pain. Transforaminal lumbar interbody fusion (TLIF) is a commonly performed procedure to treat degenerative lumbar diseases,[1] including severe degenerative disc disease, spondylolisthesis, postlaminectomy instability, pseudarthrosis, and trauma, among others.[2] The procedure involves the removal of degenerated disc material, placement of bone graft and an interbody device in the disc space, and posterior instrumentation to provide initial stability and aid in fusion.[3]

The placement of the interbody device improves sagittal alignment, restores disc and foraminal height, and provides indirect decompression of foraminal and canal stenosis.[4] TLIF increases surface area for fusion, which enhances fusion rates.[4,5]

Pseudarthrosis is a failure of bone fusion after attempted spinal arthrodesis such as in TLIF,[6] usually at a minimum of 6 months after surgery.[7] Pseudarthrosis occurrs in 3% to 22% of single-level TLIF patients,[8–10] and revision for pseudarthrosis occurs in 8% of patients with single- or double-level TLIF.[11] Surgical technique, instrumentation type, biologics, nutrition, smoking, past medical history, revision surgery, radiographic parameters, and medications have all been identified as influencing the rate of fusion after spine surgery.[6,12–14] Pseudarthrosis commonly presents with symptoms of new pain or neurological change, but about 22% can be asymptomatic.[15] Pseudarthrosis accounts for 45% to 56% of all revisions, and it remains a common problem after spinal fusion.[16] Pseudarthrosis is also associated with a significantly higher cost for patients.[17]

Recombinant human bone morphogenetic protein-2 (rhBMP-2, or BMP for short; Infuse, Medtronic, Minneapolis, MN, USA, and Sofamor Danek, Memphis, TN, USA) is a transforming growth factor-β used to induce bone formation in spine fusion.[18] Only a select few of more than 20 BMPs have been shown to have properties related to fusion.[19] BMP has been used in orthopedic fusions as in maxillofacial reconstruction.[17,19] BMP is approved by the Food and Drug Administration for anterior lumbar interbody fusions, but surgeons commonly use it off-label in open and minimally invasive (MIS) TLIF as an adjunct for allograft and autograft bone with hopes of increasing fusion rates.[20,21] BMP has a higher fusion rate than iliac crest bone graft (ICBG) in posterior lumbar fusion and anterior lumbar interbody fusion, but BMP's role in TLIF remains controversial.[20,21]

The purpose of the present study was to investigate whether BMP use reduces the rate of pseudarthrosis in single-level TLIF and to identify other factors associated with pseudarthrosis.

# METHODS

## Inclusion and Exclusion Criteria

This is a retrospective analysis at a single high-volume tertiary care center in the United States of adult patients undergoing primary single-level TLIF for degenerative pathologies with a minimum of 1-year follow-up. Adult patients undergoing MIS/hybrid single-level TLIF with a minimum of 1-year follow-up were included. Patients were excluded if they were younger than 18 years, had less than 1 year of clinical follow-up, underwent open TLIF procedure, underwent ICBG use without BMP, or had a history of prior fusion, infection, trauma, or malignancy. Patients with prior microdiscectomy and laminectomy were not excluded.

## Data Source

All orthopedic and neurosurgical spine patients undergoing primary single-level TLIF surgery from 2012 to 2019 were included in the analysis. Data were collected by manual review of electronic medical records for demographics, intraoperative variables, surgical outcomes, and 90-day perioperative outcomes. Demographics include age, medical comorbidities, Charlson Comorbidity Index, American Society of Anesthesiologists classification, and tobacco use. Intraoperative variables included surgical technique, graft choice, interbody cage, blood loss, and length of stay. When possible, the volumes of BMP and cancellous allograft were recorded.

Complications for single-level TLIF patients were reviewed from the time of surgery until their last follow-up date. Medical complication was defined as cardiac, pulmonary, urinary, or any other nonsurgical complications. Wound complications were defined as superficial or deep infection and wound dehiscence. Motor neurological complications included weakness on physical examination and cauda equina syndrome. Other neurological complications tracked were radiculitis, sensory deficit, and persistent pain. Reoperation and the reason for reoperation were reviewed from the operation reports until the final clinical follow-up. Development of pseudarthrosis and revision for pseudarthrosis were tracked until final clinical follow-up. Patients were classified as having pseudarthrosis in our study if they had a minimum of 6 months of postoperative[7] radiographic evidence of progressive radiolucent lines around implants, with incomplete graft integration on radiographs or computed tomography images. Patients who underwent revision for pseudarthrosis all had intraoperative evidence of pseudarthrosis noted in their surgical note by incomplete bridging bone and persistent motion at the index surgical level.

## Surgical Technique

MIS-TLIF was performed via dual lumbar posterior paramedian or Wiltse incision of approximately 2 to 3 cm using a muscle-sparing approach and limited exposure of the facet capsule and lamina. Interbody fusion was performed with endplate preparation in which

the intervertebral disc was removed, and the vertebral endplates were prepared to expose bleeding bone. The hybrid midline technique utilizes both the midline approach for decompression and insertion of interbody device, as well as the paramedian incisions for screw placement. This technique combines the advantages of a midline decompression while avoiding lateral dissection and minimizing soft-tissue trauma with MIS screw insertion.[22] Cage placement was performed after placing allograft and autograft (±BMP) anterior and contralateral to the cage to provide graft and BMP containment. All TLIF procedures were performed with bilateral pedicle screw placement. Depending on surgeon preference, pedicle screws were placed either before or after interbody implantation.

### Statistical Analysis

Statistical analysis was conducted to compare patients who had reoperation for pseudarthrosis and those who did not in terms of BMP use, demographics, and surgical factors. Independent sample *t* test was used to compare quantitative variables, and $\chi^2$ test was used for categorical variables. Multiple logistic regression was used to find the odds ratios for predictors of reoperation for pseudarthrosis. Kaplan-Meier survival curve and Mantel-Cox test were used to determine the difference in survivorship to reoperation. SPSS software was used for statistical analysis (IBM, Armonk, New York). Statistical significance was set at $P < 0.05$.

## RESULTS

### Demographics

There were 148 primary single-level TLIFs: 81 (54.7%) with BMP use and 67 (45.3%) with no BMP use. No differences in demographics or medical comorbidities were found between patients who received BMP and those who did not (Table 1). The mean age was 59.3 years, and 52.0% were women. Smoking status was similar between BMP and non-BMP groups (BMP 40.7% vs non-BMP 38.8%, $P = 0.811$). Mean body mass index was 29.2 and was not different between groups (BMP 30.0 vs non-BMP 28.2, $P = 0.125$). Charlson Comorbidity Index (BMP 2.2 vs non-BMP 2.8, $P = 0.113$) and American Society of Anesthesiologist (BMP 2.3 vs non-BMP 2.3, $P = 0.818$) were similar. There were similar proportions of patients who were diabetic (BMP 12.3% vs non-BMP 16.4% $P = 0.480$) or had chronic obstructive pulmonary disease (COPD) (BMP 6.2% vs non-BMP 7.5%, $P = 0.756$). BMP patients had longer average follow-up (BMP 790.4 vs non-BMP 560.3 days, $P < 0.001$).

### Surgical Outcomes

Patients who received BMP had lower estimated blood loss (EBL; Table 2; BMP 169.6 ± 133.2 vs non-BMP 257.3 ± 206.6 mL, $P = 0.002$). The average volume of BMP used was 1.5 mL, and cancellous allograft used was on average 32.1 mL in non-BMP cases and 38.0 mL in BMP cases ($P = 0.182$). BMP cases were more likely to have local autograft ($P = 0.001$), ICBG ($P = 0.014$), and cellular bone allograft ($P < 0.001$). BMP patients received expandable interbody cages more often (77.8% vs 34.4%, $P < 0.001$). There were no differences in other operative characteristics between BMP and non-BMP groups.

### Complications

Postoperative complication rates at 90 days were 14.8% in the BMP group and 22.4% in the non-BMP group (Table 3, $P = 0.235$). There was no difference in wound complications, medical complications, or neurological complications in the perioperative 90-day period until the last follow-up. Of the neurological complications, the most common was new or recurrent

**Table 1.** Comparison of demographics among single-level TLIFs with and without BMP use.

| Demographics | No BMP | BMP | Total | *P* |
|---|---|---|---|---|
| *N* | 67 (45.3%) | 81 (54.7%) | 148 | |
| Age, y | 60.4 ± 11.7 | 58.5 ± 12.0 | 59.3 ± 11.9 | 0.339 |
| Female gender | 39 (56.7%) | 39 (48.1%) | 77 (52.0%) | 0.299 |
| Body mass index | 28.2 ± 5.7 | 30.0 ± 8.3 | 29.2 ± 7.3 | 0.125 |
| Current/past smoker | 26 (38.8%) | 33 (40.7%) | 59 (39.9%) | 0.811 |
| Charlson Comorbidity Index | 2.8 ± 2.5 | 2.2 ± 1.5 | 2.5 ± 2.1 | 0.113 |
| Diabetes mellitus | 11 (16.4%) | 10 (12.3%) | 21 (14.2%) | 0.480 |
| Diabetes with end-organ damage | 3 (4.5%) | 2 (2.5%) | 5 (3.4%) | 0.501 |
| History of chronic obstructive pulmonary disease | 5 (7.5%) | 5 (6.2%) | 10 (6.8%) | 0.756 |
| American Society of Anesthesiologists classification | 2.3 ± 0.7 | 2.3 ± 0.6 | 2.3 ± 0.6 | 0.818 |
| Days of follow-up | 560.3 ± 275.4 | 790.4 ± 440.2 | 686.2 ± 390.8 | <0.001 |

Abbreviations: BMP, recombinant human bone morphogenetic protein 2; TLIF, transforaminal lumbar interbody fusion.
*Note:* Data presented as *n* (%) or mean ± SD.

**Table 2.** Comparison of surgical outcomes among single-level TLIFs with and without BMP use.

| Surgical Outcomes | No BMP | BMP | Total | *P* |
|---|---|---|---|---|
| Operative time, min | 219.1 ± 60.2 | 220.6 ± 70.7 | 219.9 ± 65.9 | 0.894 |
| Estimated blood loss, mL | 257.3 ± 206.6 | 169.6 ± 133.2 | 209.0 ± 175.0 | 0.002 |
| Fluoroscopic dosage, mGy | 54.6 ± 42.2 | 54.9 ± 57.1 | 54.8 ± 51.6 | 0.973 |
| Tranexamic acid, mL | 1746.7 ± 1074.2 | 2152.2 ± 979.5 | 1922.4 ± 1037.0 | 0.297 |
| Intraoperative complications | 4 (6.0%) | 4 (4.9%) | 8 (5.4%) | 0.782 |
| Durotomy | 2 (3.0%) | 2 (2.5%) | 4 (2.7%) | 0.847 |
| Neuromonitoring changes | 2 (3.0%) | 2 (2.5%) | 4 (2.7%) | 0.847 |
| BMP volume, mL | 0 ± 0 | 1.5 ± 0.4 | 1.5 ± 0.4 | <0.001 |
| Cancellous allograft use | 6 (9.0%) | 6 (7.4%) | 12 (8.1%) | 0.731 |
| Cancellous allograft volume, mL | 32.1 ± 8.2 | 38.0 ± 18.7 | 36.8 ± 17.2 | 0.182 |
| Local autograft use | 46 (68.7%) | 73 (90.1%) | 119 (80.4%) | 0.001 |
| Iliac crest bone graft use | 0 (0.0%) | 7 (8.6%) | 7 (4.7%) | 0.014 |
| Demineralized bone matrix use | 6 (9.0%) | 6 (7.4%) | 12 (8.1%) | 0.731 |
| Bone marrow aspirate use | 8 (11.9%) | 16 (29.8%) | 24 (16.2%) | 0.199 |
| Cellular bone allograft | 35 (52.2%) | 4 (4.9%) | 39 (26.4%) | <0.001 |
| Expandable cage use | 33 (34.4%) | 63 (77.8%) | 96 (64.9%) | <0.001 |
| Length of stay, d | 3.5 ± 3.1 | 3.0 ± 2.1 | 3.2 ± 2.6 | 0.219 |

Abbreviations: BMP, recombinant human bone morphogenetic protein 2; TLIF, transforaminal lumbar interbody fusion.
*Note:* Data presented as *n* (%) or mean ± SD.

radiculopathy, which occurred in 9.9% in BMP vs 19.4% in non-BMP ($P$ = 0.098). Of those, 23.8% of radiculopathy (BMP 25.0% vs non-BMP 23.1%, $P$ = 0.920) resolved without surgical intervention.

## Return to Operating Room

BMP use did not affect pseudarthrosis diagnosed at a minimum of 1-year follow-up (Table 3, BMP 6.2% vs no BMP 7.5%, $P$ = 0.756). The majority (4.1%) of pseudarthrosis occurred in the 1- to 2-year postoperative period. Of the 10 total patients who showed clinical evidence of pseudarthrosis, 8 needed reoperation and 2 were treated nonoperatively (Table 4). BMP use did not reduce reoperation for pseudarthrosis (BMP 3.7% vs no BMP 7.5%, $P$ = 0.314), did not alter the time to reoperation ($P$ = 0.877, Figure), and did not affect revision rates at any time point until the last follow-up. The revision rate at follow-up was 11.1% for BMP and 17.9% for non-BMP patients ($P$ = 0.238). Reasons for reoperation did not differ between the BMP and non-BMP groups. A total of 12.8% of patients underwent reoperations involving the same level, while 6.1% had reoperations at an adjacent level. A total of 6.1% of patients had revision for adjacent segments stenosis, while 5.4% had revisions for central or foraminal stenosis.

Patients who underwent revision for pseudarthrosis tended to be younger (Table 5, revised 55.1 ± 12.9 vs not revised 59.6 ± 11.8 years old, $P$ = 0.304), had diabetes

**Table 3.** Comparison of perioperative complications among single-level TLIFs with and without BMP use.

| Postoperative Complications | No BMP | BMP | Total | *P* |
|---|---|---|---|---|
| Postoperative complications 0–90 d | 15 (22.4%) | 12 (14.8%) | 27 (18.2%) | 0.235 |
| Wound complications 0–90 d | 1 (1.5%) | 0 (0.0%) | 1 (0.7%) | 0.270 |
| Medical complications 0–90 d | 5 (7.5%) | 4 (4.9%) | 9 (6.1%) | 0.522 |
| Neurological complication 0–90 d | 3 (4.5%) | 5 (6.2%) | 8 (5.4%) | 0.650 |
| **Complications at 90-d Follow-Up** | | | | |
| Any readmission to follow-up | 11 (16.4%) | 8 (9.9%) | 19 (12.8%) | 0.236 |
| All postoperative complications or readmission to follow-up | 29 (43.3%) | 26 (32.1%) | 55 (37.2%) | 0.161 |
| Any neurological complications postoperative follow-up | 20 (29.9%) | 17 (21.0%) | 37 (25.0%) | 0.215 |
| Motor weakness | 2 (3.0%) | 1 (1.2%) | 3 (2.0%) | 0.452 |
| Stenosis | 0 (0.0%) | 1 (1.2%) | 1 (0.7%) | 0.361 |
| Radiculopathy | 13 (19.4%) | 8 (9.9%) | 21 (14.2%) | 0.098 |
| Radiculopathy resolved spontaneously without surgery | 3 (23.1%) | 2 (25.0%) | 5 (23.8%) | 0.920 |
| Sensory deficit | 2 (3.0%) | 3 (3.7%) | 5 (3.4%) | 0.810 |
| Persistent pain | 4 (6.0%) | 3 (3.7%) | 7 (4.7%) | 0.518 |
| Pseudarthrosis at a minimum of 1-y follow-up | 5 (7.5%) | 5 (6.2%) | 10 (6.8%) | 0.756 |
| 0–1 y | 1 (1.5%) | 2 (2.5%) | 3 (2.0%) | 0.549 |
| 1–2 y | 4 (6.0%) | 2 (2.5%) | 6 (4.1%) | |
| 2+ y | 0 (0.0%) | 1 (1.2%) | 1 (0.7%) | |
| Medical complications, postoperative to follow-up | 5 (7.5%) | 4 (4.9%) | 9 (6.1%) | 0.522 |
| Wound complications, postoperative to follow-up | 2 (3.0%) | 1 (1.2%) | 3 (2.0%) | 0.452 |

Abbreviations: BMP, recombinant human bone morphogenetic protein 2; TLIF, transforaminal lumbar interbody fusion.
*Note:* Data presented as n (%).

**Table 4.** Comparison of reoperations among single-level TLIFs with and without BMP use.

| Reoperation | No BMP | BMP | Total | *P* |
|---|---|---|---|---|
| Return to OR 30 d | 2 (3.0%) | 3 (3.7%) | 5 (3.4%) | 0.810 |
| Return to OR 90 d | 3 (4.5%) | 3 (3.7%) | 6 (4.1%) | 0.812 |
| Return to OR to follow-up | 12 (17.9%) | 9 (11.1%) | 21 (14.2%) | 0.238 |
| Levels Involved | | | | |
| Reoperation at the same level as index surgery | 11 (16.4%) | 9 (9.9%) | 19 (12.8%) | 0.236 |
| Reoperation at the adjacent level of index surgery | 5 (7.5%) | 4 (4.9%) | 9 (6.1%) | 0.522 |
| Reason for reoperation | | | | |
| Any neurological symptom | 10 (14.9%) | 8 (9.9%) | 18 (12.2%) | 0.350 |
| Pseudarthrosis | 5 (7.5%) | 3 (3.7%) | 8 (5.4%) | 0.314 |
| Adjacent segment stenosis | 5 (7.5%) | 4 (4.9%) | 9 (6.1%) | 0.522 |
| Central or foraminal stenosis | 3 (4.5%) | 5 (6.2%) | 8 (5.4%) | 0.65 |
| Wound infection/complication | 0 (0.0%) | 1 (1.2%) | 1 (0.7%) | 0.361 |
| Instrumentation (migration/prominence/failure) | 0 (0.0%) | 1 (1.2%) | 1 (0.7%) | 0.361 |
| Hematoma/seroma | 0 (0.0%) | 1 (1.2%) | 1 (0.7%) | 0.361 |
| Days to revision surgery | 400.3 ± 260.4 | 394.6 ± 297.0 | 398.0 ± 267.9 | 0.965 |

Abbreviations: BMP, recombinant human bone morphogenetic protein 2; OR, operating room; TLIF, transforaminal lumbar interbody fusion.
*Note:* Reoperations and reason for reoperation were recorded by clinical and operative notes at the study institution.

with end-organ damage (revised 37.5% vs not revised 1.4%, $P < 0.001$), and had a history of COPD (revised 25.0% vs not revised 5.7%, $P = 0.035$). Clinical diagnosis of pseudarthrosis occurred 1 to 2 years after index surgery in 60.0% (6/10) of patients later revised for pseudarthrosis. Time to reoperation for pseudarthrosis was on average 536.3 days after index surgery, though that was not significantly different from time to revision for other reasons (305.8 days, $P = 0.057$).

Multiple logistic regression analysis demonstrated that diabetes mellitus with end-organ damage (Table 6; OR 122.6, $P = 0.001$) was the strongest risk factor for later revision for pseudarthrosis. BMP use was not protective (OR = 0.2, $P = 0.269$), nor was the use of an expandable cage (OR 2.6, $P = 0.412$). History of COPD, smoking, and bone marrow aspirate use also did not affect the risk of reoperation for pseudarthrosis.

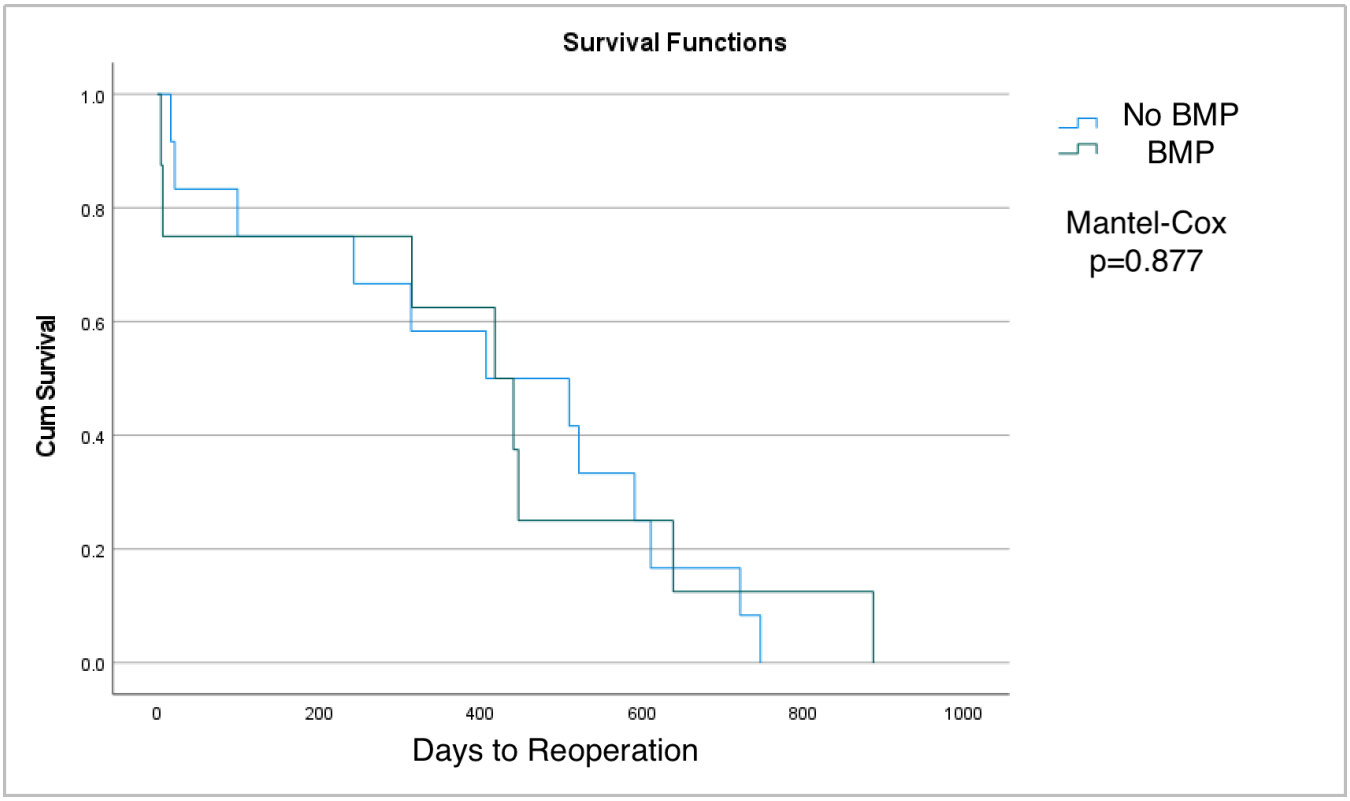


**Figure.** Kaplan-Meier survivorship curve for days to reoperation between patients who received recombinant human bone morphogenetic protein 2 (BMP) and those who did not in the index surgery. Abbreviation: Cum, cumulative.

**Table 5.** Comparison of single-level transforaminal lumbar interbody fusions that underwent reoperation for pseudarthrosis vs those that did not.

| Variable | No Pseudarthrosis Reoperation | Reoperation for Pseudarthrosis | Total | *P* |
|---|---|---|---|---|
| *N* | 140 (94.6%) | 8 (5.4%) | 148 | |
| **Demographic Characteristics** | | | | |
| Age, y | 59.6 ± 11.8 | 55.1 ± 12.9 | 59.3 ± 11.9 | 0.304 |
| 18–29 | 0 (0%) | 0 (0%) | 0 (0%) | 0.876 |
| 30–41 | 10 (7.1%) | 1 (9.1%) | 11 (7.4%) | |
| 42–53 | 34 (24.3%) | 2 (25.0%) | 36 (24.3%) | |
| 54–65 | 44 (31.4%) | 3 (37.5%) | 47 (31.8%) | |
| ≥66 | 52 (37.1%) | 2 (25.0%) | 54 (36.5%) | |
| Female Gender | 74 (52.9%) | 3 (37.5%) | 77 (52.0%) | 0.398 |
| BMI | 29.0 ± 7.2 | 32.7 ± 8.5 | 39.2 ± 7.3 | 0.155 |
| Current/past smoker | 55 (39.3%) | 4 (50.0%) | 59 (399%) | 0.547 |
| Charlson Comorbidity Index | 2.4 ± 2.1 | 2.9 ± 2.2 | 2.4 ± 2.1 | 0.565 |
| Diabetes mellitus | 18 (12.9%) | 3 (37.5%) | 21 (14.2%) | 0.052 |
| Diabetes with end-organ damage | 2 (1.4%) | 3 (37.5%) | 5 (3.5%) | <0.001 |
| History of COPD | 8 (5.7%) | 2 (25.0%) | 10 (6.8%) | 0.035 |
| American Society of | | | | 0.298 |
| Anesthesiologist classification | 2.2 ± 0.6 | 2.5 ± 0.9 | 2.3 ± 0.6 | |
| Days of follow-up | 679.3 ± 295.1 | 806.9 ± 299.9 | 686.2 ± 390.8 | 0.371 |
| **Index Surgery Operative Characteristics** | | | | |
| Operative time, min | 218.1 ± 63.5 | 251.8 ± 98.7 | 219.9 ± 65.9 | 0.160 |
| Estimated blood loss, mL | 208.0 ± 178.8 | 225.0 ± 92.6 | 208.9 ± 175.0 | 0.791 |
| Fluoroscopic dosage, mGy | 50.8 ± 45.8 | 110.5 ± 91.2 | 54.8 ± 51.6 | 0.003 |
| BMP use | 78 (55.7%) | 3 (37.5%) | 81 (54.7%) | 0.314 |
| Average BMP volume, mL | 1.5 ± 0.4 | 1.4 ± 0.0 | 1.5 ± 0.4 | 0.565 |
| Cancellous allograft use | 98 (70.0%) | 5 (62.5%) | 103 (69.3%) | 0.654 |
| Cancellous allograft volume, mL | 37.1 ± 17.6 | 33.0 ± 6.7 | 36.8 ± 17.2 | 0.612 |
| Local autograft use | 113 (80.7%) | 6 (75.0%) | 119 (80.4%) | 0.692 |
| Iliac crest bone graft use | 6 (4.3%) | 1 (12.5%) | 8 (4.7%) | 0.287 |
| Demineralized bone matrix use | 12 (8.6%) | 0 (0.0%) | 12 (8.1%) | 0.388 |
| Tranexamic acid, mL | 1776.9 ± 961.4 | 3240.2 ± 827.0 | 1922.4 ± 1037.0 | 0.017 |
| Bone marrow aspirate use | 22 (15.7%) | 2 (25.0%) | 24 (16.2%) | 0.488 |
| Cellular bone allograft | 37 (26.4%) | 2 (25.0%) | 39 (26.4%) | 0.929 |
| Expandable cage use | 90 (64.3%) | 6 (75.0%) | 96 (64.9%) | 0.537 |
| Length of stay, d | 3.2 ± 2.7 | 4.3 ± 1.8 | 3.2 ± 2.6 | 0.261 |
| Pseudarthrosis at a minimum of 1 | 2 (1.4%) | 8 (80%) | 10 (6.8%) | < 0.001 |
| y follow-up | | | | |
| 0–1 y | 1 (0.75%) | 2 (25.0%) | 3 (2.0%) | < 0.001 |
| 1–2 y | 1 (0.7%) | 5 (62.5%) | 6 (4.1%) | |
| 2+ y | 0 (0.0%) | 1 (12.5%) | 1 (0.7%) | |
| Days to revision surgery | 305.8 ± 279.3 | 536.3 ± 189.1 | 398.0 ± 267.9 | 0.057 |
| **Neurological Symptoms After Index Surgery** | | | | |
| Motor deficit | 2 (1.4%) | 1 (12.5%) | 3 (2.0%) | 0.031 |
| Stenosis | 1 (0.7%) | 0 (0.0%) | 0 (0.0%) | 0.810 |
| Radiculopathy | 19 (13.6%) | 2 (25.0%) | 21 (14.2%) | 0.368 |
| Radiculopathy resolved | 5 (26.3%) | 0 (0.0%) | 5 (23.8%) | |
| spontaneously without surgery | | | | 0.406 |
| Sensory deficit | 3 (2.1%) | 2 (25.0%) | 5 (3.4%) | <0.001 |
| Persistent pain | 7 (5.0%) | 0 (0.0%) | 7 (4.7%) | 0.517 |

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; TLIF, transforaminal lumbar interbody fusion.
*Note:* Data presented as *n* (%) or mean ± SD.

## DISCUSSION

This retrospective study demonstrated no significant benefit from the use of BMP in single-level TLIF on developing complications or clinically significant pseudarthrosis. Chang et al reviewed the use of BMP with allograft or autograft in posterior MIS interbody fusions, showing a fusion rate of 65% to 100%, which was statistically similar to ICBG alone, autograft plus allograft, and bone marrow aspirate.[23] Overley et al also found no difference in radiographic fusion and rate of revision surgery with BMP use in single-level MIS-TLIF.[24] In our data, the fusion rate was 93.6% with BMP and 92.5% without BMP, which corresponds well to the prior findings of 3% to 22% pseudarthrosis after single-level TLIF.[8–10] However, Nandyala et al showed BMP to achieve superior arthrodesis (92%) compared with silicate-substituted calcium phosphate (65%) in single-level MIS-TLIF.[25]

Singh et al reported a 6.8% revision rate for pseudarthrosis and 8.6% total revision rate in 610 single- to double-level MIS-TLIF with a minimum of 1-year follow-up.[26] This rate is slightly higher than the 5.4% revision for pseudarthrosis and lower than the 14.2% total revision rate in our study at a similar follow-up

**Table 6.** Multiple logistic regression analysis of outcome variables given use of BMP.

| Variable | OR (95 % CI) | *P* |
|---|---|---|
| BMP use | 0.2 (0.01–3.7) | 0.269 |
| Age 18–41 y (ref: age >41 y) | 0.6 (0.03–15.2) | 0.782 |
| Smoking history | 2.2 (0.3–18.1) | 0.461 |
| History of COPD | 7.8 (0.4–147.5) | 0.170 |
| Diabetes with end-organ damage | 112.6 (5.7–2225.8 ) | **0.002** |
| Bone marrow aspirate use | 1.1 (0.1–15.9 ) | 0.918 |
| Local autograft use | 0.3 (0.02–4.1 ) | 0.346 |
| Iliac crest bone graft use | 21.9 (0.7–694.5 ) | 0.080 |
| Cellular bone allograft use | 0.4 (0.02–7.3) | 0.534 |
| Expandable cage use | 2.6 (0.3–25.5) | 0.412 |
| ASA classification>3 (ref: ≤3) | 0.6 (0.001–391.0) | 0.874 |

Abbreviations: ASA, American Society of Anesthesiologists; BMP, recombinant human bone morphogenetic protein 2; COPD, chronic obstructive pulmonary disease; ref, reference.
*Note:* Values in boldface represent statistical significance at $P < 0.05$. Nagelkerke $R^2 = 0.381$. Hosmer Lemeshow test $P = 0.731$.

time. The use of bilateral pedicle screw fixation in our study and unilateral pedicle screw fixation in Singh et al may account for this difference.[26] In Singh et al, patients undergoing revision for pseudarthrosis were significantly younger and had higher rates of smoking trending toward significance ($P = 0.054$).[26] These data support our findings; additionally, we demonstrated that diabetes mellitus with end-organ damage was an independent risk factor. Smoking did not affect the rate of pseudarthrosis or BMP use in our study. Emami et al also failed to show smoking to be a risk factor for pseudarthrosis after MIS-TLIF.[6]

Technical differences in arthrodesis and pedicle screw could indeed account for pseudarthrosis rates. Gologorsky et al demonstrated higher rates of pseudarthrosis in TLIF using unilateral pedicle screw fixation compared with bilateral screw fixation.[27] Bilateral pedicle screw fixation was standard in the current study. This helps explain why the revision rate for pseudarthrosis is lower in the current study compared with the results from unilateral screw fixation in Singh et al.[28] The expandable cage was also identified to possibly affect pseudarthrosis rates, but the results of the bivariate and multivariate analysis did not show an increased risk of pseudarthrosis requiring revision from use of expandable interbody cage. Hawasli et al reported similarly in a study of MIS-TLIF that use of an expandable cage did not increase the risk of pseudarthrosis.[29]

Poorly controlled diabetes with end-organ damage was a risk factor for revision for pseudarthrosis. Glassman et al found significantly higher rates of nonunion in diabetics after lumbar spine surgery, but no difference was found in fusion rates between insulin-dependent and noninsulin-dependent diabetics.[30] Contrarily, Bendo et al reported that diabetic patients did not show worse outcomes after posterior lumbar fusions.[31] Takahashi et al noted pseudarthrosis rates of 20% in diabetes vs 3% in nondiabetics ($P = 0.095$) after lumbar surgery.[32] Freedman et al noted no difference in infection or nonunion rates in diabetic patients with spondylolisthesis in the Spine Patients Outcomes Research Trial.[33]

With no consensus for radiographic criteria for diagnosis of pseudarthrosis, most diagnoses are made clinically with correlation with multiple imaging modalities.[34] Computed tomography can show subsidence or lucency around the fusion construct, and plain radiographs provide evidence of deficient fusion mass morphology. Surgical exploration remains the gold standard of diagnosis, but it is rarely performed due to morbidity.[34] Most pseudarthrosis patients in our study (8/10) underwent revision and had intraoperative evidence of incomplete bony integration and movement at the fused segment, confirming pseudarthrosis.

It is unclear why some pseudarthroses remain asymptomatic. Prior data have shown that younger age and noninstrumented fusions increased the likelihood of symptomatic pseudarthrosis.[35,36] All patients in Singh et al who presented with radiographically confirmed pseudarthrosis were symptomatic and needed revision arthrodesis.[26] Pseudarthrosis revision surgery was reported to cost $20,267.[26] Emami et al identified revision surgery to be a risk factor for pseudarthrosis (8%) in MIS-TLIF patients at a minimum of 1-year follow-up.[11] Patient satisfaction and symptoms are also related to psychosocial factors.[37–39]

Chun et al conducted a meta-analysis of pseudarthrosis in lumbar fusions and found that BMP-2 has a higher fusion rate (94%) compared with autograft (89%) and demineralized bone matrix (89%).[37,40] Surgical techniques reviewed[40] were single-[41,42] and multi-level[43] posterolateral lumbar arthrodesis with pedicle screw and rods using BMP vs ICBG. BMP group had significantly lower EBL in our study, in which open TLIF procedures were excluded entirely. Several studies found higher use of BMP[44,45] and lower blood loss in MIS-TLIF compared with open TLIF.[45–47] Hey et al attributed differences in EBL to intraoperative factors and not BMP use.[48]

Given the absence of protection against reoperation, pseudarthrosis, or complications, BMP use was not demonstrated by the authors as a cost-effective strategy in single-level TLIF. Glassman et al reported an average cost of $4,764.90 for BMP use in 1- to 4-level lumbar fusions.[30] Furthermore, BMP has been associated with clinical side effects including inflammatory complications such as cervical spine swelling and seromas,

postoperative radiculitis, ectopic bone formation, vertebral bone resorption, subsidence, retrograde ejaculation, bladder retention, hematoma, wound dehiscence, and infection.[49] Singh et al reported 1.7% revision for heterotopic ossification and osteolysis after small kit (4.2 mg) and large kit (12 mg) BMP use in index MIS-TLIF.[26] Hegelson et al reported a 41% osteolysis rate at 1 to 2 years with 6 mg of BMP use in TLIF.[50] Mindea et al report 11.4% radicular symptoms not attributable to structural etiologies with 4.2 mg BMP used per level.[51] In our data, BMP use did not increase perioperative or postoperative complications. Postoperative radiculitis rate was 14.2% with or without BMP use. Hofstetter et al showed a positive correlation between dosage of BMP used and complications in a meta-analysis of spinal arthrodesis.[52] Small (4.2 mg or 2.8 mL) and extra small (2.1 mg or 1.4 mL) dosages used in our study may result in no discernable increase in complication rates with BMP.

### Limitations

The retrospective design limits this study's ability to randomize patients and determine causation. This study results are from a high-volume single center and may not be applicable to a smaller, low-volume center. It is difficult to control for technique differences among surgeons, and BMP application to contralateral posterior elements and disc space was not analyzed. The definition of clinical pseudarthrosis as a surgeon depends on documentation with radiographic correlation of pseudarthrosis. Not all patients noted to have pseudarthrosis were revised. Although the volume of some grafts such as BMP and cancellous allograft was routinely included, the documentation of the amounts of other grafts used (demineralized bone matrix, bone marrow aspirate, local autograft, etc) was noted to be inaccurate and inconsistent. Therefore, those graft variables were analyzed as binomial variables instead of characterizing volumetric differences. Biological use is subject to surgeon preference, and selection bias may exist for which the patient receives BMP or other grafts. BMP is often used in conjunction with other biologics and grafts, which may confound the relationship between BMP and pseudarthrosis. Furthermore, surgeon techniques for pedicle screw placement, rod materials, and arthrodesis techniques could all affect pseudarthrosis rates but were out of the scope of the analysis in the current article. Surgeon preference and contractual obligations to certain cage types and brands could not be adequately accounted for, but this does represent real practice environments where such factors can influence implant choice.

## CONCLUSION

BMP did not reduce pseudarthrosis and associated reoperations in single-level TLIF or affect rates of postoperative complications. Patients with a history of diabetes with end-organ damage are at higher risk of needing reoperation for pseudarthrosis after single-level TLIF.

## REFERENCES


1. Uçar BY, Özcan Ç, Polat Ö, Aman T. Transforaminal lumbar Interbody fusion for lumbar degenerative disease: patient selection and perspectives. *Orthop Res Rev*. 2019;11:183–189. doi:10.2147/ORR.S204297

2. Garg B, Mehta N. Minimally invasive transforaminal lumbar interbody fusion (MI-TLIF): a review of indications, technique, results and complications. *J Clin Orthop Trauma*. 2019;10(Suppl 1):S156–S162. doi:10.1016/j.jcot.2019.01.008

3. Mobbs RJ, Phan K, Malham G, Seex K, Rao PJ. Lumbar interbody fusion: techniques, indications and comparison of interbody fusion options including PLIF. *J Spine Surg*. 2015;1(1):2–18. doi:10.3978/j.issn.2414-469X.2015.10.05

4. Derman PB, Albert TJ. Interbody fusion techniques in the surgical management of degenerative lumbar spondylolisthesis. *Curr Rev Musculoskelet Med*. 2017;10(4):530–538. doi:10.1007/s12178-017-9443-2

5. Macki M, Bydon M, Weingart R, et al. Posterolateral fusion with interbody for lumbar spondylolisthesis is associated with less repeat surgery than posterolateral fusion alone. *Clin Neurol Neurosurg*. 2015;138:117–123. doi:10.1016/j.clineuro.2015.08.014

6. Emami A, Faloon M, Sahai N, et al. Risk factors for pseudarthrosis in minimally-invasive transforaminal lumbar interbody fusion. *Asian Spine J*. 2018;12(5):830–838. doi:10.31616/asj.2018.12.5.830

7. Rager O, Schaller K, Payer M, Tchernin D, Ratib O, Tessitore E. SPECT/CT in differentiation of pseudarthrosis from other causes of back pain in lumbar spinal fusion: report on 10 consecutive cases. *Clin Nucl Med*. 2012;37(4):339–343. doi:10.1097/RLU.0b013e318239248b

8. Challier V, Boissiere L, Obeid I, et al. One-level lumbar degenerative spondylolisthesis and posterior approach: is transforaminal lateral Interbody fusion mandatory? A randomized controlled trial with 2-year follow-up. *Spine (Phila Pa 1976)*. 2017;42(8):531–539. doi:10.1097/BRS.0000000000001857

9. Rihn JA, Patel R, Makda J, et al. Complications associated with single-level transforaminal lumbar interbody fusion. *Spine J*. 2009;9(8):623–629. doi:10.1016/j.spinee.2009.04.004

10. Overley SC, McAnany SJ, Anwar MA, et al. Predictive factors and rates of fusion in minimally invasive transforaminal lumbar interbody fusion utilizing rhBMP-2 or mesenchymal stem cells. *Int J Spine Surg*. 2019;13(1):46–52. doi:10.14444/6007

11. Emami A, Faloon M, Sahai N, et al. Risk factors for pseudarthrosis in minimally-invasive transforaminal lumbar interbody fusion. *Asian Spine J*. 2018;12(5):830–838. doi:10.31616/asj.2018.12.5.830

12. Adogwa O, Buchowski JM, Lenke LG, et al. Comparison of rod fracture rates in long spinal deformity constructs after transforaminal versus anterior lumbar interbody fusions: a single-institution analysis. *J Neurosurg Spine*. 2019;32(1):1–8. doi:10.3171/2019.7.SPINE19630

13. Jenkins NW, Parrish JM, Mayo BC, et al. The identification of risk factors for increased postoperative pain following minimally invasive transforaminal lumbar interbody fusion. *Eur Spine J*. 2020;29(6):1304–1310. doi:10.1007/s00586-020-06344-4

14. Teton ZE, Cheaney B, Obayashi JT, Than KD. PEEK Interbody devices for multilevel anterior cervical discectomy and fusion: association with more than 6-fold higher rates of pseudarthrosis compared to structural allograft. *J Neurosurg Spine*. 2020:1–7. doi:10.3171/2019.11.SPINE19788

15. Jung J-M, Chung CK, Kim CH, Yang SH, Ko YS. Prognosis of symptomatic pseudarthrosis observed at 1 year after lateral lumbar interbody fusion. *Spine (Phila Pa 1976)*. 2021;46(18):E1006–E1013. doi:10.1097/BRS.0000000000003980

16. Leven D, Cho SK. Pseudarthrosis of the cervical spine: risk factors, diagnosis and management. *Asian Spine J*. 2016;10(4):776–786. doi:10.4184/asj.2016.10.4.776

17. Jain A, Yeramaneni S, Kebaish KM, et al. Cost-utility analysis of rhBMP-2 use in adult spinal deformity surgery. *Spine (Phila Pa 1976)*. 2020;45(14):1009–1015. doi:10.1097/BRS.0000000000003442

18. Cohen LL, Yang BW, O'Neill NP, Proctor MR, Glotzbecker MP, Hedequist DJ. Use of recombinant human bone morphogenetic protein for revision cervical spine fusion in children with down syndrome: a case series. *J Neurosurg Pediatr*. 2020:1–5. doi:10.3171/2019.11.PEDS19622

19. Herford AS. The use of recombinant human bone morphogenetic protein-2 (rhBMP-2) in maxillofacial trauma. *Chin J Traumatol*. 2017;20(1):1–3. doi:10.1016/j.cjtee.2016.05.004

20. Oliveira O de, Martins SPR, Lima W de, Gomes MM. The use of bone morphogenetic proteins (BMP) and pseudarthrosis, a literature review. *Rev Bras Ortop*. 2017;52(2):124–140. doi:10.1016/j.rboe.2016.03.005

21. Vaz K, Verma K, Protopsaltis T, Schwab F, Lonner B, Errico T. Bone grafting options for lumbar spine surgery: a review examining clinical efficacy and complications. *SAS J*. 2010;4(3):75–86. doi:10.1016/j.esas.2010.01.004

22. Reinshagen C, Ruess D, Walcott BP, Molcanyi M, Goldbrunner R, Rieger B. A novel minimally invasive technique for lumbar decompression, realignment, and navigated interbody fusion. *J Clin Neurosci*. 2015;22(9):1484–1490. doi:10.1016/j.jocn.2015.03.019

23. Chang KY, Hsu WK. Spinal biologics in minimally invasive lumbar surgery. *Minim Invasive Surg*. 2018;2018:5230350. doi:10.1155/2018/5230350

24. Overley SC, McAnany SJ, Anwar MA, et al. Predictive factors and rates of fusion in minimally invasive transforaminal lumbar interbody fusion utilizing rhBMP-2 or mesenchymal stem cells. *Int J Spine Surg*. 2019;13(1):46–52. doi:10.14444/6007

25. Nandyala SV, Marquez-Lara A, Fineberg SJ, Pelton M, Singh K. Controlled trial of silicate-substituted calcium phosphate versus rhBMP-2 in a minimally invasive transforaminal lumbar interbody fusion. *Spine (Phila Pa 1976)*. 2014;39(3):185–191. doi:10.1097/BRS.0000000000000106

26. Singh K, Nandyala SV, Marquez-Lara A, et al. Clinical sequelae after rhBMP-2 use in a minimally invasive transforaminal lumbar interbody fusion. *Spine J*. 2013;13(9):1118–1125. doi:10.1016/j.spinee.2013.07.028

27. Gologorsky Y, Skovrlj B, Steinberger J, et al. Increased incidence of pseudarthrosis after unilateral instrumented transforaminal lumbar interbody fusion in patients with lumbar spondylosis: clinical article. *J Neurosurg Spine*. 2014;21(4):601–607. doi:10.3171/2014.6.SPINE13488

28. Singh K, Nandyala SV, Marquez-Lara A, et al. Clinical sequelae after rhBMP-2 use in a minimally invasive transforaminal lumbar interbody fusion. *Spine J*. 2013;13(9):1118–1125. doi:10.1016/j.spinee.2013.07.028

29. Hawasli AH, Khalifeh JM, Chatrath A, Yarbrough CK, Ray WZ. Minimally invasive transforaminal lumbar interbody fusion with expandable versus static interbody devices: radiographic assessment of sagittal segmental and pelvic parameters. *Neurosurg Focus*. 2017;43(2):E10. doi:10.3171/2017.5.FOCUS17197

30. Glassman SD, Carreon LY, Campbell MJ, et al. The perioperative cost of infuse bone graft in posterolateral lumbar spine fusion. *Spine J*. 2008;8(3):443–448. doi:10.1016/j.spinee.2007.03.004

31. Bendo JA, Spivak J, Moskovich R, Neuwirth M. Instrumented posterior arthrodesis of the lumbar spine in patients with diabetes mellitus. *Am J Orthop (Belle Mead NJ)*. 2000;29(8):617–620.

32. Takahashi S, Suzuki A, Toyoda H, et al. Characteristics of diabetes associated with poor improvements in clinical outcomes after lumbar spine surgery. *Spine (Phila Pa 1976)*. 2013;38(6):516–522. doi:10.1097/BRS.0b013e318273583a

33. Freedman MK, Hilibrand AS, Blood EA, et al. The impact of diabetes on the outcomes of surgical and nonsurgical treatment of patients in the spine patient outcomes research trial. *Spine (Phila Pa 1976)*. 2011;36(4):290–307. doi:10.1097/BRS.0b013e3181ef9d8c

34. Peters MJM, Bastiaenen CHG, Brans BT, Weijers RE, Willems PC. The diagnostic accuracy of imaging modalities to detect pseudarthrosis after spinal fusion-a systematic review and meta-analysis of the literature. *Skeletal Radiol*. 2019;48(10):1499–1510. doi:10.1007/s00256-019-03181-5

35. Phillips FM, Carlson G, Emery SE, Bohlman HH. Anterior cervical pseudarthrosis. *Spine*. 1997;22(14):1585–1589. doi:10.1097/00007632-199707150-00012

36. Raizman NM, O'Brien JR, Poehling-Monaghan KL, Yu WD. Pseudarthrosis of the spine. *J Am Acad Orthop Surg*. 2009;17(8):494–503. doi:10.5435/00124635-200908000-00003

37. Chun DS, Baker KC, Hsu WK. Lumbar pseudarthrosis: a review of current diagnosis and treatment. *Neurosurg Focus*. 2015;39(4):E10. doi:10.3171/2015.7.FOCUS15292

38. Carpenter CT, Dietz JW, Leung KY, Hanscom DA, Wagner TA. Repair of a pseudarthrosis of the lumbar spine. A functional outcome study. *J Bone Joint Surg Am*. 1996;78(5):712–720. doi:10.2106/00004623-199605000-00011

39. Adogwa O, Verla T, Thompson P, et al. Affective disorders influence clinical outcomes after revision lumbar surgery in elderly patients with symptomatic adjacent-segment disease, recurrent stenosis, or pseudarthrosis: clinical article. *J Neurosurg Spine*. 2014;21(2):153–159. doi:10.3171/2014.4.SPINE12668

40. Hsu WK, Nickoli MS, Wang JC, et al. Improving the clinical evidence of bone graft substitute technology in lumbar spine surgery. *Global Spine J*. 2012;2(4):239–248. doi:10.1055/s-0032-1315454

41. Dawson E, Bae HW, Burkus JK, Stambough JL, Glassman SD. Recombinant human bone morphogenetic protein-2 on an absorbable collagen sponge with an osteoconductive bulking agent in posterolateral arthrodesis with instrumentation: a prospective

randomized trial. *J Bone Joint Surg Am*. 2009;91(7):1604–1613. doi:10.2106/JBJS.G.01157

42. Boden SD, Kang J, Sandhu H, Heller JG. Use of recombinant human bone morphogenetic protein-2 to achieve posterolateral lumbar spine fusion in humans: a prospective, randomized clinical pilot trial 2002 Volvo award in clinical studies. *Spine (Phila Pa 1976)*. 2002;27(23):2662–2673. doi:10.1097/00007632-200212010-00005

43. Glassman SD, Carreon L, Djurasovic M, et al. Posterolateral lumbar spine fusion with INFUSE bone graft. *Spine J*. 2007;7(1):44–49. doi:10.1016/j.spinee.2006.06.381

44. Wu RH, Fraser JF, Härtl R. Minimal access versus open transforaminal lumbar interbody fusion: meta-analysis of fusion rates. *Spine (Phila Pa 1976)*. 2010;35(26):2273–2281. doi:10.1097/BRS.0b013e3181cd42cc

45. Price JP, Dawson JM, Schwender JD, Schellhas KP. Clinical and radiologic comparison of minimally invasive surgery with traditional open transforaminal lumbar interbody fusion: a review of 452 patients from a single center. *Clin Spine Surg*. 2018;31(2):E121–E126. doi:10.1097/BSD.0000000000000581

46. Hockley A, Ge D, Vasquez-Montes D, et al. Minimally invasive versus open transforaminal lumbar interbody fusion surgery: an analysis of opioids, nonopioid analgesics, and perioperative characteristics. *Global Spine J*. 2019;9(6):624–629. doi:10.1177/2192568218822320

47. Ge DH, Stekas ND, Varlotta CG, et al. Comparative analysis of two transforaminal lumbar interbody fusion techniques: open TLIF: versus: wiltse MIS TLIF. *Spine (Phila Pa 1976)*. 2019;44(9):E555–E560. doi:10.1097/BRS.0000000000002903

48. Hey HWD, Hee HT. Open and minimally invasive transforaminal lumbar interbody fusion: comparison of intermediate results and complications. *Asian Spine J*. 2015;9(2):185–193. doi:10.4184/asj.2015.9.2.185

49. James AW, LaChaud G, Shen J, et al. A review of the clinical side effects of bone morphogenetic protein-2. *Tissue Eng Part B Rev*. 2016;22(4):284–297. doi:10.1089/ten.TEB.2015.0357

50. Helgeson MD, Lehman RA, Patzkowski JC, Dmitriev AE, Rosner MK, Mack AW. Adjacent vertebral body osteolysis with bone morphogenetic protein use in transforaminal lumbar interbody fusion. *Spine J*. 2011;11(6):507–510. doi:10.1016/j.spinee.2011.01.017

51. Mindea SA, Shih P, Song JK. Recombinant human bone morphogenetic protein-2-induced radiculitis in elective minimally invasive transforaminal lumbar interbody fusions: a series review. *Spine (Phila Pa 1976)*. 2009;34(14):1480–1484. doi:10.1097/BRS.0b013e3181a396a1

52. Hofstetter CP, Hofer AS, Levi AD. Exploratory meta-analysis on dose-related efficacy and morbidity of bone morphogenetic protein in spinal arthrodesis surgery. *J Neurosurg Spine*. 2016;24(3):457–475. doi:10.3171/2015.4.SPINE141086

**Funding:** The authors received no financial support for the research, authorship, and/or publication of this article.

**Declaration of Conflicting Interests:** A.J.B. is a paid consultant for Nuvasive, K2M-Stryker, Medtronic, Altus Spine, Evolution Spine, and EOS Imaging. Additionally, he reports contracts/grants from Nuvasive (paid to institution); royalties/licenses from Nuvasive, Evolution Spine, and Altus Spine; support for attending meetings/travel from Nuvasive and Medtronic; serving as director and chair of the Spine and Scoliosis Research Associates Australia (nonprofit); and received fellowship support from Nuvasive paid to the institution. T.S.P. is a paid consultant for Globus Medical, Innovasis, K2M-Stryker, Medicrea International, and Nuvasive and owns stocks/stock options with Torus Medical. C.R.F. is a presenter or speaker for Expert Connect; a paid consultant for Stryker and Nuvasive; has received payment/honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Amplify; and has received payment for expert testimony from the departments of Justice in the southern and eastern districts of New York. Y.H.K. receives IP royalties and is a paid consultant of Biomet. The remaining authors have no disclosures.

**Corresponding Author:** Aaron J. Buckland, Melbourne Orthoapaedic Group, 33 The Ave, Windsor, Vic 3181, Melbourne, Australia; aaron.buckland@spineandscoliosis.org