Structural Allograft Versus PEEK Implants in Anterior Cervical Discectomy and Fusion: A Systematic Review

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Abstract

Study Design: Systematic literature review.

Objective: Our primary objective was to compare reported fusion rates after anterior cervical discectomy and fusion (ACDF) using structural allograft versus polyetheretherketone (PEEK) interbody devices in patients with cervical spine degeneration. Our secondary objectives were to compare differences in rates of subsidence and reoperation and in patient-reported outcomes between the 2 groups.

Methods: Through a systematic review of the English-language literature using various databases, we identified 4702 articles. After we applied inclusion and exclusion criteria, 14 articles (7 randomized controlled trials, 4 prospective studies, and 3 retrospective studies) reporting fusion rates of structural allograft or PEEK interbody devices were eligible for our analysis. No randomized controlled trials compared outcomes of structural allograft versus PEEK interbody devices. Extracted data included authors, study years, study designs, sample sizes, patient ages, duration of follow-up, types of interbody devices used, fusion rates, definition of fusion, reoperation rates, subsidence rates, and patient-reported outcomes.

Results: Fusion rates were 82% to 100% for allograft and 88% to 98% for PEEK interbody devices. The reported data were insufficient to perform meta-analysis. Structural allograft had the highest reported rate of reoperation (14%), and PEEK interbody devices had the highest reported subsidence rate (18%). Patient-reported outcomes improved in both groups. There was insufficient high-quality evidence to compare the associations of various PEEK modifications with fusion rates.

Conclusion: Fusion rates were similar between structural allograft and PEEK interbody devices when used for ACDF for cervical spine degeneration. Currently, there is insufficient high-quality evidence to assess associations of PEEK modifications with fusion rates.

Level of Evidence: II.

Keywords
allograft, anterior cervical discectomy and fusion, cervical spine degeneration, fusion rate, interbody device, patient-reported outcome, polyetheretherketone interbody device, structural allograft, systematic review

Introduction

Anterior cervical discectomy and fusion (ACDF) is a common surgical treatment for cervical spine degeneration and associated cervical nerve root or spinal cord compression.1,2 Indications for ACDF include cervical radiculopathy or myelopathy secondary to degenerative disc disease, disc herniation, spondylosis, and spinal stenosis. Interbody devices used in ACDF facilitate fusion, correct kyphosis, and restore foraminal height.3,4 When ACDF was initially described by Cloward5

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in 1958, structural autograft bone was used for interbody support. However, during the past several decades, various alternatives to structural autograft have gained popularity, including structural cadaveric allograft, polyetheretherketone (PEEK) interbody devices, and metal interbody devices. A 2017 survey of AOSpine members found that PEEK interbody devices were commonly used worldwide and structural allografts were commonly used in North America. PEEK has multiple theoretical advantages, including biocompatibility, radiolucent, favorable elasticity, and ease of procurement and storage. The major drawback of PEEK is that it is bio-inert and limits host bone integration. Various strategies have been proposed to improve the biologic integration of PEEK, including augmenting PEEK devices with graft extenders, such as demineralized bone matrix or cellular products, as well as modifications to the PEEK device. Proposed modifications include surface enhancements, such as increased surface porosity or titanium coating, and impregnation of PEEK with bioactive materials such as hydroxyapatite. The effects of these modifications on fusion success and clinical outcomes are unclear.

Structural allograft, including cortical allograft, corticocancellous or composite grafts, and dense cancellous grafts, is an effective alternative to autograft to achieve bony fusion in ACDF. Among surgeons who use allograft, cortical and corticocancellous composite grafts are more popular because they provide additional structural support and resistance against subsidence, whereas dense cancellous grafts have been reported to have high rates of resorption.

Our primary objective was to compare reported fusion rates after ACDF using structural allograft versus PEEK interbody devices in patients with cervical spine degeneration. Our secondary objectives were to compare differences in the rates of subsidence and reoperation and in patient-reported outcomes between the 2 groups.

### Methods

Our study used publicly available information and thus was not subject to review by our institutional review board.

### Search Strategy

We designed our literature search in accordance with the Preferred Reporting Items of Systematic Reviews and Meta-Analyses guidelines (PRISMA). With the assistance of a clinical informationist, we performed a comprehensive literature search using PubMed, Embase, The Cochrane Library, Web of Science, Scopus, ClinicalTrials.gov, and CINAHL Plus databases in October 2018 (see Appendix 1 in the online version of the article). We identified 4702 articles (Figure 1).

### Inclusion and Exclusion Criteria

We included studies that reported results of ACDF using structural allograft, PEEK interbody devices, or modified PEEK interbody devices; analyzed patients aged ≥18 years; included results of >20 patients; were published in 1993 or later; were written in English; were randomized controlled trials or retrospective, prospective, or observational cohort studies; and reported 2-year radiographic follow-up. (For comparative studies in which only 1 of the study groups met the eligibility criteria, we limited our data abstraction and analysis to that group.)

We excluded studies that reported on ACDF using zero-profile or stand-alone devices; ACDF performed without anterior cervical plating; cervical corpectomy; circumferential (360° or 540°) fusion; interventions to facilitate fusion in addition to the interbody device (eg, bone morphogenic protein, stem cells, autograft, platelets); ACDF for nondegenerative conditions; ACDF for adjacent-segment disease (adjacent to previous ACDF); or revision ACDF for nonunion or other conditions. We also excluded animal studies, cadaveric studies, case reports, correspondence, letters to the editor, technical notes, abstracts, and poster presentations. Level of evidence of the articles included in this systematic review was assessed using the Oxford Centre for Evidence-Based Medicine.

### Study Selection

Two independent reviewers screened the studies for eligibility. A third reviewer served as an arbitrator when there was disagreement between the 2 primary reviewers. Each article’s title and abstract were reviewed. Articles that could not be excluded on the basis of this review were retrieved for full-text review (n = 101). Covidence Systematic Review Software (Veritas Health Innovation, Melbourne, Victoria, Australia) was used to facilitate the screening and selection process. Fourteen articles (7 randomized controlled trials, 4 prospective studies, and 3 retrospective studies) met our eligibility criteria and were included in the review (Table 1).

### Data Extraction and Analysis

Using a standardized data extraction form, we extracted the following information: authors, study years, study designs, sample sizes, patient ages, duration of follow-up, types of interbody device used, fusion rates, definitions of fusion, reoperation rates, subsidence rates, and patient-reported outcomes (ie, visual analogue scale [VAS] for pain, Neck Disability Index [NDI], Patient-Reported Outcomes Measurement Information System, and Odom’s criteria). Descriptive statistics were calculated and reported as appropriate. There were insufficient data to perform a meta-analysis.

### Results

#### Fusion Rates

In 11 studies, fusion was assessed by an independent or blinded physician. Criteria for fusion success differed slightly among studies, although motion (commonly defined as <2° or <4° change in angulation between the spinous processes)
on flexion-extension radiographs is the commonly used method to determine fusion success (Table 2).

**Structural Allograft.** Nine studies (1354 patients) reported fusion data with the use of structural allograft: 5 used corticocancellous allograft, 2 used unspecified cortical allograft, and 1 did not report the type of allograft used. The fusion rates among these 9 studies were 82% to 100%. Among the 5 studies that used corticocancellous allograft, fusion rates at 2 years or more were 82% to 97% (Table 1).

A prospective comparison of 1-level and 2-level ACDF using corticocancellous allograft reported fusion rates of 89% and 79%, respectively, at 2 years, and 93% and 86%, respectively, at 5 years. The reported fusion rates for unspecified cortical grafts at 2 years were 82% to 97%. In a prospective study, Suchomel et al assessed fusion rates of fibular allograft versus structural autograft and found that the fibular allograft group had fusion rates of 85.5% at 1 year and 93.4% at 2 years.

**PEEK Interbody Devices.** Five studies using PEEK interbody devices (146 patients) were included in our final analysis, including 1 randomized controlled trial, 2 prospective studies, and 2 retrospective studies. Rates of fusion for PEEK interbody devices in these 5 studies were 88% to 98%.

In a prospective study by El-Tantawy, 10 patients underwent 2-level fusion, 10 underwent 3-level fusion, and 8 underwent 4-level fusion with stand-alone PEEK cage. Fusion was achieved at a mean of 14.9 weeks for 2-level, 15.2 weeks for
Table 1. Studies of Fusion Rates in Patients Who Underwent Anterior Cervical Discectomy and Fusion for Cervical Spine Degeneration.

| First Author, Year | Design | Study Groups | Sample Size | Mean Age (Years) | Follow-up (Years) | Indications (No. of Patients) | Levels (No. of Patients) | 2-Year Fusion | Reoperation | Subsidence |
|--------------------|--------|--------------|-------------|------------------|-------------------|-------------------------------|--------------------------|--------------|------------|------------|
| Feiz-Erfan, 2007   | RCT    | Allograft with vs without platelets | 50          | 46               | 2                 | DDD (29); herniated disc (21) | 1 (18); 2 (29)          | 85           | 4          | NR         |
| Campbell, 2009     | RCT    | Allograft with vs without cervical collar | 257         | 44               | 2                 | Radiculopathy or myelopathy    | 1 (257)                 | 96 (braced); 100 (nonbraced) | 0.7          | NR         |
| Feng, 2018         | RCT    | PEEK with vs without tricalcium phosphate | 23          | 64               | 2                 | Radiculopathy (12); myelopathy (5); radiculomyelopathy (6) | 1 (5); 2 (12); 3 (6) | 98           | NR         | 0          |
| Coric, 2011        | RCT    | Allograft vs arthroplasty | 133         | 44               | 2                 | Radiculopathy or myelopathy    | 1 (133)                 | 82           | 5          | NR         |
| Gornet, 2017       | RCT    | Allograft vs arthroplasty | 188         | 47               | 2                 | Radiculopathy or myelopathy    | 2 (188)                 | 98           | NR         | 0          |
| Hisey, 2015        | RCT    | Allograft vs arthroplasty | 81          | 44               | 4                 | Radiculopathy or myelopathy    | 1 (81)                  | 94*          | NR         | NR         |
| Mummaneni, 2007    | RCT    | Allograft vs arthroplasty | 265         | 44               | 2                 | Radiculopathy or myelopathy    | 1 (265)                 | 98           | 8.6        | NR         |
| Suchomel, 2004     | PC     | Allograft vs autograft | NA          | 48               | 2                 | Spondylosis and/or cervical disc prolapse/protrusion | 1 or 2 (NA³) | 93           | NR         | 0          |
| Zigler, 2016       | PC     | 1- vs 2-level allograft | 186         | 45               | 5                 | Radiculopathy or myelopathy    | 1 (81); 2 (105)         | 89 (1-level); 79 (2-level) | 14          | NR         |
| Schlosser, 2006    | RC     | Allograft | 219         | 52               | 6                 | Unknown                       | 1 (80); 2 (57); 3 (53); 4 (29) | 98*          | 8          | NR         |
| El-Tantawy, 2015   | PC     | 2- vs 3- vs 4-level PEEK implant | 28          | 40               | 2                 | Neck pain and radiculopathy    | 2 (10); 3 (10); 4 (8) | 93           | 0          | 2          |
| Niu, 2010          | PC     | PEEK vs titanium implant | 25          | 52               | 2                 | Radiculopathy or myelopathy    | 1 (16); 2 (9)           | 100*         | 0          | 0          |
| Cabraja, 2012      | RC     | PEEK vs titanium implant | 42          | 58               | 2                 | Radiculopathy or myelopathy    | 1 (42)                  | 88*          | NR         | 14         |
| Dufour, 2010       | RC     | PEEK implant | 28          | 48               | 2.7               | Radiculopathy or myelopathy    | 1 (19); 2 (9)           | 94           | NR         | 0          |

Abbreviations: ACDF, anterior cervical discectomy and fusion; DDD, degenerative disc disease; NA, not available; NR, none reported; PC, prospective cohort; PEEK, polyetheretherketone; RC, retrospective cohort; RCT, randomized controlled trial.

³Fusion rate reported at 4 years.

⁴Eighty patients were included in the study. The number of patients allocated to each group was not reported.

⁵Fusion rate reported at unknown time period.

⁶Fusion rate reported at 1 year.

⁷Fusion rate reported at 2.4 years.
Table 2. Definitions of Fusion in Studies of Structural Allograft and PEEK Interbody Devices in Patients With Cervical Spine Degeneration Who Underwent Anterior Cervical Discectomy and Fusion.

| First Author, Year | Definition of Fusion |
|--------------------|----------------------|
| Feiz-Erfan, 2007   | Absence of major angular motion (≤2°) on flexion/extension radiographs and <50% lucency at each potential fusion surface. |
| Campbell, 2009     | “The presence of bridging trabecular bone as evidenced by continuous bony connection of the vertebral bodies above and below in at least one of the following areas: lateral, anterior, posterior, and/or through the allograft ring implant; angulation of less than 4° on flexion-extension radiographs; and absence of radiolucency covering more than 50% of either the superior or inferior surface of the graft.” |
| Feng, 2018         | “1) rotation <4° and <1.25 mm translation with the absence of motion adjacent to interspinous processes (>3 mm) in the flexion-extension view and (2) the presence of continuous trabecular bone bridging was revealed by CT scan in at least one of the following locations: anterior, within, or posterior to the PEEK cage.” |
| Coric, 2011        | “1) bridging trabecular bone; 2) angular motion less than 5°; 3) translational motion less than 3 mm; and 4) less than 50% radiolucency along the bone-implant interface.” |
| Gornet, 2017       | “1) angulation ≤4°, 2) bridging bone as a continuous bony connection with the vertebral bodies above and below, and 3) no radiolucency covering more than 50% of either the superior or inferior surface of the graft.” |
| Hisey, 2015        | “Bridging bone across the disk space, <2 degrees angular motion measured from flexion to extension, and <50% radiolucency lines at the graft vertebral endplate interfaces.” |
| Mummaneni, 2007    | “1) bone spanning the two VBs in the treated segment; 2) less than 4° of motion on dynamic radiographs; and 3) radiolucencies covering no more than 50% of the implant surface.” |
| Suchomel, 2004     | According to criteria of Brown et al48: “Complete: Complete bridging of trabeculae between adjacent vertebral bodies and bone graft; Partial: Less than 50% bridging trabeculae; Non-union: Lack of trabecular bridging.” |
| Zigler, 2016       | Unknown |
| Schlosser, 2006    | No radiolucency within the construct and no evidence of instrumentation failure. |
| Niu, 2010          | “Lack of a radiolucent line between the cage and endplate as well as the lack of translation or angulation change in the lateral cervical flexion-extension radiographs at the 1-year follow-up.” |
| Cabraja, 2012      | “Movement of less than 2° was measured, and by the absence of motion between the spinous processes on lateral flexion-extension radiographs.” |
| El-Tantawy, 2015   | “…continuity of the trabeculae between end-plates with the absence of lucency at the cage/end-plate interface. This was confirmed by stability on dynamic views (not more than 2 mm widening of the inter-spinous distance) or by CT in suspected fusions.” |

Note: All definitions are based on a combination of clinical examination and imaging findings. Variations in terminology and criteria may exist among different studies. CT, computed tomography; PEEK, polyetheretherketone; VB, vertebral body.

Subsidence Rates

Structural Allograft. Among the studies of structural allograft, only 2 reported subsidence rates. Gornet et al22 reported the highest subsidence rate (4.3%, 6/138 patients) at 2-year follow-up. In the study by Suchomel et al30 none of the patients developed subsidence at 2-year follow-up.

PEEK Interbody Devices. High subsidence rates were reported in the study of PEEK interbody devices by El-Tantawy,32 occurring at 7 fusion levels in 5 patients (18%); however, no patient underwent revision surgery. Cabraja et al34 reported a subsidence rate of 14% (6/42), with no reoperations. The remaining articles discussing PEEK fusion rates did not report any subsidence among their patients.27,29,33

Reoperation Rates

Structural Allograft. In studies using structural allograft interbody, the incidence of reoperation for all reasons was 0.7% (1/149 patients) to 13.9% (26/186 patients) (Table 1).23,28 Overall, the rates of reoperation for pseudarthrosis with structural allograft interbody were 1.8% to 6.4%.28,31

PEEK Interbody Devices. Among the 5 studies involving PEEK devices, 2 reported no reoperations29,32 and 3 did not monitor for reoperation27,33,34 (Table 1).

Patient-Reported Outcomes

Eleven studies reported patient-reported outcomes, with VAS and NDI being the most frequently used measures.21-29,32,34

Structural Allograft. Seven studies described patient-reported outcomes, with an overall significant improvement in clinical outcomes assessed by VAS and NDI scores.21,26,28 Feiz-Erfan et al32 reported subjective improvements overall. In VAS scores ranging from 3 to 30, the mean VAS score at baseline
Table 3. Power Calculation, Sample Size, and Reporting of Patients Lost to Follow-up.

| First Author, Year | OCEBM Level of Evidence | Who Assessed Fusion | Power Calculation and Sample Size | Follow-up Rate, % (Follow-up duration, y) |
|--------------------|-------------------------|---------------------|-----------------------------------|------------------------------------------|
| Feiz-Erfan,24 2007 | II                      | Physician not in study | NR                               | 85 (2)                                   |
| Campbell,23 2009  | I                       | Physician not in study | NR                               | NR                                       |
| Feng,37 2018      | II                      | 2 Blinded physicians  | NR                               | NR                                       |
| Coric,26 2011     | II                      | Physician not in study | NR                               | 87 (2)                                   |
| Gornet,22 2017    | I                       | Physician not in study | Reported                         | 85 (2)                                   |
| Hisey,21 2015     | II                      | Physician not in study | Reported                         | 79 (4)                                   |
| Mummene,35 2004   | III                     | Treating surgeon and independent radiologist | NR | 99 (2)                                   |
| Suchomel,30 2004  | III                     | Physician not in study | NR                               | 99 (2)                                   |
| Suchomel,30 2004  | III                     | Physician not in study | NR                               | 99 (2)                                   |
| Zipper,36 2016    | III                     | Physician not in study | NR                               | 99 (2)                                   |
| Schlosser,31 2006 | IV                      | Physician not in study | NR                               | 94 (2)                                   |
| Niu,29 2010       | IV                      | Physician not in study | NR                               | NR                                       |
| Cabraja,34 2012   | IV                      | NR                   | NR                               | NR                                       |
| El-Tantawy,32 2015| IV                      | NR                   | NR                               | 100 (2)                                   |
| Dufour,33 2010    | IV                      | NR                   | NR                               | 100 (1)                                   |

Abbreviations: NR, not reported; OCEBM, Oxford Centre for Evidence-Based Medicine.

for all patients was 15.5; at 2-year follow-up the mean score had improved to 7.0.24 Similarly, Coric et al26 showed a >20% improvement in NDI scores at 2-year follow-up. The methods used for assessing patient-reported outcomes were heterogeneous, limiting quantitative analysis of association of allograft interbody with clinical outcomes.

**PEEK Interbody Devices.** Overall outcomes improved among the 4 studies that reported patient-reported outcomes.27,29,32,34 The success rate of surgery as measured by Odom’s criteria was 64% in the study by Cabraja et al.34 In the randomized controlled trial comparing an empty PEEK cage with PEEK packed with β-tricalcium phosphate, patients in both groups showed improvements in VAS, NDI, and Japanese Orthopaedic Association scores.27

**Discussion**

We conducted a systematic review of the literature to compare fusion rates of structural allograft versus PEEK interbody devices in patients with cervical spine degeneration who underwent ACDF. Of the 14 studies included in our review, the overall fusion rates were 82% to 100% for structural allograft and 88% to 98% for PEEK interbody devices. The lack of randomized controlled trials comparing these 2 interbody devices, in addition to the variability in methodology to assess fusion, sample sizes, and other methods among studies, precluded meta-analysis.

Because fusion is a key determinant of success after ACDF, a standard for determining fusion rate is needed in cervical spine fusion studies. Several widely varying criteria for determining radiographic fusion were reported (Table 2). The most common components of the definitions included <50% radiolucency along the bone-implant surface and a specified degree of angular motion on dynamic radiographs (<2° or <4°). Most studies classified fusion as a binary variable; however, some studies classified fusion as “complete,” “partial,” and “nonunion” or “excellent,” “good,” and “no fusion.”30 Most studies used multiple observers to determine radiographic fusion, and none of the 14 studies reported intraobserver differences in determination of fusion. In 2008, it was presumed that a consensus definition of cervical fusion was beginning to form.36 In a recently published systematic review by Oshina et al,10 criteria were described for fusion assessment in ACDF. Most commonly, the surgeon’s subjective assessment of bridging trabecular bone between endplates and the absence of a radiolucent gap were used to assess fusion. The problem of heterogeneity in fusion assessment is commonly described in systematic reviews and meta-analyses reporting fusion rates in ACDF.28-40 A universally accepted criterion for fusion assessment is needed to standardize studies and allow for comparison.36

Patient-reported outcomes were reported in only 10 of the 14 studies, indicating that patient-reported outcomes are often not the focus of studies that describe interbody devices, even among those with 2-year follow-up. In the studies that described patient-reported outcomes, the results were not always directly comparable, further illustrating the need for reporting and standardizing outcomes in cervical spine surgery studies. A recent review by Nayak et al also acknowledged that the numerous patient-reported outcome measures and the variability in minimal clinically important differences between these measures limit comparisons of clinical outcomes in spine surgery research.

We required minimum radiographic follow-up of 2 years for inclusion in our review (Table 3). The 1 high-quality study excluded because of a lack of 2-year radiographic follow-up was the PIERCE-PEEK Study (Prospective International Multicenter Evaluation of Radiological and Clinical Effects of Stand-Alone PEEK Intervertebral Spacers for ACDF) by Suess et al. The authors followed a cohort of 356 patients who underwent ACDF with PEEK interbody devices without any
Although PEEK provides good biocompatibility and strength, it is unable to bond directly to bone and to osseointegrate. Modifications to PEEK designed to address the issue of osseointegration have gained popularity. These modifications include hydroxyapatite-coated PEEK, porous PEEK, titanium plasma-coated PEEK, carbon fiber–reinforced PEEK, and polyetherketone. Our study did not control for these variations because there is insufficient high-quality evidence comparing these modifications. We hypothesize that modifications to PEEK result in superior biomechanical properties and superior osseointegration compared with unmodified, legacy PEEK devices.

Although we excluded patients who underwent ACDF without anterior plating, the use of stand-alone interbody devices without anterior plating is common in Europe. Studies of autograft report that use of an anterior cervical plate improved fusion rates from 93.5% to 98%. To our knowledge, no high-quality studies have compared the outcomes of plated versus un plated 1- and 2-level ACDF with modern implants, indicating an important area for future research.

In addition to the potential differences in fusion rates between structural allograft and PEEK interbody devices, these devices may differ greatly in cost. Although studies comparing costs between structural allograft and PEEK devices are limited, a 2015 study by Virk et al estimated the costs per quality-adjusted life-year for ACDF using PEEK ($3328), allograft ($2492), and autograft ($2492). However, they did not account for regional variations in cost. In some regions, because of storage, regulatory, and cultural reasons, obtaining structural allograft can be difficult or cost prohibitive. Future studies focusing on cost differences among interbody devices are needed.

When pooling results from the studies we analyzed, the subsidence rate was higher in patients who had PEEK versus allograft devices; however, none of the studies included in this review directly compared subsidence rates of PEEK versus allograft. It is important to note that although structural allograft had lower reported subsidence rates, it is difficult to assess for subsidence on radiographs because of the resemblance of allograft to native bone on imaging. In contrast, PEEK cages have embedded radiopaque markers, which potentially allow for better visualization of subsidence. In a direct comparative study that did not meet criteria for inclusion in our review, no significant difference in subsidence rates was seen between allograft and PEEK interbody devices used in ACDF. It is also important to consider that although subsidence after ACDF procedures has been well studied, the effects of subsidence on clinical outcomes and fusion rates after ACDF remain unclear.

Limitations are inherent in systematic reviews. In our study, heterogeneity of fusion assessment, stringent inclusion and exclusion criteria, and possible missed cases contribute to the limitations. The discrepancy in fusion assessment prevented us from performing a meta-analysis. In addition, the lack of level-I evidence with a direct comparison of structural allograft versus PEEK makes it difficult to form robust conclusions. Further high-quality evidence is required to provide evidence-based treatments for patients with cervical spine degeneration undergoing ACDF. A thorough search and review of the literature, as well as strict adherence to the Preferred Reporting Items of Systematic reviews and Meta-Analyses guidelines contributed to the strengths of this systematic review.

**Conclusions**

Similar fusion rates have been reported for structural allograft and PEEK interbody devices for ACDF in patients with cervical spine degeneration. No high-quality randomized controlled trials or high-quality cohort comparisons directly compared structural allograft versus PEEK interbody devices in ACDF. Future research is needed to assess the outcomes of various modified PEEK devices and bone graft substitutes and extenders.

**Authors’ Note**

This study used publicly available information and thus was not subject to review from our institutional review board.

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Supplemental Material
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