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February 28, 2022

Gift Tee
Director
Division of Practitioner Services
Centers for Medicare & Medicaid Services
7500 Security Boulevard
Baltimore, Maryland 21244

Attention: Division of Practitioner Services, Potentially Misvalued Codes

Dear Director Tee:

On behalf of LifeNet Health, I am writing to submit comments requesting agency review of **CPT 20931** (*Allograft, structural, for spine surgery only (List separately in addition to code for primary procedure)*) as a potentially misvalued service as part of its annual Medicare Physician Fee Schedule rulemaking process.

LifeNet Health has been a trusted source of transplant and surgical solutions for nearly 40 years. We have provided more than seven million allograft implants to help restore patients' wellbeing and, in many cases, save lives. We work closely with clinicians and healthcare organization to understand clinical needs and provide the resources needed for efficient, effective, economical care.

POTENTIALLY MISVALUED SERVICES IN THE MEDICARE PHYSICIAN FEE SCHEDULE

As we have previously shared, we believe that there is a code and value misalignment related to spine procedures in need of review. This relates to anterior cervical discectomy and fusion (ACDF) procedures, one of the most common spine surgeries performed. In particular, we are concerned the coding schema that results under the use of primary procedure CPT 22551 (*Arthrodesis, anterior interbody, including disc space preparation, discectomy, osteophytectomy and decompression of spinal cord and/or nerve roots; cervical below C2*) can result in cumulative RVUs that do not sufficiently reflect physician work, time, or outcomes, and we believe that this misalignment can be traced to **CPT 20931**.

Cervical degenerative disc disease is one of the most common diagnoses for patients suffering from neck and back pain. In addition to pain, patients may suffer from lack of function, immobility, and sensory loss. Initial treatments tend to be conservative, focusing on anti-inflammatory medicine and/or physical therapy. However, when these options fail, a surgical intervention may be needed. Such a procedure usually involves a discectomy and fusion, whereby the affected disc is excised, and the nerve root or spinal cord is decompressed. Following disc removal, the vertebral space is typically implanted with allograft bone or another option.

Historically, autografts, meaning implants from the patient's own body, have been a standard practice. However, autografts have several disadvantages, such as extended operating time, donor site pain, limited supply, and variable quality depending upon the patient's health. Thus, there has been a shift

toward the use of alternative interbody spacers for treatment of degenerative disc disease. Two of the most common choices are structural allograft bone or synthetic cages.

Both allograft bone and synthetic cages have mechanical properties similar to autograft. However, synthetic cages may not integrate into the bone as well as autografts, which can lead the patient back to experiencing pain, immobility, and sensory loss, and potentially necessitating further surgery. By contrast, structural allografts will integrate into the surrounding bone, which may result in superior clinical outcomes.[1,2,3]

However, the values assigned to the codes for these different implant approaches vary. The primary procedure under either clinical scenario is CPT 22551 (*Arthrodesis, anterior interbody, including disc space preparation, discectomy, osteophytectomy and decompression of spinal cord and/or nerve roots; cervical below C2*). The table below illustrates the coding scenarios for the use of 3 devices depending on whether the device selected is a synthetic material or structural allograft and how it results in wRVU differentials.

Work RVU Differentials Based on Implant Selection	
3 synthetic cage devices with plate	**3 structural allografts with plate**
CPT 22551 (*Arthrodesis, anterior interbody, including disc space preparation, discectomy, osteophytectomy and decompression of spinal cord and/or nerve roots; cervical below C2*) (50.42) **wRVUs: 25.00**	**CPT 22551** (*Arthrodesis, anterior interbody, including disc space preparation, discectomy, osteophytectomy and decompression of spinal cord and/or nerve roots; cervical below C2*) **wRVUs: 25.00**
+CPT 22552 (x2) (*Arthrodesis, anterior interbody, including disc space preparation, discectomy, osteophytectomy and decompression of spinal cord and/or nerve roots; cervical below C2, each additional interspace (List separately in addition to code for separate procedure)*) **wRVUs (6.5 x2): 13**	**+CPT 22552 (x2)** (*Arthrodesis, anterior interbody, including disc space preparation, discectomy, osteophytectomy and decompression of spinal cord and/or nerve roots; cervical below C2, each additional interspace (List separately in addition to code for separate procedure)*) **wRVUs (6.5 x2): 13**
+CPT 22846 w Modifier 59[4] (*Anterior instrumentation; 4 to 7 vertebral segments (List separately in addition to code for primary procedure)*) **wRVUs: 12.4**	**+CPT 22846 w Modifier 59** (*Anterior instrumentation; 4 to 7 vertebral segments (List separately in addition to code for primary procedure)*) **wRVUs: 12.4**

[1] Nigeste Carter, Elena C. Gianulis and Mark A. Moore (July 16. 2019). Allograft Structural Interbody Spacers Compared to PEEK Cages in Cervical Fusion: Benchtop and Clinical Evidence [Online First], IntechOpen, DOI: 10.5772/intechopen.88091. Available from: https://www.intechopen.com/online-first/allograft-structural-interbody-spacers-compared-to-peek-cages-in-cervical-fusion-benchtop-and-clinic

[2] Katie L. Krause, MD, PhD, James T. Obayashi, BS, Kelly J. Bridges, MD, Ahmed M. Raslan, MD, and Khoi D. Than, MD (January 2019). Fivefold higher rate of pseudarthrosis with polyetheretherketone interbody device than with structural allograft used for 1-level anterior cervical discectomy and fusion. J Neurosurg Spine 30:46–51, 2019 (Attached).

[3] Nida Fatima, Elie Massaad, Ganesh M. Shankar, John H. Shin (April 2020). Structural Allograft versus Polyetheretherketone Implants in Patients Undergoing Spinal Fusion Surgery: A Systematic Review and Meta-Analysis. World Neurosurgery136: 101-109, 2020 (Attached).

[4] Modifier 59 (*Distinct Procedural Service*)

+CPT 22853 (x3) (*Insertion of interbody biomechanical device(s) (e.g., synthetic cage, mesh) with integral anterior instrumentation for device anchoring (e.g., screws, flanges), when performed, to intervertebral disc space in conjunction with interbody arthrodesis, each interspace (List separately in addition to code for primary procedure)*) **wRVUs (4.25x3): 12.75**	N/A
+CPT 20930/6 (*Allograft, morselized, or placement of osteopromotive material, for spine surgery only (List separately in addition to code for primary procedure)*) (0.00)	**+CPT 20931** (*Allograft, structural, for spine surgery only (List separately in addition to code for primary procedure)*) **wRVUs: 1.81**.
Total wRVUs: 63.15	**Total wRVUs: 52.21**

We are concerned that the variance in the RVUs assigned to these procedures as outlined above do not reflect a variance in work, resources, or intensity. Therefore, we urge CMS to encourage review of CPT 20931 to address this variance, which can provide a financial incentive to select a synthetic implant, particularly when multiple levels are involved. Because we support CMS' efforts to ensure patient safety and quality of care, we have attached a list of articles which highlight the clinical outcomes for patients based on implant selection that we believe support development of a payment policy that does not undervalue the selection of structural allografts.

Sincerely,

Bud Brame
Vice-President of Strategic Product Planning and Reimbursement Services

- *Nonunion Rates After Anterior Cervical Discectomy and Fusion: Comparison of Polyetheretherketone vs Structural Allograft Implants* (2021)

- *Structural Allograft Versus Synthetic Interbody Cage for Anterior Cervical Discectomy and Fusion: A Comparison of 1-Year Outcomes From a National Database* (2020)

- *Structural Allograft versus Polyetheretherketone Implants in Patients Undergoing Spinal Fusion Surgery: A Systematic Review and Meta-Analysis* (2020)

- *Fivefold higher rate of pseudarthrosis with polyetheretherketone interbody device than with structural allograft used for 1-level anterior cervical discectomy and fusion* (2018)

- *Cages in ACDF are Associated With a Higher Nonunion Rate Than Allograft* (2018)

- *PEEK-Halo effect in interbody fusion* (2015)

- Articles in Review:
    - *Greater risk of pseudarthrosis using PEEK spacers vs structural allografts in 1-level ACDF*
    - *Higher nonunion rate using cages versus allografts in ACDF*
    - *Lower revision rate with structural allografts vs synthetic cages in multilevel ACDF procedures*
    - *Structural allografts provide better outcomes than PEEK cages in spinal fusion procedures*

Nonunion Rates After Anterior Cervical Discectomy and Fusion: Comparison of Polyetheretherketone vs Structural Allograft Implants

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BACKGROUND: Although advances in implant materials, such as polyetheretherketone (PEEK), have been developed aimed to improve outcome after anterior cervical discectomy and fusion (ACDF), it is essential to confirm whether these changes translate into clinically important sustained benefits.

OBJECTIVE: To compare the radiographic and clinical outcomes of patients undergoing up to 3-level ACDF with PEEK vs structural allograft implants.

METHODS: In this cohort study, radiographic and symptomatic nonunion rates were compared in consecutive patients who underwent 1 to 3 level ACDF with allograft or PEEK implant. Prospectively collected clinical data and patient-reported outcome (PRO) scores were compared between the allograft and PEEK groups. Regression analysis was performed to determine the predictors of nonunion.

RESULTS: In total, 194 of 404 patients met the inclusion criteria (79% allograft vs 21% PEEK). Preoperative demographic variables were comparable between the 2 groups except for age. The rate of radiographic nonunion was higher with PEEK implants (39% vs 27%, $P = .0035$). However, a higher proportion of nonunion in the allograft cohort required posterior instrumentation (14% vs 3%, $P = .039$). Patients with multilevel procedures and PEEK implants had up to 5.8 times the risk of radiographic nonunion, whereas younger patients, active smokers, and multilevel procedures were at higher risk of symptomatic nonunion.

CONCLUSION: Along with implant material, factors such as younger age, active smoking status, and the number of operated levels were independent predictors of fusion failure. Given the impact of nonunion on PRO, perioperative optimization of modifiable factors and surgical planning are essential to ensure a successful outcome.

KEY WORDS: Allograft, Anterior cervical discectomy and fusion, PEEK, Nonunion

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For degenerative cervical pathologies causing neurological symptoms, surgery remains the primary treatment modality with anterior cervical discectomy and fusion (ACDF) being one of the most commonly utilized techniques.[1,2] An ongoing challenge of ACDF is achieving successful fusion as nonunion is associated with poor outcome.[3-5] The reported rates of nonunion range from 0.9% to >50%.[4,6,7]

Polyetheretherketone (PEEK) has become popular for fusion because of ease of use, radiolucency, and low elastic modulus. However, some have cautioned potential risk of implant failure because of the hydrophobic property of PEEK preventing osteointegration.[8] Indeed, 2 recent studies reported a significantly higher rate of nonunion with PEEK implants.[6,9] There remains a lack of research examining fusion rates and patient-reported outcomes (PRO) with respect to the use of PEEK in the setting of multilevel ACDF. The objective of

ABBREVIATIONS: ACDF, anterior cervical discectomy and fusion; **MCS,** Mental Health Score; **mJOA,** modified Japanese Orthopedic Association; **NDI,** Neck Disability Index; **PCS,** Physical Health Score; **PEEK,** polyetheretherketone; **PRO,** patient-reported outcome; **SF-12,** Short Form-12

Supplemental digital content is available for this article at www.neurosurgery-online.com.

TABLE 1. Radiographic Determinants of Fusion

	CT scan	X-ray
Fusion criteria (presence of all specified requirements)	1. Bridging bone across the disc space 2. Lack of radiolucent line at graft-vertebral body interface	1. Bridging bone across the disc space 2. Lack of radiolucent line at graft-vertebral body interface 3. Motion less than 1 mm between adjacent spinous processes on flexion—extension lateral views

this study was to compare the radiographic and clinical outcomes of patients undergoing up to 3-level ACDF with PEEK vs allograft implants.

METHODS

Study Design

This is an analysis of a single-center, prospectively collected database of patients undergoing cervical spine procedures between 2014 and 2018 by 5 spine surgeons. The inclusion criteria were (1) age ≥18 yr with cervical disc herniation or spondylosis causing radiculopathy or myelopathy; (2) ACDF involving up to 3 disc levels; and (3) follow-up greater than 1 yr with X-ray or computed tomography (CT). Exclusion criteria were (1) procedures for congenital anomalies, tumor, infection, and trauma; (2) ACDF without anterior plate; (3) combined anterior posterior procedures; and (4) posterior instrumentation prior to 1-yr follow-up. All patients failed at least 6 mo of nonoperative management before surgery. The timing of surgery and graft material was determined by the surgeons. No patient received bone morphogenic protein or titanium-coated PEEK implants. All patients were advised to stop taking nonsteroidal anti-inflammatory (NSAID) medication for 6 wk after surgery. This study was approved by the Institutional Review Board with a waiver of patient consent (ORA19091102).

Data Collection

Patient demographics, clinical, and radiographic data were extracted from medical records. PRO measures were gathered from a prospectively collected database. These included a numeric rating scale for neck and arm pain, modified Japanese Orthopedic Association (mJOA) scale, Neck Disability Index (NDI) scale, Short Form-12 (SF-12) Physical Health Score (PCS), and SF-12 Mental Health Score (MCS).

The primary outcome was nonunion after ACDF. Postoperative fusion status was assessed by a fellow and a senior resident (W.H.A.R. and M.G.K.) using either X-ray including flexion-extension views or CT scan at the latest follow-up (Table 1).[10,11] For patients who underwent posterior instrumentation, the latest imaging before the procedure was used to assess for fusion. Patients were categorized as symptomatic nonunion if they required posterior instrumentation because of their nonunion as noted by the preoperative dictation. Secondary outcomes were PRO scores at the same time point as their imaging. Clinical data included smoking status, number of operated levels, and intraoperative complications.

Statistical Analysis

Descriptive statistics were performed to characterize demographic, clinical, and PRO data. Comparative analyses were performed using unpaired *t*-test for continuous variables, Mann-Whitney *U*-test for nonparametric variables, and chi-square tests for categorical variables. Radiographic nonunion rates were compared between the allograft and PEEK cohorts based on the number of patients and the number of operated levels. All patients included in the study had a minimum of 1-yr follow-up imaging and PRO data. Distribution of fusion, asymptomatic, and symptomatic nonunion was compared based on implant material, smoking history, and number of operated levels. Subgroup analyses were performed on the PEEK cohort comparing the graft material placed within the PEEK cage and comparing 5 participating surgeons to determine the impact of differences in surgical technique. For the subgroup analysis, overall nonunion rate was used, as not all surgeons had symptomatic nonunions preventing chi-square analysis. Post hoc analysis was performed in the patients with radiographic nonunion to assess for the presence of graft subsidence and graft resorption along with changes in anterior intervertebral height from immediate postoperative X-ray to latest follow-up X-ray. A multinomial regression analysis was performed to determine the relative risk of nonunion based on age, smoking status, implant material, and number of operated levels against base case of successful fusion. Post hoc regression was performed using the above variables along with individual surgeons to determine the relative risk of symptomatic nonunion to account for practice variability. For the comparative analyses, a P-value $< .05$ was set as statistically significant. Statistical analysis was performed using STATA 14.3 (StataCorp, 2018).

RESULTS

In total, 194 of 404 patients met the inclusion criteria with 79% receiving allograft vs 21% receiving PEEK (Figure 1). The average follow-up was 20 ± 11.0 and 17 ± 6.5 mo for the allograft and PEEK group, respectively. Baseline demographics and clinical data were comparable between the groups except for age and the number of operated levels (Table 2). Of the participating surgeons, 2 surgeons only had patients with allograft, 1 surgeon only had patients with PEEK, and 2 surgeons used both implant materials.

Radiographic Outcomes

The radiographic outcomes are summarized in Tables 3 and 4. In total, 366 disc levels were operated with 64% undergoing multilevel procedures. Seventy-four patients (38%) had a CT scan to assess for fusion. There was no difference in the distribution of imaging modality between groups ($P = .275$). The overall rate of nonunion was higher in the PEEK group based on the number of patients but did not reach significance (Table 3). The rate of radiographic nonunion was significantly higher in the PEEK group based on the number of operated levels for 3-level ACDF and the total sum of the cohort ($P = .026$ and $P = .035$, Table 4). The distribution of patients with radiographic and symptomatic nonunions was significantly different with more patients with

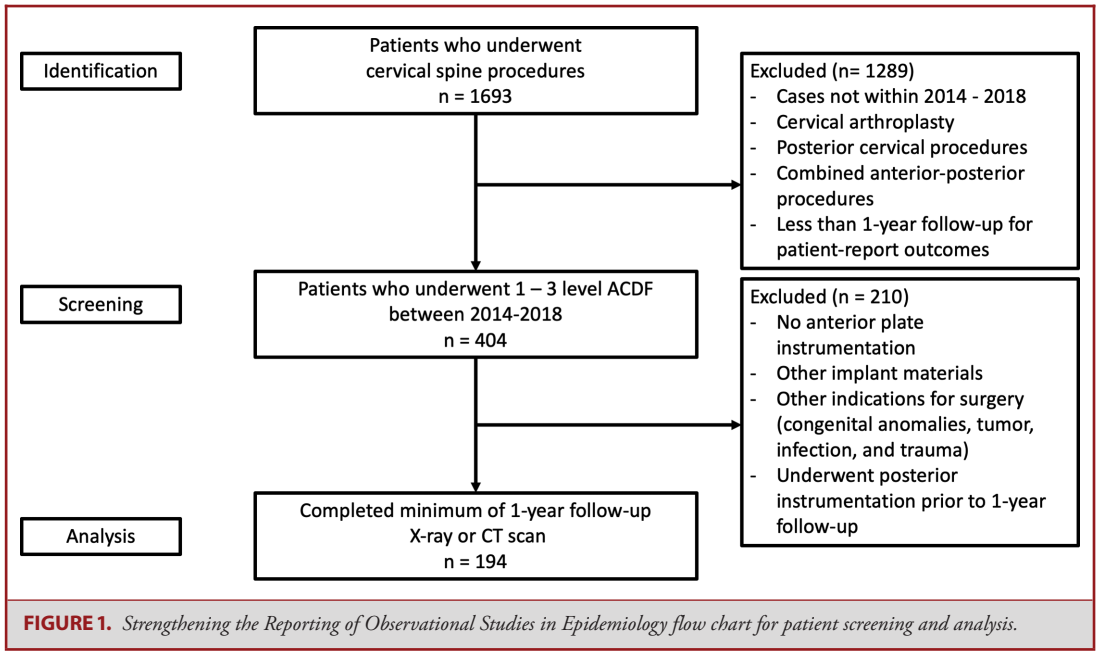


FIGURE 1. *Strengthening the Reporting of Observational Studies in Epidemiology flow chart for patient screening and analysis.*

TABLE 2. Patient Demographic and Clinical Data

	Allograft (n = 154)	PEEK (n = 40)	*P* value
Age (yr)	56.7 (10.7)	61.8 (8.9)	**.007***
Gender (M:F)	64:90	19:21	.499
Smoker	Active: 30 Ex-smoker: 32 No: 92	Active: 4 Ex-smoker: 9 No: 27	.371
Number of levels operated	1: 62 2: 59 3: 33	1: 6 2: 21 3: 13	**.011***
Additional graft material (no. of patients)	None	Morselized allograft: 26 Morselized autograft: 11 i-Factor™: 28** BM aspirate: 4**	
Intraoperative complications (no. of patients)	Yes: 0 No: 154	Yes: 1 (durotomy) No: 39	
Additional surgeries (no. of patients)	PSI: 20 Facet fusion: 2	PSI: 1	**.039***

BM: bone marrow, EBL: estimated blood loss, PEEK: polyetheretherketone, PSI: posterior spinal instrumentation.
*$P < .05$.
**These materials were used in conjunction with morselized autograft or allograft.

allograft undergoing posterior instrumentation ($P < .001$, Figure 2). The rates of symptomatic nonunion in smokers were higher compared to nonsmokers ($P < .001$, Figure 3). Combining the allograft and PEEK cohorts, patients with multilevel ACDF had higher rates of nonunion ($P < .001$, Figure 4). Fusion rate based on graft material in the PEEK implant (morselized allograft vs autograft) did not show a significant difference (64% vs 54%, $P = .936$). Fusion rate between cases with i-Factor™ (Cerapedics), bone marrow aspirate, or no additional packing material did not show a significant difference (63% vs 71% vs 44%, $P = .307$). Comparing the fusion rates based on surgeons, there were no significant differences between the 4 surgeons who used allograft or for the 3 surgeons who used PEEK ($P = .283$, $P = .614$). Within the subset of 83 patients with radiographic

TABLE 3. Radiographic Nonunion Rates Based on Number of Patients

	Allograft		PEEK		
	Fused (%)	Not fused (%)	Fused (%)	Not fused (%)	*P* value
1 level	48 (77.4)	14 (22.6)	5 (83.3)	1 (16.7)	.739
2 levels	30 (50.8)	29 (49.2)	7 (33.3)	14 (66.7)	.167
3 levels	18 (54.5)	15 (45.5)	3 (23.1)	10 (76.9)	.054
Total	96 (62.3)	58 (37.7)	15 (37.5)	25 (62.5)	.053

PEEK: polyetheretherketone.

TABLE 4. Radiographic Nonunion Rates Based on Number of Operated Levels

	Allograft		PEEK		
	Fused (%)	Not fused (%)	Fused (%)	Not fused (%)	*P* value
1 level	48 (77.4)	14 (22.6)	5 (83.3)	1 (16.7)	.739
2 levels	76 (64.4)	42 (35.6)	24 (57.1)	18 (42.9)	.404
3 levels	79 (79.8)	20 (20.2)	24 (61.5)	15 (38.5)	**.026***
Total	203 (72.8)	76 (27.2)	53 (60.9)	34 (39.1)	**.035***

PEEK: polyetheretherketone.
*$P < .05$.

nonunion, 45% of patients with structural allograft and 35% of patients with PEEK implants had radiographic findings of graft subsidence or graft resorption. Comparing the change in anterior intervertebral height from immediate postoperative to the latest follow-up X-ray, the allograft group had significantly greater height loss (1.9 ± 1.7 mm vs 0.6 ± 1.1 mm, $P < .0001$). Furthermore, significantly higher proportion of patients with allograft had intervertebral height loss greater than 3 mm than those with PEEK implants (41% vs 4%, $P = .006$).

The regression analyses results are summarized in Table 5. With the fused group as the reference case, the relative risks of radiographic nonunion in patients with 2- or 3-level ACDF were 5.85 and 5.77 times higher, whereas the relative risk of radiographic nonunion in patients with PEEK was 3.39 times higher than with allograft. The relative risk of symptomatic nonunion in active smokers was 4.68 times higher than nonsmokers. Also, the relative risk of symptomatic nonunion in patients with 3-level ACDF was 4.24 times higher. However, the implant material was not associated with higher rate of symptomatic nonunion. There was a decrease in the relative risk of developing symptomatic pseudarthrosis with increasing age. Post hoc analysis that included individual surgeons in the regression analysis did not reveal significant impact of individual surgeons in symptomatic nonunion (see **Table**, **Supplemental Digital Content**).

Clinical Outcomes

The PRO scores are summarized in Table 6. The allograft group reported significantly higher NDI scores compared to the

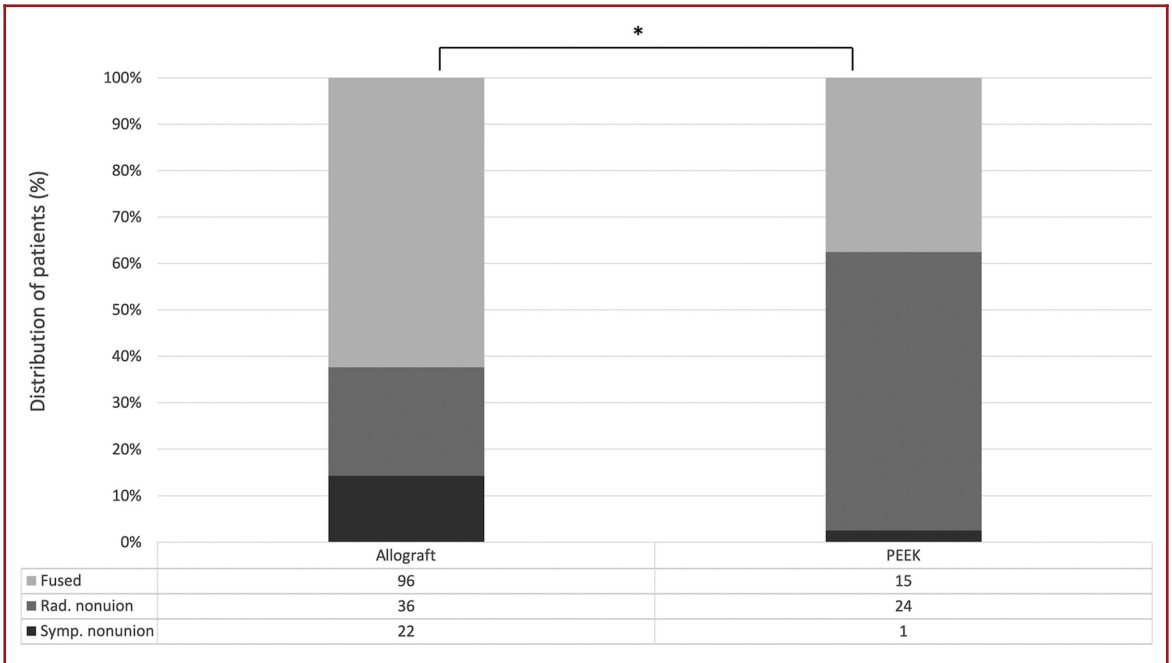
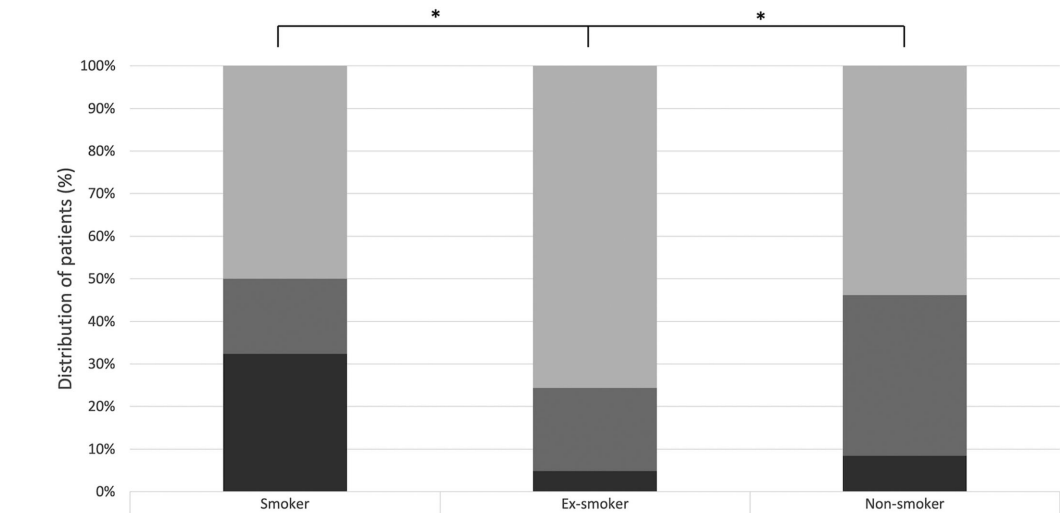
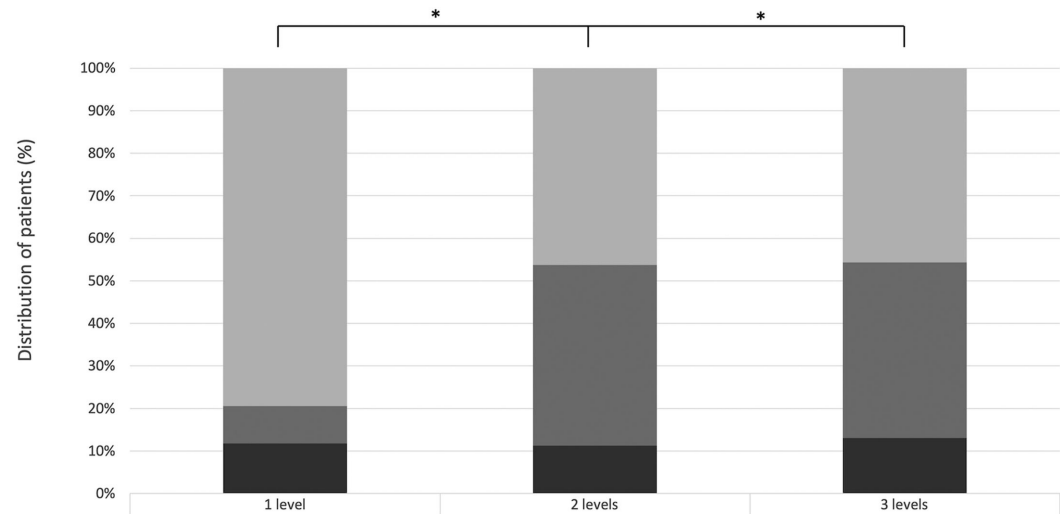


FIGURE 2. *Distribution of patients with fusion, radiographic nonunion, and symptomatic nonunion requiring posterior instrumentation after ACDF with allograft vs PEEK cage. Symp. nonunion: symptomatic nonunion, rad. nonunion: radiographic nonunion.* *$P < .001$.



	Smoker	Ex-smoker	Non-smoker
Fused	17	31	64
Rad. nonunion	6	8	45
Symp. nonunion	11	2	10

FIGURE 3. *Distribution of patients with fusion, radiographic nonunion, and symptomatic nonunion requiring posterior instrumentation after ACDF based on smoking status. The rates of symptomatic nonunion in smokers were significantly higher compared to nonsmokers and ex-smokers. Symp. nonunion: symptomatic nonunion, rad. nonunion: radiographic nonunion. *P < .001.*



	1 level	2 levels	3 levels
Fused	54	37	21
Rad. nonunion	6	34	19
Symp. nonunion	8	9	6

FIGURE 4. *Distribution of patients with fusion, radiographic nonunion, and symptomatic nonunion requiring posterior instrumentation after ACDF based on number of levels operated. Patients with multilevel ACDF had significantly higher rates of pseudarthrosis compared to one-level ACDF. Symp. nonunion: symptomatic nonunion, rad. nonunion: radiographic nonunion. *P < .001.*

TABLE 5. Regression Analysis for Radiographic Nonunion and Symptomatic Nonunion Against Base Reference of Successful Fusion

	Relative risk	*P* value	95% CI	
Radiographic nonunion				
Age	.9898972	.600	.9530057	1.028217
Smoking status				
Nonsmoker				
Ex-smoker	.4263481	.068	.1707208	1.064737
Active smoker	.5909651	.344	.1988122	1.756631
Number of levels operated				
1				
2	5.850819	**.000***	2.278294	15.02531
3	5.772748	**.001***	2.014829	16.53968
Implant material				
Allograft				
PEEK	3.39479	**.004***	1.480423	7.784665
Symptomatic nonunion				
Age	.9417858	**.017***	.8963938	.9894764
Smoking status				
Nonsmoker				
Ex-smoker	.5180977	.425	.1031163	2.60313
Active smoker	4.682879	**.005***	1.598184	13.72143
Number of levels operated				
1				
2	2.316957	.163	.7113221	7.546921
3	4.237785	**.039***	1.076868	16.6769
Implant material				
Allograft				
PEEK	.360489	.353	.0418859	3.102531

CI: confidence interval, PEEK: polyetheretherketone.
*$P < .05$.

TABLE 6. Patient-Reported Health-Related Quality of Life Measures

Outcome parameters	Allograft (n = 154) Mean (SD)	PEEK (n = 40) Mean (SD)	*P* value
Preoperative			
NDI	41.73 (19.42)	33.33 (18.22)	**.020***
mJOA	14.60 (3.89)	14.22 (2.28)	.447
NRS neck pain	6.11 (3.01)	5.38 (3.25)	.263
NRS arm pain	5.11 (3.15)	4.97 (2.95)	.779
SF-12 MCS	46.52 (11.79)	50.46 (10.69)	.095
SF-12 PCS	31.31 (8.56)	31.26 (7.66)	.978
Postoperative follow-up			
Mean follow-up (mo)	20 (11.0)	17 (6.5)	.280
NDI	33.29 (21.92)	22.1 (16.55)	**.003***
mJOA	14.83 (2.92)	15.18 (2.60)	.603
NRS neck pain	4.30 (2.92)	3.43 (2.87)	.103
NRS arm pain	3.04 (2.97)	2.60 (2.85)	.430
SF-12 MCS	48.95 (11.44)	51.61 (10.47)	.171
SF-12 PCS	36.29 (11.48)	38.52 (11.75)	.282

MCS: mental health composite score, mJOA: modified Japanese Orthopedic Assessment scale, NDI: Neck Disability Index, NRS: numeric rating scale, PCS: physical health composite score, PEEK: polyetheretherketone, SD: standard deviation, SF-12: Short Form-12.
*$P < .05$.

PEEK group at the preoperative period and at the final follow-up. Comparing patients categorized based on fusion status (ie, fused, radiographic nonunion, and symptomatic nonunion), patients with symptomatic nonunion had significantly worse NDI, SF-12 PCS, and neck pain compared to the other 2 groups (Figure 5). Patients with symptomatic nonunion also had worse SF-12 MCS and mJOA scores compared to the radiographic nonunion group. Lastly, patients with symptomatic nonunion had worse arm pain compared to the fused group.

DISCUSSION

This prospectively collected database documents a higher incidence of radiographic nonunion in patients treated with PEEK implants. Regression analysis suggests that factors associated with greater risk of radiographic nonunion are the use of PEEK implant and multilevel procedures, whereas younger age, smoking status, and multilevel ACDF was predictive of symptomatic nonunion. Furthermore, PROs were significantly worse in individuals with symptomatic nonunion.

Nonunions after spinal fusion procedures can result in recurrent pain, radiculopathy, and kyphotic deformity. Some of the findings of this study parallel published reports such as the impact of graft material, the number of levels operated, and smoking history. Two recent studies compared fusion rates between allograft and PEEK for single-level or multilevel ACDF.[6,9] Both retrospective cohort studies highlighted significantly higher rates of nonunion in the PEEK cohort.[6,9] The results of our findings share a similar extent of nonunion at >50% in patients with PEEK implant. This is in contrast to the findings of Wang et al,[12] with the differences being postulated to be due to a longer follow-up period, institutional policy on smoking cessation, and exclusion of standalone implants.

One proposed theory for the difference in fusion is the hydrophobic property of PEEK preventing osteointegration.[8] The lack of osteointegration of PEEK implants also creates a unique challenge in the radiographic assessment called the PEEK-halo effect in CT scans.[13] Given that one of the criteria for assessing fusion is a lack of radiolucent line at the graft/vertebral body interface, the halo effect around the PEEK implant may cause greater difficulty in determining fusion status. Lastly, the relatively greater surface area for graft/vertebral body interface with structural allograft may allow an enhanced rate of fusion.

An increase in the number of operated levels has also been found to be associated with nonunion.[14,15] The results of this study further support that patients undergoing multilevel ACDF experience higher rates of nonunion. In the univariate analysis, differences in the rate of nonunion were significant in the 3-level ACDF, which lead to differences in the overall rates of

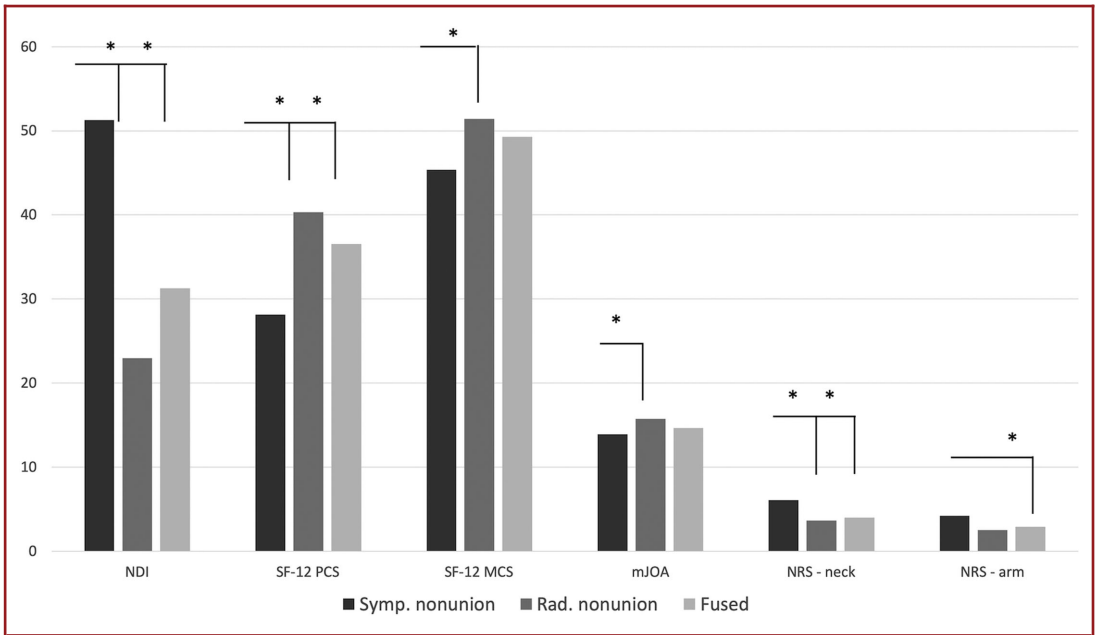


FIGURE 5. *Postoperative PRO measures based on fusion status. Symp. nonunion: symptomatic nonunion, rad. nonunion: radiographic nonunion, *P < .05.*

nonunion. The subset of patients undergoing multilevel ACDF with PEEK graft had a 4.6-fold risk of symptomatic nonunion. History of smoking has been linked as an independent predictor of nonunion.[16-18] Smoking is believed to contribute to osteoporosis with the destruction of osteoblast.[18] In our study, active smokers had 4.7 times the risk of symptomatic nonunion. Unique to this study is the incorporation of ex-smoker status, which did not confer the risk of symptomatic nonunion. Lastly, age was found to be a significant predictor of symptomatic nonunion, which is consistent with the findings of Phillips et al,[5] who hypothesized that younger age may be related to symptomatic nonunion because of the increased biomechanical demand from greater activity levels. Older patients with lower activity levels may experience sufficient stability with fibrous nonunion to prevent tipping into symptomatic pseudarthrosis.

There is one finding in this study that differs from previous reports, including that of Krause et al[6] and Teton et al.[9] Specifically, the rate of symptomatic nonunion was higher in the allograft group in our univariate analysis, whereas other recent studies noted higher reoperation rates with PEEK. This may be postulated as differences in individual surgeon's threshold for reoperation as not all participating surgeons used both implant materials. However, our subgroup and post hoc analyses did not reveal the impact of the individual surgeon in fusion rates or reoperation. Considering the clinical data of the 2 groups may also provide potential explanations. Examining the PRO of the allograft cohort, patients reported significantly worse disability compared to the PEEK group. This may have contributed to the surgeons offering posterior instrumentation for nonunion more readily in the allograft cohort. The studies by Krause et al[6] and Teton et al[9] did not include clinical outcomes nor included regression analysis. Furthermore, cases of nonunion with allograft may be associated with resorption of the graft, which does not occur with PEEK.[19] The loss of intervertebral height in such cases may have contributed toward worsening symptomatology. In fact, in our post hoc analysis, the intervertebral height loss for patients with structural allografts was significantly greater. Although the differences in the number of posterior instrumentations between the 2 groups are worth noting, it is important to highlight that the use of allograft was not found to be predictive of symptomatic nonunion in our regression analysis. Furthermore, the rate of reoperation in this study is in keeping with the finding of a recent systematic review of ACDF that noted the highest revision rates in the allograft group.[20]

The variability in the definition of fusion remains a challenge in research.[4,20,21] Although radiographic and symptomatic nonunion rates in this study are within the range reported in the literature, they are at the higher end of that spectrum. This may reflect our strict criteria for fusion using change in interspinous distance on flexion-extension X-rays along with the use of a CT scan in 38% of patients. This is in contrast to previous studies that relied on neutral lateral radiographs and using CT scans in a minority of patients. As highlighted in the literature, standardizing the definition of fusion will improve future comparison of study results.

Limitations

There are a number of limitations in the study. First, the distribution of patients with implant material was not equal with 79% receiving allograft. Although the majority of preoperative variables were comparable between the 2 groups, age, number of operated levels, and NDI were different. The differences in

patient characteristics were addressed using regression analysis. Even with the disparity in the sample size, the regression analysis supports that PEEK implant may lead to greater radiographic nonunion, but other factors such as number of operated levels and smoking status play a greater role in symptomatic nonunion. Along with the use of multivariate analysis, this study presents the largest study to date with prospectively collected data. Secondly, determining the need for posterior instrumentation subject to variations in practice patterns. Although preoperative clinic notes were analyzed to confirm that all posterior instrumentations were intended to address nonunion, the threshold for offering surgery was not standardized. Given that patients treated by 5 surgeons were included in the study, standardization of operating procedures was not feasible. However, our subgroup analyses of fusion rates based on individual surgeons and also based on graft material in the PEEK cage did not show statistically significant differences. Lastly, other potential patient factors such as steroid or NSAID use and co-morbidities (ie, renal failure and osteoporosis) may impact fusion. Although all patients in this study were advised to stop using NSAID for 6 wk after surgery, the other variables were not assessed.

CONCLUSION

Radiographic nonunion in patients with PEEK implant after ACDF was significantly higher than those with allograft implants. Along with implant material, factors such as younger age, active smoking status, and the number of operated levels were independent predictors of fusion failure. Given the impact of nonunion in PRO, perioperative optimization of modifiable factors and surgical planning are essential to ensure successful outcome.

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Supplemental Digital Content. Table. Post hoc regression analysis for symptomatic nonunion against base reference of successful fusion accounting for individual surgeons. PEEK: polyetheretherketone, CI: confidence interval, $^{*}P < .05$.

Original Article

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Structural Allograft Versus Synthetic Interbody Cage for Anterior Cervical Discectomy and Fusion: A Comparison of 1-Year Outcomes From a National Database

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Abstract

Study Design: Observational cohort study.

Objective: To compare 1-year perioperative complications between structural allograft (SA) and synthetic cage (SC) for anterior cervical discectomy and fusion (ACDF) using a national database.

Methods: The TriNetX Research Network was retrospectively queried. Patients undergoing initial single or multilevel ACDF surgery between October 1, 2015 and April 30, 2019 were propensity score matched based on age and comorbidities. The rates of 1-year revision ACDF surgery and reported diagnoses of pseudoarthrosis, surgical site infection (SSI), and dysphagia were compared between structural allograft and synthetic cage techniques.

Results: A comparison of 1-year outcomes between propensity score matched cohorts was conducted on 3056 patients undergoing single-level ACDF and 3510 patients undergoing multilevel ACDF. In single-level ACDF patients, there was no difference in 1-year revision ACDF surgery ($P = .573$), reported diagnoses of pseudoarthrosis ($P = .413$), SSI ($P = .620$), or dysphagia ($P = .529$) between SA and SC groups. In multilevel ACDF patients, there was a higher rate of revision surgery (SA 3.8% vs SC 7.3%, odds ratio = 1.982, $P < .001$) in the SC group, and a higher rate of dysphagia in the SA group (SA 15.9% vs SC 12.9%).

Conclusion: While the overall revision and complication rate for single-level ACDF remains low despite interbody graft selection, SC implant selection may result in higher rates of revision surgery in multilevel procedures despite yielding lower rates of dysphagia. Further prospective study is warranted.

Keywords

anterior cervical discectomy and fusion, ACDF, structural allograft, interbody spacer, surgical site infection, pseudoarthrosis

Introduction

Anterior cervical discectomy and fusion (ACDF) has emerged as the most commonly performed surgical treatment for degenerative cervical spine disease.[1] Each year, over 132 000 ACDFs are performed in the United States and volumes have increased 5.7% annually from 2006 to 2013.[2] Since early descriptions of anterior surgical approaches in the 1950's, advancements in techniques, instrumentation, and implant materials have focused primarily on achieving more reliable fusion of unstable or symptomatic segments.[3-5] Options for interbody grafts have evolved from tricortical iliac crest autograft to structural allograft (SA) or synthetic cages (SC) of various materials.

Autograft harvested from the iliac crest is biocompatible and nonimmunogenic and has been reported to have high

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fusion rates with relatively few incidences of graft complications.[5-7] Hence, autograft is considered to be the gold standard for ACDF. However, in addition to a second surgical site with increased blood loss and operative time, the donor site is frequently reported to have complications such as pain, hematomas, seromas, infections, and fractures contributing to potential functional disability.[8,9]

The potential for graft site complications and additional operative time has led surgeons to increasingly substitute autograft with structural allograft or synthetic cages of various materials such as polyetheretherketone (PEEK) and titanium alloys.[10,11] In a retrospective review examining geographic variation in anterior cervical fusion procedures, McGuire et al[12] demonstrated a marked decrease in autograft utilization from 86% in 1999 to 10% in 2008. During the same time period, they reported a significant increase in the use of structural allograft and synthetic cages from 14% to 59% and 0% to 31%, respectively. In a 2017 international survey of spine surgeons, PEEK cages (64.1%) were the most commonly used interbody implant worldwide.[11] While respondents universally agreed that achieving fusion was successful to a good clinical outcome, only half of respondents were satisfied with comparative effectiveness data available on graft materials.

While the use of structural allograft and synthetic cages for single- and multilevel ACDF has been individually reported in multiple studies with favorable outcomes,[13-15] there are few direct comparisons of complications and rates of revision surgery between structural allografts and synthetic cages. Krause et al[16] recently reported that the use of PEEK implants in single-level ACDF is associated with significantly higher rate of pseudoarthrosis and need for revision surgery when compared with the use of structural allografts. In their study, 29 of 56 (51.8%) PEEK implants demonstrated radiographic evidence of pseudoarthrosis compared to 7 of 71 (10%) structural allograft. Furthermore, 7 patients from the PEEK group required revision (12.5%) while 1 patient with structural allograft required revision (1.4%). To increase sample size, other authors have utilized a large-scale administrative database (PearlDiver Patient Record Database) to compare outcomes between structural allograft and synthetic cages.[17,18] Goz et al[17] included 17 000 patients from 2007 to 2014, while Pirkle et al[18] included 6130 patients from 2007 to 2016. After correcting for age, gender, comorbidity burden, and number of levels fused, Goz et al[17] reported that graft choice was not an independent predictor of complications, with an overall rate of revision surgery of <1% in both groups. In contrast, Pirkle et al[18] found a higher rate of revision surgery for synthetic cages (5.32%) compared with structural allograft (1.97%), and this difference remained significant after controlling for confounding variables such as levels fused and smoking status.

In an era of maximizing value, our objective was to further understand potential differences in one-year clinical outcomes between structural allograft and synthetic cages. We selected the TriNetX platform, a multicenter, longitudinal database, to obtain the most recent comparative data across a large patient sample.

Methods

This research was deemed exempt from institutional review board review by the institution's clinical research committee. The TriNetX Research database was retrospectively queried as of May 22, 2020 to evaluate all patients undergoing single or multilevel ACDF surgery between October 1, 2015 and April 30, 2019. All patients had a minimum of one-year follow up data available, and the study time period aligned with the implementation of International Classification of Diseases 10th edition (ICD-10) to maintain consistency in code-based definitions. Patients were then grouped by receipt of structural allograft or synthetic cage. Analysis was performed using propensity score matched cohorts. Propensity score matching was performed based on age, race, gender, and the presence or absence of the following diagnoses within the year prior to ACDF surgery: cervical disc disorders; spondylosis; cervical radiculopathy; hypertension; chronic pain; anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders; diabetes mellitus, mood (affective) disorders; overweight or obesity; nicotine dependence; disorders of bone density and structure, and malnutrition. The primary outcome measure was revision ACDF surgery within 1 year of the initial procedure. Revision surgeries included ACDF, posterior decompression and fusion, posterior decompression without fusion and other procedures (osteotomy, posterior open treatment of fracture or dislocation, laminectomy for lesions and neoplasm, anterior decompression). Secondary outcome measures included reported diagnoses of pseudoarthrosis, surgical site infection (SSI), or dysphagia within the 1-year postoperative period. Adjacent segment disease was considered for evaluation as a secondary endpoint but excluded due to the lack of a specific ICD-10 code for this condition. Primary and secondary outcomes were identified by relevant diagnosis or procedure codes. A full list of definitions for the surgical procedures, comorbidities, and outcomes is presented in Table 1. All statistical analysis was performed using TriNetX Analytics. Significance was assessed at an alpha of .05.

About TriNetX

TriNetX is a "global health research network that optimizes clinical research and enables discoveries through the generation of real-world evidence."[19] The research platform includes longitudinal data from 26 health care organizations and includes over 37 million patients. As a federated network, TriNetX received a waiver from Western Institutional Review Board since only aggregated counts, statistical summaries of de-identified information, but no protected health information is received, and no study-specific activities are performed in retrospective analyses. De-identified, HIPAA (Health Insurance Portability and Accountability Act) compliant electronic health record (EHR) data is collected from participating health care organizations who submit structured and unstructured data elements. On average, participants submit data retrospectively for 7 years, with some providing historical data 13 years or

Table 1. Coding Definitions: CPT and ICD-10 Code Definitions Provided for Single-Level Structural Allograft and Synthetic Interbody Spacer, Multilevel Structural Allograft and Synthetic Interbody spacer, Patient Comorbidities, and Procedure Outcomes.

	CPT and ICD-10 code definitions
Surgical procedures	
Single level with structural allograft	22 551 (ACDF) and 20 931 (structural allograft) and cannot have 22 552 (multilevel) or 22 853 (biomechanical spacer); and cannot have any history of previous 22 551 or 22 552 (no prior ACDF)
Single level with interbody spacer	22 551 (ACDF) and 22 853 (biomechanical spacer) and cannot have 20 931 (structural allograft) or 22 552 (multilevel); and cannot have any history of previous 22 551 or 22 552 (no prior ACDF)
Multilevel with structural allograft	22 551 (ACDF) and 20 931 (structural allograft) and 22 552 (multilevel) and cannot have 22 853 (biomechanical spacer); and cannot have any history of previous 22 551 or 22 552 (no prior ACDF)
Multilevel with interbody spacer	22 551 (ACDF) and 22 853 (biomechanical spacer) and 22 552 (multilevel) and cannot have 20 931 (structural allograft); and cannot have any history of previous 22 551 or 22 552 (no prior ACDF)
Comorbidities and risk factors (diagnosis present 1 day to 1 year prior to surgery)	
Spondylosis	M47
Cervical disc disorders	M50
Radiculopathy, cervical region	M54.12
Chronic pain, not elsewhere classified	G89.2
Hypertensive diseases	I10-I16
Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders	F40-F48
Mood (affective) disorders	F30-F39
Overweight and obesity	E66
Diabetes mellitus	E08-E13
Nicotine dependence	F17
Disorders of bone density and structure	M80-85
Malnutrition	E40-46
Outcomes (diagnosis or procedure present 1 day to 1 year after surgery)	
Revision	22 210, 22 216, 22 226, 22 326, 22 548,22 551, 22 552, 22 590, 22 595,22 600, 22 614, 63 001, 63 015, 63 020, 63 035, 63 040, 63 043, 63 045, 63 048, 63 050, 63 051, 63 075, 63 076, 63 250, 63 265, 63 270, 63 275, 63 280, 63 285
Pseudoarthrosis	M96.0
Dysphagia	R13
Surgical site infection	T81.4

Abbreviations: CPT, Current Procedural Terminology; ICD-10, International Classification of Diseases–10th Revision; ACDF, anterior cervical discectomy and fusion.

older. Variables captured include demographics, diagnoses (all mapped to ICD-10 coding) procedures (ICD-10 PCS and CPT), medications, lab values, and genomics information. Statistical analysis is performed within the analytics platform using parallel R and Python queries triangulated to maximize test accuracy.[19]

Results:

A total of 8103 patients were included in this observational cohort study. Of the 3775 patients undergoing single-level ACDF, structural allograft was used in 2213 (59%) patients and synthetic cages in 1562 (41%) patients. Of the 4328 multilevel ACDF procedures, structural allograft (SA) was used in 2482 (57%) patients and synthetic cages (SC) in 1846 (43%) patients.

To control for differences in comorbidities across the sample, the cohorts were propensity score matched based on age, gender, race, and comorbid conditions. Prior to propensity score matching, patients undergoing single-level ACDF using structural allograft were significantly younger (SA 53.9 $\pm$ 12.9 vs SC 55.1 $\pm$ 13.0 years, $P = .004$), had higher rates of cervical disc disorders (SA 62.7% vs SC 59.0%, $P = .020$), higher rates of cervical radiculopathy (SA 43.6% vs SC 40.2%, $P = .040$), higher rates of nicotine dependence (SA 17.6% vs SC 10.7%, $P < .001$), lower rates of spondylosis (SA 49.9% vs SC 55.1%, $P = .002$), and lower rates of disorders of bone density and structure (SA 4.4% vs SC 6.7%, $P = .002$). After propensity score matching, no significant differences remained (Table 2). Prior to propensity score matching, patients undergoing multilevel ACDF using synthetic cage were significantly

Table 2. Patient Characteristics and Comorbidities Before and After Propensity Score Matching: Demographics and Comorbidities Data Provided for Single- and Multilevel ACDF With the Original Cohorts and Propensity Score Matched Cohorts.

Single-level ACDF	Initial sample			Propensity score matched cohort		
Demographics and comorbidities	Structural allograft (n = 2213), n (%)	Synthetic interbody spacer (n = 1562), n (%)	P[a]	Structural allograft (n = 1528), n (%)	Synthetic interbody spacer (n = 1528), n (%)	P[a]
Age, years, mean ± SD	53.9 ± 12.9	55.1 ± 13.0	**.004**	55.2 ± 12.9	55.0 ± 13.0	.609
White race	1797 (81.2)	1270 (81.3)	.936	1245 (81.5)	1240 (81.2)	.817
Female gender	1021 (46.1)	757 (48.5)	.158	736 (48.2)	737 (48.2)	.971
Cervical disc disorders	1388 (62.7)	921 (59.0)	**.020**	905 (59.2)	910 (59.6)	.854
Spondylosis	1105 (49.9)	861 (55.1)	**.002**	850 (55.6)	828 (54.2)	.424
Cervical radiculopathy	964 (43.6)	628 (40.2)	**.040**	611 (40.0)	624 (40.8)	.632
Hypertension	836 (37.8)	611 (39.1)	.404	578 (37.8)	592 (38.7)	.602
Chronic pain	457 (20.7)	343 (22.0)	.333	340 (22.3)	328 (21.5)	.599
Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders	354 (16.0)	263 (16.8)	.491	246 (16.1)	248 (16.2)	.922
Mood (affective) disorders	383 (17.3)	253 (16.2)	.370	252 (16.5)	248 (16.2)	.845
Diabetes mellitus	373 (16.9)	251 (16.1)	.522	245 (16.0)	248 (16.2)	.883
Overweight or obese	295 (13.3)	187 (12.0)	.218	177 (11.6)	185 (12.1)	.654
Nicotine dependence	389 (17.6)	167 (10.7)	**<.001**	179 (11.7)	167 (10.9)	.493
Disorders of bone density and structure	97 (4.4)	104 (6.7)	**.002**	82 (5.4)	88 (5.8)	.636
Malnutrition	30 (1.4)	13 (0.8)	.136	12 (.8)	13 (.9)	.841

Multilevel ACDF	Initial sample			Propensity score matched cohort		
Demographics and comorbidities	Structural allograft (n = 2482), n (%)	Synthetic interbody spacer (n = 1846), n (%)	P	Structural allograft (n = 1755), n (%)	Synthetic interbody spacer (n = 1755), n (%)	P
Age, years, mean ± SD)	55.8 ± 11.0	57.8 ± 10.9	**<.001**	57.4 ± 10.8	57.3 ± 10.8	.731
White race	1966 (79.2)	1527 (82.7)	**.004**	1423 (81.1)	1438 (81.9)	.514
Female gender	1197 (48.2)	925 (50.1)	.221	847 (48.3)	869 (49.5)	.458
Cervical disc disorders	1444 (58.2)	1175 (63.7)	**<.001**	1109 (63.2)	1100 (62.7)	.753
Spondylosis	1674 (67.4)	1283 (69.5)	.150	1201 (68.5)	1215 (69.2)	.636
Cervical radiculopathy	1258 (50.7)	848 (45.9)	**.002**	815 (46.4)	817 (46.5)	.946
Hypertension	1081 (43.6)	822 (44.5)	.523	780 (44.4)	770 (43.9)	.734
Chronic pain	531 (21.4)	502 (27.2)	**<.001**	430 (24.5)	448 (25.5)	.483
Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders	427 (17.2)	334 (18.1)	.447	308 (17.6)	316 (18.0)	.724
Mood (affective) disorders	435 (17.5)	350 (19.0)	.226	314 (17.9)	322 (18.3)	.726
Diabetes mellitus	423 (17.0)	319 (17.3)	.837	302 (17.2)	303 (17.3)	.964
Overweight or obese	375 (15.1)	250 (13.5)	.147	229 (13.0)	240 (13.7)	.585
Nicotine dependence	423 (17.0)	222 (12.0)	**<.001**	201 (11.5)	219 (12.5)	.349
Disorders of bone density and structure	123 (5.0)	143 (7.7)	**<.001**	110 (6.3)	121 (6.9)	.454
Malnutrition	31 (1.3)	10 (0.5)	**.018**	11 (0.6)	10 (0.6)	.827

Abbreviation: ACDF, Anterior cervical discectomy and fusion.
[a] Statistical significance with $P < .05$ in boldface.

older (SA 55.8 ± 11.0 vs SC 57.8 ± 10.9 years, $P < .001$), more likely to be White (SA 79.2% vs SC 82.7%, $P = .004$) and had higher rates of cervical disc disorders (SA 58.2% vs SC 63.7%, $P < .001$), higher rates of chronic pain (SA 21.4% vs SC 27.2%, $P < .001$), higher rates of disorders of bone density and structure (SA 5.0% vs SC 7.7%, $P < .001$), lower rates of cervical radiculopathy (SA 50.7% vs SC 45.9% $P = .002$), lower rates of nicotine dependence (SA 17.0% vs. SC 12.0%, $P < .001$), and lower rates of malnutrition (SA 1.3% vs SC 0.5%, $P = .018$). After propensity score matching none of these differences remained (Table 2).

Following propensity score matching, 3056 patients underwent single-level ACDF, with 1528 (50%) patients in the structural allograft group and 1528 (50%) in the synthetic cage group. Comparing 1-year outcomes, there was no difference in the rate of revision surgery ($P = .573$) or reported diagnoses

Table 3. Propensity Score Matched Cohorts, 1-Year Outcomes: Data Provided for Propensity Score Matched Patient Cohorts With Single- and Multilevel ACDF Utilizing Structural Allograft or Synthetic Interbody Spacer.

	Structural allograft, n (%)	Synthetic interbody spacer, n (%)	Odds Ratio (95% CI)	P[a]
Single level (n = 3056)	1528 (100.0)	1528 (100.0)		
Revision	56 (3.7)	62 (4.1)	1.112 (0.769-1.607)	.573
Pseudoarthrosis	232 (15.2)	216 (14.1)	0.920 (0.753-1.124)	.413
Surgical site infection	17 (1.1)	20 (1.3)	1.179 (0.615-2.259)	.620
Dysphagia	177 (11.6)	166 (10.9)	0.930 (0.743-1.165)	.529
Multilevel (n = 3510)	1755 (100.0)	1755 (100.0)		
Revision	67 (3.8)	128 (7.3)	1.982 (1.464-2.684)	**<.001**
Pseudoarthrosis	372 (21.2)	413 (23.5)	1.144 (0.976-1.341)	.097
Surgical site infection	18 (1.0)	23 (1.3)	1.281 (0.689-2.383)	.432
Dysphagia	279 (15.9)	226 (12.9)	0.782 (0.647-0.945)	**.011**

Abbreviation: ACDF, anterior cervical discectomy and fusion.
[a] Statistical significance with $P < .5$ in boldface.

of pseudoarthrosis ($P = .413$), SSI ($P = .620$), or dysphagia ($P = .529$) (Table 3).

A total of 3510 patients remained in the multilevel ACDF cohort following propensity score matching, with equal distribution among the SA and SC groups. For patients in the SC group, there was a higher likelihood of revision surgery (SA 3.8% vs SC 7.3%, OR = 1.982, $P < .001$) and lower likelihood of dysphagia (SA 15.9% vs SC 12.9%, OR = 0.782, $P = .011$). No significant differences in SSI ($P = .439$) or pseudoarthrosis ($P = .097$) were observed (Table 3).

Discussion

Outcomes following ACDF have been shown to be effective in patients with degenerative cervical disease.[5,13,20] With an increasing number of synthetic cage materials and implants available to surgeons, our study represents an analysis of the most recent data available comparing 1-year complications between structural allografts and synthetic cages. Compared with structural allograft, patients undergoing multilevel ACDF with synthetic cage were at increased risk for 1-year revision surgery, while those receiving structural allograft were at increased risk for dysphagia.

For single-level ACDF, our comparison of 1-year outcomes between structural allografts and synthetic cages did not reveal any differences in the risk of revision surgery, pseudoarthrosis, SSI, or dysphagia. In contrast to our results, Krause et al[16] demonstrated radiographically higher rate of pseudoarthrosis (SA 10% vs PEEK 51.8%, $P < .001$) and greater need for revision surgery (SA 1.4% vs PEEK 12.5%, $P = .01$) with the use of PEEK in single-level ACDF. Based on these results, Krause and colleagues concluded that PEEK devices are associated with significantly higher rates of pseudoarthrosis and need for revision surgery compared with the use of allograft for single-level ACDF. Similarly, an administrative database study by Pirkle et al[18] suggested the use of structural allograft to be superior over synthetic cages after finding higher pseudoarthrosis rates in patients who underwent single-level ACDF with synthetic cages compared to structural allograft (SA 1.9% vs SC 4.2%, $P = .0007$) after controlling for number of levels treated, diabetes status, and tobacco use. We posit that our results may have deviated from these findings given the relatively low rates of complications observed in our cohort of single-level ACDFs, especially over the 1-year time horizon. In addition, our study employed more extensive propensity score matching than the Pirkle and Krause studies, suggesting that previously unexamined comorbidities and risk factors beyond smoking status, sex, diabetes, age, and body mass index—which were controlled for in the prior studies—may be important in determining the optimal implant for single-level ACDF.

Previous studies have observed significantly higher rates of pseudoarthrosis and need for revision surgery in multilevel ACDF compared to single-level ACDF utilizing structural allografts and synthetic cages.[21-23] In our present comparative study, we observed higher rates of pseudoarthrosis and likelihood of revision surgery in the multilevel ACDF cohort. Our results further show that the patients who underwent multilevel ACDF with synthetic cages have a significantly higher likelihood of revision surgery when compared with structural allografts. Our results are directionally in line with the Pirkle et al[18] comparative review which demonstrated significantly higher pseudoarthrosis rate with 2-level (SA 1.7% vs SC 6.1%, $P < .001$), and 3+ level (SA 2.9% vs SC 6.3%, $P < .001$) ACDF. Similar to this study,[18] we included both anterior and posterior procedures in our criteria for revision surgery in order to broadly capture these clinical scenarios.

In another comparison, Goz et al[17] evaluated the rate of perioperative complications in patients undergoing ACDF found a statistically significant correlation with larger overall rate of complications in the synthetic cage (SA 7.76% vs SC 8.71%, $P < .01$) group and higher likelihood of revision surgery in the structural allograft (SA 0.56% vs SC 0.50%, $P = .03$) group. However, the authors considered these differences to be clinically insignificant given the low absolute differences observed. Based on these results, they concluded that synthetic

cages are associated with a marginally higher overall rate of complications with similar revision rates, but acknowledged that additional large studies are necessary to further elucidate which graft combination provides the ultimate combination of fusion rates, low complications, and low cost. In contrast, our study showed significantly higher revision rate with synthetic cages in multilevel ACDF that may affect clinical practice. Beyond revision rate, our study evaluated the secondary outcomes of SSI, pseudoarthrosis, and dysphagia. While no significant differences between the structural allograft and synthetic cage groups were observed, with the exception of dysphagia in multilevel surgeries, these endpoints are limited in that they are grossly underreported postoperatively. In addition, the broad evaluation of SSI encompasses a wide variety of complications from benign superficial infections to deep infections requiring surgical intervention. Our observation of higher rates of dysphagia in patients undergoing multilevel ACDF with structural allograft is in alignment with Goz et al's evaluation of dysphagia rates in the single- and multilevel population (SA 0.64% vs SC 0.33%, $P < .01$), but in contrast to previous studies.[24] This finding must be interpreted cautiously as our study design precludes control for factors that influence dysphagia such as surgical time, number of levels fused, and operative level, especially above C3.[25,26]

Given our finding of potentially higher one-year revision rates in ACDF with synthetic cages, we suggest further economic investigation of these devices, in parallel with clinical evaluation, is warranted. Limited data comparing the cost-effectiveness of ACDF with structural allograft or synthetic cage is currently available. Using a 10-year-Markov state transition model, Virk et al[27] found that PEEK cages had an incremental cost-effectiveness ratio over $100 000/quality-adjusted life year gained compared with autograft or structural allograft, leading to the conclusion that the technique is not cost effective compared with these alternatives. Beyond the differences in implant costs—structural allograft has been cited to cost up to $2552 and synthetic cages up to $7928 per implant[28]—operative time, hospital length of stay, complication rates, and post-discharge resource utilization are important cost drivers that require further direct comparison.

Synthetic cages that widely exist on the market today are composed of PEEK, titanium alloys, and carbon fiber with numerous studies attesting for their efficacy in spinal fusion.[29] One systematic review assessing clinical and radiographic outcomes of synthetic cages in ACDF found no differences in outcomes between PEEK, titanium, and carbon fiber cages, but titanium and carbon fiber cages were correlated with increased cost and higher subsidence rate in comparison to PEEK cages.[30] Given its radiolucency, low elastic modulus resulting in stress shielding, and similarities to cancellous bone, PEEK has been more widely used as an implant material for spinal fusion.[11,29,31] However, PEEK has been demonstrated to have a hydrophobic surface preventing protein absorption and promotion of cell adhesion interfering host-bone integration by the formation of an encapsulating fibrous layer.[32,33] While coating PEEK with a bioactive substance such as titanium has shown to be effective in improving its biocompatibility, it is also associated with biological and inflammatory reactions in human and animal studies.[34] In addition to these drawbacks, fusion mass may not form in the space occupied by the synthetic cage with less endplate surface area and intervertebral volume available, as hypothesized in Pirkle et al[18] study. On the contrary, allograft possess osteoinductive properties and provides osteoconductive scaffold for new bone formation with relatively high fusion rates comparable to autografts, especially with plating techniques.[29,35] In addition to implant material, the use of an anterior plate and the type of nonstructural biologic material used in conjunction with a synthetic cage are other important aspects of the surgical procedure that influence postoperative outcomes. In a meta-analysis of 19 studies, patients who underwent ACDF with a cage-only technique had significantly lower rates of postoperative dysphagia and adjacent segment disease compared with patients who underwent ACDF with a cage-plate technique, but the cage-plate technique had better radiographic outcomes with significantly less subsidence and better restoration of cervical lordosis. No other significant differences in outcomes or postoperative complications were observed.[36] The choice of nonstructural biologic graft for use with synthetic cages is considered an important factor that influences postoperative fusion rates, but surgeons report there is insufficient comparative data to help select between grafts.[11] Due to small sample sizes and potential for bias, much of the evidence regarding biologic selection is of limited quality, making this an important area of future research.[37] Given the complex interaction between multiple factors that influence ACDF success, our findings are unable to pinpoint a precise reason for the trends observed and highlight the need for a prospective randomized controlled trial comparing structural allograft and synthetic cages before adequate evidence supporting the superiority of either implant is generated.

The analysis of any administrative database comes with several limitations. First, the TriNetX database relies heavily on coded data from multiple institutions yet this data carries the potential lack of fidelity associated with coding and may not be a representative sample of all patients undergoing ACDF surgery. Second, using coded data we were unable to differentiate between various implant materials, important aspects of the surgical procedure performed (such as the type of biologic used in conjunction with a synthetic cage or whether a plate was used), or the number of levels involved in multilevel procedures. The inability to differentiate between the number of segments involved in multilevel fusions is a significant limitation, as previous studies have identified multilevel surgeries as a risk factor for revision,[22,23,38,39] and a 27% increased risk of revision has been reported for 3 or more level compared with 2-level ACDF.[23] Third, our data set did not allow for specification of the diagnosis associated with revision surgery, and therefore limits our ability to infer the reason for revision. This is especially important in the context of the postoperative pseudoarthrosis rates presented, as these may or may not have been symptomatic or required further intervention. Fourth, while we

feel that the use of propensity score matching provides valuable control for confounding factors that may influence outcomes after surgery, the inherent limitations of observational studies and potential influence of unmeasured confounding covariates remains.

While few studies have directly compared complications and outcomes of structural allografts and synthetic cages, our findings further contribute to a growing body of literature that highlights the apparent increased risk of revision surgery following ACDF with synthetic cages compared with structural allograft bone. Despite the widespread use of synthetic cages, further large-scale, prospective studies that include parallel cost-effectiveness analysis are needed to determine if there are additional clinical benefits that outweigh the additional cost and potential increased risk of complications, including revision surgery.

Conclusion

Compared with structural allograft, patients undergoing multilevel ACDF with synthetic cage may be at increased risk for 1-year revision surgery, while those receiving structural allograft may be at increased risk for dysphagia. No differences in postoperative complication rates between implants were observed in single-level ACDF. Further large-scale, prospective comparison of structural allografts and synthetic cages for ACDF is warranted before the superiority of either implant can be concluded.

Declaration of Conflicting Interests

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Structural Allograft versus Polyetheretherketone Implants in Patients Undergoing Spinal Fusion Surgery: A Systematic Review and Meta-Analysis

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Key words
- Allograft
- Fusion
- PEEK implant
- Spinal fusion surgery
- Subsidence

Abbreviations and Acronyms
CI: Confidence interval
OR: Odds ratio
PEEK: Polyetheretherketone

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OBJECTIVE: **Interbody spacers have been successfully used in spinal fusion procedures with the aim to restore disc height, provide stability, and promote bone fusion. The authors evaluated the efficacy of structural body allograft versus polyetheretherketone (PEEK) implants in patients undergoing spinal fusion surgery.**

METHODS: **A systematic review of electronic databases was conducted using different Medical Subject Headings terms from January 1970 to August 2019. Pooled and subgroup analyses were performed using random-effects and fixed-effects models based on I^2 heterogeneity.**

RESULTS: **The analysis included 6640 patients (structural allograft 64% and PEEK cage 36%) from 7 comparative studies. There were no statistically significant differences in age ($P = 0.27$), sex ($P = 0.31$), body mass index ($P = 0.82$), and smoking status ($P = 0.27$) between the 2 groups. Overall, the mean follow-up was 12.9 ± 1.5 months. Pooled meta-analysis revealed that patients with structural allograft had 2.59-fold higher likelihood of fusion compared with patients with PEEK cages (odds ratio [OR] 2.59, 95% confidence interval [CI] 1.02–6.57, $P = 0.05$) at last follow-up evaluation. Patients with structural allograft had 61% less likelihood of pseudarthrosis (OR 0.39, 95% CI 0.15–0.98, $P = 0.05$) and 74% lower incidence of reoperation compared with patients with PEEK implants (OR 0.26, 95% CI 0.09–0.79, $P = 0.02$). Our results suggest that patients with structural allografts had a higher subsidence rate compared with patients with PEEK implants, but this was statistically insignificant (OR 1.07, 95% CI 0.45–2.53, $P = 0.89$).**

CONCLUSIONS: **Our results corroborate that structural allografts are highly effective in promoting bony fusion compared with PEEK implants in patients undergoing spinal fusion surgery.**

INTRODUCTION

The evolution of interbody spacers has revolutionized spinal fusion surgery, as these spacers restore disc height, provide stability, and promote bony fusion.[1] With comparable elastic modulus values and mechanical properties similar to autologous bone, structural bone allograft and polyetheretherketone (PEEK) synthetic cages have gained immense popularity over other alternatives, such as autograft.[2] The osteoconductive scaffold demonstrating osseointegration in a rat model by structural allograft has shown a long history of successful clinical use.[3] However, in vivo models of PEEK implants demonstrate lack of osseointegration as well as the growth of fibrous tissue.[4,5] Therefore, modifications of surface enhancement through titanium coating, increased surface porosity, and impregnation of PEEK with bioactive materials such as hydroxyapatite have been proposed.[6] Although the restoration and maintenance of disc space height are the main goals of fusion surgeries, literature exists regarding the failure of mechanical function in supporting the anterior column through bone graft while assuming an essential biologic role to promote bone growth.[7,8] Nonetheless, there is insufficient evidence supporting the use of structural allograft over PEEK implants in spinal fusion procedures. To evaluate the differences between these spacers, we conducted a systematic review and meta-analysis of all available literature comparing structural body allograft and PEEK implants in spinal fusion surgery and associated surgical and radiographic outcomes, including subsidence, pseudarthrosis, fusion rate, reoperation, and patient-reported outcomes.

MATERIALS AND METHODS

Data Source and Search Strategy

We conducted a literature search according to the guidelines provided by the Preferred Reporting Items for Systematic Review and Meta-Analysis.[9] Two reviewers (N.F. and J.H.S.) conducted a detailed systematic review of electronic databases (PubMed, Embase, Scopus, Medline, and

Google Scholar) for articles published between January 1990 and November 2019. We used different Medical Subject Headings terms (with Boolean operators "AND" and "OR") including "allograft," "structural body allograft," "polyetheretherketone," "PEEK," "femoral cortical allograft," "femoral ring allograft," "cage," "cervical fusion," "lumbar fusion," and "interbody fusion." We included only articles that were published in English.

Eligibility Criteria

Eligible studies were of spinal fusion procedures that compared structural allograft and PEEK cages for primary diagnoses of degenerative spinal disease, trauma, herniated disc, and ossified posterior longitudinal ligament. We included only studies that reported at least 1 of the following clinical or radiographic outcomes: subsidence, pseudarthrosis, fusion rate, or patient-reported outcomes. Exclusion criteria were case reports, case series, and implantation of the cage in the setting of spinal infection.

Data Extraction and Outcome Measures

The data were extracted by 2 authors (N.F. and J.H.S.) using a structured template form based on Cochrane Consumers and Communication Group. Any disagreement between the 2 authors was resolved by discussion. The following data were extracted from each article: 1) demographic characteristics of each cohort, 2) clinical conditions, 3) intraoperative parameters (surgical approaches and number of levels involved), 4) type of allograft used during each study, and 5) outcome parameters (subsidence rate, mean change in lordotic angle, pseudarthrosis, reoperation, fusion rates, and patient-reported outcome measures).

Evidence Quality Assessment

The Grades of Recommendation, Assessment, Development and Evaluation protocol[10] was used to assess the quality of evidence for each study independently by the 2 reviewers. Each study was given an overall rating based on study design, limitations, and results as high, moderate, low, or very low.

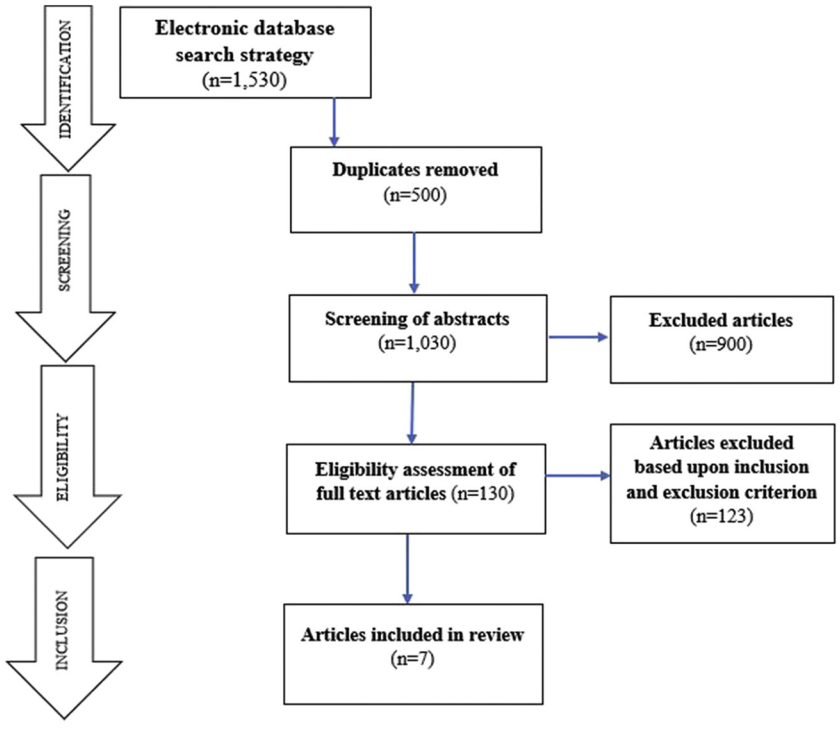

Figure 1. Database search strategy of the included studies according to Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines.

Statistical Analysis

RevMan 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used for comparing data from the included studies. Dichotomous data were reported as odds ratio (OR) with 95% confidence interval (CI). Heterogeneity among studies was evaluated using I^2 statistics. A fixed-effects model was used for $I^2 < 50\%$, and a random-effects model was used for $I^2 \geq 50\%$. All tests were 2-tailed, and $P < 0.05$ was considered as statistically significant. Subsidence was defined as decrease in anterior and/or posterior disc heights by >2 mm. Radiographic fusion was defined as presence of bridging bone in front of or through the radiolucent cage or allograft incorporation into the surrounding bone. IBM SPSS Version 25 software (IBM Corporation, Armonk, New York, USA) was used to evaluate for differences between groups using independent sample t tests, and χ^2 statistical analysis was used for assessment of categorical variables.

Risk of Bias Across Studies

No randomized controlled trials were included in our analysis. Furthermore, double blindness was not achieved in any study. The high heterogeneity among studies was further analyzed using funnel plots, which showed the asymmetric distribution. This bias can be attributable to the sample size, as the removal of the smaller sized cohort significantly decreased the heterogeneity.

RESULTS

Literature Search

A flow diagram in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines[9] was plotted as shown in **Figure 1**. The reviewers retrieved 1530 articles from PubMed, Embase, Scopus, Medline, and Google Scholar. Of 1530 articles, 500 articles were removed owing to duplication in different electronic databases, and a further 900 articles were excluded because of data not related to spinal fusion surgery. Lastly, 123 of the remaining130 articles were excluded owing to lack of quantitative data and absence of comparison groups.

Table 1. Baseline Characteristics of Included Studies

Reference	Type of Study	Levels	Patients (*N*)	Case/Control*	F/M Sex	Mean Age (years)	BMI	Smokers	Mean FU (months)	Type of Surgery	Type of Allograft	Indications of Surgery
Cutler et al., 2006[8]	Retro	Single-level	39	21 (53.8)/18 (46.2)	12 (57)/9 (23): 10 (55.5)/8 (20.5)	45.8/50.2	NA	4 (19)/5 (27.7)	15.1	TLIF	Femoral cortical bone allograft	DDD: 27; recurrent disc herniation: 7; grade I or II degenerative spondylolisthesis: 5
Wan et al., 2014[11]	Retro	Multilevel	48 (83)	30 (36.1)/53 (63.8)	38 (79.2)/10 (20.8)	56.3	24.3	1 (2.1)	12	ALIF	Femoral ring allografts	Spine deformities including scoliosis, kyphosis and flat-back syndrome
Yson et al., 2017[12]	Retro	Multilevel	67 (117)	19 (32)/48 (85)	12 (63.2)/7 (36.8): 27 (56.3)/21 (43.7)	48.6/52.5	NA	NA	14.7	ACDF	Structural fibular allograft	Herniated nucleus pulposus: 24; multilevel cervical spondylosis: 24; foraminal stenosis: 7, adjacent segment disease: 5; myelopathy: 4; degenerative spondylolisthesis: 2; DDD: 1
Pirkle et al., 2019[13]	Retro†	Multilevel	6130	4063 (66)/2067 (34)	NA	NA	NA	60/2195 (2.7)/69/1034 (6.7)	12	ACDF	Structural allograft	NA
Teton et al., 2019[14]	Retro	Multilevel	62	31 (50)/31 (50)	NA	NA	NA	NA	NA	ACDF	Structural allograft	NA
Hill et al., 2019[15]	Retro	Multilevel	167	39 (23.4)/128 (76.6)	22 (56.4)/17 (43.6): 75 (58.6)/53 (41.4)	53.8/55.0	31.0/29.9	8 (20.5)/12 (9.4)	12	ACDF	Structural allograft	DDD and cervical trauma
Krause et al., 2019[16]	Retro	Single-level	127	71 (55.9)/56 (44.1)	37 (52.1)/34 (47.8): 35 (62.5)/21 (37.5)	53/51	28.4/29.1	17 (23.9)/15 (26.7)	16/21	ACDF	Structural allograft composed of composite, cortical, or cancellous materials	DDD and cervical trauma

Numbers in parentheses are percentages.

F, female; M, male; BMI, body mass index; FU, follow-up; Retro, retrospective; TLIF, transforaminal lumbar interbody fusion; DDD, degenerative disc disease; ALIF, anterior lumbar interbody fusion; NA, not available; ACDF, anterior cervical disc fusion.

*Case: structural allograft; Control: polyetheretherketone cage.

†Pearl Driver National Database.

Table 2. Outcome Characteristics Including Clinical and Radiographic Factors of Included Studies

Reference	Subsidence Rate	Mean NDI Improvement	Mean Change in Lordotic Angle (°)	Pseudarthrosis	Reoperation	Fusion Rate
Cutler et al., 2006[8]	2/21:0/18	ODI: 42.3/40.2	2.68/1.72	1/21: 0/18	1/21: 0/18	95.2%/100%
Wan et al., 2014[11]	NA	NA	1.8 ± 1.7/2.5 ± 4.2	5/30: 3/53	NA	84.2%/94.9%
Yson et al., 2017[12]	9/32:25/85	Subsidence: 7.1; nonsubsidence: 16.6	NA	1/19: 4/48	1/19: 4/48	94.7%/91.6%
Pirkle et al., 2019[13]	NA	NA	NA	80/4063: 110/2067	NA	98.0%/94.7%
Teton et al., 2019[14]	NA	NA	NA	6/31: 20/31	0/31: 4/31	81%/35%
Hill et al., 2019[15]	NA	0.4/0.6	NA	NA	NA	NA
Krause et al., 2019[16]	NA	NA	NA	7/71: 29/56	1/71: 7/56	90%/48.3%

NDI, Neck Disability Index; ODI, Oswestry Disability Index; NA, not available.

Hence, 7 comparative studies were included in our meta-analysis.[8,11-16]

Study Characteristics

All studies were retrospective in nature. These studies were carried out in the United States ($n = 6$), and China ($n = 1$). The baseline characteristics, outcome characteristics, and comparison of both groups are presented in Tables 1–3.

Our analysis included 6640 patients; 4250 (64.0%) underwent procedures with structural allograft, and 2390 (36.0%) underwent procedures with PEEK cages. The mean follow-up in both groups was 12.9 ± 1.5 months. The quality of evidence as assessed by the Grades of Recommendation, Assessment, Development and Evaluation assessment was deemed very low in 4 studies and low in 3 studies.

Of the available data ($n = 448$), χ^2 statistical analysis was performed to look at the comparative analysis of male versus female patients in structural allograft and PEEK cage groups, with 121 female and 77 male patients in the structural allograft group and 103 female and 147 male patients in the PEEK cage group. There was no statistically significant difference in gender distribution between the structural allograft group and PEEK group ($P = 0.31$). Furthermore, the mean age (SD) for the structural allograft and PEEK groups was 51.5 (4.3) and 53.0 (2.6), respectively. There was no statistically significant difference in age between the 2 groups ($P = 0.27$).

The mean body mass index was 27.9 ± 3.4 kg/m^2 among patients with structural allograft and 27.8 ± 3.1 kg/m^2 among patients with PEEK cages. There was no statistically significant difference between the 2 cohorts ($P = 0.82$). Similarly, there was no statistically significant difference in data related to smoking between the 2 groups ($P = 0.27$).

Table 3. Demographic, Radiographic, and Clinical Characteristics of Included Studies Comparing the 2 Cohorts

Parameter	Structural Allograft	PEEK Cage	*P* Value
Number of patients	4250	2390	—
Sex, F/M*	121/77	103/147	0.31
Age, years, mean ± SD	51.5 ± 4.3	53.0 ± 2.6	0.27
BMI, kg/m^2, mean ± SD	27.9 ± 3.4	27.8 ± 3.1	0.82
Smokers	90	102	0.27
Follow-up, months, mean ± SD	12.9 ± 1.5	12.9 ± 1.5	—
Pseudarthrosis	120	213	0.02†
Reoperation	3	15	0.13
Fusion rate, mean ± SD	90.5 ± 6.7	77.4 ± 28.2	0.24

PEEK, polyetheretherketone; F, female; M, male; BMI, body mass index.
*Sample size is smaller than the total number of patients owing to lack of data provided in the included studies.
†Statistically significant.

Operative Data

The spinal fusion surgeries in our meta-analysis included anterior cervical discectomy and fusion ($n = 5$),[12-16] anterior lumbar interbody fusion ($n = 1$),[11] and thoracolumbar interbody fusion ($n = 1$).[8] Five studies[11-15] involved multilevel spinal fusion surgery, and 2 studies[8,16] involved single-level spinal fusion surgery. The structural allografts included femoral cortical bone allograft ($n = 1$), femoral ring allograft ($n = 1$), fibular allograft ($n = 1$), and unspecified ($n = 4$). Owing to the inclusion of 1 study with data from a national database,[13] there was moderate heterogeneity in terms of type and number of PEEK cages for comparative analysis. Data regarding estimated blood loss and operative time was scarce, and therefore analysis could not be performed.

Postoperative Patient-Reported Outcomes

The study design revealed significant heterogeneity about patient-reported outcomes, and therefore clinically meaningful

Table 4. Patient-Reported Outcome Characteristics of Included Studies

Reference	Mean NDI Improvement	Neck VAS	Arm VAS	Mean ODI Improvement	Mean Prolo Scale Improvement
Cutler et al., 2006[8]	—	—	—	42.3/40.2	—
Wan et al., 2014[11]	—	—	—	—	3.1 ± 1.1/3.5 ± 0.8
Yson et al., 2017[12]	7.1/16.6*	1.8/2.8*	5.9/1.6*	—	—
Pirkle et al., 2019[13]	—	—	—	—	—
Teton et al., 2019[14]	—	—	—	—	—
Hill et al., 2019[15]	0.4/0.6	—	—	—	—
Krause et al., 2019[16]	—	—	—	—	—

NDI, Neck Disability Index; VAS, visual analog scale; ODI, Oswestry Disability Index.
*Subsidence/nonsubsidence.

statistical analysis could not be performed. However, none of the included studies reported a significant difference between the 2 groups in Neck Disability Index, visual analog scale, Oswestry Disability Index, and Prolo Scale. Patient-reported outcome characteristics of the included studies are presented in Table 4.

Radiologic Outcome

Fusion Rate. The fusion rate at the last follow-up was 81%–98% (pooled proportion: 90.5%) in patients with structural allograft compared with 35%–100% in patients with PEEK cages (pooled proportion: 77.4%). The pooled meta-analysis revealed that patients with structural allograft had 2.59-fold higher likelihood of fusion compared with patients with PEEK cages (OR 2.59, 95% CI 1.02–6.57, P = 0.05) at the last follow-up evaluation (Figure 2). Furthermore, patients with structural allograft had 61% less likelihood of pseudarthrosis compared with patients with PEEK cages (OR 0.39, 95% CI 0.15–0.98, P = 0.05) (Figure 3). Hence patients with structural allograft had 74% less likelihood of reoperation compared with patients with PEEK cages (OR 0.26, 95% CI 0.09–0.79, P = 0.02) (Figure 4).

Subsidence. Only 2 studies[8,12] had sufficient data related to subsidence. There was no statistically significant difference in terms of subsidence between the study cohorts with structural allograft and PEEK cages (OR 1.07, 95% CI 0.45–2.53, I^2 = 0%, P = 0.89) (Figure 5).

Subgroup Analysis Based on Location. Subgroup analysis to determine the fusion rate based on the spinal location was performed. Four included studies[12–14,16] reported the comparative fusion rates in the cervical spine region, and 2 studies reported fusion rates in the lumbar spine area.[8,11] Our results corroborated the reported rates for the cervical spine region; the patients with structural allograft had 4.68-fold higher likelihood of fusion compared with the patients with PEEK cages (OR 4.68, 95% CI 2.08–10.54, P = 0.0002) (Figure 6A). In contrast, the patients with structural allograft in the lumbar spine region had 69% less likelihood of fusion at the last follow-up than the patients with PEEK cages. This was borderline statistically significant (OR 0.31, 95% CI 0.08–1.22, P = 0.09) (Figure 6B).

DISCUSSION

This meta-analysis sought to determine 2 important outcome parameters associated with interbody spacers during spinal fusion surgery: 1) subsidence and fusion rate through radiographic evaluation, and 2) patient-reported outcomes. Furthermore, we did a comparative analysis of preoperative demographic parameters including age, sex, body mass index, and smoking status between the 2 groups.

This review included 6640 patients from 7 comparative studies. Most of the patients had structural allograft during spinal fusion surgery (n 4250; 64%), while the remaining patients (n = 2390; 36%) had PEEK implants. The studies included in our meta-analysis involved interbody spacers following anterior cervical discectomy and fusion (n = 5), anterior lumbar interbody fusion (n = 1), and

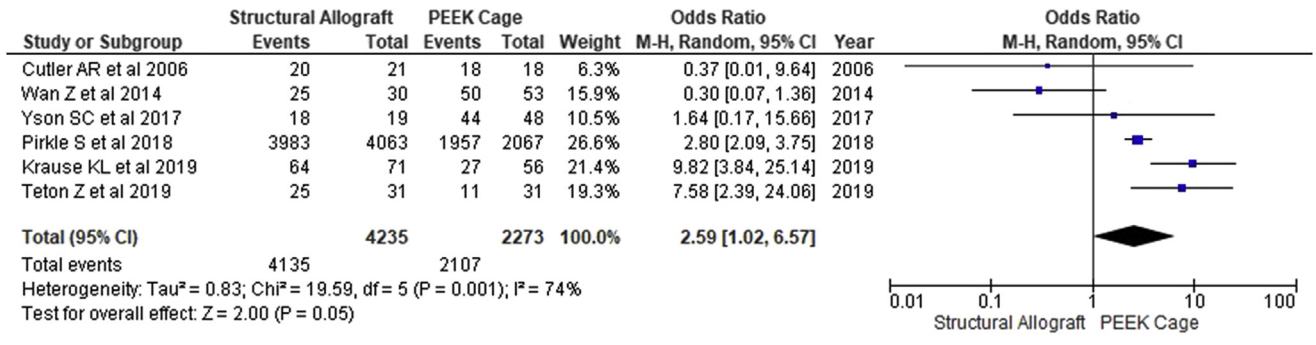

Figure 2. Pooled analysis of fusion rate. A statistically significant difference exists in fusion rate between the cohorts with structural allograft and polyetheretherketone cage (odds ratio 2.59, 95% confidence interval 1.02–6.57, I^2 74%, P = 0.05). PEEK, polyetheretherketone; M-H, Mantel-Haenszel; CI, confidence interval.

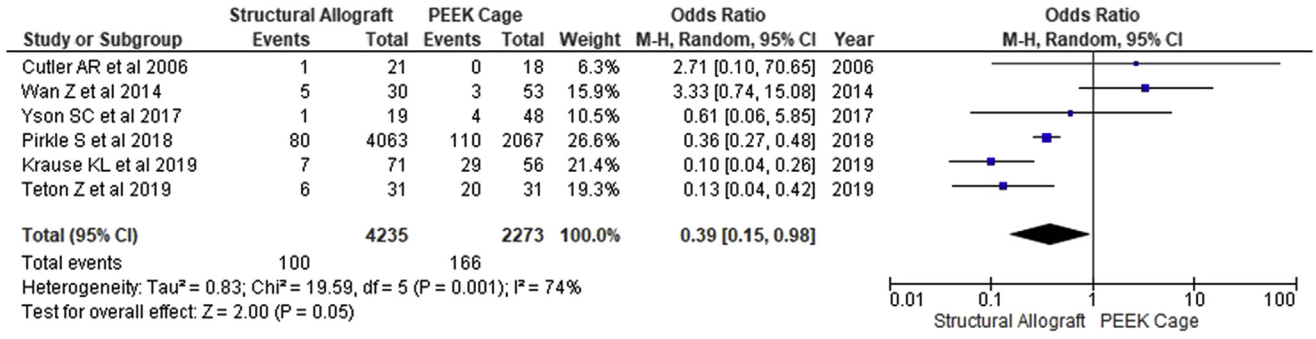

Figure 3. Pooled analysis of pseudarthrosis. A statistically significant difference exists in terms pseudarthrosis between the cohorts with structural allograft and polyetheretherketone cage (odds ratio 0.39, 95% confidence interval 0.15–0.98, I^2 74%, $P = 0.05$). PEEK, polyetheretherketone; M-H, Mantel-Haenszel; CI, confidence interval.

transforaminal lumbar interbody fusion ($n = 1$) for degenerative disc disease and trauma. Degenerative disc disease and trauma are the most common diagnoses for patients experiencing neck and back pain.[2,17] These patients usually present with radiculopathic and myelopathic symptoms following compression of the nerve roots and spinal cord, respectively. The spinal fusion procedure involves removing the affected disc, excising the osteophytes, and decompressing the nerve root or spinal cord.[2] The residual disc space is implanted with a bone or synthetic graft for preservation and maintenance of the vertebral space height, with or without the additional support of plates and screws.[2]

Following interbody spacer placement, the fusion rate is a key determinant of success.[12] However, a standardized criterion for fusion assessment does not exist.[2] In our review, most of the surgeons subjectively assessed fusion through bridging trabecular bone and the absence of a radiolucent gap between endplates. Pooling results from our studies revealed that fusion rate was higher among patients with structural allograft by 2.59-fold compared with patients with PEEK implants ($P = 0.05$). Thus, there was 61% less likelihood of pseudarthrosis ($P < 0.05$) and 76% lower risk of reoperation among patients with structural allograft compared with patients with PEEK implants. PEEK is a nonabsorbable, semicrystalline polymer with elastic modulus similar to native bone (3.84 GPa). However, its inert nature and low surface energy affect the body's biologic response. Furthermore, the hydrophobic nature of PEEK potentially limits the protein-surface and cell-surface interactions, which eventually limit the cellular adhesions. In contrast, the structural allograft provides an osteoconductive scaffold for neovascularization and osseointegration and thus performs better. Hence PEEK is associated with lower fusion rates regardless of providing excellent mechanical stability. The modifications to improve PEEK bioactivity in terms of surface coating with synthetic osteoconductive material, increasing the surface porosity and roughness through chemical modifications, and incorporating bioactive particles have gained widespread popularity.[2,18,19] However, our review did not control for these variations owing to lack of high-quality evidence comparing these modifications.

The patients with structural allograft had significantly better fusion rates in the cervical region (OR 4.68, 95% CI 2.08–10.54, $P = 0.0002$) compared with patients with PEEK cages in the lumbar region (OR 0.31, 95% CI 0.08–1.22, $P = 0.09$). This could be explained by the fact that the strong polymer material of the PEEK cage is able to withstand the compressive load of the vertebral column in the lumbar region, thus offering a higher fusion rate

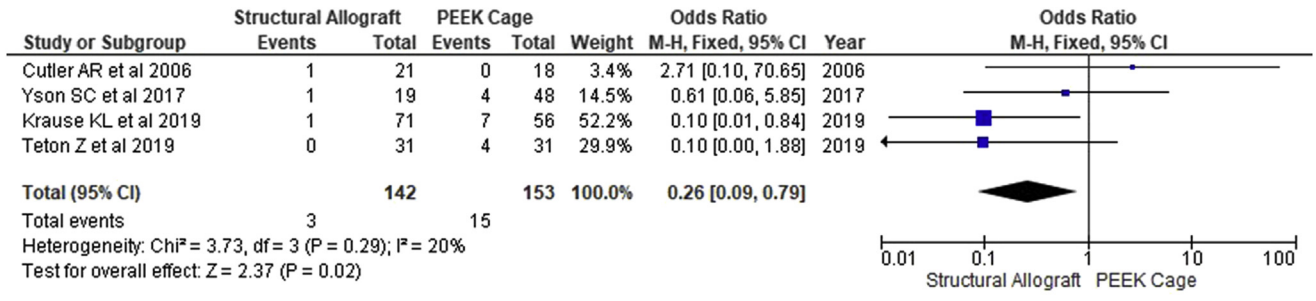

Figure 4. Pooled analysis of reoperation. A statistically significant difference exists in reoperation owing to nonunion between the cohorts with structural allograft and polyetheretherketone cage (odds ratio 0.26, 95% confidence interval 0.09–0.79, I^2 20%, $P = 0.02$). PEEK, polyetheretherketone; M-H, Mantel-Haenszel; CI, confidence interval.

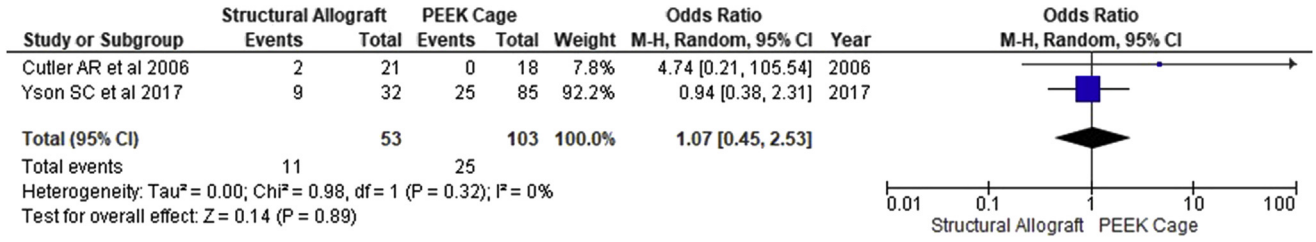

Figure 5. Pooled analysis of subsidence. A statistically insignificant difference exists in rate of subsidence between the cohorts with structural allograft and polyetheretherketone cage (odds ratio 1.07, 95% confidence interval 0.45–2.53, I^2 0%, $P = 0.89$). PEEK, polyetheretherketone; M-H, Mantel-Haenszel; CI, confidence interval.

compared with structural allograft.[8] On the contrary, some studies suggest that the fusion rate is less with the PEEK cage in the cervical region, as it represents a mechanical block for fusion formation.[13] Furthermore, the PEEK cage provides less endplate surface area and less available intervertebral volume for arthrodesis, which is the possible cause of the lower fusion rate compared with the structural allograft.[13]

The mean radiographic follow-up after fusion in our included studies was 12.9 ± 1.5 months. All included studies reported the fusion based on plain x-ray. In general, spinal arthrodesis takes at least 3 months to 1 year to achieve a solid fusion; hence it is appropriate to repeat a plain x-ray after 1 year to determine the fusion rate.[20] However, in the assessment of patients who have undergone spinal arthrodesis, the clinical picture along with radiographic assessment should be considered for the further management plan.[21] The sensitivity and specificity of predicting the fusion rate with a plain radiograph were reported in the literature as 89% and 60%, respectively.[22] A few studies[23,24] have reported a lower fusion rate on computed tomography scans than on dynamic radiographs following spinal fusion procedures, whereas others have reported an equivalent fusion rate with computed tomography scan and plain dynamic radiographs with a positive predictive value of 100% and negative predictive value of 85%.[25]

Furthermore, our meta-analysis revealed that the subsidence rate was 1.07-fold higher among patients with structural allograft compared with patients with PEEK implants. Although the results of our pooled analysis related to subsidence were statistically insignificant ($P = 0.89$) owing to small sample sizes and lack of studies with high-quality evidence, our analysis highlights an important finding. As the structural bone allograft has an essential biologic role to promote bone growth, the disc height is mostly lost to achieve osseous fusion.[8]

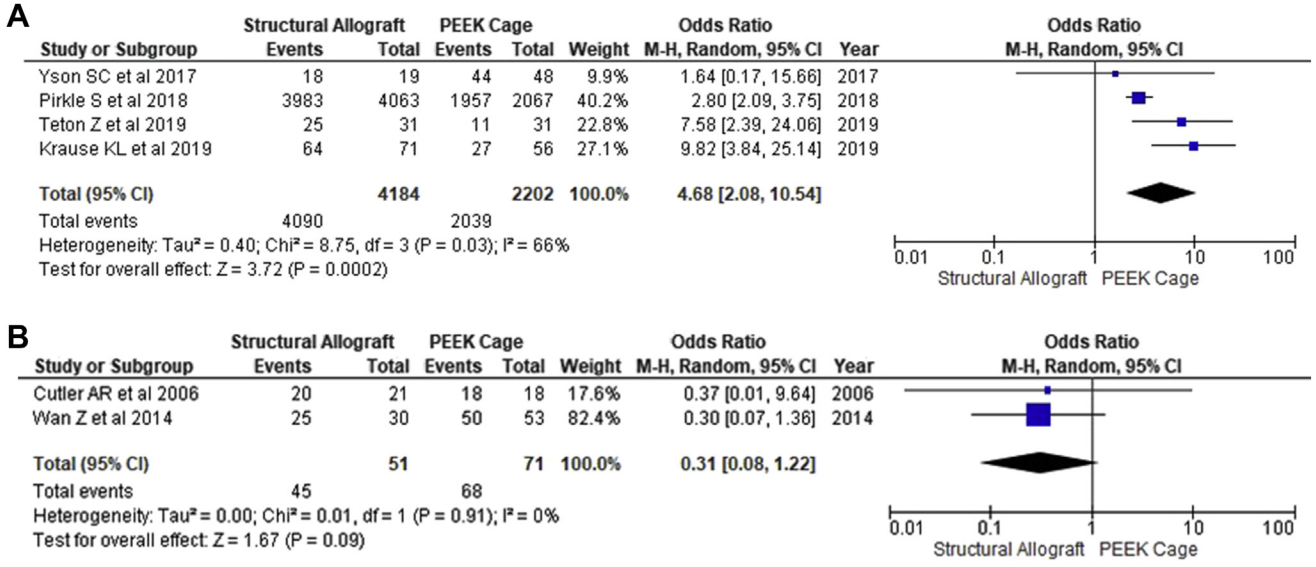

Figure 6. Subgroup analysis of fusion rate based on the spinal location. (**A**) Cervical spine region. A statistically significant difference exists in rate of fusion between the cohorts with structural allograft and polyetheretherketone cage (odds ratio 4.68, 95% confidence interval 2.08–10.54, I^2 66%, $P = 0.0002$). (**B**) Lumbar region. A borderline statistically significant difference exists in rate of fusion between the cohorts with structural allograft and polyetheretherketone cage (odds ratio 0.31, 95% confidence interval 0.08–1.22, I^2 0%, $P = 0.09$). PEEK, polyetheretherketone; M-H, Mantel-Haenszel; CI, confidence interval.

Thus, allografts are associated with more postoperative disc height loss compared with PEEK cages. This is further strengthened by McAfee et al.,[26] who reported a 66% increase in intraoperative disc space height at 2-year follow-up in patients who underwent transforaminal lumbar interbody fusion using PEEK cages.[26] However, further studies are needed to compare the subsidence rates between structural allograft and PEEK implants in patients following spinal fusion surgery.

Patient-reported outcomes were described in only 4 studies[8,11,12,15] suggesting that these clinical outcomes are often not the focus of the studies. The scales for outcome assessment were different among these studies and included Neck Disability Index, visual analog scale, Oswestry Disability Index, and Prolo Scale, and a comparative analysis could not be performed. Tracking surgical outcomes, including the patient-reported outcome, is pivotal to understanding the clinical progress and has been in increasing use in clinical practice. However, variability exists in determining the clinical outcomes through these patient-reported outcome measures in spine surgery because they depend exclusively on the patient's response. This is acknowledged by Nayak et al.,[27] who reported the limitation in comparison of clinical outcomes in spine surgery research owing to variability in patient-reported outcome measures. In addition, although the subsidence rate after spinal fusion procedures has been well studied, the effects of subsidence on the clinical outcomes and fusion rate remain unclear.[28] Further studies are needed to determine the reliability, validity, and responsiveness of these patient-reported outcome measures.

In addition to the surgical effectiveness, structural allografts are cost-effective compared with PEEK cages in spinal fusion surgeries. Our included studies did not report the cost data; however, it is of paramount importance to highlight the cost savings of these spinal implants for surgical decision making. The individual surgeon instrumentation costs varied 10-fold based on the fusion construct used.[29] However, previous literature reported that PEEK cages were much more costly than structural allograft.[29] PEEK spacers cost $4930–$5246, whereas structural allograft spacers are estimated to cost $1220–$3640.[29] Further studies are needed to determine the surgical effectiveness and cost savings related to the use of PEEK cages versus structural allograft in patients undergoing spinal fusion surgery.

Our study has several limitations. 1) No randomized controlled trials were included. 2) Only retrospective studies were included. which could be a source of selection bias. 3) The studies did not provide sufficient data regarding the different surgical approaches adopted between the 2 cohorts. 4) The indications for surgery and underlying clinical conditions were not always clear in the studies. 5) There was heterogeneity of PEEK cage assessment in one of the studies owing to inclusion of a national database.[13] 6) There were differences in the fusion assessment among the studies. 6) High-quality evidence for comparative analysis to form robust conclusions was lacking. Further prospective studies comparing structural allograft and PEEK implants following spinal fusion surgery with regard to subsidence rate, fusion assessment, and patient-reported outcome at long-term follow-up are required to better assess the effectiveness of each interbody spacer.

CONCLUSIONS

At a mean follow-up of 12.9 months, structural body allograft provides better bony fusion compared with PEEK implants following spinal fusion surgery. However, further prospective studies are needed to compare the effectiveness of the 2 interbody spacers in patients undergoing single-level and multilevel spinal fusion procedures.

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JNS SPINE

CLINICAL ARTICLE

J Neurosurg Spine 30:46–51, 2019

Fivefold higher rate of pseudarthrosis with polyetheretherketone interbody device than with structural allograft used for 1-level anterior cervical discectomy and fusion

Presented at the 2018 AANS/CNS Joint Section on Disorders of the Spine and Peripheral Nerves

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OBJECTIVE Common interbody graft options for anterior cervical discectomy and fusion (ACDF) include structural allograft and polyetheretherketone (PEEK). PEEK has gained popularity due to its radiolucency and its elastic modulus, which is similar to that of bone. The authors sought to compare the rates of pseudarthrosis, a lack of solid bone growth across the disc space, and the need for revision surgery with the use of grafts made of allogenic bone versus PEEK.

METHODS The authors retrospectively reviewed 127 cases in which patients had undergone a 1-level ACDF followed by at least 1 year of radiographic follow-up. Data on age, sex, body mass index, tobacco use, pseudarthrosis, and the reoperation rate for pseudarthrosis were collected. These data were analyzed by performing a Pearson's chi-square test.

RESULTS Of 127 patients, 56 had received PEEK implants and 71 had received allografts. Forty-six of the PEEK implants (82%) were stand-alone devices. There were no significant differences between the 2 treatment groups with respect to patient age, sex, or body mass index. Twenty-nine (52%) of 56 patients with PEEK implants demonstrated radiographic evidence of pseudarthrosis, compared to 7 (10%) of 71 patients with structural allografts ($p < 0.001$, OR 9.82; 95% CI 3.836–25.139). Seven patients with PEEK implants required reoperation for pseudarthrosis, compared to 1 patient with an allograft ($p = 0.01$, OR 10.00; 95% CI 1.192–83.884). There was no significant difference in tobacco use between the PEEK and allograft groups ($p = 0.586$).

CONCLUSIONS The results of this study demonstrate that the use of PEEK devices in 1-level ACDF is associated with a significantly higher rate of radiographically demonstrated pseudarthrosis and need for revision surgery compared with the use of allografts. Surgeons should be aware of this when deciding on interbody graft options, and reimbursement policies should reflect these discrepancies.

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KEYWORDS ACDF; anterior cervical discectomy and fusion; pseudarthrosis; PEEK; allograft

Anterior cervical discectomy and fusion (ACDF) is one of the most common neurosurgical procedures performed for the treatment of cervical myelopathy and radiculopathy.[1] Although immediate symptomatic relief is generally due to decompression of the affected neural structures, long-term success is dependent on the placement of an appropriate interbody graft within the disc space to maintain disc and foraminal height, restore cervical lordosis, and promote bone fusion.[11,13]

As surgeons continue to refine this common procedure, options for graft material have increasingly multiplied. An autograft, often obtained from the patient's anterior iliac crest, is considered to be the gold standard due to its lack of histocompatibility difference from the removed disc,

ABBREVIATIONS ACDF = anterior cervical discectomy and fusion; DBM = demineralized bone matrix; PEEK = polyetheretherketone; QALY = quality-adjusted life-year; rhBMP-2 = recombinant human bone morphogenetic protein–2.

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which could lead to graft rejection, and its ability to form a solid fusion construct.[17,22] Harvesting bone for an autograft, however, comes with added morbidity, including donor site pain, stress fractures, and injury to the lateral femoral cutaneous nerve, as well as increased operative time, blood loss, and rate of surgical infection.[13,19,22] Allograft substitutes, including cortical, cancellous, and composite cadaver bone, have been employed to circumvent these complications, but they come with the theoretical risk of increased disease transmission, such as hepatitis and HIV, for which the estimated risks of disease spread are reported to be 0.01% and 0.03%, respectively.[6,14]

More recently, synthetic interbody fusion devices have been developed, which are primarily made from carbon fiber, titanium, or polyetheretherketone (PEEK).[28] The PEEK cage, in particular, has gained significant popularity due to its radiolucent properties and its elastic modulus, which is similar to that of bone.[4,8,12] Furthermore, the use of PEEK cages results in increased billing per surgical level compared to allograft,[23] which may further drive graft selection. Of note, for single-level cases, if a PEEK cage is used without a plate, the number of work relative value units is fewer than if a structural allograft is used with a plate (approximately 36 vs 49, depending on the payor). It seems conceivable that PEEK, a plastic material, would promote less bone fusion than a structural cadaveric bone allograft, even if the PEEK cage were packed with bone. Thus, we performed the largest retrospective cohort study to date to examine the incidence of radiographically demonstrated pseudarthrosis and subsequent reoperations in patients who underwent a 1-level ACDF with either a PEEK or structural allograft implant.

Methods

In this retrospective, single-center study, all consecutive 1-level ACDF procedures performed at the Oregon Health & Science University between July 2011 and July 2016 were reviewed. Thirteen different attending surgeons (9 neurological surgeons and 4 orthopedic surgeons) performed the operative procedures. Any adult patient undergoing a 1-level ACDF for degenerative disease or trauma was included. Patients who did not have at least 1 year of follow-up with either a cervical x-ray study or CT scan were excluded. Implant selection, duration of follow-up, and the acquisition of follow-up imaging were dependent on the practice pattern of the individual surgeon. The study was approved by the local institutional review board, with a waiver of consent.

Electronic medical records were reviewed for demographic data, patient smoking status, type of graft material used, and evidence of pseudarthrosis. The presence of pseudarthrosis was defined as the lack of solid bone growth across the disc space at 1 or more years of radiographic follow-up. The primary investigators and an attending neuroradiologist independently reviewed all postoperative imaging studies. Records were further reviewed for any additional surgical intervention that was warranted beyond the index surgery. All records were also reviewed for the occurrence of postoperative infection.

Statistical analysis was undertaken using SPSS Statistics version 24 (IBM Corp.), and p values were considered significant at < 0.05. Pearson correlation tests were used to determine whether there were statistically significant correlations between the rates of pseudarthrosis and of reoperations, and the graft materials (PEEK vs allograft materials). A Pearson correlation test was also used to determine if there was a statistically significant level of correlation between smoking history and graft material in patients in whom pseudarthrosis was confirmed. A Fisher exact test was used to determine the correlation between pseudarthrosis and the reoperation rate for PEEK grafts associated with a plate. A Student t-test was used to determine differences between the times of radiographic follow-up.

Mean results for the treatment groups are expressed as means ± standard deviations.

Results

Four hundred eight patients underwent 1-level ACDF during the collection period; of these, 211 (51.7%) received PEEK implants, 185 (45.3%) received structural allograft implants, and 12 (2.9%) received iliac crest autografts. Of the 408 patients, 127 (31%) met the study's inclusion criteria: 56 (44%) with PEEK implants and 71 (56%) with structural allograft implants. The allograft implants included composite (61/71), cortical (8/71), or cancellous (2/71) materials. All PEEK cages were filled with nonstructural allograft in the form of demineralized bone matrix (DBM; 47/56) or a local autograft (9/56). The mean age of patients was 51 ± 14.9 years in the PEEK group and 53 ± 13.0 years in the allograft group. There was no significant difference in body mass index or smoking status between patients in the PEEK and allograft groups (Table 1). The overall 25% rate of smokers was slightly higher than the 17% rate in the overall US population.[9] In both groups, the majority of procedures were performed for degenerative changes: 1 procedure was performed for trauma in the PEEK group (2%) and 11 procedures were performed for trauma in the allograft group (15.5%) ($p = 0.009$). Excluding patients who underwent ACDF for trauma yielded similar pseudarthrosis rates: 27 (48.2%) of 56 patients in the PEEK group and 5 (8%) of 62 patients in the structural allograft group.

Patient imaging at the 1-year follow-up included x-ray studies in 110 patients (86.6%) and CT scanning in 17 patients (13.4%). In the PEEK group, 45 (80.4%) of 56 pa-

TABLE 1. Patient demographics

Factor	Structural Allograft Group	PEEK Group	Total
Patients	71	56	127
Age in yrs (mean ± SD)	51 ± 14.9	53 ± 13.0	51.7 ± 14.2
Males	34	21	55
Females	37	35	72
Smokers	17 (24)	15 (27)	32 (25)
BMI (mean ± SD)	28.4 ± 0.6	29.1 ± 0.7	28.7 ± 0.6

Unless otherwise specified, values represent numbers of patients (%, if given). There was no statistically significant difference between groups in any category.

tients underwent x-ray studies compared to 65 (91.5%) of 71 patients in the structural allograft group; the difference in these values was not statistically significant ($p = 0.115$). Average radiographic follow-up was longer in the PEEK group than in the structural allograft group: 21 versus 16 months, respectively ($p = 0.02$). Of the 56 patients who received PEEK implants, 29 (51.8%) had demonstrated radiographic evidence of pseudarthrosis at 1 or more years after follow-up, as seen on a cervical x-ray film or CT scan (Fig. 1). In contrast, only 7 (10%) of the 71 patients with structural allograft implants had radiographic evidence of pseudarthrosis ($p < 0.001$, OR 9.82; 95% CI 3.8–25.1). Of patients with pseudarthrosis, 7 patients with PEEK implants (24.1%) required a revision operation for pseudarthrosis, compared to only 1 patient with a structural allograft (14.3%) ($p = 0.01$, OR 10.00; 95% CI 1.192–83.884) (Table 2). Clinical indications for revision surgery for the 7 patients with PEEK implants included persistent radiculopathy (6/7), myelopathy (2/7), or chronic, debilitating neck pain (1/7). One of the 7 patients required revision surgery to correct completely fractured hardware with radiculopathy. The types of revision surgery included a redo ACDF, a posterior instrumented fusion, and a combination of redo anterior fusion combined with posterior fusion.

The 1 patient who underwent revision ACDF surgery in the allograft group initially received a composite bone graft and displayed clinical indications of persistent radiculopathy. Interestingly, the graft for this patient was changed to a PEEK implant upon revision surgery. This was also the only patient in whom a postoperative wound infection developed after revision surgery; the infection was treated with operative washout and a course of antibiotics. There were no reports of postoperative transmission of hepatitis or HIV in either group.

The incidence of pseudarthrosis in patients who had received PEEK implants requiring plate and screw fixation was also examined. The majority of PEEK implants were stand-alone devices with no associated plate devices (46/56 implants, 82.1%). Of the 10 patients who received PEEK implants with an associated plate, there was radiographic evidence of pseudarthrosis in 3 patients, 2 of whom required revision surgery. Compared to stand-alone PEEK implants, there was no significant correlation between a PEEK implant associated with a plate and the incidence of pseudarthrosis ($p = 0.171$) or revision surgery ($p = 0.596$). In other words, PEEK implants led to higher pseudarthrosis rates than structural allografts regardless of whether the PEEK implants were stand-alone or supplemented with a plate and screws. However, the number of patients with a plated PEEK implant was very small ($n = 10$) and insufficient to draw strong conclusions.

Smoking status was further examined in patients with radiographic pseudarthrosis: 11 (37.9%) of 29 patients with pseudarthrosis in the PEEK group smoked tobacco, whereas 4 (57.1%) of 7 patients with pseudarthrosis in the allograft group smoked ($p = 0.586$) (Table 2). Of all patients with pseudarthrosis, only 1 patient in the PEEK group was on a long-term regimen of steroids for lupus.

Discussion

This retrospective study—the largest ever in which PEEK implants have been compared with structural allografts for ACDF—demonstrates an alarmingly high rate of radiographic evidence of pseudarthrosis in patients who received PEEK grafts while undergoing a 1-level ACDF compared to those who received structural allografts. After at least 1 year of radiographic follow-up, there was a fivefold higher incidence of pseudarthrosis in patients with PEEK cages and almost a doubled rate of subsequent revision surgery.

Since their approval by the US Food and Drug Administration in 1998,[12,21] PEEK implants have been a widely accepted choice as an interbody spacer. A recent study surveying 5334 surgeons from the Global AO Spine database found that PEEK cages make up 84% of cages selected for the graft component of an ACDF.[28] PEEK implants have gained popularity because their elastic modulus is close to that of human bone, and in contrast to metallic cages, PEEK cages are composed of radiolucent material and produce less artifact on postoperative imaging.[5] Furthermore, PEEK does not come with the risk of disease transmission that allograft spacers theoretically carry. However, the inherent bio-inertness of PEEK comes with the significant disadvantage of its being less likely to integrate with organic bone tissue.[21] In vitro studies have demonstrated that when mesenchymal cells are cultured on PEEK material, they do not express known markers of bone formation, including alkaline phosphatase or osteocalcin.[15] Furthermore, mesenchymal cultures grown on PEEK have significantly higher levels of interleukin-1β, which is associated

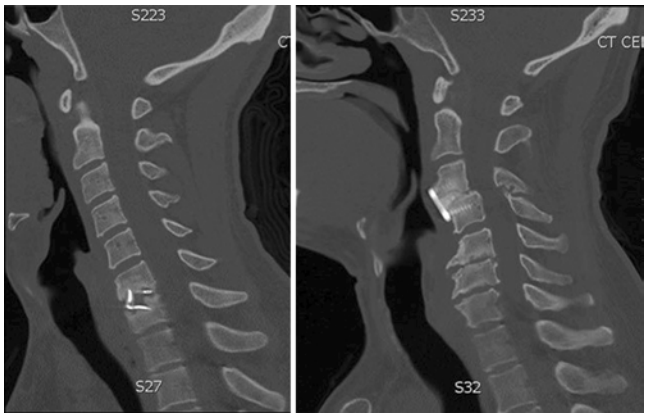

FIG. 1. Sagittal x-ray films obtained in a patient with a PEEK interbody graft and pseudarthrosis (**left**) and a patient with a structural allograft implant (**right**) healed 1 year after surgery.

TABLE 2. Comparison of pseudarthrosis, need for revision surgery, and smoking status between the structural allograft and PEEK implant groups

Factor	Structural Allograft Group	PEEK Group	p Value
Pseudarthrosis on imaging studies	7 (10)	29 (52)	≤0.001
Revision surgery	1 (14)	7 (24)	0.01
Smokers w/ pseudarthrosis	4 (57)	11 (38)	0.59

Unless otherwise specified, values represent numbers of patients (%).

with the formation of fibrous tissue rather than bone tissue. Cells cultured on PEEK have also been demonstrated to have significantly higher levels of necrosis, DNA damage, and apoptosis.[16] These in vitro studies are supported in an in vivo sheep model, which also demonstrated PEEK cages surrounded by fibrous connective tissue, preventing bone integration and potentially resulting in nonunion.[24]

In the clinical setting, there is little evidence for the superiority of PEEK over allograft, although studies describing well-controlled, direct comparisons between PEEK and allograft are limited. A recent meta-analysis found only 10 studies that directly compared PEEK to autograft, allograft, or other synthetic cages (titanium and carbon fiber). However, within those 10 studies there were no significant differences in fusion rates or clinical outcomes between PEEK and other graft materials.[10] In only 2 of those 10 studies did researchers directly compare PEEK to allograft. Vaidya et al.[25] performed a retrospective chart review of 46 consecutive cases of ACDF in which they compared patients treated with PEEK cages filled with recombinant human bone morphogenetic protein–2 (rhBMP-2) with patients treated with allograft interbody spacers and DBM at a single institution. Follow-up x-ray studies at 1.5–6 months postoperatively demonstrated that the PEEK cages filled with rhBMP-2 consistently exhibited 100% endplate resorption, which was said to have often been mistaken as infection by radiologists' interpretations. In contrast, there was no endplate resorption in any of the patients treated with allograft and DBM, with only "simple and progressive blurring" of the endplate junction, indicating ongoing fusion. However, at the 2-year follow-up, there was no significant difference in radiographic or clinical outcomes between the two groups, as measured by Cervical Oswestry Scale scores or visual analog scale scores. Subsequent cost analysis demonstrated that the cost of implants treated with PEEK and rhBMP-2 was more than 3 times the cost of those treated with allografts and DBM, which led the authors to ultimately abandon the use of PEEK and rhBMP-2 in lieu of the less expensive and equally effective allograft spacer. Another retrospective review[20] compared PEEK and rhBMP-2 with allograft and rhBMP-2 for both ACDF and lumbar interbody fusion. In those patients who underwent an ACDF (n = 34), the PEEK and rhBMP-2 groups had slightly higher fusion rates than the allograft group (91% vs 81%, respectively), with 1 PEEK cage displaying cage migration. Similar to the findings of Vaidya et al.,[25] there was 100% endplate resorption with the use of rhBMP-2. There was a 50% subsidence rate in all patients.[20]

This potential for subsidence is one main concern cited in the literature as a disadvantage of allografts, which can lead to loss of disc and foraminal height, increased angulation, and nonunion.[2,3,18] However, in a recent retrospective study, researchers compared subsidence rates between PEEK and allograft cages and found that there was no significant difference between the PEEK (29%) and allograft (28%) groups. Furthermore, this study by Yson et al. demonstrated that even those patients who did have subsidence did not display any clinical difference from those who did not, as measured by the Neck Disability Index and the visual analog scale.[29]

Our findings have a wider implication on a systems level, as the number of ACDF procedures performed continues to increase, and reimbursement policies continue to evolve. Between 1992 and 2005, the rate of ACDFs grew by 206% in patients older than 65 years,[27] which is in line with the significant increase in general American healthcare spending, which rose to $2.6 trillion in 2010. As such, there has been increased scrutiny regarding the cost-effectiveness of all spinal procedures.[26] In 1 study, a Markov decision model was used to determine the most effective graft (PEEK, allograft, or autograft) for a 1-level ACDF in terms of cost and quality of life. Cost was defined as the total sum of hospital, physician, and graft fees based on Current Procedural Terminology codes. The code designated for a PEEK interbody cage (22851) has a significantly higher reimbursement rate than that for a structural allograft (20931),[23] with a work relative value unit of 6.7 versus 1.8, respectively. As such, there was a significantly higher total cost for an ACDF with a PEEK cage (estimated total cost of $18,314) than for the same procedure in which an allograft cage was used (estimated total cost of $12,539). Virk et al. further examined the cost of quality-adjusted life-years (QALYs) gained by each graft type. PEEK was reported to be the most expensive, costing $3220/QALY, compared to allograft at $2358/QALY and autograft at $2413/QALY.[26] This economic discrepancy is further widened by synthetic cage billing per level of placement, while allograft billing is once per surgery, regardless of the number of levels instrumented.

As Kersten et al. described in the review accompanying their meta-analysis, data regarding clinical outcomes of PEEK cages come mostly from noncomparative cohort studies and a few randomized control trials.[10] Compared with data from previous studies, the advantage of the data we present here is that it offers a direct comparison of the incidence of radiographic pseudarthrosis between patients who received a PEEK cage and those who received a structural allograft in a 1-level ACDF. Furthermore, according to our review of previous studies, our study has the largest cohort of patients. However, our study does have limitations, which are inherent to its retrospective nature. A total of 13 different surgeons performed these procedures, making standardization of graft selection and the operative procedure difficult, although the similarity of the results across multiple surgeons does suggest generalizability of our findings. Differences between surgeons and changes in practice patterns were not evaluated. Confounders may stem from the lack of uniformity of physical graft placement, the type of structural allograft used (although the vast majority were composite), and the materials used to pack the PEEK cages (although the vast majority were packed with allograft and DBM). Many patients did not have 1 year of follow-up and thus were not included in the final analysis.

Another limitation of this study is that 2 different imaging modalities (x-ray and CT) were used to evaluate fusion. Ideally, all patients would have received gold-standard CT scanning, although the use of CT leads to increased costs as well as greater radiation exposure. One might even argue that complete bone bridging from endplate to endplate is not essential. As is the case with de-

vices covered by plasma spray or sintered beads, PEEK does not undergo creeping bone substitution, as it just needs to be anchored at the ends to bone and will continue its load-bearing support irrespective of bone growth through the cage itself. As such, another imaging modality that could have been useful for assessing pseudarthrosis in this study, and which may be considered in future studies, is the flexion-extension x-ray study, which has been shown to provide a higher level of evidence for fusion.[7]

Also, as mentioned, the rate of cigarette smoking in the patient population of this study is slightly higher than the percentage of smokers in the overall US population, which may affect the generalizability of the results. In addition, the PEEK group in the present study also had a higher percentage of cigarette smokers than the structural allograft group. Although this finding was not statistically significant, it suggests that the two groups were not ideally matched. One should note, however, that the prevalence of smoking in patients with pseudarthrosis was higher in patients with structural allografts than in those with PEEK devices. This study is also lacking objective clinical data with validated outcome surveys, which will be a focus of future prospective studies. The ideal future study would be a multicenter study with a minimum of 2 years of follow-up and a better definition of the goal of the implants.

Conclusions

The results of this study suggest that the use of PEEK cages is associated with a significantly increased risk for bone nonunion and revision surgery compared to the use of structural allograft implants, at least at our institution. Thus, surgeons should consider these risks when deciding among the many graft choices available for an ACDF. Furthermore, reimbursement policies to reduce the cost discrepancy between PEEK and allograft should be advocated.

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Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article. Dr. Raslan reports being a consultant to Abbott, and Dr. Than reports being a consultant to Bioventus.

Author Contributions

Conception and design: Than. Acquisition of data: Krause, Bridges. Analysis and interpretation of data: Than, Krause, Obayashi. Drafting the article: Than, Krause. Critically revising the article: Than, Krause, Bridges. Reviewed submitted version of manuscript: Than, Obayashi, Bridges, Raslan. Approved the final version of the manuscript on behalf of all authors: Than. Statistical analysis: Than, Krause, Obayashi, Raslan. Administrative/technical/material support: Than. Study supervision: Than.

Supplemental Information

Previous Presentations

Data shown in this report were presented by Dr. Krause at the Spine Summit 2018—34th Annual Meeting of the Section on Disorders of the Spine and Peripheral Nerves (Abstract no. 122, Top Abstracts Concurrent Session), March 14–17, 2018, Orlando, Florida; and in Abstracts of the 2018 AANS/CNS Joint Section on Disorders of the Spine and Peripheral Nerves Annual Meeting. *Neurosurg Focus 44(3):*A1–A109, 2018.

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Cages in ACDF are Associated With a Higher Nonunion Rate Than Allograft

A Stratified Comparative Analysis of 6130 Patients

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Study Design. A retrospective database review.

Objective. The purpose of this study was to analyze the rate of nonunion in patients treated with structural allograft and intervertebral cages in anterior cervical discectomy and fusion (ACDF).

Summary of Background Data. Existing literature consists primarily of single-center studies with inconsistent findings.

Methods. We performed a retrospective analysis of 6130 patients registered in the PearlDiver national database through Humana Insurance from 2007 to 2016. All ACDF patients with anterior plating who were active in the database for at least 1 year were included in the study. Patients with a fracture history within 1 year of intervention, past arthrodesis of hand, foot, or ankle, or a planned posterior approach were excluded from the study. Patients were stratified by number of levels treated, tobacco use, and diabetic condition. Nonunion rates of structural allograft and intervertebral cage groups after 1 year were compared using Chi-squared analyses.

Results. Four thousand sixty-three patients were included in the allograft group, while 2067 were included in the cage group. Overall nonunion rates were significantly higher in the cage group (5.32%) than in allograft group (1.97%) ($P < 0.01$). When controlling for confounders, increased rates of nonunion were consistently observed in the cage group, achieving statistical significance in 25 of the 26 analyses.

Conclusion. The increased rate of nonunion associated with intervertebral cages may suggest the superiority of allograft over cages in ACDF.

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Key words: ACDF, allograft, anterior cervical discectomy and fusion, cervical spine, fusion rate, intervertebral cage, nonunion, PEEK cage.

Level of Evidence: 3

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Anterior cervical discectomy and fusion (ACDF) is widely recognized as a highly successful surgical treatment of cervical radiculopathy and myelopathy.[1,2] Anterior decompression alone of the neural elements may result in spinal instability and pain, and thus, a concurrent arthrodesis is performed to achieve stability. The technique, initially performed with harvesting of autologous bone graft from the ilium, has since been modified by the utilization of allograft, and more recently, intervertebral cages with bone graft material. The importance of achieving fusion is generally agreed upon[3] in that the failure to achieve fusion is associated with a higher likelihood of symptoms and a higher likelihood for revision surgery.

Although allograft does not share the same osteoinductive and osteogenetic properties as autologous iliac crest bone graft, the distinct advantage of the use of allograft is the avoidance of the morbidity of iliac crest bone graft harvest. Allograft, despite its biological inferiority to autograft, does retain osteoconductivity and has been demonstrated in the literature to have high fusion rates.[4] Intervertebral cages in the cervical spine are designed to provide structural support between vertebral bodies and to allow bone fusion to occur within and around the cage. However, the cage itself carries no biological properties to promote fusion formation. Furthermore, the cage itself does occupy surface area and intervertebral volume for fusion mass to form that would otherwise have been occupied by a structural graft, auto or allo. This may decrease the likelihood of achieving solid arthrodesis as compared to structural bone graft. Despite these theoretical concerns, there has been a widespread enthusiasm for the use of intervertebral cages in anterior cervical discectomy and arthrodesis. Yoon *et al*, [3] in an international survey of spine surgeons, reported that the majority (64%) utilize cages as the

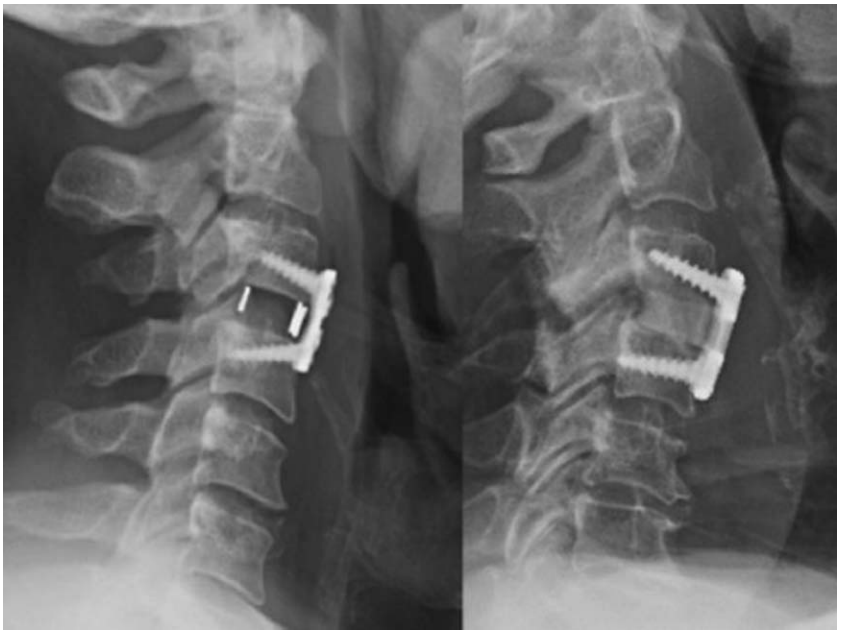

Figure 1. Single-level ACDF with cage and anterior instrumentation (left). Single-level ACDF with allograft and anterior instrumentation (right).

structural graft component. In North America, 36% of surgeons reported using cages in ACDF.[3]

Although there is extensive literature on fusion rates in ACDF, there are few studies comparing fusion rates in ACDF when using a cage *versus* a structural bone graft.[5–9] In addition, as fusion rates are fairly high for ACDF in general, small comparative studies are unlikely to have sufficient power to ascertain whether a difference in fusion rate exists or not. A higher sample size is needed to statistically demonstrate a significant difference or nondifference in fusion rates between the two techniques.

Using the PearlDiver database, we hypothesized that the use of an intervertebral cage in ACDF would be associated with a higher nonunion rate when compared with the fusion rates of ACDF using structural bone graft.

MATERIALS AND METHODS

We performed a retrospective review of the Humana subset of the PearlDiver Patient Record Database. This is a commercially available dataset with millions of records from the nationwide Humana health insurance provider. In this dataset, queries can be conducted by Current Procedural Terminology (CPT) coding and International Classification of Diseases (ICD) 9th and 10th revision coding.

We utilized CPT 22551 and queried for patients who had undergone ACDF. Specifically, we selected for patients who had undergone (1) ACDF (22551), (2) structural allograft only (20931) or allograft with cage placement (22851), and (3) anterior instrumentation (22845, 22846) (Figure 1). In this population, we selected only patients who had at least 1-year follow-up after their index ACDF procedure. Any use of autologous iliac crest bone graft in ACDF was excluded from this study.

As our goal was to examine the effect of the intervertebral cage, we excluded patients who had a posterior arthrodesis (22600) within 3 months of their ACDF, as this may have been a part of a planned staged procedure. We also excluded patients who may have had other concurrent orthopedic arthrodesis CPT codes in this perioperative period as well. In addition, we excluded patients with an ICD-9 or ICD-10 coding of fracture (Supplementary Table 1, http://links.lww.com/BRS/B383). The reason for these exclusions was to ensure to ensure that a ''nonunion'' code was in reference to the ACDF and not another source such as fracture healing or an alternate body site of fusion.

After our initial univariate analysis, we then performed a stratified analysis controlling for one significant variable (Table 1), then two (Table 2), and then three significant variables (Table 3). In order to determine differences in nonunion rates between the no cage and cage groups, we conducted Chi-squared tests of independence with an alpha level of 0.05 in all of our analyses.

RESULTS

We identified 6130 patients who underwent ACDF with cage or allograft, anterior plating, and without concurrent or delayed posterior arthrodesis in the Humana subsection of the PearlDiver data registry. Of these, 66% (4063) were treated with allograft and 34% (2067) were treated with a cage device. The distribution of tobacco users, diabetics, and different levels of surgery were not observed to be statistically different between the cage group and allograft group ($P > 0.05$).

In our univariate analysis of nonunion, we observed that patients with a cage experienced a rate of 5.32% and those with allograft 1.97% ($P < 0.0001$). We also observed statistically increased rates of nonunion for diabetics, multiple levels, and tobacco use ($P < 0.0001$). In all subanalyses controlling for confounding variables, we observed a higher rate of nonunion with the use of the cage as compared to the

TABLE 1. Stratified Analysis; Nonunion Rates Between Allograft and Cage, After Controlling for Number of Levels Treated, Diabetes Status, and Tobacco Use

	Allograft	Cage	*P*
One-level ACDF	1.9% (35/1835)	4.2% (35/843)	0.0007
Two-level ACDF	1.7% (28/1641)	6.1% (56/921)	<0.0001
3+ level ACDF	2.9% (17/587)	6.3% (19/303)	0.0155
Diabetes +	2.6% (44/1692)	8.3% (61/738)	<0.0001
Diabetes −	1.5% (36/2371)	3.7% (49/1329)	<0.0001
Tobacco +	2.7% (60/2195)	6.7% (69/1034)	<0.0001
Tobacco −	1.1% (20/1868)	4.0% (41/1033)	<0.0001

ACDF indicates anterior cervical discectomy and fusion.

allograft group. When controlling for one additional variable (Table 1), we observed that the use of the cage was significantly associated with a higher rate of nonunion in all subanalyses.

When controlling for two additional variables, we observed the use of the cage to be significantly associated with a higher rate of nonunion in 12 of the 13 possible subanalyses (Table 2). Three subanalyses were not possible (three-level ACDF/Tobacco −; three-level ACDF Diabetes −; Tobacco −/Diabetes −) group because the number of nonunions was less than 11. For patient privacy compliance in the PearlDiver data, when the sample size is less than 11, the true value is rendered as "−1." In these cases, the number may be anywhere between 1 and 11 patients. In some cases, we were able to use the 11 values as a conservative estimate and still perform our analysis. For example, in the two-level ACDF/Tobacco − group, there were 11 or less patients with nonunion in the allograft group, whereas there were 22 patients with nonunion in the cage group. In this case, we assigned the highest possible nonunion rate (11 patients) in the allograft group and still observed a statistically significant difference between the allograft and cage group.

When controlling for three additional variables (Table 3), we observed a statistically higher nonunion rate in the cage group in all subanalyses that were possible. Of the 12 possible permutations, only five subanalyses had sufficient data to allow for analysis. The remaining seven subanalyses had nonunion numbers of less than 11 in both groups. As the true numerator is not known in both groups, we could not estimate a comparison in these subanalyses.

DISCUSSION

In anterior cervical discectomy and arthrodesis, the achievement of stability is of obvious importance for the maintenance of long-term benefit. Nonunion has been associated

TABLE 2. Stratified Analysis; Nonunion Rates Between Allograft and Cage, After Controlling for Two Variables

	Allograft	Cage	*P*
One-level ACDF/Tobacco +	2.2% (22/1001)	5.5% (23/420)	0.0013
One-level ACDF/Tobacco −	1.6% (13/834)	2.8% (12/423)	0.1253
One-level ACDF/Diabetes +	3.1% (23/747)	6.2% (17/273)	0.0219
One-level ACDF/Diabetes −	1.1% (12/1088)	3.1% (18/570)	0.0029
Two-level ACDF/Tobacco +	3.0% (26/870)	7.3% (34/467)	0.0003
Two-level ACDF/Tobacco −	1.4% (11*/771)	4.8% (22/454)	0.0004
Two-level ACDF/Diabetes +	1.6% (11*/673)	8.6% (29/339)	<0.0001
Two-level ACDF/Diabetes −	1.9% (18/968)	4.6% (27/582)	0.0016
3+ level ACDF/Tobacco +	3.7% (12/324)	8.1% (12/147)	0.0416
3+ level ACDF/Tobacco −	NA	NA	NA
3+ level ACDF/Diabetes +	4.0% (11/272)	11.9% (15/126)	0.0032
3+ level ACDF/Diabetes −	NA	NA	NA
Tobacco +/Diabetes +	2.6% (25/957)	7.6% (30/396)	<0.0001
Tobacco +/Diabetes −	2.8% (35/1238)	6.1% (39/638)	0.0005
Tobacco −/Diabetes +	2.6% (19/735)	9.1% (31/342)	<0.0001
Tobacco −/Diabetes −	NA	NA	NA

*The * indicates that this number was less than 11 and thus not exactly known. In some cases, statistical analysis was still possible assuming the highest possible value. NA represents comparisons that could not be made because the numerators in both populations were less than 11.*

ACDF indicates anterior cervical discectomy and fusion.

TABLE 3. Stratified Analysis; Nonunion Rates Between Allograft and Cage, After Controlling for Three Variables

	Allograft	Cage	*P*
One-level ACDF/Tobacco +/Diabetes +	3.0% (13/430)	7.7% (11/143)	0.0159
One-level ACDF/Tobacco +/Diabetes −	1.9% (11*/571)	4.7% (13/277)	0.0228
One-level ACDF/Tobacco −/Diabetes +	NA	NA	NA
One-level ACDF/Tobacco −/Diabetes −	NA	NA	NA
Two-level ACDF/Tobacco +/Diabetes +	3.0% (11/368)	9.7% (18/186)	0.0009
Two-level ACDF/Tobacco +/Diabetes −	3.2% (16/502)	7.5% (21/281)	0.0067
Two-level ACDF/Tobacco −/Diabetes +	3.6% (11*/305)	10.5% (16/153)	0.0034
Two-level ACDF/Tobacco −/Diabetes −	NA	NA	NA
3+ level ACDF/Tobacco +/Diabetes +	NA	NA	NA
3+ level ACDF/Tobacco +/Diabetes −	NA	NA	NA
3+ level ACDF/Tobacco −/Diabetes +	NA	NA	NA
3+ level ACDF/Tobacco −/Diabetes −	NA	NA	NA

*The * indicates that this number was less than 11 and thus not exactly known. In some cases, statistical analysis was still possible assuming the highest possible value. NA represents comparisons that could not be made because the numerators in both populations were less than 11.*

ACDF indicates anterior cervical discectomy and fusion.

with poor clinical outcome and the need for revision surgery,[10–12] whether posterior or anterior, presents an additional risk to the patient.

The use of an intervertebral cage in anterior discectomy and arthrodesis has gained popularity.[3] Although the nonresorbable nature of the cage may allow for stability as the fusion mass forms, it may also represent a literal mechanical block for fusion formation. Fusion mass cannot form in the space occupied by the synthetic cage. With less endplate surface area and less intervertebral volume available for arthrodesis, we hypothesized that the use of a cage in ACDF would be significantly associated with the development of a nonunion.

Our study using the Humana data within the PearlDiver registry suggests that the use of an intervertebral cage in ACDF is statistically associated with a higher nonunion rate as compared to allograft. In every analysis and subanalyses, we observed a higher rate of nonunion in patients treated with a cage as opposed to allograft. These observations were statistically significant in 25 of the 26 possible permutations of analysis.

This finding is in contrast with prior literature. To date, there have been five studies that compared union rates in ACDF using cages *versus* bone graft and none of them were able to demonstrate a difference between the two techniques.[5–9] However, the sample size in these studies are low. Even when the data from these five studies are pooled, there are only 122 patients in the bone graft ACDF group and 147 patients in the cage group. This low combined sample size precludes sufficient analysis and control for confounding variables, whereas our study allows for a larger stratified analysis.

Our study observed that ACDF with structural allograft results in a significantly higher rate of arthrodesis than ACDF with a cage. Despite this finding, ACDF cages may continue to have a role in cervical spine arthrodesis. In situations where structural allograft may not be readily available, cervical cages represent a reasonable alternative with a well-documented fusion rate, though perhaps not as high as allograft. However, as autologous iliac crest is widely available, a larger structured study with sufficient power, comparing the pros and cons of ACDF with cages and autologous iliac crest would be of great interest.

With any large database, there are weaknesses. The reliability of the reporting and coding is dependent upon multiple sources in an administrative data registry. We were unable to obtain radiographic evidence of nonunion for individual patients and instead relied on the diagnosis codes for nonunion, an important assumption we have made in this study. As this was an observational database study, we were also unable to determine the constitution of each cage placed, whether that be PEEK, titanium, mesh, or porous material. In our analysis, we stratified our initial population to account for the three most likely confounding variables for nonunion. It is entirely possible that other confounding variables exist and this may affect the analysis. Even with this large database, the nonunion patients whittled down to less than 11 patients in some subanalyses. One of the limitations of PearlDiver is when patient population size is less than 11, the true number is not revealed because of the potential for patient identification. We encountered this in some of our subanalyses and this did limit our ability to analyze the data, particularly in Tables 2 and 3 where we attempted to control for multiple confounders.

Future studies utilizing other data sources with sufficient sample size may be of value in further investigation. However, the PearlDiver data have been widely utilized in peer-reviewed publication.[13,14] To date, this study is the largest comparative study examining the fusion rates of ACDF using cages and structural bone graft. Our practice, like the majority of spine surgeons in North America,[3] is to utilize structural bone graft in ACDF. These data suggest that allograft, when available, may be a superior option than

the use of a cage in achieving arthrodesis in the cervical spine.

➢ Key Points

- ❑ In this study, both structural allograft and intervertebral cage groups experienced high fusion rates.
- ❑ When comparing nonunion rates, these data suggest the superiority of allograft in ACDF.
- ❑ While the use of a cage and nonstructural bone graft material remains an important surgical option, the use of allograft, when donor bone is available, may be preferable in achieving solid arthrodesis.

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Technical Note

PEEK-Halo effect in interbody fusion

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ABSTRACT

Recent developments have seen poly[aryl-ether-ether-ketone] (PEEK) being increasingly used in vertebral body fusion. More novel approaches to improve PEEK have included the introduction of titanium-PEEK (Ti-PEEK) composites and coatings. This paper aims to describe a potential complication of PEEK based implants relating to poorer integration with the surrounding bone, producing a "PEEK-Halo" effect which is not seen in Ti-PEEK composite implants. We present images from two patients undergoing anterior lumbar interbody fusion (ALIF). The first patient underwent an L5/S1 ALIF using a PEEK implant whilst the second patient underwent L4/L5 ALIF using a Ti-PEEK composite implant. Evidence of osseointegration was sought using CT imaging and confirmed using histological preparations of a sheep tibia model. The PEEK-Halo effect is demonstrated by a halo effect between the PEEK implant and the bone graft on CT imaging. This phenomenon is secondary to poor osseointegration of PEEK implants. The PEEK-Halo effect was not demonstrated in the second patient who received a Ti-PEEK composite graft. Histological analysis of graft/bone interface surfaces in PEEK *versus* Ti-PEEK implants in a sheep model further confirmed poorer osseointegration of the PEEK implant. In conclusion, the PEEK-Halo effect is seen secondary to minimal osseointegration of PEEK at the adjacent vertebral endplate following a PEEK implant insertion. This effect is not seen with Ti-PEEK implants, and may support the role of titanium in improving the bone–implant interface of PEEK substrates.

1. Introduction

Since the approval of spinal implants for medical use there has been continuous development and advancement in their biomaterial construction. There are a number of properties which are sought when designing an ideal biopolymer for use in spinal implantation. These biopolymers aim to be strong, yet match the mechanical properties (elastic modulus) of bone; inert; biocompatible; and amenable to formation of a strong bone-implant interface (osseointegration) for long term fusion.

Traditional materials include titanium alloy cages, which achieve good rates of fusion [1]. However they have been associated with a number of disadvantages including (1) a higher subsidence rate of the cage into adjacent vertebrae [2]; (2) higher stiffness, reducing mechanical stimulation of the surrounding vertebral bone, and shielding the bone graft with implications on fusion in accordance with Wolff's Law [3]; (3) difficulties in radiological evaluation due to lack of radiolucency; and (4) subject to *in vivo* corrosion and hydrogen embrittlement [4].

Poly[aryl-ether-ether-ketone] (PEEK) biomaterials emerged and for use in medical applications as early as the 1980s [5], though they did not see widespread use as spinal cages until the late 1990s with the introduction of the Brantigan cage [6]. PEEK cages possess a number of mechanical advantages over traditional implants including (1) lower stiffness than titanium alloy, allowing better transfer of loading forces to the bone graft; (2) an elastic modulus much closer to that of cortical bone than titanium implants (4.3 GPa *versus* 18.6 GPa *versus* 110 GPa) [7]; and (3) minimisation of stress shielding compared to solid titanium implants [3].

PEEK implants also possess a number of cytological advantages, and have been shown to be as safe, non-cytotoxic and non-mutagenic as traditional implants [8,9] and have excellent *in vitro* and *in vivo* biocompatibility, that can be further improved with the addition of other materials including titanium [10,11].

Recent developments have seen PEEK being increasingly used in vertebral body fusion, mini-spine implants, as well as some pedicle based rod systems [12], interspinous spacers and disc arthroplasty [13,14]. More novel approaches to improve PEEK have included the introduction of titanium-PEEK (Ti-PEEK) composites and coatings [15].

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In order to optimise outcomes for patients, there must be continual evaluation of the properties of PEEK. This paper aims to describe a potential complication of PEEK based implants relating to poorer integration with the surrounding bone, producing a "PEEK-Halo" effect which is not seen in Ti-PEEK composite implants.

2. Technical note

Two patients were referred to the senior author for anterior lumbar interbody fusion procedures performed at L4/L5 and L5/S1, respectively. The first patient received a SYNFIX PEEK INTERBODY graft (SYNTHES, USA), whilst the second patient received a Ti-PEEK composite implant (REDMOND ALIF, A-SPINE ASIA, TAIWAN). CT images were captured at 12 month follow-up to assess for any evidence of poor osseointegration. Consent was obtained from both patients.

The histological methods have been described previously [19]. In brief, PEEK and Ti-sprayed PEEK implants were placed in a line-to-line manner in cortical bone and cancellous bone of adult sheep tibia using an established ovine model. Histomorphometric analysis was performed to assess the extent of osseointegration between the PEEK/composite material and cortical and cancellous implantation sites. Appropriate ethical approval was obtained for this study at the local hospital ethics board.

We describe in this article a phenomenon termed the "PEEK-Halo" effect. This phenomenon is represented by a halo effect between the PEEK implant and the bone graft on CT scan (Fig. 1). This phenomenon is secondary to poor osseointegration of PEEK implants, and has not been described in Ti-PEEK composites.

Figure 2 represents a Ti-PEEK composite implant which does not demonstrate the above described PEEK-Halo effect. We hypothesise that this is secondary to improved osseointegration of composite implants with the surrounding vertebral bone and bone graft placed within the cage device.

This effect was confirmed by a pre-clinical ovine tibia model histologically. In Figure 3A, a distinguishable fibrous tissue layer and gap has formed across the PEEK/bone interface of the inserted PEEK implants, corresponding to a radiolucent halo observed on CT scan. However the plasma sprayed titanium-coated implants illustrated in Figure 3B demonstrated on-growth and in-growth of bone across the Ti-PEEK/bone interface and the absence of a radiolucent rim on CT scan. Therefore, this histological analysis further substantiates the link between PEEK, fibrous tissue formation, reduced osseointegration and the development of the halo effect.

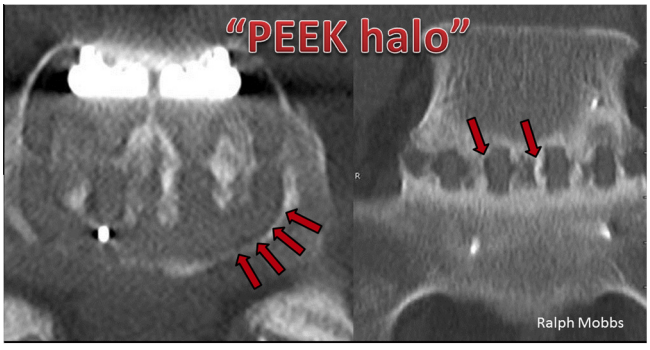

Fig. 1. (Left) Transverse and (right) coronal CT images at 12 months post L5/S1 anterior lumbar interbody fusion for discogenic low back pain. The presence of bridging bone between endplates confirms fusion through the construct with an excellent clinical outcome, however at the bone graft/poly[aryl-ether-ether-ketone] (PEEK) interface, a radiolucent rim is evident (delineated by the arrows) confirming no bone/PEEK integration, the so called "PEEK-Halo" effect.

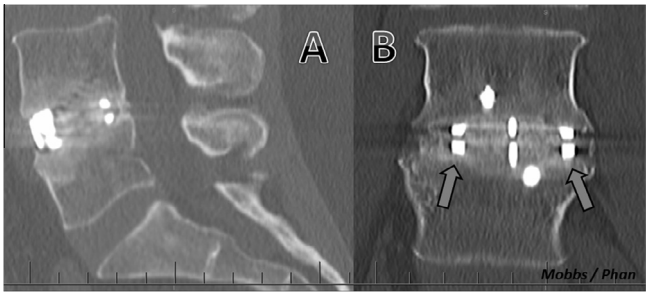

Fig. 2. (A) Midsagittal and (B) coronal fine cut CT images at 12 months post L4/5 anterior lumbar interbody fusion demonstrating adjacent endplate sclerosis and the absence of radiolucency at the titanium-poly[aryl-ether-ether-ketone] (Ti-PEEK)–bone endplate interface (arrows).

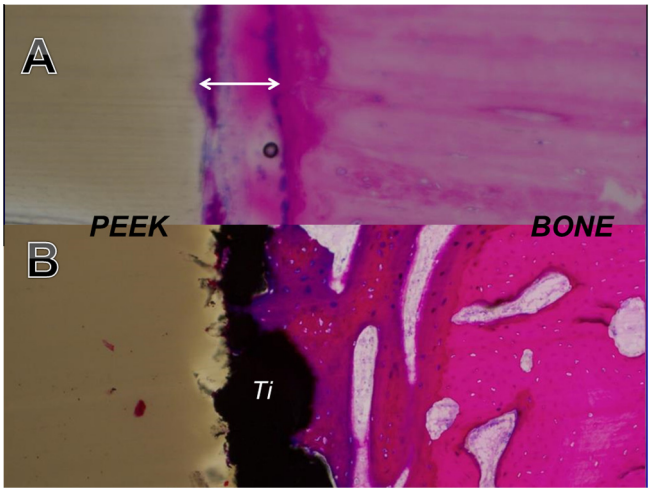

Fig. 3. Histology of poly[aryl-ether-ether-ketone] (PEEK)/bone interface at 4 weeks post-implantation into a sheep tibia model. Histology processing of samples began with fixation in phosphate-buffered formalin, dehydration through increasing concentrations of ethanol (70% to 100%) and embedding in polymethylmethacrylate (PMMA) resin before being sectioned and stained with methylene blue and basic fuchsin. (A) Well-established rim of fibrous tissue (white arrow) between the PEEK implant and adjacent bone – the rim of fibrous tissue results in the halo effect seen on CT imaging. (B) Titanium (Ti)-PEEK/bone interface demonstrating on-growth and ingrowth of bone at the Ti-PEEK/bone interface, with no radiolucent rim evident on CT imaging. Adapted from Walsh et al. (2015) [19].

3. Comment

We hypothesise that there are a number of potential explanations for the existence of the PEEK-Halo effect seen between the vertebral bone and the PEEK implant. Implant materials generate peri-implant inflammatory factors, and it is these factors that are postulated to be responsible for the degree of osseointegration and therefore the rates of fusion long-term.

There is considerable debate however regarding the interaction between PEEK and osteoblastic differentiation. Sagomonyants et al. [16] showed that PEEK implants have comparable *in vitro* bone forming capacity to that of rough titanium. These data are supported by other studies which show that PEEK is capable of induction of osteoblast differentiation *in vitro* [17]. However, more recent studies have found that osteoblasts differentiate to a lesser degree when cultured on PEEK *versus* titanium surfaces, suggesting that the former has a lower level of support for osteogenic tissues [18]. If a Ti-PEEK composite does indeed allow better osteoblastic differentiation than PEEK, this could provide one possible explanation for the observed PEEK-Halo effect.

Another recent study demonstrated that plasma-sprayed titanium coating to PEEK implants improves the bone implant

interface. This study assessed shear strength in cortical sites at 4 and 12 weeks post-implantation in cancellous bone of adult sheep. The titanium coating was found to dramatically improve the shear strength at the bone-implant interface at 4 weeks, with further improvement at 12 weeks also observed when compared to PEEK alone [19].

A recent study compared *in vitro* and *in vivo* effects of PEEK *versus* PEEK with the addition of titanium via electron beam deposition. They found *in vitro* cellular responses of cell attachment, proliferation and osteoblastic differentiation to be superior in the Ti-PEEK implants compared to pure PEEK substrate. The *in vivo* bioactivity was also improved, with a significant difference observed in bone-in-contact ratio [20]. These findings, combined with those of Wu et al. [21] suggest better biocompatibility of Ti-PEEK implants, and give further weight to the presence of PEEK-Halo being secondary to poorer osseointegration of pure PEEK substrates.

4. Conclusion

In summary we describe the PEEK-Halo effect which is seen secondary to minimal osseointegration of PEEK at the adjacent vertebral endplate following a PEEK implant insertion. This effect is not seen with Ti-PEEK implants, and may support the role of titanium in improving the bone–implant interface of PEEK substrates. Furthermore, the PEEK-Halo effect may provide incremental evidence for poor or reduced fusion rates on radiological imaging of patients who have received a pure PEEK implant.

Conflicts of Interest/Disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

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Articles in Review

"Five-fold Greater Risk of Pseudoarthrosis with PEEK"

Dr. Than – 1 Level Allograft vs PEEK; 127 Patients

"PEEK IBD Associated w 7-Fold Higher Rate of Pseudoarthrosis"

Dr. Than – Multi Level Allograft vs PEEK; 81 Patients

"5.32% Non-Union Rate for Cages; Allograft < 2%"

Pirkle et al. – Allograft vs Cage; 6130 Patient Database

"Allograft Rate of Fusion 90.5%; PEEK – 77.4%"

Fatima et al. – Allograft vs PEEK; 6640 Patient Database

"The Likelihood of Revision was Nearly Double for Synthetics when Compared to Allograft"

Menon et al.; 8130 Patient Database

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ARTICLE IN REVIEW:

Higher nonunion rate using cages versus allografts in ACDF

PUBLICATION: Spine Journal, March 2019

TITLE: Cages in ACDF are Associated with a Higher Nonunion Rate than Allograft. A Stratified Comparative Analysis of 6130 Patients.

AUTHORS: Pirkle S, Kaskovich S, Cook DJ, Ho A, Shi LL, Lee MJ.

STUDY DESIGN: Retrospective database review, 6130 patients.

SUMMARY: Anterior cervical discectomy and fusion (ACDF) is a common treatment for cervical degenerative disc disease (CDDD). Use of an interbody spacer provides support and promotes fusion. This retrospective review evaluated the rate of nonunion in 6130 patients who had undergone ACDF surgery using either structural allograft bone (n=4063) or synthetic cages (n=2067). After at least one year follow-up, overall nonunion rates were significantly higher in the cage group (5.32%) compared to the allograft group (1.97%; $p < 0.01$). Increased rates of nonunion were consistently observed in the cage group regardless of confounding factors, such as levels treated, tobacco use, and diabetes. This study demonstrates a significantly greater risk of nonunion with the use of synthetic cages in ACDF procedures compared to structural allografts, supporting the use of structural allografts in cervical fusion procedures.

Greater nonunion rate with synthetic cages:

Nonunion rates were significantly higher in the cage group (5.32%) than in the structural allograft group (1.97%; $p < 0.01$).

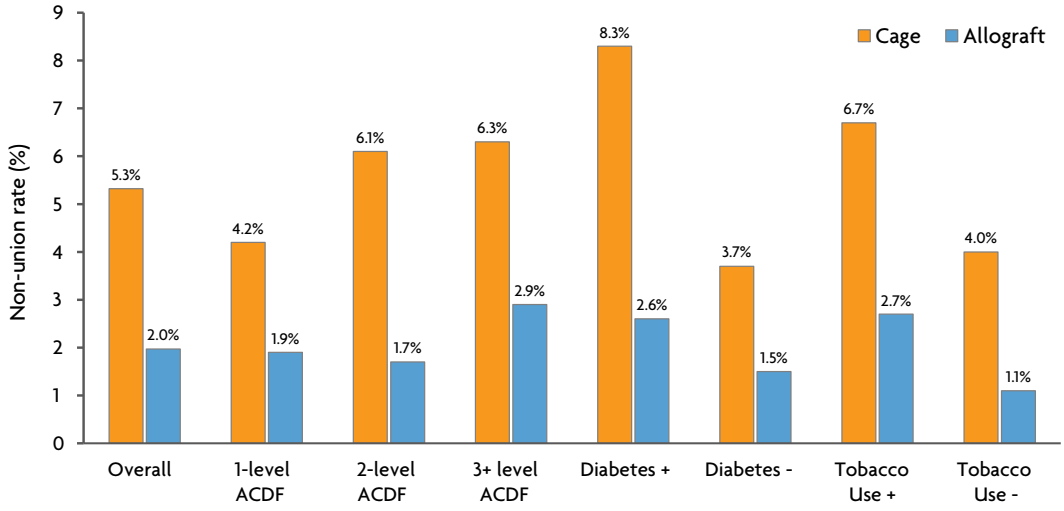
Allograft outperformed cage regardless of confounding factors:

Cage group showed consistently higher nonunion rate regardless of confounding factors, such as levels treated, tobacco use, and diabetes.

Structural allografts are an effective choice in ACDF:

The results suggest that allograft may be a superior option over a cage in achieving arthrodesis in the cervical spine.

Structural allografts have a lower rate of nonunion compared to synthetic cages.



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ARTICLE IN REVIEW:

Greater risk of pseudarthrosis using PEEK spacers vs structural allografts in 1-level ACDF

PUBLICATION: Journal of Neurosurgery Spine, January 2019

TITLE: Five-fold higher rate of pseudarthrosis with polyetheretherketone interbody device than with structural allograft used for 1-level anterior cervical discectomy and fusion.

AUTHORS: Krause KL, Obayashi JT, Bridges KJ, Raslan AM, Than KD.

STUDY DESIGN: Retrospective, single center, multisurgeon, 127 patients.

SUMMARY: Anterior cervical discectomy and fusion (ACDF) is one of the most common treatments for cervical degenerative disc disease (CDDD). Long term success depends on the placement of an interbody spacer to provide support and promote fusion. Structural bone allografts and synthetic polyetheretherketone (PEEK) are two of the most common interbody spacers used in ACDF. This retrospective study evaluated the rates of pseudarthrosis and the need for revision surgery in 127 patients who had undergone a 1-level ACDF surgery using either structural allograft bone (n=71) or PEEK (n=56) interbody spacers. After at least 1 year follow-up, 29 out of 56 (52%) patients with PEEK implants demonstrated radiographic evidence of pseudarthrosis, which was 5-fold greater than that seen in patients with structural allografts (7 out of 71; 10%). Of these, 7 patients with PEEK implants (out of 29; 24%) required reoperation versus 1 patient with structural allografts (out of 7; 14%). This study demonstrates a significantly greater risk of pseudarthrosis ($p < 0.001$) and increased rate of revision surgery ($p = 0.01$) with the use of PEEK interbody spacers in 1-level ACDF procedures compared to structural allografts, supporting the use of structural allografts in cervical fusion procedures.

Five-fold greater risk of pseudarthrosis with PEEK:

52% of patients with PEEK implants had radiographic pseudarthrosis, compared to 10% of those with structural allografts.

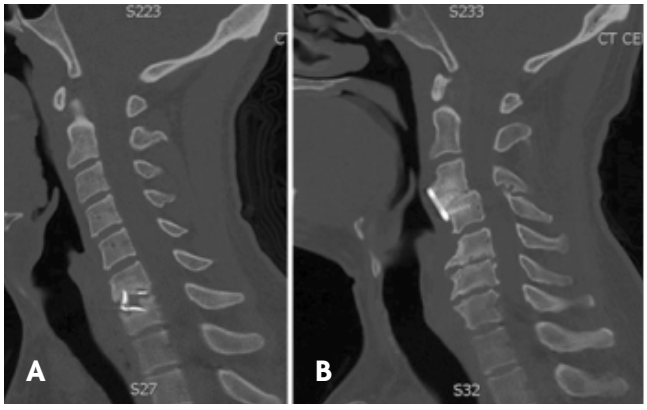
Rate of subsequent revision nearly doubled with PEEK:

Of those with pseudarthrosis, only 1 patient with a structural allograft (14%) required revision surgery, compared to 7 patients in the PEEK group (24%).

No significant differences between patient demographics:

Patients' age, sex, BMI, and tobacco use were similar between the two groups ($p > 0.05$).

Greater risk of pseudarthrosis with use of PEEK vs structural allograft



Radiographs showing use of (A) PEEK interbody spacer and pseudarthrosis and (B) structural allograft bone and fusion after 1 year.
Reprinted with permission from Krause et al. J Neurosurg Spine 2019.

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ARTICLE IN REVIEW:

Structural allografts provide better outcomes than PEEK cages in spinal fusion procedures

PUBLICATION: World Neurosurgery, April 2020

TITLE: Structural Allograft versus Polyetheretherketone Implants in Patients Undergoing Spinal Fusion Surgery: A Systematic Review and Meta-Analysis

AUTHORS: Fatima N, Massaad E, Shankar GM, Shin JH.

STUDY DESIGN: Meta-analysis

SUMMARY: Interbody spacers, such as structural allografts or polyetheretherketone (PEEK) cages, are a popular alternative to autograft for spinal fusion. Comparisons of clinical success of these two materials are scarce. This systematic review of 7 studies included 6640 patients who underwent single-level or multilevel spinal fusion procedures with structural allografts (n=4250), or PEEK cages (n=2390). There were no significant differences in the patient demographics between the groups, including age, gender, BMI, and smoking status. By the final followup, the rate of fusion in the structural allograft group was 2.59-fold higher compared to the PEEK cages group (OR 2.59, 95% CI 1.02-6.57, p=0.05). Structural allografts were 61% less likely to results in pseudarthrosis (OR 0.39, 95% CI 0.15-0.98, p=0.05) and were 74% less likely to result in reoperation (OR 0.26, 95% CI 0.09-0.79, p=0.02). In an analysis of patients who underwent fusions in the cervical spine, those treated with structural allografts had 4.68-fold higher likelihood of fusion than patients treated with PEEK cages (OR 4.68, 95% CI 2.08-10.54, p=0.0002). These results align with previously reported fusion rates in the cervical spine. While prospective studies are needed, this analysis concludes structural allografts provide higher fusion rates and lower rates of pseudarthrosis compared to PEEK cages.

Better fusion rates:

The pooled fusion rate in patients treated with structural allografts was 90.5% compared to 77.4% in patients with PEEK cages.

Lower risk of pseudarthrosis and revision:

Patients treated with structural allografts were 61% less likely to have pseudarthrosis and 74% less likely to require reoperation.

Greater rate of fusion in the cervical spine:

Patients with structural allografts had 4.68-fold higher likelihood of fusion than those with PEEK cages.

Structural allografts provide better outcomes than PEEK cages

Parameter	Structural Allograft	PEEK
Patients (n)	4250	2390
Rate of pseudarthrosis	2.82%	8.91%
Rate of reoperation	0.07%	0.2%
Rate of fusion	90.5%	77.4%

Adapted from Table 3.

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ARTICLE IN REVIEW:

Lower revision rate with structural allografts vs synthetic cages in multilevel ACDF procedures

PUBLICATION: Global Spine Journal, August 2020

TITLE: Structural Allograft Versus Synthetic Interbody Cage for Anterior Cervical Discectomy and Fusion: A Comparison of 1-Year Outcomes from a National Database[1]

AUTHORS: Menon N, Turcotte J, Patton C.

STUDY DESIGN: Observational cohort study

SUMMARY: The TriNetX database, a global health research network, was used to identify 8,103 patients who had undergone single-level or multilevel anterior cervical discectomy and fusion (ACDF) procedures. The authors used these data to compare the rates of 1-year revision, pseudarthrosis, surgical site infection (SSI), and dysphagia between procedures using structural allograft and synthetic cage. Differences in patient age, gender, race, and comorbidities were controlled for using propensity score matching. In the single-level cohort, there was no significant difference ($p>0.05$) in revision rates, pseudarthrosis rates, SSI, or dysphagia between patients who received structural allograft (n=1,528) or synthetic cage (n=1,528). In the multilevel cohort (n=3,510; 50% synthetic cage/50% structural allograft), there was a significantly higher likelihood of revision surgery with synthetic cages compared to structural allografts (7.3% vs 3.8%, odds ratio=1.982, $p<0.001$). However, there was significantly lower likelihood of dysphagia with synthetic cages (12.9% vs 15.9%, odds ratio=0.782, $p=0.011$). There were no differences in SSI or the rate of pseudarthrosis. While the results were comparable in single-level procedures, the multilevel results were in line with previous reports in which higher rates of revisions were observed with synthetics.[2-4] Combined with reports of greater fusion rates[4], structural allografts may be the superior option for ACDF procedures.

Single-level procedures:

In single-level procedures, the likelihood of revision, pseudarthrosis, surgical site infection, and dysphagia were similar in both cohorts.

Multilevel procedures:

The likelihood of revision was nearly double when using synthetics compared to structural allografts (7.3% vs 3.8%), but the likelihood of dysphagia was 3% lower with synthetics (12.9% vs 15.9%). There were no differences in surgical site infection or pseudarthrosis.

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Significant differences in multilevel procedures

	Structural	Synthetic
Revision	3.8%	7.3%
Pseudarthrosis	No difference	
Surgical Site Infection	No difference	
Dysphagia	15.9%	12.9%

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