Original Study

Clinical outcomes for lumbar fusion using silicon nitride versus other biomaterials

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Background: In lumbar fusion surgery, intervertebral spacer cages made of silicon nitride (Si_3N_4) ceramic are an available option among other biomaterials. While the surface chemistry of Si_3N_4 is known to favor bone fusion, large-scale clinical studies attesting to its efficacy are lacking. This multicenter retrospective study compared lumbar fusion outcomes for Si_3N_4 cages to previously reported data for other cage materials.

Methods: Pre-operative patient demographics, comorbidities, changes in visual analog scale (ΔVAS) pain scores, complications, adverse events, and secondary surgical interventions (SSI) were compiled from the records of 450 patients who underwent Si_3N_4 lumbar spinal fusion at four separate U.S. surgical centers. For comparison, MEDLINE/PubMed and Google Scholar searches identified studies reporting similar outcomes for other biomaterials. A total of 1,025 patients from 26 cohorts reported in 14 publications met inclusion criteria for this control group.

Results: Overall, the mean last-follow-up for all patients was 341±293 days (11.4±9.8 months), with the longest follow-up being 6.4 years. Patients with Si_3N_4 implants were similar in gender and age distribution to the control group but had higher BMI values (30.9±6.1 *vs.* 25.8±4.1, P<0.01) and lower tobacco use (15.8% *vs.* 30.0%, P<0.01). Both the Si_3N_4 and control groups showed significant improvements in VAS pain scores from preoperative to last follow-up. For the Si_3N_4 group, ΔVAS was 36.8±35.4 points compared to 37.6±22.5 points (P=0.63) for the metadata group. Complications and reoperations for the Si_3N_4 and the control groups were similar (i.e., 9.8% and 3.1% versus 12.4% and 2.9%, P=0.16 and P=0.84, respectively).

Conclusions: Lumbar fusion with Si_3N_4 spacers compared favorably with the improvements reported with other commonly used biomaterial cages.

Keywords: Lumbar discectomy and fusion; clinical outcomes; silicon nitride (Si_3N_4)

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Introduction

Lumbar spinal fusion is typically performed for intractable low-back pain (LBP) or radicular symptoms after failure of extended conservative treatments (1). Symptoms can result from degenerative intervertebral disc disease (DDD), disc herniation, stenosis, vertebral endplate sclerosis, osteophytes, spondylolisthesis, spondylosis, scoliosis, infection, tumors, or trauma (2-4). A central lumen in the intervertebral spacers holds bone graft, while the implant provides segmental stability and restores disc height, lordotic curvature, and sagittal balance (5,6).

Spacer design and biomaterials have evolved over the past 30 years (7). Early use of structural iliac crest autogenous bone graft was limited by donor site morbidity, leading to interest in allograft and synthetic biomaterials. Today, polyetheretherketone (PEEK), titanium (Ti), tantalum (Ta), and silicon nitride (Si_3N_4) reflect biomaterial choices for cage manufacture (8,9). Of these, Si_3N_4 has the longest clinical history. It was originally implanted in patients who underwent lumbar fusion beginning in 1986 (10). Despite design limitations, those early Si_3N_4 implants proved to be safe and efficacious at thirty years of follow-up (11). The U.S. FDA cleared Si_3N_4 intervertebral spinal spacers in 2008, followed by the European Union in 2009, Brazil in 2015, and Australia in 2017. To date, over 35,000 Si_3N_4 spinal fusion devices have been implanted, with <0.07% reportable adverse events (SINTX Technologies, Inc., 2019, unpublished data).

Because of a paucity of prior clinical results, the purpose of this study was to augment existing data with a significant retrospective review of lumbar fusion outcomes using Si_3N_4 cages (450 patients, 519 implants) at four U.S. centers. Preoperative patient demographics, pain scores, comorbidity data along with post-operative last follow-up pain scores, complications, adverse events, and secondary surgical interventions (SSI) were obtained from chart reviews of 450 patients who received Si_3N_4 implants. Results were compared to lumbar fusion reported with other biomaterials in 26 cohorts comprised of 1,025 patients, reported in 14 publications. The null hypothesis was that Si_3N_4 lumbar fusion outcomes would not be different from those reported in the control group.

Methods

Review of medical records

In accordance with the study protocol, an experienced medical records examiner was independently contracted to retrieve data from the charts of all patients who received a Si_3N_4 lumbar fusion implant by four surgeons at different medical centers between November 2017 and June 2018. Although IRB approval was not required for this study, patient information and data remained anonymous and in compliance with IRB standards. Inclusion criteria are listed in *Table 1*. There were no exclusion criteria. Data were recorded from both digital and active or archival hard copy files.

Several different surgical approaches were utilized including anterior lumbar interbody fusion (ALIF), transforaminal lumbar interbody fusion (TLIF), and posterior lateral interbody fusion (PLIF). Two generations of Si_3N_4 spacers were used in this study (*Figure 1*). *Figure 2* provides a breakdown of the number of single and multilevel surgeries by center. Over 85% of the patients were operated on at one level and about 13% at two levels. Three and four level procedures were a rarity at <1.0%. A total of 519 Si_3N_4 devices were implanted as shown in *Figure 3*, with over 80% of the implantations occurring between L4 and S1. Of this total, approximately 59.5% were PLIF, 37.4% TLIF, and 3.1% ALIF implants.

Surgical procedures

The surgical procedure varied based on the approach and implant type chosen by the surgeon (12). For PLIF, patients were placed in a prone position and either an open midline incision with bilateral muscle dissection or a MIS paramedian muscle splitting incision was used to access the posterior vertebral column. A laminectomy was generally performed based on surgeon preference and the dura retracted to expose the disc space. A complete discectomy was performed followed by endplate preparation. A sizer was used to determine the appropriate height, width, depth, and lordosis of the intervertebral space. Based on these measurements, a Si_3N_4 cage was selected. Local osteophytes that were removed during endplate preparation were morselized and, along with burr shavings, packed into the lumen of the implant. Demineralized bone matrix (DBM) was added based on surgeon preference. After placement of the interbody device, bilateral pedicle screws and rods were inserted into the superior and inferior segments for added stabilization. For TLIF, the patients were also placed in a prone position and a midline or paramedian incision was conducted. A unilateral laminectomy and inferior facetectomy were then performed to expose the spinal

Table 1 Inclusion and exclusion criteria

Inclusion criteria
≥18 years of age
Patients presenting with lumbar spondylolisthesis, stenosis, degenerative disc disease including herniation, spinal instability, spondylosis, radiculopathy and/or myelopathy as diagnosed by their respective spine surgeon based on patient history, physical examination, and radiographic assessment
Patients receiving Valeo I or II Si_3N_4 interbody fusion devices
No improvement in symptoms within ≥6 weeks of conservative therapy
All studies with a surgical date at least 6 months prior to initiation of the data collection process
Exclusion criteria
None

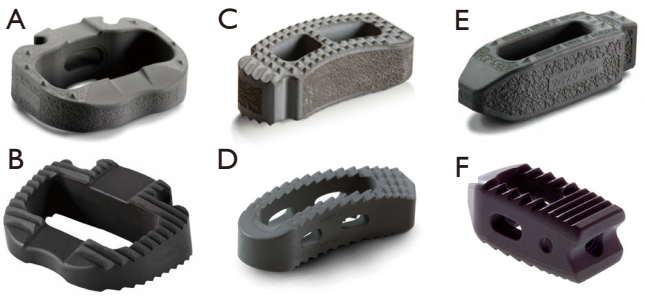

Figure 1 Silicon nitride implants used in this study: (A) Valeo I AL; (B) Valeo II AL; (C) Valeo I TL; (D) Valeo II TL; (E) Valeo I PL/OL; and (F) Valeo II PL/OL. AL, anterior lumbar; TL, transforaminal lumbar; PL, posterior lateral; OL, oblique lateral.

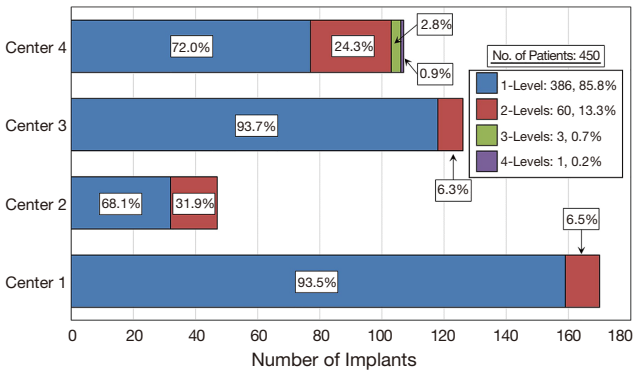

Figure 2 Number of patients, levels, and percentages at each of the four surgical centers.

canal followed by removal of the natural disc and endplate preparation. The remaining operative steps were similar to the PLIF approach. For ALIF (13), patients were placed in the supine position. This anterior approach involved midline, paramedian, or minimally invasive incisions to split the oblique abdominal muscle followed by retraction of retroperitoneal organs and vasculature to form a corridor to the spinal column. The technique provided a direct view of disc space and lateral exposure of the vertebral segments which permitted removal of the disc and endplate preparation. Appropriately sized Si_3N_4 implants, packed with morselized bone and DBM, were then placed in the disc space. A subsequent posterior operative procedure was used to place bilateral pedicle screws and rods for added stabilization. Patients were mobilized soon after surgery without orthoses. Upon discharge, they were instructed to restrict bending, twisting and lifting efforts during the recovery period of no more than ~11.3 kg (25 lbs.) for between 6 and 12 weeks.

Data acquisition

Each patient's preoperative demographic data (age, gender, height, weight, BMI, and diagnoses), comorbidity conditions (smoking, diabetes, hypertension, osteoporosis, osteopenia, tumor, and other), along with their post-operative results (days to last follow-up, pain scores, complications, adverse events, and SSIs) were extracted from their respective medical charts. Pain scores were assessed using the visual analog scale (VAS), zero being "no pain" and ten being the "worst pain imaginable". Pain scores were taken as the maximum of either back, leg, or bodily pain at each follow-up visit. For consistency with the metadata, scores were converted to a zero to 100-point scale. Complications and adverse events included recurrent symptoms, adjacent level disease (ALD), subsidence, infection, migration or non-

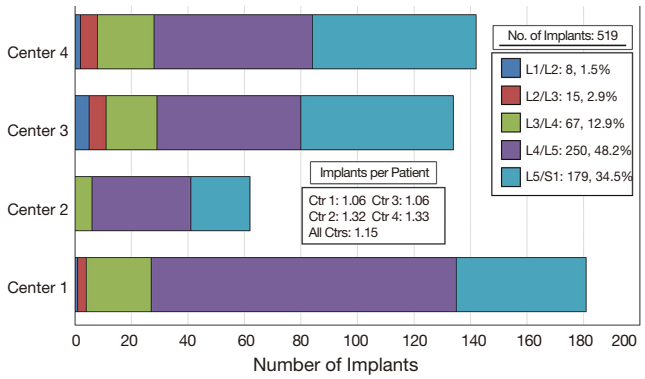

Figure 3 Number of implants per level at each of the four surgical centers.

union, and hematoma. SSIs were compiled for patients experiencing ALD and pain associated with pedicle screw position or removal.

Meta-analysis

A meta-analysis was performed to quantitatively assess and compare differential changes in pain scores, complications, adverse events, and SSI for patients implanted with Si_3N_4 cages versus other commonly used lumbar interbody devices. MEDLINE/PubMed was searched for relevant publications using a human clinical query with the search terms of "(Lumbar Spinal Fusion) AND (Pain) AND (VAS)" along with filters for years (2000 to 2019), abstract and full text in English, and Adults (≥19 years of age). The output was augmented by a Google Scholar search with the added terms of "(Standard Deviation) OR (Confidence Interval)". Article titles and abstracts were then compared, and duplicates removed. Additional clinical papers were identified from a number of published systematic reviews and meta-analyses (14-17) and by manual searches. Papers were excluded if the reported studies were for follow-up periods of <6 months or if they lacked quantifiable statistical data for pre-op and follow-up pain scores. Of the remaining articles, those selected for inclusion had statistically similar pre-op demographics. Fourteen studies consisting of 26 cohorts and 1,025 patients were selected (18-31). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for included articles is shown in *Figure 4* (32).

Statistical analysis

Statistical analyses including metadata comparisons were performed using MedCalc Ver. 18.6-64 bit (Ostend, Belgium). Ordinal data were analyzed using Student's *t*-tests whereas nominal results used proportionality assessments including Chi-squared and Fisher's exact tests. Significance was set at P values of <0.05. An independent statistician (Biomedical Statistical Consulting, Wynnewood, PA USA) assisted in performing the meta-analysis.

Results

Preoperative diagnosis, demographics, and comorbidities

Four lumbar spine disorders (spondylolisthesis, spinal stenosis, degenerative disc disease, and disc herniation) accounted for over 85% of patient diagnoses. The entire etiological data are provided in *Table 2*. Of the 450 patient records included in the study, the average age was 58.2± 12.4 years, 56.2% were female, and the average BMI score was 30.9±6.1. There were no statistical gender differences between the four surgical centers and only center 4 had a slightly younger population (55.5 years, P=0.04). Pre-op comorbidities are presented in *Table 3*. The patient count in this and subsequent tables or charts do not total to the original enrollment due to the fact that some data were missing from patients' records. Patients from all four centers bordered on being clinically obese. However, centers 1 and 3 were at opposite ends of the statistical spectrum (32.2, P=0.02, and 29.4, P=0.01, respectively) when compared to the average of all four centers. For pre-op comorbidities, *Table 3* shows that 15.8% of the patients were smokers, 32.9% had high blood pressure, 12.9% were diabetic, and 2.0% were diagnosed with osteoporosis or osteopenia. Center 2 had the highest percentage of smokers (31.9%, P=0.01) whereas center 3 had the fewest (4.8%, P<0.01). While nearly one-third of all patients were hypertensive, center 2 had the smallest statistical proportion of patients with this morbidity (i.e., 14.9%, P=0.01). There were no statistical differences between the centers for patients with diabetes or osteoporosis/osteopenia. Heterogeneity tests conducted for differences in these demographic and

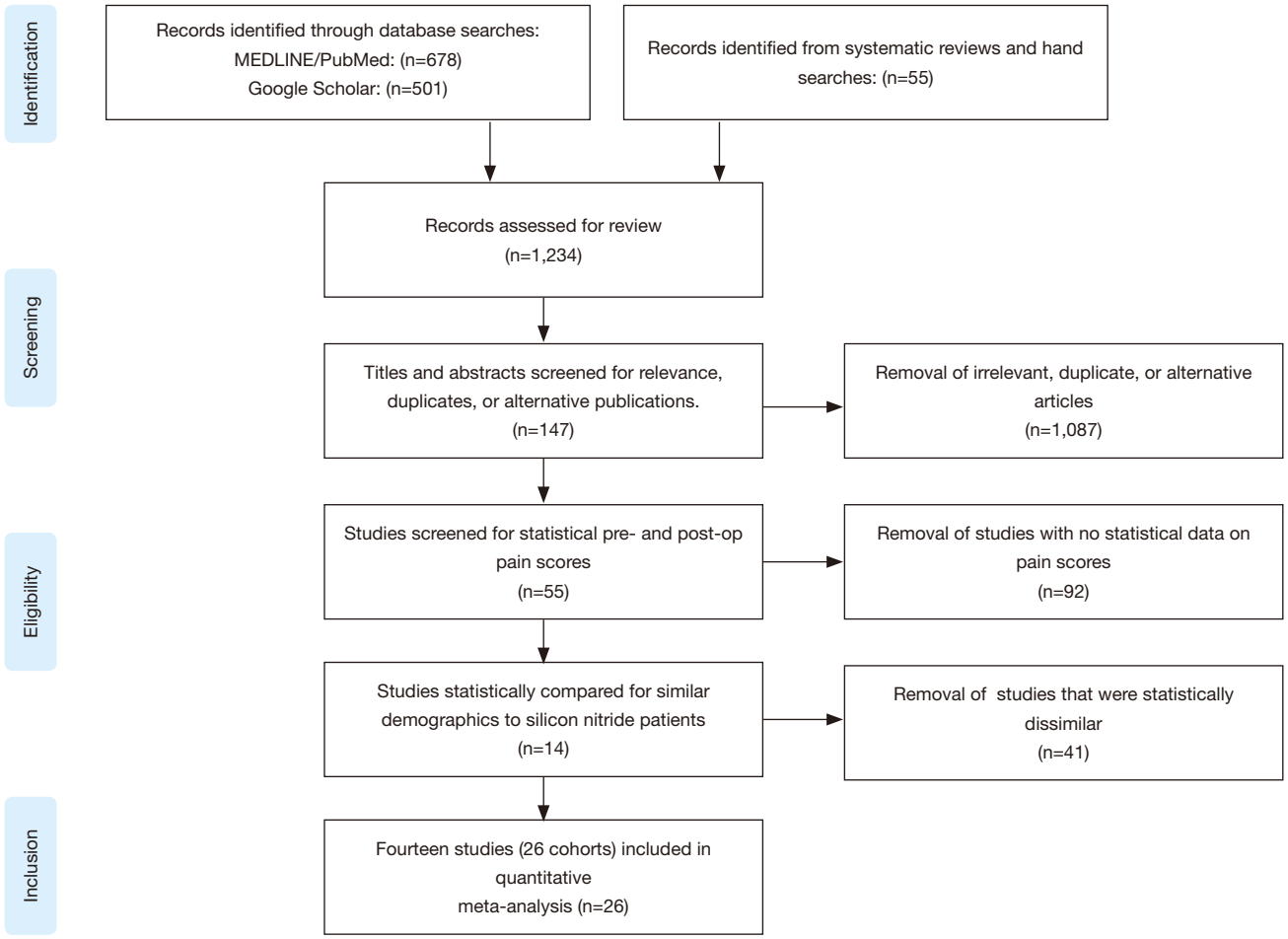

Figure 4 PRISMA flow diagram for selection of included studies. PRISMA, Preferred Reporting Items for Systematic Review and Meta-analysis.

Table 2 Patient diagnoses

Diagnosis	n	%
Spondylolisthesis	174	38.7
Spinal stenosis	137	30.4
Degenerative disc disease	46	10.2
Disc herniation	32	7.1
Spinal instability	26	5.8
Spondylosis	22	4.9
Radiculopathy	10	2.2
Infectious discitis	2	0.4
Post-traumatic deformity	1	0.2

pre-op comorbidities showed homogeneous statistics for gender (I^2=45.8%, P=0.14), diabetes (I^2=4.1%, P=0.37), and osteoporosis/osteopenia (I^2=0.0%, P=0.52), whereas heterogeneous values were observed for age (I^2=60.9%, P=0.05), BMI (I^2=76.3%, P<0.01), smoking (I^2=90.2%, P<0.01), and hypertension (I^2=71.9%, P=0.01). However, the incidence of these morbidities was fairly representative of the greater US population as shown in *Table 4*.

Clinical outcomes

Average time to last-follow-up for each of the four surgical centers is presented in *Table 5*. Significant differences

Table 3 Pre-op comorbidities by surgical center

Center	Smoking			Hypertension			Diabetes			Osteoporosis osteopenia			Total n
	n	%	P†	n	%	P†	n	%	P†	n	%	P†	
1	23	13.5	0.48	64	37.6	0.27	26	15.3	0.44	4	2.4	0.76	170
2	15	31.9	0.01	7	14.9	0.01	7	14.9	0.70	2	4.3	0.31	47
3	6	4.8	<0.01	45	35.7	0.56	16	12.7	0.95	1	0.8	0.36	126
4	27	25.2	0.12	32	29.9	0.55	9	8.4	0.20	2	1.9	0.95	107
Total	71	15.8	1.00	148	32.9	1.00	58	12.9	1.00	9	2.0	1.00	450

†, P value for each center in comparison to average value for all centers.

Table 4 Incidence of morbidities in this study compared to the general US population

Morbidity	This study	US population
BMI	30.9	29.4 (33)
Tobacco use	15.8%	19.3% (34)
Hypertension	32.9%	33.0% (35)
Diabetes	12.9%	9.4% (36)
Osteoporosis/osteopenia	2.0%/NA	3.2%/10.6% (37)†

†, based on a 2010 US population of 309.3 million.

Table 5 Days to last follow-up by surgical center

Center	n	Average	SD	Max	Min	P value†
1	169	305	225	1,151	9	0.15
2	45	729	504	2,292	29	<0.01
3	126	261	215	1,120	27	<0.01
4	105	327	216	14	840	0.65
Total/average	445	341	293	2,292	9	1.00

†, P value for each center in comparison to average for all centers.

Table 6 Change in pain scores (ΔVAS) from pre-op to last follow-up by surgical center

Center	n	Average	SD	Max	Min	P value†
1	148	46.8	33.3	100	−30	<0.01
2	43	39.8	33.1	100	−50	0.60
3	44	36.1	33.8	100	−60	0.90
4	107	22.1	35.2	100	−50	<0.01
Total/average	342	36.8	35.4	100	−60	1.00

†, P value for each center in comparison to average for all centers.

were noted in last follow-up periods with center 3 having the shortest period (261±215 days, 8.7±7.2 months) and center 2 having the longest (729±504 days, or 24.3±16.8 months). The overall longest follow-up also occurred for center 2 at 2,292 days (~6.4 y). Clinical results for changes in VAS pain scores for the four centers are provided in *Table 6*. Patients from each center experienced significant reductions in VAS pain scores (P<0.01) from pre-op to last follow-up. A summary of VAS pain scores for each center along with their statistical significance is shown in *Figure 5*. Patients from center 1 had the largest reductions in pain (46.8 points) with patients from center 4 showing the smallest change (22.1 points). Overall, 77.6% of patients reported an improvement in their pain scores at ≤2 years follow-up, with 69.0% showing ≥25-point improvement and 60.0% indicating an improvement of more than 35-points. Between the four centers these results were homogeneous for pre-op pain scores (I^2=51.2%, P=0.11) but heterogeneous for last follow-up (I^2=83.8%, P<0.01) and ΔVAS (I^2=86.7%, P<0.01) pain scores.

Box and whisker plots for pain scores are provided in *Figure 6* as a function of last follow-up. The largest reduction in pain occurred in the post-operative periods up to nine-months. Mean values dropped from 75.3-point for pre-op to 34.9-, 36.7-, and 38.4-point for the periods of <3, 3–6, and 6–9 months, respectively. Thereafter, average pain scores moderately increased for the remaining patients at 1-year (45.8-point) but declined at 1–2 years (37.9-point) and increased at >2 years (42.6-point). However, they never returned to their pre-op levels. Covariant analyses were performed to assess the effects of demographics and pre-op comorbidities on follow-up pain scores. In comparing data

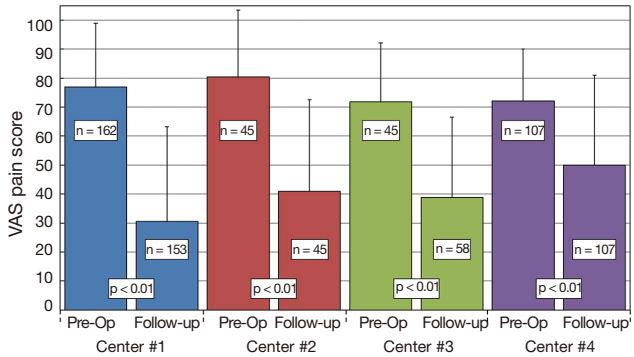

Figure 5 Pre-Op and last follow-up VAS scores for the four participating surgical centers. VAS, visual analog scale.

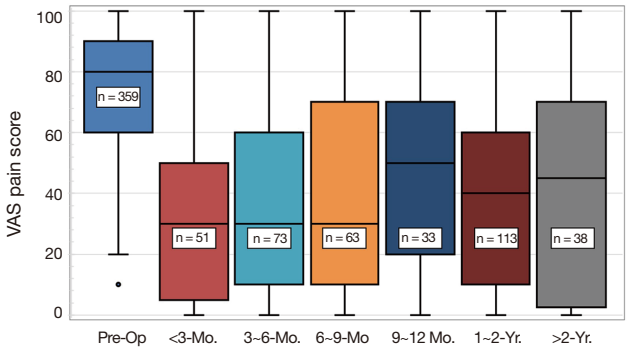

Figure 6 Box and whisker plot of VAS pain scores as a function of follow-up period. VAS, visual analog scale.

for follow-up periods of <9 to >9 months, it was discovered that there was a significantly higher proportion of patients with osteoporosis/osteopenia for patients with >9 months follow-up (i.e., 4.05% versus 0.448%, P=0.01). Poor bone quality may have been a contributing factor to the increased pain scores for the later follow-up periods because these patients showed higher last follow-up pain values (i.e., 55.0±32.1 points, n=8, P=0.15) than the average of the four centers. Eleven of the 44 total complications and one SSI for persistent pain due to a pedicle screw were also associated with follow-up periods >12 months. There were no other covariant factors that had statistically significant contributions to the higher pain scores for the later follow-up periods.

Meta-analysis

Metadata from fourteen lumbar fusion studies comprising of 26 cohorts and 1,025 patients were selected as the control group for comparison to the Si_3N_4 results. Although a larger number of studies were initially considered for inclusion, only 14 met similar demographic criteria. Most studies had much younger patient populations (typically >10-year differential). The 14 studies were composed of a mixture of single- and multicenter randomized controlled trials (RCTs) and retrospective or observational studies assessing the effectiveness of various lumbar fusion methods using a range of commonly accepted spacers or cages and surgical approaches. Details of the selected studies are provided in *Table 7*. *Table 8* compares the pre-op demographics of the Si_3N_4 group to the compiled metadata. There were no statistical differences in either age or gender between the two groups but the Si_3N_4 cohort had higher BMI values than the control (30.9 versus 25.8, P<0.01). In fact, it was difficult to locate comparative studies that matched this comorbidity. Of the 55 studies selected for final review (cf., *Figure 4*), only four cohorts had statistically similar BMI data, and from them, only one had common age and gender statistics. In contrast, patients from the Si_3N_4 group included a lower number of smokers than the control (15.8% versus 30.0%, P<0.01). *Table 9* provides clinical outcomes for both the Si_3N_4 and metadata groups in terms of changes in VAS pain scores, complications, adverse events, and SSI. There were no statistical differences in any of these comparative measures. A heterogeneity test for the metadata is provided in the funnel plot of *Figure 7*. This test compares mean and 95% confidence intervals for changes in VAS pain scores for the 26 meta-analysis cohorts to the mean and pooled 95% confidence interval from this Si_3N_4 study. The test indicates reasonable homogeneity of the data (I^2=29.1%, P=0.083). Using the same comparative data, a forest plot is provided in *Figure 8*. These results complement the statistical analysis of *Table 9* and suggest that changes in pain scores between the two groups were essentially equivalent under either fixed or random effects assumptions.

Table 9 also shows that the complications or adverse events and SSIs were statistically equivalent. The complication rate of the Si_3N_4 patients was ~9.8% compared to ~12.4% for the metadata (P=0.16). There were 14 SSI incidents for the Si_3N_4 patients and 27 for patients included in the meta-analysis (P=0.84). Additional details on complications, adverse events, and SSI are provided in *Table 10*. A recurrence of symptoms was the most common complication within the Si_3N_4 group (n=23, 5.1%), followed by a diagnosis of ALD (n=11, 2.4%). Repeat surgeries were performed on 14 patients for ALD and pedicle screw

Table 7 Summary of meta-analysis studies

Author	No. of patients	Study type, materials, and methods	Clinical outcomes
Malmivaara, *et al*. (18), 2007	50	Multicenter randomized controlled trial assessing conservative management versus single- and multi-level decompression and transpedicular fusion with 2-year follow-up	Patients in both groups improved, but the surgical intervention group had greater reductions in pain and disability
Kim, *et al*. (19), 2010	128	Single-center retrospective study of four patient cohorts undergoing mini-anterior lumbar interbody fusion (ALIF, 86), or mini-transforaminal lumbar interbody fusion (TLIF, 42) procedures at two levels with PEEK cages and >2-year follow-up	Significant improvements were seen in all cohorts with no differences in pain or disability
Sys, *et al*. (20), 2011	38	Single-center prospective randomized controlled trial assessing the clinical effectiveness of using platelet-rich plasma (PRP) and iliac crest bone (ICB) chips with carbon-fiber reinforced PEEK cages (CFRP) versus the same materials excluding the use of PRP for 2-year follow-up	Addition of PRP in posterior lumbar interbody fusion did not lead to a substantial improvement or deterioration when compared with autologous bone only
Nemoto, *et al*. (21), 2014	48	Retrospective review of prospectively collected data at a single center comparing 23 and 25 single-level TLIF cases using either Ti or PEEK cages, respectively, with 2-year follow-up	The superiority of PEEK over Ti was not demonstrated. There were unfavorable radiographic findings for PEEK associated with nonunion
Buttermann, *et al*. (22), 2015	50	Single-center prospective randomized controlled and blinded trial comparing midline and paraspinal approaches for two-level fusion using allograft cortical rings and ICB with >5 years follow-up	Midline and paraspinal approaches resulted in similar outcomes for two-level spinal fusion
Fei, *et al*. (23), 2015	176	Single-center prospective study assessing clinical outcomes for single- and multilevel degenerative disc disease treated using either posterior dynamic stabilization (PDS) with polycarbonate urethane spacers or posterior lumbar intervertebral fusion (PLIF) with an unspecified cage and autologous bone graft and 3-year follow-up	Compared with PLIF, PDS had advantages for blood loss, length of hospital stays, radiographic outcomes, and total cost; but there were no statistically significant differences in back or leg VAS pain or Oswestry disability index (ODI) scores
Lattig, *et al*. (24), 2015	89	Single-center retrospective study examining clinical outcomes for single-level decompression alone or decompression with fusion (D&F) where facet effusion was a sign of degenerative spondylolisthesis for 2-year follow-up. Only D&F cases with or without effusion were included in this analysis. The fusion method and spacer or cage was not specified	There were no significant differences in outcomes based on the presence or absence of facet effusion or surgical treatment. The effusion sign alone is not an indication for adding fusion to decompression in the treatment of lumbar degenerative spondylolisthesis.
Siepe, *et al*. (25), 2015	71	Single-center prospective study assessing mid-term (35.1 months) follow-up for a single-level stand-alone PEEK/Ti intervertebral lumbar spinal fusion cage	Overall, there was a significant improvement from baseline VAS and ODI scores and 77.5% of patients reported highly satisfactory outcomes
Försth, *et al*. (26), 2016	111	Multicenter randomized controlled trial assessing clinical effectiveness for single- and two-level decompression or decompression with fusion surgery for patients with lumbar spinal stenosis at 2- and 5-year follow-up. Only D&F cases were included in this analysis. The D&F method and spacer or cage materials were not specified. They were determined solely by the surgeon	Decompression and fusion surgery did not result in improved clinical outcomes at 2- and 5-year compared to decompression surgery alone

Table 7 (*continued*)

Table 7 (*continued*)

Author	No. of patients	Study type, materials, and methods	Clinical outcomes
Hoff, *et al*. (27), 2016	24	Single-center prospective randomized controlled trial assessing two-level hybrid stand-alone ALIF at L5/S1 with total disc replacement (TDR) at L4/L5 as an alternative to two-level circumferential TLIF at L4-S1 using a PEEK cage at 37 months follow-up. Only the TLIF data are included in this analysis	Both cohorts demonstrated significant clinical improvement at the final follow-up compared to their preoperative conditions. However, pain scores for hybrid cases were significantly lower at the final follow-up than the TLIF patients
Kim, *et al*. (28), 2016	50	Multicenter retrospective review of prospectively acquired patient data assessing the clinical effectiveness of an expandable TLIF PEEK/Ti composite cage at ≥12 months follow-up	The expandable interbody cage led to significant improvement in clinical and radiographic outcomes, including disc height restoration, fusion, and minimal device-related complications
Lee, *et al*. (29), 2016	74	Multicenter prospective randomized single-blinded controlled study evaluating the clinical effectiveness of a single-level PLIF using either a CaO-SiO_2-P_2O_5-B_2O_3 bioactive glass ceramic spacer or a traditional Ti cage for 1-year follow-up	Patients receiving the bioactive glass ceramic spacer or the Ti cage had similar fusion rates and clinical outcomes. There were no significant differences between the cohorts
Rickert, *et al*. (30), 2017	38	Single-center prospective randomized clinical pilot trial comparing clinical and radiological outcomes for one and two level TLIF using a PEEK cage with and without a Ti-coating at 12 months follow-up	Identical outcomes with high rates of fusion were seen in both groups. The Ti-coating appeared to have no safety or efficacy issues at 12 months follow-up
Kim, *et al*. (31), 2018	78	Single-center prospective, randomized, controlled trial comparing robot-assisted versus free-hand PLIF with an unspecified interbody cage for ≥1-year follow-up	Clinical outcomes including VAS and ODI scores did not differ between the two cohorts

Table 8 Pre-op demographics for lumbar fusion with Si_3N_4 versus other allogenic bone or abiotic spacers

Demographic	Si_3N_4			Meta-data			P value
	n	Total	%	n	Total	%	
Gender, female	253	450	56.2	533	910	58.6	0.40
Age, mean ± SD	450	58.2±12.4		999	57.5±10.5		0.27
BMI, mean ± SD	447	30.9±6.1		430	25.8±4.1		<0.01
Smoking, yes	71	450	15.8	116	387	30.0	<0.01

Table 9 Clinical outcomes for lumbar fusion with Si_3N_4 and other allogenic bone and or abiotic spacers

Outcome	This study			Meta-data			P value
	n	Total	%	n	Total	%	
Change in VAS pain scores, mean ± SD	342	36.8±35.4		1,025	37.6±22.5		0.63
Complications and adverse events	44	450	9.8	116	936	12.4	0.16
Secondary surgical interventions (SSI)	14	450	3.1	27	936	2.9	0.84

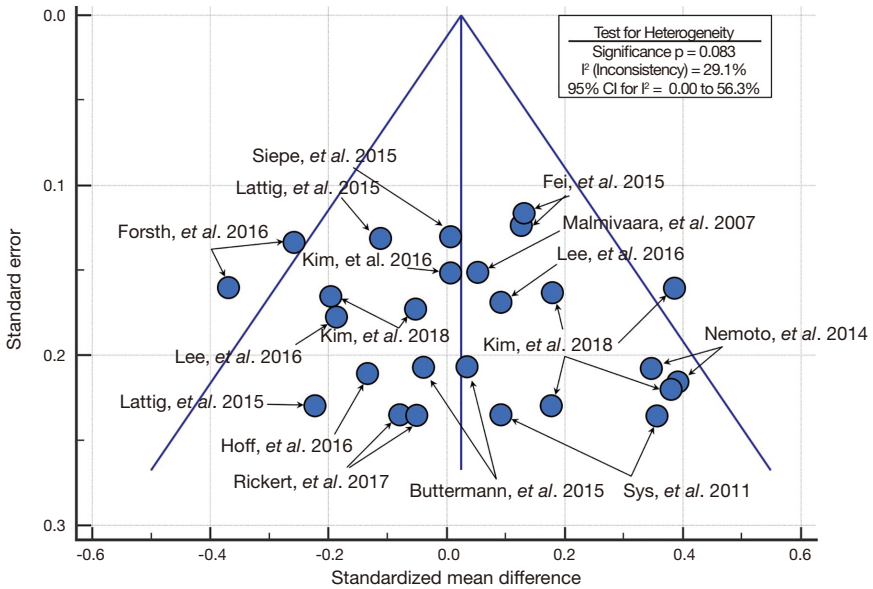

Figure 7 Funnel plot for meta-analysis studies and cohorts.

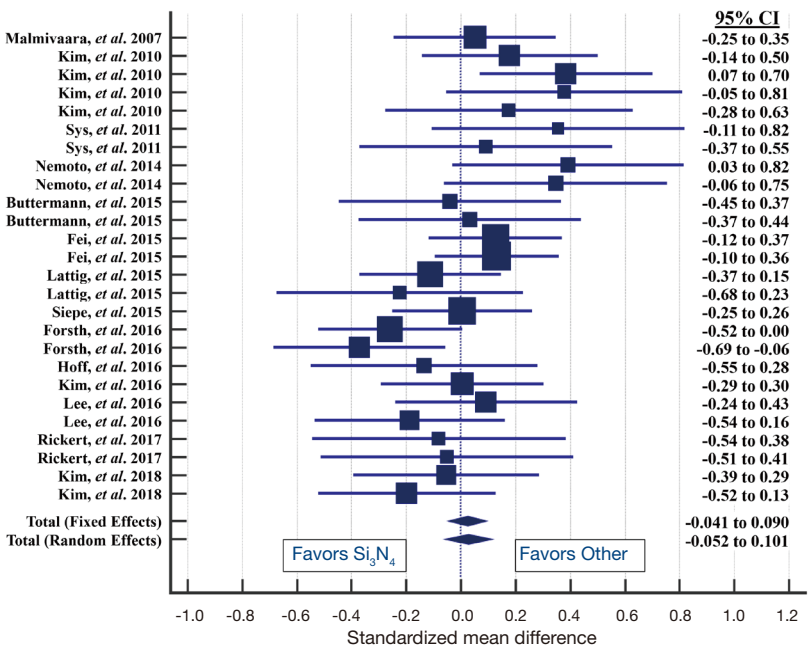

Figure 8 Forest plot comparing changes in VAS pain scores for meta-data and the four surgical centers. VAS, visual analog scale.

Table 10 Complications, adverse events and secondary surgical interventions (SSI)

Author	No. of patients	Complications and adverse events		Secondary surgical interventions (SSI)		Description of complications, adverse events, and SSI
		n	%	n	%	
This study, 2019	450	44	9.8	14	3.1	Recurrent symptoms [23]; adjacent level disease [11]; subsidence [3]; wound infection [3]; migration or non-union [3]; and hematoma [1]. SSIs were for adjacent level disease [11]; persistent pain associated with a pedicle screw [1]; screw removal [1]; and screw reposition [1]
Malmivaara, *et al*. (18), 2007	50	13	26.0	3	6.0	Dural tears [8]; screw malposition [1]; hematoma [1]; misjudged stenotic level [1]; respiratory distress due to pulmonary edema and stress ulcer [1]; secondary decompression [1]. SSIs were for hematoma [1]; misjudged stenotic level [1]; and secondary decompression [1]
Kim, *et al*. (19), 2010	128	4	3.1	0	0.0	Pedicle screw fracture [1]; and sympathetic changes [3]. No SSIs
Sys, *et al*. (20), 2011	38	10	26.3	4	10.5	Dural tear [1]; transient radiculopathy [3]; donor site pain [6]; SSIs were for removal of instrumentation [4]
Nemoto, *et al*. (21), 2014	48	15	31.3	0	0.0	Vertebral osteolysis [15]. No SSIs
Buttermann, *et al*. (22), 2015	50	11	22.0	4	7.7	Pneumonia [3]; nausea and tachycardia [1]; transient meralgia paresthetica [1]; superficial wound infection [1]; septic shoulder [1]; ileus [1]; delirium [1]; seroma [1]; deep venous thrombosis [1]. SSIs were for adjacent level decompression [1]; screw malposition [1]; fusion extension without decompression [1]; and implantation of a spinal cord stimulator [1]. Authors reported that over half the patients had SSI for instrumentation removal, but these data were not included in this analysis
Fei, *et al*. (23), 2015	176	6	3.4	3	1.7	Excessive bleeding and intraoperative death [1]; intraoperative myocardial infarction and death [1]; deep venous thrombosis [1]; motor deficient [1]; and broken screws [2]. SSIs were for motor deficient [1]; and broken screws [2]
Lattig, *et al*. (24), 2015	89	NA	NA	NA	NA	NA
Siepe, *et al*. (25), 2015	71	9	12.7	3	4.2	Radiculopathy [2]; venous laceration [2]; abdominal hernia [1]; adjacent level disc herniation [1]; hematoma [1]; persistent pain [1]; and abdominal wall hernia [1]. SSIs were for radiculopathy [1]; persistent pain [1]; and abdominal wall hernia [1]
Försth, *et al*. (26), 2016	111	32	28.8	1	0.9	Dural tears [12]; wound infections [17]; myocardial infarction, stroke, or thromboembolic events [3]. SSIs were for wound infection [1]
Hoff, *et al*. (27), 2016	24	4	16.7	0	0.0	Dural tears [2]; and prolonged wound secretion [2]. No SSIs
Kim, *et al*. (28), 2016	50	0	0.0	0	0.0	No complications or SSIs
Lee, *et al*. (29), 2016	74	3	4.1	0	0.0	Details of all minor complications were not provided. Osteolysis [1]; screw fracture [1]; hematochezia [1]; No SSIs
Rickert, *et al*. (30), 2017	38	8	21.1	8	21.1	Pseudarthrosis [4]; perforation of the iliac vein [1]; persistent leg pain and neurolysis [1]; hematoma compressing a nerve root [1]; wound infection [1]. All complications required SSIs
Kim, *et al*. (31), 2018	78	1	1.3	1	1.3	Screw malposition [1]. SSI was for screw malposition [1]

NA, data on complications, adverse events and SSI were not provided in the article.

problems. Patients from the metadata group had similar complications and SSIs.

Discussion

Clinical effectiveness of Si_3N_4

Although Si_3N_4 has only recently emerged in the past decade as an effective bioceramic, it is well-known for its capabilities as an industrial material (38). Initially, its strength and toughness made it desirable as a structural biomaterial (39), but its enhanced osteoconductivity (40-42), bacteriostasis (43-46), improved radiolucency (47,48), lack of subsidence in the cervical spine (49), and wear resistance (50,51) are more relevant properties for spinal fusion and arthroplasty. In preclinical studies, Si_3N_4's unique surface chemistry, topography, and hydrophilicity upregulate osteogenic activity to achieve faster spinal fusion, while simultaneously preventing bacterial adhesion and biofilm formation (52-57). As an orthopaedic articulation material, Si_3N_4 exhibits antioxidative characteristics which protect and potentially lengthen the service life of polyethylene liners (58). In contrast to oxide-based bioceramics which are purported to be bioinert and used solely for structural purposes (59), Si_3N_4 combines both bioactivity and structural stability in one material (60).

Although a number of recent clinical publications have reported on the performance of Si_3N_4 in cervical fusion (61-63), there are few contemporary reports on lumbar outcomes. Yet, Si_3N_4 uniquely has the longest clinical history as a spinal arthrodesis material. It was first used in a 30-patient lumbar spinal fusion study that was initiated in the mid-1980s (10). A 30+ years, follow-up of the remaining patients from this study was recently published (11). It showed that VAS pain scores and fusion effectiveness were similar to outcomes from the present study. Initial reductions of up to 47 points in VAS pain were seen during the first 5 years post-operatively with lower reductions after about 10 years (i.e., 35 points). Complication rates were slightly higher (n=11, 36.7%, P<0.01), but this is not unexpected given the design of these early devices. More recent case reports by Youssef (48) and Rambo (64) have demonstrated that Si_3N_4 was also effective in achieving solid lumbar fusion at 1-year follow-up in two patients, and it aided in the remediation of two other patients who had septic lumbar discitis, respectively. There is also an ongoing prospective randomized controlled lumbar fusion study comparing Si_3N_4 to PEEK devices that is expected to be published in the near future (65).

Minimum clinical important differences in pain scores

The present study is the largest multicenter evaluation of the safety and efficacy of Si_3N_4 for lumbar fusion to date. It demonstrates that Si_3N_4 cages implanted using various surgical approaches by different surgeons are as effective as other lumbar fusion implants and procedures from the compiled metadata of 1,025 patients in 26 cohorts and 14 published studies. The average reduction in VAS pain scores (ΔVAS) with the Si_3N_4 cages was 36.8±35.4 points compared to the average for the metadata of 37.6±22.5 points (P=0.63). The results from the present study also compare favorably with similar data from a recent systematic review of lumbar fusion by Phillips *et al.* (14). They reported that ΔVAS back pain scores for 3,060 patients compiled from 26 studies were 36.8±14.7 points (P=1.00 when compared to Si_3N_4 patients of this study, or P=0.19 when compared to the metadata of this study). This large compilation provides further evidence that clinical outcomes using Si_3N_4 cages are equivalent to other commonly used spacers or cages.

A number of studies or critical reviews have also attempted to quantify the minimum clinically important difference (MCID) for reductions in VAS back and leg pain for patients undergoing lumbar spine fusion (66-72). MCID represents "smallest change reported by patients that correlates with the patient stating that he or she is moderately better" (73), but the assessment methodology remains open to debate because there exists a considerable range in MCID values (0 to 100-point scale). As examples, Copay *et al.* suggested that a change of greater than 12 points for back pain and 16-points for leg pain were appropriate MCIDs for data retrospectively extracted from 454 lumbar fusion cases using a variety of surgical approaches (67). Hägg *et al.* recommended an 18–19-point reduction as the MCID for back pain based on the clinical evaluation of 289 lumbar cases performed using four different non-operative and surgical procedures including conservative management, instrumented and non-instrumented posterior lateral fusion (PLF), and instrumented PLIF (66). Parker proposed that the MCID values be set at 21 points for back pain and 28 points for leg pain based on 45 TLIF cases (69). Carragee *et al.* selected a 30-point decrease in pain intensity as the MCID regardless of its origin for 165 consecutive lumbar patients diagnosed with either isthmic spondylolisthesis or degenerative disc disease (68). The MCID values recommended by Solberg for 894 patients

diagnosed with herniated discs were 25 for back pain and 35 for leg-pain (71). Finally, Zannikos reviewed these and other prior studies and concluded that agreeing on specific MCID values remains an important measure but requires further study and quantification (72). However, of note, the mean change in VAS scores for the Si_3N_4 patients of the present study exceeded all of the above cited or recommended MCID values. The effectiveness of the Si_3N_4 implants from this study can also be determined by the proportion of patients exceeding preset MCID targets. Based on the review given above, MCIDs of either 10-, 20-, 30-, or even 40-point result in 77.5%, 71.6%, 59.7%, and 51.8%, of the Si_3N_4 patients with successful outcomes, respectively. Clearly, a majority of the patients in the present study had noticable clinical improvements which were on par with the other large cohort studies cited previously.

Limitations

The retrospective design of the present study is a limitation. While data were compiled from the medical charts of patients by an independent examiner using a prescribed protocol, the original recording of this information was performed by the respective medical staffs of four surgical centers without a common procedure. Consequently, the use of a consistent set of clinical evaluation methods was lacking, including standards for reporting and recording VAS pain scores. Furthermore, differentiation between back, leg, and bodily pain was not monitored. However, mitigating this limitation is the fact that numerical pain rating scales of zero to 10 (or zero to 100) are easy to administer and evaluate. An additional limitation is the lack of consistent follow-up periods between the four centers. The study was also limited by a lack of contemporaneous controls. No data were acquired on any other cage materials at the four clinical sites. Only the compiled metadata and cited systematic and other reviews in the discussion section were used as comparative controls. Lastly, although the data were acquired by an unbiased medical records contractor, subsequent analyses were done by the study authors who are users of Si_3N_4 spinal spacers. Nonetheless, the statistical analyses and comparison to previously-published metadata and reviews fairly represent expected outcomes by other practitioners and surgical centers.

Conclusions

This study reports on the multicenter clinical outcomes of 450 patients who were implanted with Si_3N_4 intervertebral spacers/cages using various lumbar spinal fusion procedures. Patient follow-up averaged 11.4±9.8 months. Pre-op demographics, comorbidities, and VAS pain scores were compiled along with last follow-up pain scores, complications, adverse events, and SSIs. As a control group, comparative metadata were collected from 26 publications comprising 14 cohorts and 1,025 patients. The results demonstrated that implanted Si_3N_4 devices were safe and provided equivalent pain reduction outcomes to other commonly used spacers or cages implanted under differing surgical approaches. Although the four centers in this study were heterogeneous in pre-op patient demographics, comorbidities, and pre- and post-op clinical outcomes, the compiled ordinal and nominal data for the Si_3N_4 patients were statistically equivalent to the selected metadata. Also, the ΔVAS outcomes from this study were also equivalent to the results from a recent comprehensive systematic review. Lastly, a comparative MCID pain analyses demonstrated that Si_3N_4 cages were as effective in achieving the same level pain reduction as other lumbar arthrodesis devices or procedures.

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Footnote

Conflicts of Interest: Drs. GC Calvert, G VanBuren Huffmon III, WM Rambo Jr, and MW Smith were consulting surgeons to Amedica Corporation during the course of this study. Dr. BJ McEntire and Dr. BS Bal were principals and employees of Amedica Corporation (now SINTX Technologies).

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Due to the retrospective nature of the study, informed consent by the respective IRBs of each surgical center was not required. However, none of the patients' personal data was disclosed, and their records remain fully secured and in compliance with IRB standards.

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