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## Original Research and Review of Literature

# An inception cohort study of patients in a military clinic treated for lower back pain with lumbar fusion and SIGNAFUSE® with a systematic review of the literature

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## ABSTRACT

**Background:** Use of synthetic bone graft substitutes for spinal fusion has increased sharply over the past 20 years. SIGNAFUSE® is one such synthetic graft material that provides an osteostimulatory effect for spinal fusion. Because clinical trials are not required for commercialization of synthetic bone graft substitutes in the United States, fusion rates attained using SIGNAFUSE for lumbar fusion are not well documented. The goal of the current study is to determine the rate of spinal fusion in a military clinic following lumbar fusion surgery augmented with SIGNAFUSE.

**Methods:** We report a retrospective chart review of 8 patients who received lumbar spinal fusion surgery augmented with SIGNAFUSE. All patients were assessed by computed tomographic (CT) imaging at least 1-year post-surgery to determine whether bony fusion had occurred. We also systematically reviewed literature sources that report fusion rate following spinal fusion surgery, for broader context.

**Results:** An average of 1.6 spinal levels were treated with SIGNAFUSE-loaded interbody cages. All patients had stabilization hardware via pedicle screws or integrated cage fixation. Seven of 8 patients successfully fused, for an overall fusion rate of 87.5% (95% confidence interval: 47.4% to 99.7%). Systematic review of 26 recent publications that included 1,126 patients treated with synthetic bone graft showed that the overall fusion rate in the literature is 84.4%.

**Conclusions:** Fusion was achieved in 87.5% of patients treated with SIGNAFUSE. This is comparable to the fusion rate in a systematic review of 1,126 patients treated with synthetic bone graft materials.

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## Introduction

About two-thirds of adults have lower back pain (LBP) at some point during their lifetime [1]. LBP may be even more prevalent in a military population, due to acute trauma in combat and stress injuries in training [2]. LBP caused more than 457,000 Americans to seek spinal fusion in 2011, with ~75% of fusion procedures for spondylolisthesis, spondylosis, or other painful disk disorders [3, 4].

Lumbar fusion surgery is done to achieve solid fusion, restore spinal stability, and enable return to normal activities. Spinal fusion procedures use various biologic materials to promote new bone growth, with iliac crest bone graft (ICBG) considered the “gold standard” of treatment, because of its osteoconductivity, osteoinductivity, osteogenicity, and angiogenic potential [5, 6]. Though ICBG is widely used, problems such as donor site morbidity, limited supply of graft material, potential increase in surgical complication rates, and the increase in surgical times

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argue against use of ICBG [5, 7]. Thus, there has been an effort to develop other bone grafting options that include allograft bone (e.g., demineralized bone matrices, allograft chips), synthetic graft materials (e.g. hydroxyapatite or HA),  $\beta$ -tricalcium phosphate ( $\beta$ -TCP), bioactive glass, collagen-based matrix, or recombinant growth factors (e.g., rhBMP-2). Synthetic graft materials provide the osteoconductive element that ICBG provides but may lack the osteoinductive and osteogenic components of ICBG [6]. To circumvent these limitations, some synthetic grafts incorporate bioactive glass to provide an osteostimulatory signal and many surgeons combine synthetics with bone marrow aspirate (BMA), to provide an osteogenic component. Synthetic graft materials are attractive because of the low risk of disease transmission, minimal immunogenicity, and superior intra-operative handling capabilities [6]. Additionally, synthetics avoid the potential adverse events reported in some patients following use of rhBMP-2, including retrograde ejaculation, ectopic bone formation, and dysphagia [8, 9].

Here we report an inception cohort study of 8 patients treated in a military clinic who underwent lumbar fusion procedures to alleviate symptoms of degenerative disk disease and other spinal disorders. All patients were treated with SIGNAFUSE® Bioactive Bone Graft (Bioventus, Durham, NC), a combination synthetic graft composed of hydroxyapatite with  $\beta$ -tricalcium phosphate (HA/ $\beta$ -TCP) and bioactive glass in a resorbable polymer carrier, and all patients were evaluated for fusion by computed tomographic (CT) imaging. We also present a systematic review of publications reporting synthetic bone graft use in lumbar fusion surgery, as a point of comparison for our observed fusion results with SIGNAFUSE.

## Patients and Methods

A planned retrospective chart review was combined with prospective computed tomographic (CT) imaging at follow-up, to evaluate the primary endpoint of radiographic fusion rate in patients treated with SIGNAFUSE at William Beaumont Army Medical Center (WBAMC) in El Paso, TX. The study received full Institutional Review Board (IRB) approval in October 2016. Potentially eligible patients were contacted after surgery by research staff to assess their interest in participating in the study. Patients were eligible for inclusion in this study if they:

- Were age 18 years of age or older;
- Were active duty military;
- Were a Department of Defense beneficiary;
- Had undergone a 1-3 level lumbar spinal fusion for a degenerative spinal process at WBAMC between August 2012 and January 2016;
- Voluntarily signed the IRB-approved informed consent document.

Patients were excluded from study if they:

- Were pregnant;
- Underwent lumbar spinal fusion surgery at 4 or more levels;
- Were diagnosed with concurrent tumor;
- Were indicated for surgery due to trauma;
- No longer resided in the WBAMC area.

Patients interested in the study were invited for an on-site visit with a follow-up CT scan at WBAMC. A total of 19 patients were consented for study participation; 8 patients met inclusion criteria and completed a follow-up CT scan. Fusion status of the patient was assessed using CT scans and the patients were considered fused if there was evidence of bilateral continuous trabecular bone across the fusion bed.

A systematic review was also performed to compare the observed healing outcomes to healing outcomes from a range of different spinal

fusion techniques that used many different commercially available synthetic bone graft substitutes. Sources were identified by several PubMed searches, augmented with sources drawn from a recent systematic review [10]. We sought to identify lumbar fusion procedures that used a range of commercially available synthetic bone grafts. Specific inclusion criteria were that studies:

- Were identified using the search phrase “lumbar spinal fusion” or “lumbar spine fusion”;
- Had been published within the last 20 years;
- Were randomized controlled trials (RCTs), prospective cohorts, or retrospective cohorts;
- Reported sufficient data to calculate fusion rate following fusion surgery;
- Used synthetic bone graft materials, bone grafts augmented with autograft, or bone marrow aspirate during the procedure;
- Assessed bony fusion by X-ray or CT;
- Were published in a peer-reviewed journal.



**Figure 1:** CT image for Patient #3, acquired 1.8 years after surgery. Patient #3 was a 34-year old male with a long history of lower back pain, beginning after an injury while on active-duty military service. His pain was midline in the lower back, with bilateral lower leg numbness and pain on the posterior aspect of both legs, with subjective muscle weakness. The patient was diagnosed with L5/S1 degenerative disc disease with herniation. The patient attempted conservative management, including physical therapy, pain medications, traction, and bracing, without relief, so he underwent an ALIF at L5/S1 without complication. Three months later, X-rays demonstrated L5/S1 incorporation of the graft into the endplates with bony fusion.



**Figure 2:** CT image for Patient #12, acquired 1.6 years after surgery. Patient #12 was a 25-year old male with bilateral leg pain and lower back pain of 2 years duration. Onset of pain was insidious, with no overt injury. Dorsal leg pain projected to the toes, with numbness and tingling, and patient had positional relief when leaning forward, but most other activities increased pain. Patient was diagnosed with L5/S1 spondylolisthesis with radiculopathy. The patient underwent an ALIF at L5/S1 without complication and CT scan demonstrated L5/S1 fusion of 40% of the disc at 20 months.

Exclusion criteria (for the whole study or for a particular study arm) were that:

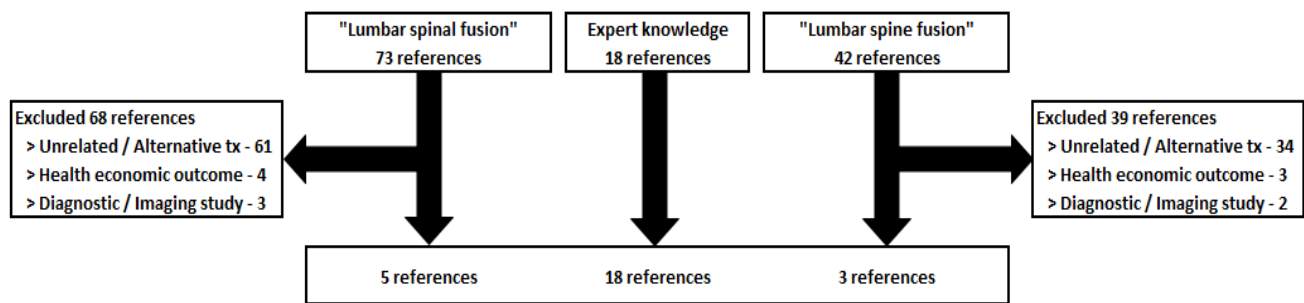
- Patient follow-up was less than 12 months;
- Surgery involved the cervical spine;
- Bone graft materials were augmented with rhBMP;
- Fusion was reported by level, not by patient;
- Radiographic assessment of fusion was not reported;
- Publication was as an abstract, conference proceeding, or editorial.

## Results

Average patient age was 41.6 years (standard deviation (SD) =  $\pm 10.6$ ) at surgery and 2 patients had prior surgery (Table 1). Diagnoses within the cohort included 6 patients with spondylosis and 2 with spondylolisthesis. In 5 patients, SIGNAFUSE was used in combination with bioglass granules and in 1 patient SIGNAFUSE was used in combination with cancellous allograft bone. Four patients received anterior lumbar interbody fusion (ALIF), 3 received transforaminal lumbar interbody fusion (TLIF), and 1 received oblique lumbar interbody fusion (OLIF) fusion surgery. An average of 1.6 spinal levels

were fused (range: 1 to 3 levels). All patients received stabilization hardware via pedicle screw instrumentation or integrated fixation built into the ALIF cages (Table 2). Average duration of surgery was 181 minutes (SD =  $\pm 94$  minutes), and operative blood loss was 164 mL ( $\pm 260$  mL SD). The average hospital stay after surgery was 2.1 days, with the longest stay being 3 days. Seven of 8 patients had successful fusion, as determined by CT, for an overall fusion rate of 87.5% (95% confidence interval: 47.4% to 99.7%) (Table 2). All 2- and 3-level fusion procedures showed evidence of radiographic fusion by CT scan within 2 years post-surgery, while 3 out of 4 patients with 1-level fusion procedures showed evidence of radiographic fusion. Figures 1 and 2 show representative CT scans of successfully fused patients.

A total of 26 published studies were identified for the systematic review (11-36). The process by which these studies were identified is shown (Figure 3). Included studies were predominantly posterolateral fusions (PLF) with instrumentation and used ceramic bone grafts augmented with autograft or bone marrow aspirate. Analysis of these published studies shows that the overall weighted average fusion rate is 84.4% in 1,126 patients (Table 3). Thus, fusion results from SIGNAFUSE-treated patients (Table 2) are comparable to fusion results in the systematic review (Table 3).



**Figure 3:** PRISMA diagram, showing how the sample of 26 studies reported in Table 3 was assembled.

**Table 1:** Patient demographics at surgery. DDD = Degenerative disk disease; Spond = Spondylolisthesis; LBP = Lower back pain.

Gender	Patient age	Pre-operative diagnosis	Pre-operative symptoms	Prior surgery
Male	42	L3/L4, L4/L5 DDD	LBP, anterolateral right thigh pain, left thigh pain	None
Male	33	L5/S1 DDD, herniation	LBP for 13 years, bilateral lower leg numbness, muscle weakness	None
Male	41	L4/L5 DDD, L5/S1 Spond	LBP for 2 years, right leg numbness, right leg tingling, right leg pain	None
Male	25	L5/S1 Spond, radiculopathy	LBP for > 2 years, bilateral leg pain, bilateral leg numbness, bilateral leg tingling	None
Male	55	L4/L5, L5/S1 DDD	LBP for 30 years, right foot numbness, right lower leg numbness	None
Male	42	L4/L5 DDD, herniated disc	LBP for 5 years, bilateral lower extremity pain	None
Female	38	L5/S1 Synostosis	LBP for > 5 years, L5/S1 synchondrosis, right leg pain, right foot pain	L4/L5 ALIF
Male	57	L3/L4, L4/L5, L5/S1 DDD	Back pain for > 1 year, right lower extremity tingling for > 1 year	L4/L5 microdiscectomy

**Table 2:** Operative characteristics and outcomes. INTERFACE = synthetic granules (45S5 bioglass) ALIF = anterior lumbar interbody fusion; TLIF = transforaminal lumbar interbody fusion; OLIF = oblique lumbar interbody fusion.

Fusion levels	Surgical Technique	SIGNAFUSE graft used	Other graft used	Spinal levels fused	Operative time (min)	Operative blood loss (mL)	Hospital stay (days)	Outcome
L3/L4, L4/L5	ALIF	15 g	INTERFACE 1 g	2	160	100	3	Fused
L5/S1	ALIF	15 g	INTERFACE 1 g	1	105	50	2	Fused
L4/5, L5/S1	ALIF	15 g	INTERFACE 1 g	2	273	75	3	Fused
L5/S1	ALIF	15 g	INTERFACE 1 g	1	104	20	2	Fused
L4/L5, L5/S1	TLIF	7.5 g	Cancellous chips 30 cc	2	232	50	2	Fused
L4/L5	TLIF	15 g	None	1	83	NA	1	Not Fused
L5/S1	TLIF	15 g	None	1	143	100	2	Fused
L3/4, L4/5, L5/S1	OLIF	30 g	INTERFACE 1 g	3	347	750	2	Fused
Average				1.6	180.9	163.6	2.1	87.5% fused
SD				0.7	94.0	260.2	0.6	35.4%

## Discussion

Our results show that a fusion rate of 87.5% can be attained in a clinical setting with a range of different lumbar fusion approaches combined with SIGNAFUSE (Table 2). The fusion rates obtained with SIGNAFUSE are thus comparable to fusion rates reported with a range of other synthetic bone grafts (Table 3). The overall weighted average of fusion in the 26 publications was 84.4% (943 of 1,126 patients fused), while the fusion success of our SIGNAFUSE-treated patients was 87.5% (7 of 8 patients fused). Sub-analysis of the systematic review by graft type (HA,  $\beta$ -TCP, or HA/ $\beta$ -TCP) showed that fusion rates did not differ appreciably, with respective average fusion rates of 80%, 86%, and 88% (Table 3).

This study has several limitations. First, the number of patients in our series is small, and patients were treated with several different surgical techniques, while most published studies were PLF procedures. Second, varying amounts of SIGNAFUSE graft material were used (range: 7.5 - 30 g) in our series (Table 2). Third, the systematic review reports a range of different synthetic graft materials which may not all be comparable to one another, but the sample size of the individual graft materials is too

small to analyze separately. Fourth, even within the cohort of patients who received SIGNAFUSE, some patients had SIGNAFUSE augmented with bioactive glass, some patients had SIGNAFUSE augmented with cancellous chips, and some patients did not have any supplemental grafting materials. Fifth, the volume and relative ratio of other materials (BMA, autograft, etc.) mixed with graft materials varied, so it is not possible to attribute fusion success to any specific synthetic materials. For example, one study used HA and  $\beta$ -TCP without other supplemental grafting materials, while all other studies in the systematic review used BMA or autograft to augment the synthetic materials [33]. Finally, few controlled trials using synthetic bone graft materials have been conducted overall, so there is a compelling need for additional research.

## Conclusions

Lumbar fusion surgery has increased in the recent past and is expected to continue to increase as the population ages [4]. Stable fusion is the goal of surgery, so there is a strong impetus to identify which types of bone grafting materials or bone graft substitutes are most effective in attaining fusion. The use of a synthetic graft such as SIGNAFUSE, alone or in combination with other grafting materials, may provide an advantage in spinal fusion surgery.

**Table 3:** Systematic review of previously published studies utilizing synthetic bone grafts in lumbar fusion approaches

HA = hydroxyapatite;  $\beta$ -TCP = beta-tricalcium phosphate; A = autograft; BMA = bone marrow aspirate;  $\beta$ -TCS = beta-tricalcium sulfate; C = collagen; DBM = demineralized bone matrix; Si-CaP = silicate substituted calcium phosphate.

First Author	Year	Ref #	Design	Approach	Graft	FU (mos)	Patients	Fused	Fusion rate (%)
Cavagna	1999	11	Prosp.	PLF	HA + $\beta$ -TCP + A + BMA	24	106	100	94
Chen	2005	12	Retro.	PLF	$\beta$ -TCS + A	30	39	34	87
	2005	12	Retro.	PLF	$\beta$ -TCS (S) + A	30	35	29	83
Hsu	2005	13	Prosp.	PLF	HA + A	12	38	25	66
Korovessis	2005	14	RCT	PLF	HA + A + BMA	12	38	38	100
Kanayama	2006	15	RCT	PLF	HA + $\beta$ -TCP + A	12	10	9	90
Kitchel	2006	16	Prosp.	PLF + PLIF	HA + C + BMA	24	25	20	80
Neen	2006	17	Prosp.	PLF	HA + C + BMA	24	15	14	93
	2006	17	Prosp.	PLIF	HA + C + BMA	24	13	11	85
	2006	17	Prosp.	ALIF	HA + C + BMA	24	22	17	77
Moro-Barrero	2007	18	Prosp.	PLF	HA + $\beta$ -TCP + A	30	35	31	89
Chang	2008	19	Retro.	PLF	$\beta$ -TCS + A	12	66	61	92
Dai	2008	20	RCT	PLF	$\beta$ -TCP + A	12	32	32	100
Epstein	2008	21	Prosp.	PLF	$\beta$ -TCP + A + BMA	24	60	51	85
Epstein	2009	22	Prosp.	PLF	$\beta$ -TCP + A + BMA	12	100	95	95

First Author	Year	Ref #	Design	Approach	Graft	FU (mos)	Patients	Fused	Fusion rate (%)
Niu	2009	23	Prosp.	PLF	β-TCS + BMA	24	22	10	45
Jenis	2010	24	Retro.	PLF	HA + BMA	24	42	34	81
Ploumis	2010	25	RCT	PLF	HA + C + BMA + A	24	12	11	92
Park	2011	26	Retro.	PLF	β-TCP + A	12	30	25	83
Yamada	2012	27	Prosp.	PLF	β-TCP + A + BMA	24	61	57	93
Kong	2013	28	Prosp.	PLF	β-TCP + A	12	42	24	57
Kunakornsawat	2013	29	Retro.	PLF	HA + C + BMA	24	27	8	30
Pimenta	2013	30	RCT	XLIF	Si-CaP	12	13	7	54
Yoo	2015	31	Retro.	TLIF	HA + A	24	77	67	87
Nam	2016	32	Prosp.	PLF	HA + A	12	41	30	73
Parker	2016	33	Prosp.	XLIF	HA + β-TCP	24	25	20	80
Epstein	2017	34	Prosp.	PLF	HA + C + A + BMA	37	59	57	97
Gatam	2017	35	Prosp.	TLIF	HA + DBM	12	17	13	76
vonderHoeh	2017	36	RCT	TLIF	HA + A	12	24	20	83
Average =						20.1	1126	950	84.4

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