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Comparative Efficacy and Safety of Osteobiologics in Posterior Lumbar Fusion: A Network Meta-Analysis of Randomized Controlled Trials

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Abstract

Study Design: Network Meta-Analysis.

Objective: To compare the efficacy and safety of osteobiologics used in posterior lumbar spinal fusion (LSF) for degenerative lumbar disorders, setting autologous iliac crest bone graft (AICBG) as the reference standard.

Methods: A systematic search of randomized controlled trials (RCTs) evaluating osteobiologics in adult patients undergoing posterior LSF was performed. Primary outcomes were radiologic fusion and osteobiologic-related complications. Secondary outcomes included disability, low back pain, operative time, blood loss, and length of stay (LOS). A frequentist random-effects network meta-analysis (NMA) was performed. Meta-regression was employed to assess the influence of surgical technique on primary outcomes. Risk of bias was evaluated using the Cochrane RoB-2 tool, and certainty of evidence was assessed with the GRADE framework.

Results: Thirty-five RCTs including 2298 patients were analyzed. Compared with AICBG, recombinant human bone morphogenetic protein-2 (rhBMP-2) showed significantly higher fusion rates (OR 3.86; 95% CI 2.60-5.74; $P < 0.0001$) and lower complication risk (OR 0.50; 95% CI 0.34-0.73; $P = 0.0004$). Disability and pain outcomes were comparable across treatments. rhBMP-2 (MD −21.8 minutes; 95% CI −28.0 to −15.7; $P < 0.0001$), autologous local bone (MD −12.0 minutes; 95% CI −21.5 to −2.5; $P = 0.0133$), and ABM/P-15 (MD −17.0 minutes; 95% CI −32.6 to −1.5; $P = 0.0322$) were associated with shorter operative time. Only rhBMP-2 significantly decreased blood loss (MD −72.6 mL; 95% CI −118.9 to −26.4; $P = 0.002$), while no treatment reduced LOS.

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Conclusions: Among evaluated osteobiologics, rhBMP-2 demonstrated superior efficacy and safety compared to AICBG in posterior LSF. Other agents showed favourable trends without statistical significance, reflecting persistent uncertainty rather than confirmed equivalence.

Keywords
lumbar spinal fusion, osteobiologics, bone graft, BMP-2, network meta-analysis, degenerative lumbar disease

Introduction

Lumbar spinal fusion (LSF) is widely performed for degenerative lumbar disorders refractory to conservative treatment. Achieving solid arthrodesis remains a critical determinant of surgical success, as pseudoarthrosis has been associated with persistent pain, mechanical failure, and increased revision rates.[1,2] Optimisation of the biological fusion environment remains central to improving outcomes following LSF. Autologous iliac crest bone graft (AICBG) has long been regarded as the reference standard for LSF owing to its osteogenic, osteoinductive, and osteoconductive properties. However, iliac crest harvesting is associated with well-documented morbidity, including donor-site pain, infection, hematoma, neurovascular injury, and increased operative time and blood loss.[3,4] These drawbacks have driven the development of alternative osteobiologics aimed at maintaining fusion efficacy while minimising donor-site complications.

Over the past decades, a wide range of osteobiologic strategies have been evaluated in randomized controlled trials (RCTs), including recombinant human bone morphogenetic proteins (rhBMP)-2 and −7, demineralised bone matrix (DBM), other biomaterials, platelet-derived products, and cell-based grafts.[5-8] Among these, rhBMP-2 has consistently demonstrated high fusion rates in posterior LSF; however, concerns regarding safety, costs, and appropriate clinical use have led to ongoing debate.[9-12] Previous systematic reviews and pairwise meta-analyses have synthesised portions of this literature but are limited by restricted comparisons, heterogeneous surgical techniques, and inability to simultaneously evaluate multiple competing osteobiologics.[6,7,13] Network meta-analysis (NMA) offers a methodological advantage by integrating direct and indirect evidence within a single analytical framework, allowing comparative ranking of multiple interventions.[14] Using this approach, our recent NMA[15] identified rhBMP-2 as the osteobiologic with the most consistent evidence for improved fusion and safety compared with AICBG, while other osteobiologics failed to reach statistical significance. Nevertheless, osteobiologics for LSF were evaluated in a pooled manner, combining anterior, lateral, and posterior surgical techniques. While this strategy allowed broad comparison, it might obscure approach-specific differences in biological requirements and risk profiles. Anterior LSF techniques primarily rely on interbody support and indirect decompression, and are associated with approach-specific considerations and distinct complication profiles.[16] In contrast, posterior LSF is the most commonly performed approach and depends largely on graft placement within interbody devices and posterolateral gutters, instrumentation, and local osteoinductive processes to achieve arthrodesis, often in the setting of direct neural decompression. Moreover, the biomechanical and biochemical environments of fusion differ substantially between approaches, including variations in load sharing, graft vascularization, and local biological processes.[16]

In light of these differences, we performed a focused, approach-restricted sub-analysis of our previously published NMA.[15] Accordingly, the present study represents an updated sub-analysis of RCTs evaluating osteobiologics used specifically in posterior LSF for degenerative lumbar conditions. Using AICBG as the reference comparator, we aimed to compare fusion efficacy and complication profiles, assess secondary clinical and perioperative outcomes, and evaluate the consistency of these findings relative to our previously published NMA pooled analysis.

Materials and Methods

This study represents an approach-restricted sub-analysis of our previously published NMA,[15] using the same methodological framework and eligibility criteria. The systematic literature search was updated, and all newly identified and previously included studies were rescreened to retain only RCTs evaluating osteobiologics in posterior LSF. The systematic review was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines[17] and the Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions.[18] The review protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the ID CRD 420251163972.

Electronic Literature Search

The updated systematic search was conducted on October 3, 2025, across PubMed/MEDLINE, Scopus, EMBASE, and Web of Science to identify studies published from database inception through October 2025. Following the PICOS framework, eligible studies included adult patients (≥18 years) with lumbar degenerative disorders (P) who underwent single- or multilevel LSF (between L1 and S1) using osteobiologic

augmentation via a posterior approach (I), compared with the same procedure employing a different osteobiologic (C), with studies reporting at least radiographic fusion outcomes and complication rates (O). Detailed inclusion and exclusion criteria are provided in the Supplemental Materials.

Study Selection

Article screening was conducted using the Rayyan platform. Duplicate records were automatically identified by the software and manually verified by the first author to confirm their inclusion or exclusion during the initial screening phase. Subsequently, three reviewers (LA, SM, and JS) independently assessed the titles and abstracts of all retrieved studies based on the predefined eligibility criteria. Studies recommended for inclusion by at least two reviewers advanced to the full-text screening stage. Any discrepancies among reviewers were resolved through discussion until unanimous agreement was achieved. The overall screening process is illustrated in a PRISMA flow diagram.

Data Extraction

Extracted general study characteristics included author names, year of publication, country, funding sources, study design, sample size, mean patient age, sex distribution, body mass index, smoking status, follow-up duration, loss to follow-up rate, and underlying diagnoses. Surgery-related data comprised the type of fusion procedure, details of spinal instrumentation and interbody devices (if applicable), and the osteobiologic materials used, including their volume, concentration, dosage, application, and anatomical site of use. Additional data collected included the number of fused levels and the use of postoperative lumbar orthoses (if reported).

Definitions and assessment methods of fusion, along with corresponding fusion rates, were also recorded. For quantitative synthesis, fusion rates at the latest follow-up were included only when at least 10 fusion events per group were reported. A summary of radiologic fusion definitions across studies is provided in Supplemental Table 1. Perioperative variables extracted included complication rates, intraoperative blood loss, operation time, and length of stay (LOS). Patient-reported outcome measures (PROMs) of disability (assessed via the Oswestry Disability Index [ODI]), and LBP intensity (measured using a numeric rating scale [NRS] or visual analogue scale [VAS]) were also collected. When results were presented solely in graphical form, numerical values were approximated using WebPlotDigitizer (v4.7; https://automeris.io/WebPlotDigitizer, A. Rohatgi).

Risk of Bias and Certainty of the Evidence

The methodological quality of the included studies was evaluated using the Cochrane Risk of Bias 2 (RoB-2) tool.[19] To minimize subjectivity, three reviewers (LA, SM, and JS) independently performed the risk of bias assessment. Any discrepancies were resolved through discussion until a consensus was reached. The "Robvis" visualization tool was used to generate traffic light plots in accordance with Cochrane guidelines. The overall certainty of the evidence for the primary outcomes was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.[14]

Statistical Analysis

The NMA was conducted following the methodology described in our previous work.[15] Odds ratios (ORs) were calculated for dichotomous outcomes, and mean differences (MDs) were used for continuous outcomes, each presented with corresponding 95% confidence intervals (CIs). When studies reported multiple follow-up time points, only data from the latest available assessment were included in the analysis. In studies comparing treatment groups that shared a common osteobiologic component (eg, AICBG + rhBMP-2 vs. AICBG + allograft), the shared component was excluded to enable a direct comparison between the remaining agents (eg, rhBMP-2 vs. allograft). Data were structured in a contrast-based format for pairwise comparisons, and the NMA was performed using a frequentist random-effects model to account for the anticipated methodological and clinical heterogeneity across studies. AICBG, considered the gold standard for LSF, served as the reference comparator. Network plots were generated for each primary outcome to visualize network geometry, while forest plots illustrated effect estimates of each osteobiologic relative to AICBG. Direct head-to-head comparisons among osteobiologics were summarized in a league table. Treatments were ranked for each primary outcome using the surface under the cumulative ranking curve (SUCRA). Heterogeneity and inconsistency were evaluated using Cochran's Q statistic and the back-calculation method to differentiate direct from indirect evidence. To investigate whether the surgical technique influenced the primary outcomes and to justify the pooling of different approaches, a network meta-regression analysis was performed. The surgical technique was included as a categorical study-level covariate (moderator) with three levels: instrumented posterolateral fusion (PLF), uninstrumented PLF, and posterior lateral interbody fusion (PLIF)/transforaminal lumbar interbody fusion (TLIF). We used the Q_M statistic (Omnibus Test of Moderators) to assess the significance of the technique as a predictor of treatment effect. Publication bias was assessed using the Egger's test for outcomes analyzed in at least 10 studies, with results displayed in funnel plots. The influence of individual studies on network precision was evaluated by estimating the reduction in precision upon their exclusion, visualized in heatmaps. All statistical analyses were performed using the *netmeta* and *metafor* packages in RStudio (v. 2025.09.1 + 401, Posit Software, Boston, MA, USA).

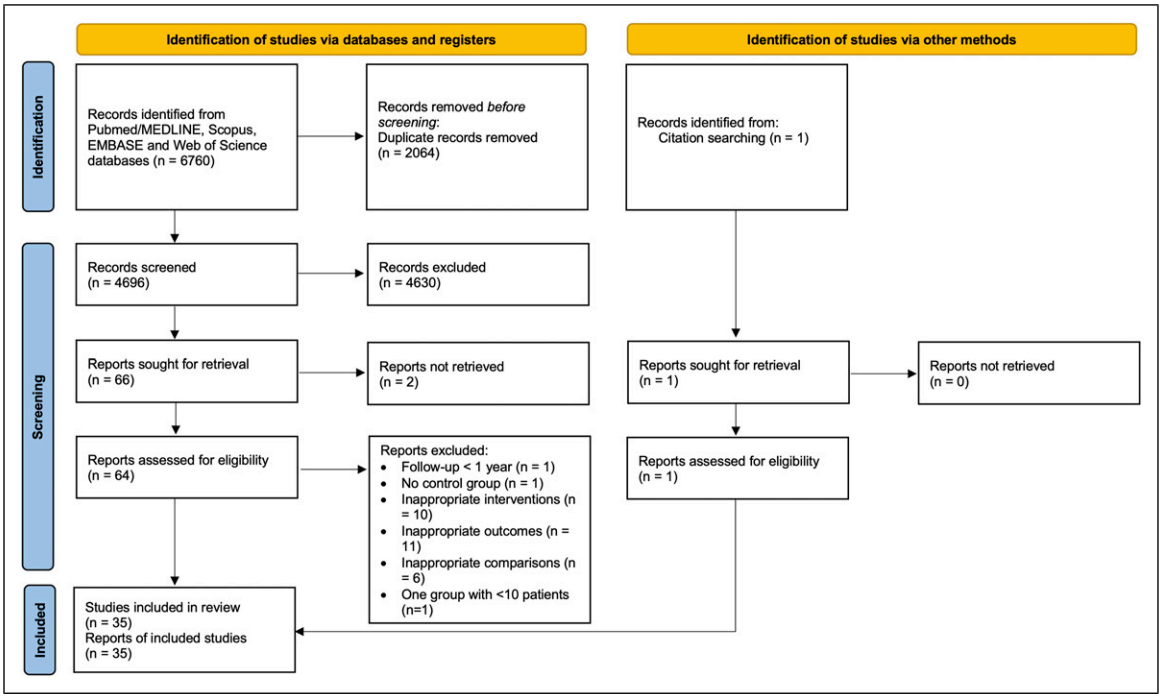


Figure 1. Search strategy flow diagram according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) protocol

Results

Study Selection

Our original NMA[15] included 43 RCTs, of which 8 evaluated anterior approaches and 2 evaluated lateral approaches, which were therefore excluded from the present sub-analysis. This resulted in 33 studies eligible for inclusion from the original dataset. The updated literature search yielded 6760 records. After removal of duplicates, 4696 unique articles remained, of which 4630 were excluded following title and abstract screening. Among the 66 reports sought for retrieval, 2 could not be found, resulting in 64 full-text assessed for eligibility. Out of these, 30 were excluded (follow-up < 1 year, n = 1; no control group, n = 1; inappropriate interventions, n = 10; inappropriate outcomes, n = 11; inappropriate comparisons, n = 6; one group with < 10 patients, n = 1). Finally, one additional study was identified through citation searching. Thus, 35 RCTs met the inclusion criteria and were eventually included (Figure 1).

Study Characteristics

Overall, 35 parallel RCTs (34 two-arm[20-53] and 1 three-arm studies[54]) published between 2002[39] and 2025[53] in Denmark,[21,38,52] Egypt,[20,54] USA,[26,29,30,32-34,40,46-50,53] Germany,[51] South Korea,[22,37,41,42] Australia,[24] China,[25] The Netherlands,[27] Spain 31, Czech Republic,[35] Canada,[36] Sweden,[39] Japan,[23,44] and Belgium[43,45] were included. Among these, 5 studies[21,42,47,48,52] were later follow-ups of previous reports.[21,38,41,46] Collectively, 3354 patients were analyzed, with follow-up ranging from 12 to 120 months. Surgical techniques performed encompassed TLIF,[20,31,37,50,51,53,54] PLF (either uninstrumented[21,38,39,46-49,52] or instrumented[22,23,25-30,32,33,35,36,40,44]), and PLIF.[24,34,41-43,45] Osteobiologics included AICBG,[20,22,25-34,36,39,40,43-49,51] autologous local bone (ALB),[20,21,23,25,27,28,33,37,38,40-42,44,50,51,53,54] rhBMP-2,[22,24,26,29,30,32-34,36,37,43,50] allograft,[21,31,35,38,50,52] rhBMP-7,[27,28,39,46-49] titanium[41,42] or polyetheretherketone cages,[50] platelet-rich plasma (PRP),[23,45,54] anorganic bone material/15-amino acid peptide fragment (ABM/P-15),[21,38,52,53] bioglass,[41,42] DBM,[37,40] silicate-substitute calcium phosphate (SiCaP),[24] β-tricalcium phosphate,[25] biphasic calcium phosphate,[36] bone marrow-derived stromal cells,[31] bone marrow concentrate,[35] platelet-rich fibrin 54, and hydroxyapatite (HA).[51] General characteristics of included studies are summarized in Tables 1 and 2. Overall, 9 studies (25.7%) displayed a low risk of bias, 9 (25.7%) presented "some concerns", and 17 (48.6%) were affected by a high risk of bias (Supplemental Figure 1).

Fusion Rate

The NMA assessing fusion rates included 23 RCTs encompassing 2298 patients and 14 osteobiologic combinations (Figure 2A; Supplemental Tables 1 and 2). Relative to AICBG, rhBMP-2 achieved a significantly higher fusion rate (OR 3.86; 95% CI 2.60-5.74; $P < 0.0001$), whereas no other intervention demonstrated a significant difference (Figure 2B). Inconsistency and

Table 1. General Characteristics and Demographics of Included Studies

Study	Country	Funding	Patient diagnosis	Type of surgery	Treatment groups	Sample size (n)	Age (mean, range or±SD)	Sex (M/F)	BMI (mean kg/m^2±SD)	Smokers (n)	Lost to follow-up	Last follow-up (months)
Abou-Madawi 2020[20]	Egypt	None	1-level grade I-II spondylolisthesis not responding to conservative treatment >3 months	TLIF	ALB	54	47.0±18.0	30/24	24.9±5.3	10	13	24+
					AICBG	54	49.0±18.0	27/27	23.5±4.5	8		
Andresen 2024[c 21]	Denmark	Cerapedics	LSS with 1- or 2-level DLS	Uninstrumented PLF	ABM/P-15 + ALB	43	71.4±6.3	8/35	27.4±4.0	2	7, 22[a]	60
					Allograft + ALB	40	70.1±6.8	8/32	26.9±3.9	0	11, 21[a]	
Andresen 2025[c 52]	Denmark	Orthotech	LSS with 1- or 2-level DLS	Uninstrumented PLF	ABM/P-15 + ALB	30	69.5±5.9	7/23	27.7±4.0	NS	0	120
					Allograft + ALB	27	67.9±5.3	5/22	26.8±3.8	NS	0	
Cho 2023[22]	South Korea	CGBio Inc./BioAlpha Inc	1-level LSS, grade 1 DLS or spondylolysis	Instrumented PLF	rhBMP-2	32	63.2±8.2	17/15	25.2±3.3	0	4	36
					AICBG	41	60.8±9.0	18/23	25.9±3.3	1	4	
Coughlan 2018[24]	Australia	Baxter Healthcare	1- or 2-level lumbar IDD, spondylolisthesis or LDH not responding to conservative treatment >6 months	PLIF	SiCaP	51	50.8±11.4	27/24	26.9±4.3	42	4	24
					rhBMP-2	52	52.3±11.6	28/24	28.6±5.0	41		
Dai 2008[25]	China	Shanghai Natural Science Foundation	1-level LSS	Instrumented PLF	β-TCP + ALB	32	48-72	14/18	23-32	5	0	36
					AICBG + ALB	30	51-73	11/19	20-31	3	0	
Dawson 2009[26]	USA	Medtronic	1- or 2-level lumbar IDD not responding to conservative treatment >6 months	Instrumented PLF	rhBMP-2	25	55.9	10/15	NS	6	3	24
					AICBG	21	56.9	9/12	NS	5	3	
Delawi 2010[27]	The Netherlands	Cooperate/industry	1-level grade I-II isthmic or DLS	Instrumented PLF	rhBMP-7 + ALB	18	53.0±18.0	10/8	26.0±4.0	8	1	12
					AICBG + ALB	16	55.0±13.0	6/10	27.0±3.0	4	0	
Delawi 2016[28]	The Netherlands	Stryker	1-level DLS or isthmic spondylolisthesis with central or foraminal LSS	Instrumented PLF	rhBMP-7 + ALB	60	54.0±14.0	27/33	26.6±4.0	29	3	12
					AICBG + ALB	59	55.0±13.0	25/34	25.2±5.0	18	3	
Dimar 2006[29]	USA	None	1-level symptomatic lumbar IDD >6 months	Instrumented PLF	AICBG	45	52.7	20/25	NS	10	NS	24
					rhBMP2	53	50.9	22/31	NS	17	NS	
Dimar 2009[30]	USA	Medtronic	1-level symptomatic lumbar IDD >6 months	Instrumented PLF	rhBMP-2	239	53.2 (20-81)	108/131	NS	63	23	24
					AICBG	224	52.3 (18-86)	95/129	NS	59	33	
Garcia de Frutos 2020[31]	Spain	Government funding	Grade I-II DLS ± lumbar 1- or 2-level(s) IDD	TLIF	BM-MSCs + allograft	34	61.0±14.6	9/25	NS	NS	2	12
					AICBG	35	60.5±10.3	14/21	NS	NS	2	
Glassman 2005[32]	USA	Cooperate/industry	1-level lumbar IDD ± grade 1 DLS not responding to conservative treatment >6 months	Instrumented PLF	rhBMP-2	38	53	14/24	NS	8	0	12
					AICBG	36	53	16/20	NS	8	0	

(continued)

Table 1. (continued)

Study	Country	Funding	Patient diagnosis	Type of surgery	Treatment groups	Sample size (n)	Age (mean, range or±SD)	Sex (M/F)	BMI (mean kg/m^2±SD)	Smokers (n)	Lost to follow-up	Last follow-up (months)
Glassman 2008[33]	USA	Norton Healthcare	IDD, LSS, DLS, deformity, post-decompression revision between L1-S1	Instrumented PLF	rhBMP-2 + ALB	50	69.2±5.5	15/35	29.4±5.7	11	3	24
					AICBG + ALB	52	69.9±5.8	17/35	28.1±6.1	9	3	
Haid 2004[34]	USA	NS	1-level lumbar IDD not responding to conservative treatment >6 months	Standalone PLIF	rhBMP-2	34	46.3 (25.8-66.1)	17/17	NS	18	4	24
					AICBG	33	46.1 (28.5-70.9)	15/18	NS	15	0	
Harrop 2025[53]	USA	Cerapedics	1-level lumbar IDD, instability, spondylosis, LSS, or LDH	TLIF	ABM/P-15	141	58.8±12.3 (26-80)	66/75	31.2±6.5	16	22	24
					ALB ± allograft	149	59.6±10.9 (30-79)	75/74	31.2±5.8	23	21	
Hart 2014[35]	The Czech Republic	NS	Lumbar IDD	Instrumented PLF	Allograft	40	62.7 (47-77)	10/30	NS	NS	0	24
					Allograft + BMC	40	58.5 (42-80)	12/28	NS	NS	0	
Hurlbert 2013[36]	Canada	Medtronic	1- or 2-level lumbar IDD	Instrumented PLF	rhBMP-2 + BCP	98	53.0	35/63	NS	NS	3	48
					AIBCG	99	53.0	48/51	NS	NS	6	
Hyun 2021[37]	South Korea	Government funding	1- or 2-level IDD between L3-S1	TLIF	DBM + rhBMP-2 + ALB	40	64.0±10.3	23/17	24.3±2.7	15	7	12
					DBM + ALB	36	62.7±9.3	19/17	26.2±4.2	11	3	
Jacobsen 2020[38]	Denmark	Orthotech	LSS with 1- or 2-level DLS	Uninstrumented PLF	ABM/P-15 + ALB	49	71.4±6.3	14/35	27.4±4.0	NS	0	24
					Allograft + ALB	49	70.1±6.8	10/39	26.9±3.9	NS	0	
Johnsson 2002[39]	Sweden	Cooperate/industry	Grade I-II isthmic spondylolisthesis	Uninstrumented PLF	rhBMP-7	10	42.9±10.8	3/7	NS	4	0	12
					AICBG	10	40.4±9.6	5/5	NS	3	0	
Kang 2012[40]	USA	Osteotech Inc.	1-level DLS with LSS	Instrumented PLF	DMB + ALB	28	64.3	10/18	NS	0	2	24
					AICBG	13	65.3	5/8	NS	0	3	
Kubota 2017[23]	Japan	None	LSS with unstable DLS	Instrumented PLF	PRP + ALB	25	65.1±2.1	15/10	NS	NS	6	24
					ALB	25	65.3±2.0	14/11	NS	NS	6	
Lee 2016[41]	South Korea	CGBio Inc./BioAlpha Inc	Severe disc extrusion, LSS or grade I-II DLS	PLIF	Bioglass + ALB	39	61.5±9.4	12/27	NS	4	0	12
					Titanium cage + ALB	35	61.1±8.3	14/21	NS	2	0	
Lee 2020[b] [42]	South Korea	CGBio Inc./BioAlpha Inc	Severe disc extrusion, LSS or grade I-II DLS	PLIF	Bioglass + ALB	32	61.5±8.9	8/24	NS	2	7	48
					Titanium cage + ALB	30	61.1±8.3	12/18	NS	2	5	
Mohi El Din 2021[54]	Egypt	None	1-level isthmic or DLS or IDD not responding to conservative treatment >6 months	TLIF	ALB	40	45.1±9.9	17/23	NS	NS	10	12
					PRF	20	47.4±6.2	10/10	NS	NS	5	
					PRP	20	44.1±4.5	9/11	NS	NS	6	
Michielsen 2013[43]	Belgium	None	1-level isthmic or DLS, lumbar IDD not responding to conservative treatment >6 months, LDH with severe IDD not responding to ESI	PLIF	rhBMP-2	19	43.2±8.8	6/13	27.0±3.2	5	0	24
					AICBG	19	42.2±9.7	10/9	24.6±3.4	10	0	

(continued)

Table 1. (continued)

Study	Country	Funding	Patient diagnosis	Type of surgery	Treatment groups	Sample size (n)	Age (mean, range or±SD)	Sex (M/F)	BMI (mean kg/m^2±SD)	Smokers (n)	Lost to follow-up	Last follow-up (months)
Ohtori 2010[44]	Japan	NS	L4-L5 DLS with LSS and chronic LBP >12 months	Instrumented PLF	ALB	42	66.0±5.5	22/20	NS	NS	0	24
					ALB + AICBG	40	67.0±6.0	18/22	NS	NS	0	
Sys 2011[45]	Belgium	None	1-level isthmic or DLS, lumbar IDD not responding to conservative treatment >6 months, LDH with severe IDD not responding to ESI	PLIF	PRP + AICBG	19	NS	12/7	27.2±5.0	8	1	24
					AICBG	19	NS	12/7	25.4±3.6	9	1	
Vaccaro 2004[46]	USA	Cooperate/industry	Grade I-II DLS with LSS not responding to conservative treatment	Uninstrumented PLF	rhBMP-7	24	63.0±11.0	11/13	NS	Excluded	2	24
					AICBG	12	66.0±7.0	5/7	NS	Excluded	5	
Vaccaro 2005[b] [47]	USA	Cooperate/industry	Grade I-II L3-L4 DLS + LSS	Uninstrumented PLF	rhBMP-7	24	63.0±11.0	11/13	NS	Excluded	3	36
					AICBG	12	66.0±7.0	5/7	NS	Excluded	1	
Vaccaro 2008[a] [49]	USA	None	Grade I-II DLS with LSS not responding to conservative treatment	Uninstrumented PLF	rhBMP-7	207	68.0±9.8	71/136	NS	NS	63	36+
					AICBG	86	71.0±8.3	26/60	NS	NS	28	
Vaccaro 2008[b] [48]	USA	NS	Grade I-II DLS with LSS not responding to conservative treatment	Uninstrumented PLF	rhBMP-7	24	63.0 (43-80)	11/13	NS	Excluded	5	48
					AICBG	12	67.0 (51-79)	5/7	NS	Excluded	4	
Villaviciencio 2021[50]	USA	None	Chronic LBP due to IDD with LSS, spondylolisthesis or recurrent LDH not responding to conservative treatment >6 months	TLIF	Allograft + rhBMP-2 + ALB	60	59.9±10.4	31/29	NS	3	3	24
					PEEK + rhBMP-2 + ALB	61	62.2±10.7	32/29	NS	1	3	
vonderHoeh 2017[51]	Germany	Medtronic	1- or 2-level lumbar IDD not responding to conservative treatments >6 months	TLIF	ALB + HA	24	64.3±12.6	7/17	NS	1	1	12
					AICBG	24	65.6±14.4	5/19	NS	0	1	

Table adapted from Ambrosio et al[15].

Abbreviations: ABM = anorganic bone material; ALB = autologous local bone; AICBG = autologous iliac crest bone graft; BCP = biphasic calcium phosphate; β-TCP = β-tricalcium phosphate; BM-MSCs = bone marrow-derived mesenchymal stromal cells; BMC = bone marrow concentrate; BMI = body mass index; DBM = demineralized bone matrix; DLS = degenerative spondylolisthesis; ESI = epidural steroid injection; HA = hydroxyapatite; IDD = intervertebral disc degeneration; LBP = low back pain; LDH = lumbar disc herniation; LSS = lumbar spinal stenosis; NS = not specified; PEEK = polyetheretherketone; PLF = posterolateral fusion; PLIF = posterior lumbar interbody fusion; PRF = platelet-rich fibrin; PRP = platelet-rich plasma; rhBMP = recombinant human bone morphogenetic protein; SiCaP = silicate-substituted calcium phosphate; SD = standard deviation; TLIF = transforaminal lumbar interbody fusion.

[a]At the last follow-up, clinical outcomes were available for 7 and 11 patients and fusion outcomes were available for 22 and 21 patients in the ABM/P-15 + ALB and allograft groups, respectively.

[b]Later follow-up report of the abovementioned study.

[c]Later follow-up report of the study by Jacobsen et al.

Table 2. Specification of Osteobiologics Used, Operated Spinal Levels, and Post-operative Bracing Strategies in Included Studies

Study	Instrumentation	Type of osteobiologic	Osteobiologic specifications	Number of operated levels (segments)	Post-operative bracing
Abou-Madawi 2020[20]	Pedicle screw-rod instrumentation with a PEEK cage (EgiFix, Egypt)	ALB	5-7 cc of ALB were placed in the disc space and the cage filled with additional ALB was then implanted	1 level (L3-L4: 2, L4-L5: 14, L5-S1: 38)	NS
		AICBG	5-7 cc of AICBG were placed in the disc space and the cage filled with additional AICBG was then implanted	1 level (L3-L4: 4, L4-L5: 33, L5-S1: 17)	
Andresen 2024[21]	None	ABM/P-15 (i-Factor, Cerapedics, USA) + ALB	ALB mixed with 5 cc of ABM/P-15 putty were placed at each level	1 level 32/43 2 levels 11/43 (L3-L4: 10, L4-L5: 40, L5-S1: 4)	Soft brace for 3 months
		Allograft + ALB	ALB mixed with 30 grams of morselized fresh frozen femoral head were placed at each level	1 level 34/40 2 levels 6/40 (L3-L4: 13, L4-L5: 32, L5-S1: 1)	
Andresen 2025[52]	None	ABM/P-15 (i-Factor, Cerapedics) + ALB	ALB mixed with 5 cc of ABM/P-15 putty were placed at each level	1 or 2 levels (NS)	Soft brace for 3 months
		Allograft + ALB	ALB mixed with 30 grams of morselized fresh frozen femoral head were placed at each level	1 or 2 levels (NS)	
Cho 2023[22]	NS	E. coli-derived rhBMP-2 with an HA carrier (Novosis, CG Bio Co., Ltd., South Korea)	Approximately 3 g (8 cc) of HA were soaked in one vial (3.0 mg) of rhBMP-2 and carefully applied in the intertransverse space of each side	1 level (NS)	NS
		AICBG	Approximately 8 cc of AICBG were applied in the intertransverse space of each side	1 level (NS)	
Coughlan 2018[24]	NS	SiCaP (Actifuse, Baxter Healthcare, USA)	The amount of SiCaP ranged between 5-10 mL. Up to 10 mL of SiCaP per level per side were packed into the decorticated posterolateral gutters in contact with bleeding decorticated TPs at the operated levels	1 or 2 levels (NS)	NS
		rhBMP-2/ACS (InFUSE bone graft, Medtronic, Ireland) + 15% HA/85% β-TCP granules (Mastergraft, Medtronic)	After binding with 12 mg rhBMP-2, the collagen sponge was cut into two equal segments and up to 10 mL Mastergraft granules were used to wrap the absorbable collagen sponge. The graft was then placed in contact with bleeding decorticated TPs at the operated levels	1 or 2 levels (NS)	

(continued)

Table 2. (continued)

Study	Instrumentation	Type of osteobiologic	Osteobiologic specifications	Number of operated levels (segments)	Post-operative bracing
Dai 2008[25]	Pedicle screw-rod instrumentation with the tenor or TSRH systems (Medtronic)	β-TCP (BioLu, China) + ALB	A stick type of β-TCP (5 × 5 × 20-mm block) was mixed with ALB with a ratio of 2:1 and placed in the decorticated fusion area	1 level (L4-L5: 20, L5-S1: 12)	NS
		AICBG + ALB	AICBG was mixed with ALB with a ratio of 2:1 and placed in the decorticated fusion area	1 level (L4-L5: 17, L5-S1: 15)	
Dawson 2009[26]	Pedicle screw-rod instrumentation with the CD horizon system (Medtronic)	rhBMP-2/ACS (InFUSE bone graft, Medtronic) + 15% HA/85% β-TCP granules (Mastergraft, Medtronic)	After binding with 6 mg rhBMP-2 (1.5 mg/mL), each collagen sponge was mixed with 5 cm^3 of Mastergraft granules. Two sponges (12 mg rhBMP-2 + 10 cm^3 of Mastergraft granules) were placed into the lateral gutters and along the pars interarticularis in each patient	1 level (NS)	NS
		AICBG	The morselized AICBG was placed into the lateral gutters and along the pars interarticularis in each patient	1 level (NS)	
Delawi 2010[27]	Pedicle screw-rod instrumentation with the Xia spinal System, Stryker, USA)	rhBMP-7 (Osigraft, Stryker) + ALB	3.5 mg lyophilized rhBMP-7 in 1 g of type I collagen carrier was applied per side, combined with morselized ALB and 2.5 mL fresh blood, in the lateral gutters on the decorticated bony surfaces of the TPs, pedicles, and along the pars interarticularis	1 level (L3-L4: 4, L4-L5: 5, L5-S1: 10)	Brace or orthosis for 8 weeks
		AICBG + ALB	AICBG was implanted in the lateral gutters on the decorticated bony surfaces of the TPs, pedicles, and along the pars interarticularis	1 level (L3-L4: 2, L4-L5: 12, L5-L6: 1, L5-S1: 1)	
Delawi 2016[28]	Pedicle screw-rod instrumentation with the Xia spinal System (Stryker)	rhBMP-7 (Osigraft, Stryker) + ALB	After the addition of 2.5 mL of fresh blood, ALB was mixed with the graft containing 3.5 mg of lyophilized rhBMP-7 in 1 g of type I collagen carrier (per each side)	1 level (L3-L4: 9, L4-L5: 24, L5-S1: 27)	Unspecified lumbar orthosis for 8 weeks
		AICBG + ALB	Bone was harvested from the iliac crest, morselized, mixed with ALB, and implanted in each side	1 level (L3-L4: 6, L4-L5: 43, L5-L6:1, L5-S1: 18)	
Dimar 2006[29]	Pedicle screw-rod instrumentation with the CD horizon system (Medtronic)	rhBMP-2 + 15% HA/85% β-TCP matrix (Amplify, Medtronic)	After reconstitution, 40 mg rhBMP-2 (2 mg/mL) were distributed onto two equal matrix pieces and placed on the decorticated osseous surface of the TPs and pars interarticularis (20 mg per side)	1 level (NS)	NS
		AICBG	AICBG morselized and placed on the decorticated osseous surface of the TPs and pars interarticularis	1 level (NS)	

(continued)

Table 2. (continued)

Study	Instrumentation	Type of osteobiologic	Osteobiologic specifications	Number of operated levels (segments)	Post-operative bracing
Dimar 2009[30]	Pedicle screw-rod instrumentation with the horizon M8 system (Medtronic)	rhBMP-2 + 15% HA/ 85% β-TCP matrix (Amplify, Medtronic)	After reconstitution, 40 mg rhBMP-2 (2 mg/mL) were distributed onto two equal matrix pieces and placed on the decorticated osseous surface of the TPs and pars interarticularis (20 mg per side)	1 level (NS)	NS
		AICBG	AICBG morselized and placed on the decorticated osseous surface of the TPs and pars interarticularis	1 level (NS)	
Garcia de Frutos 2020[31]	NS	BM-MSCs + allograft + AICBG	Autologous BM-MSCs were isolated from iliac crest BMA, cultured for 21 days, and seeded at 3-10 × 10^5 MSCs/cm^3 onto 10 cc cancellous allograft bone cubes. The product was placed in the intertransverse space on the opposite side to the transforaminal approach. 10 cc AICBG were implanted anterior to the interbody device	1 or 2 levels (NS)	NS
		AICBG	20 cc of AICBG were positioned both in the intertransverse space and anterior to the interbody device	1 or 2 levels (NS)	
Glassman 2005[32]	Pedicle screw-rod instrumentation with the CD horizon system (Medtronic)	rhBMP-2/ACS (InFUSE bone graft, Medtronic) + HA/ β-TCP CRM	20 mg of 2 mg/mL rhBMP-2 were combined with 10 mL of the CRM and placed in each lateral gutter (40 mg per level)	1 level (NS)	NS
		AICBG	NS	1 level (NS)	
Glassman 2008[33]	NS	rhBMP-2/ACS + ALB	rhBMP-2/ACS was prepared according to the manufacturer's instruction. ALB extenders were used at the surgeon's discretion	Mean: 1.96 (NS)	NS
		AICBG + ALB	No specific information provided. ALB extenders were used at the surgeon's discretion	Mean: 1.98 (NS)	
Haid 2004[34]	Two paired INTER FIX devices (Medtronic)	rhBMP-2/ACS (InFUSE bone graft, Medtronic)	The dose of rhBMP-2 varied depending on cage size (4.0-8.0 mg). The rhBMP-2–soaked sponge was then placed in the hollow central portion of the INTER FIX device before its insertion into the disc space	1 level (NS)	Soft lumbar corset
		AICBG	AICBG was morselized using a rongeur and was tightly packed into the cages before their insertion	1 level (NS)	

(continued)

Table 2. (continued)

Study	Instrumentation	Type of osteobiologic	Osteobiologic specifications	Number of operated levels (segments)	Post-operative bracing
Harrop 2025[53]	Unspecified pedicle screw-rod instrumentation with a PEEK cage	ABM/P-15 (PearlMatrix, Cerapedics)	The central cavity of the interbody cage was filled with the bone graft.	1 level (L2-L3: 6, L3-L4: 12, L4-L5: 88, L5-S1: 35)	NS
		ALB ± allograft	The central cavity of the interbody cage was filled with ALB; if deemed insufficient, allograft chips were allowed as graft extenders	1 level (L1-L2: 1, L2-L3: 3, L3-L4: 20, L4-L5: 88, L5-S1: 38)	
Hart 2014[35]	Pedicle screw-rod instrumentation with the S4 (B/Braun-Aesculap, Germany) system	Allograft	Spongious allograft bone chips derived from fresh frozen proximal or distal femurs alone were applied to the decorticated fusion beds	Mean: 1.25 (1-2)	Standard soft orthotic device for 3 months
		Allograft + BMC	From 100 mL of BMA, 9 mL of BMC were mixed with allograft bone chips (90 g) that were subsequently applied to the decorticated fusion beds	Mean: 1.83 (1-3)	
Hurlbert 2013[36]	Pedicle screw-rod instrumentation with TSRH or CD horizon (Medtronic) systems	rhBMP-2 + BCP (60% HA/40% β-TCP/80% porosity, Medtronic)	Each side was implanted with 10 mL (2.1 mg/mL) of rhBMP-2 on a BCP carrier, resulting in a total rhBMP-2 dose of 42 mg for 1 level and 63 mg for 2 levels	1 level: 88% 2 levels: 12%	Upon physician preference
		AIBCG	Corticocancellous AICBG was implanted in each side	1 level: 87% 2 levels: 13%	
Hyun 2021[37]	Unspecified screw-rod instrumentation + PEEK cage (Capstone, Medtronic)	DBM + rhBMP-2 (RAFUGEN BMP-2; Cellumed Co., Ltd., South Korea) + ALB	1.5 mL DBM and 0.055 mg rhBMP-2 were injected into the PEEK cage. ALB was packed into the surrounding disc space	1 level (L3-L4: 3, L4-L5: 18, L5-S1: 4) 2 levels (L3-L5: 10, L4-S1: 4) 3 levels (L3-S1: 1)	NS
		DBM (RAFUGEN DMB; Cellumed Co., Ltd.) + ALB	1.5 mL DBM were injected into the PEEK cage. ALB was packed into the surrounding disc space	1 level (L3-L4: 5, L4-L5: 10, L5-S1: 4) 2 levels (L3-L5: 8, L4-S1: 9)	
Jacobsen 2020[38]	None	ABM/P-15 (i-Factor, Cerapedics) + ALB	ALB was mixed with 5 cc of ABM/P-15 putty at each level	1 level: 35, 2 levels: 14	Soft brace for 3 months
		Allograft + ALB	ALB mixed with 30 grams of morselized fresh frozen femoral head at each level	1 level: 41, 2 levels: 8	
Johnsson 2002[39]	None	rhBMP-7	3.5 mg rhBMP-7 was reconstituted within 1g type I bone collagen, 2.5 mL saline, and implanted per each side (7 mg total)	1 level (L5-S1)	Soft lumbosacral brace for 5 months
		AICBG	AICBG was prepared as a cancellous bone paste and applied on the decorticated fusion sites	1 level (L5-S1)	

(continued)

Table 2. (continued)

Study	Instrumentation	Type of osteobiologic	Osteobiologic specifications	Number of operated levels (segments)	Post-operative bracing
Kang 2012[40]	NS	DBM (Grafton Matrix, Medtronic) + ALB	Approximately 30 cm^3 of a DBM + ALB were divided evenly and implanted in the lateral gutters. The facets were packed with 2-3 pieces of ALB and one 10 mm-DBM plug per side	1 level (NS)	NS
		AICBG	AICBG was placed evenly over the posterolateral fusion bed and the facets	1 level (NS)	
Kubota 2017[23]	Pedicle screw-rod instrumentation with CD horizon Legacy or CD horizon Solera (Medtronic) systems	PRP + ALB	Activated PRP (10 mL per side) was mixed with the ALB from the decompression site and placed on both sides over the transverse processes together with the ALB from the decompression site	1 level: 18, 2 levels: 7	NS
		ALB	ALB from the decompression site was implanted in the intertransverse space in each side	1 level: 15, 2 levels: 10	
Lee 2016[41]	Unspecified pedicle-screw rod instrumentation + bioglass spacer	Bioglass (BGS-7, NovoMax; CGBio Inc.) + ALB	The bioactive glass spacer was filled with 10 mL ALB and implanted in the disc space	1 level (NS)	NS
	Unspecified pedicle-screw rod instrumentation + titanium cage (4CIS; Solco Biomedical, South Korea)	Titanium cage + ALB	The titanium cage was filled with 10 mL ALB and implanted in the disc space	1 level (NS)	
Lee 2020[42]	Unspecified pedicle-screw rod instrumentation + bioglass spacer	Bioglass (BGS-7, NovoMax; CGBio Inc.) + ALB	The bioactive glass spacer was filled with 10 mL ALB and implanted in the disc space	1 level (NS)	NS
	Unspecified pedicle-screw rod instrumentation + titanium cage (4CIS; Solco Biomedical)	Titanium cage + ALB	The titanium cage was filled with 10 mL ALB and implanted in the disc space	1 level (NS)	
Mohi El Din 2021[54]	NS	ALB	ALB alone was packed into the cage	1 level (L4-L5: 36, L5-S1: 4)	NS
		PRF	10 mL of PRF were added to ALB and packed into the cage	1 level (L4-L5: 15, L5-S1: 5)	
		PRP	10 mL of PRP were added to ALB and packed into the cage	1 level (L4-L5: 15, L5-S1: 5)	
Michielsen 2013[43]	Pedicle screw-rod instrumentation with the Colorado II system (Medtronic) and two PEEK cages (Telamon, Medtronic)	rhBMP-2/ACS (InductOs, Wyeth Europa, UK)	The total amount of rhBMP-2 was 8 mg per level. Two cages of the appropriate size were filled with 2 mg of rhBMP-2 in each cage, applied on an absorbable collagen sponge. In front of each cage, another 2 mg of rhBMP-2 were applied	1 level (NS)	Lumbosacral orthosis during activity for 6 weeks
		AICBG	Two cages of the appropriate size were filled with 2.5 mL of AICBG. Before implantation, bone chips were applied in front of each cage	1 level (NS)	

(continued)

Table 2. (continued)

Study	Instrumentation	Type of osteobiologic	Osteobiologic specifications	Number of operated levels (segments)	Post-operative bracing
Ohtori 2010[44]	NS	ALB	ALB was obtained from the L4 lamina and L4-L5 spinous process and implanted	1 level (L4-L5: 42)	NS
		ALB + AICBG	Corticocancellous AICBG was mixed with ALB and implanted	1 level (L4-L5: 40)	
Sys 2011[45]	Pedicle screw-rod instrumentation with the Monarch rod system + two Saber cages (DePuy Synthes Inc., USA)	PRP + AICBG	The cages were filled with AICBG chips and steeped in the plasma-thrombin solution until clotting occurred visually	1 level (L3-L4: 0, L4-L5: 3, L5-S1: 16)	Lumbar orthosis during activity for 6 weeks
		AICBG	The cages were filled with AICBG chips and implanted after approximately 10 min, without incubation in a plasma-thrombin solution	1 level (L3-L4: 1, L4-L5: 4, L5-S1: 14)	
Vaccaro 2004[46]	None	rhBMP-7	3.5 mg rhBMP-7 with 1 g of type I bovine-collagen and 230 mg caboxymethylcellulose mixed with saline to form 0.875 mg/mL rhBMP-7. A total dose of 7 mg OP-1 was transplanted between the decorticated TPs and on the lateral border of the facets (3.5 mg per side)	1 level (L3-L4: 1, L4-L5: 23)	Rigid lumbosacral orthosis for 3 months
		AICBG	Corticocancellous AICBG was transplanted between the decorticated TPs and on the lateral border of the facets	1 level (L3-L4: 3, L4-L5: 9)	
Vaccaro 2005[47]	None	rhBMP-7	3.5 mg rhBMP-7 with 1 g of type I bovine-collagen and 230 mg caboxymethylcellulose mixed with saline to form 0.875 mg/mL rhBMP-7. A total dose of 7 mg OP-1 was transplanted between the decorticated TPs and on the lateral border of the facets (3.5 mg per side)	1 level (L3-L4: 1, L4-L5: 23)	Rigid lumbosacral orthosis for 3 months
		AICBG	Corticocancellous AICBG was transplanted between the decorticated TPs and on the lateral border of the facets	1 level (L3-L4: 9, L4-L5: 3)	
Vaccaro 2008a[49]	None	rhBMP-7	3.5 mg rhBMP-7 with 1 g of type I bovine-collagen and 230 mg caboxymethylcellulose mixed with saline to form 0.875 mg/mL rhBMP-7. A total dose of 7 mg OP-1 was transplanted between the decorticated TPs and on the lateral border of the facets (3.5 mg per side)	1 level (L3-L4: 21, L4-L5: 178, L5-S1: 8)	Lumbosacral orthosis of choice for 3 months
		AICBG	Corticocancellous AICBG was transplanted between the decorticated TPs and on the lateral border of the facets	1 level (L3-L4: 10, L4-L5: 74, L5-S1: 2)	

(continued)

Table 2. (continued)

Study	Instrumentation	Type of osteobiologic	Osteobiologic specifications	Number of operated levels (segments)	Post-operative bracing
Vaccaro 2008b[b48]	None	rhBMP-7	3.5 mg rhBMP-7 with 1 g of type I bovine-collagen and 230 mg caboxymethylcellulose mixed with saline to form 0.875 mg/mL rhBMP-7. A total dose of 7 mg OP-1 was transplanted between the decorticated TPs and on the lateral border of the facets (3.5 mg per side)	1 level (L3-L4: 1, L4-L5: 23)	Rigid lumbosacral orthosis for 3 months
		AICBG	Corticocancellous AICBG was transplanted between the decorticated TPs and on the lateral border of the facets	1 level (L3-L4: 3, L4-L5: 9)	
Villaviciencio 2021[50]	NS	Cortical allograft + rhBMP-2/ACS + ALB	An ACS with 2.1 mg rhBMP-2 was placed in the anterior disc space (1/4) with ALB, within the cortical allograft (2/4), and on the decorticated fusion site posterolaterally (1/4)	1 level (L3-L4: 2, L4-L5: 16, L5-S1: 17) 2 levels (L3-L4: 1, L4-L5: 9, L5-S1: 15)	NS
		PEEK + rhBMP-2/ACS + ALB	An ACS with 2.1 mg rhBMP-2 was placed in the anterior disc space (1/4) with ALB, within the PEEK cage(s) (2/4), and on the decorticated fusion site posterolaterally (1/4)	1 level (L2-L3: 2, L3-L4: 1, L4-L5: 21, L5-S1: 14) 2 levels (L3-L4: 3, L4-L5: 4, L5-S1: 6)	
vonderHoeh 2017[51]	Unspecified pedicle screws + oblique cage (Mectalif Ti PEEK, Medacta, Switzerland)	ALB + HA	Milled ALB (5 cc) and HA paste (5 cc; Nanostim, Medtronic)	1 level: 18, 2 levels: 6	None
		AICBG	10 cc cancellous AICBG	1 level: 17, 2 levels: 7	

Table adapted from Ambrosio et al[15].
Abbreviations: ABM/P-15 = anorganic bone matrix/15-amino acid peptide fragment, ACS = absorbable collagen sponge, AICBG = autologous iliac crest bone graft, ALB = autologous local bone, BCP = biphasic calcium phosphate, β-TCP = β-tricalcium phosphate, BM-MSCs = bone marrow-derived mesenchymal stromal cells, BMA = bone marrow aspirate, BMC = bone marrow concentrate, CRM = compression resistant matrix, DBM = demineralized bone matrix, HA = hydroxyapatite, NH-SiO_2 = silica gel matrix, NS = not specified, OP-1 = Osteogenic Protein 1, a rhBMP-7 product, PEEK = polyethyletherketone, PRF = platelet-rich fibrin, PRP = platelet-rich plasma, rhBMP = recombinant human bone morphogenetic protein, SiCaP = silicate-substituted calcium phosphate, TP = transverse process.

heterogeneity were minimal (τ^2 = 0; I^2 = 0% [95% CI 0.0-58.3%]; P = 0.77). A meta-regression analysis was performed to investigate the influence of surgical technique on fusion rates. The test of moderators was not significant (Q_M = 0.34, df = 2, P = 0.84), suggesting that the relative efficacy of osteobiologics is consistent across different posterior fusion techniques. No evidence of publication bias was observed (P = 0.64; Supplemental Figure 2). The importance of individual studies within the network is presented in Supplemental Figure 3. The certainty of evidence was rated as moderate for rhBMP-2 and low to very low for the other osteobiologics (Supplemental Table 3).

Complication Rate

The NMA examining complication rates included 20 RCTs involving 2297 patients and 10 osteobiologic combinations (Figure 3A; Supplemental Table 4). rhBMP-2 was associated with a significantly reduced risk of complications (OR 0.50; 95% CI 0.34-0.73; P = 0.0004), whereas no other intervention differed significantly from AICBG (Figure 3B). Heterogeneity was low (τ^2 = 0.0478; I^2 = 15.4% [95% CI 0.0-55.2%]; P = 0.2928), and no evidence of publication bias was found (P = 0.93; Supplemental Figure 4). Similar to fusion rate, meta-regression analysis confirmed that the effect of osteobiologics was likely independent of the specific posterior surgical approach (Q_M = 0.70, df = 2, P = 0.70). The importance of individual studies within the network is shown in Supplemental Figure 5. The certainty of the evidence was moderate for rhBMP-2 and low to very low for the other osteobiologics (Supplemental Table 5).

Direct pairwise comparisons for the primary outcomes are presented in Supplemental Figure 6. SUCRA values for each

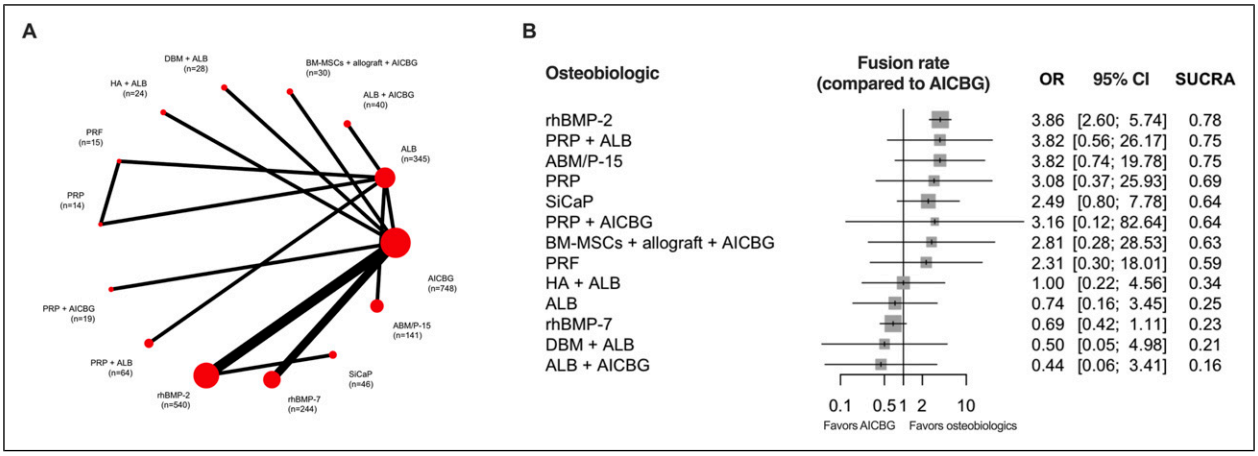


Figure 2. NMA of RCTs investigating fusion. (A) Network structure showing treatment comparisons among included studies. Line width corresponds to the number of RCTs comparing each treatment with AICBG, while circle size reflects the total number of patients receiving that treatment, indicated below each circle. (B) Forest plot of fusion assessing the effect of included osteobiologics vs. AICBG. The size of each square is inversely proportional to the precision of the effect estimate (i.e., narrower confidence intervals correspond to larger squares). Osteobiologics are ranked from highest to lowest SUCRA score. Abbreviations: ABM/P-15 = anorganic bone matrix/15-amino acid peptide fragment, AICBG = autologous iliac crest bone graft, ALB = autologous local bone, BM-MSCs = bone marrow-derived mesenchymal stromal cells, CI = confidence interval, DBM = demineralized bone matrix, HA = hydroxyapatite, NMA = network meta-analysis, OR = odds ratio, PRF = platelet-rich fibrin, PRP = platelet-rich plasma, RCT = randomized controlled trial, rhBMP = recombinant human bone morphogenetic protein, SiCaP = silicate-substituted calcium phosphate, SUCRA = surface under the cumulative ranking curve

osteobiologic were combined to generate the cluster ranking plot in Figure 4, illustrating their relative efficacy and safety. rhBMP-2 and SiCaP emerged as the top performers, achieving more than 50% in both safety and efficacy. In contrast, rhBMP-7, HA + ALB, AICBG, and ALB showed comparatively poorer overall performance, with scores below 50% for both safety and efficacy.

Secondary Outcomes

The NMA evaluating LBP severity included 8 studies with 669 patients across 7 osteobiologic combinations (Figure 5A). No treatment showed a significant difference compared with AICBG, although heterogeneity was substantial ($\tau^2 = 7.779$; $I^2 = 96.9\%$ [95% CI 93.6-98.5%]; $P < 0.0001$). Likewise, no significant differences emerged for ODI scores (12 studies,

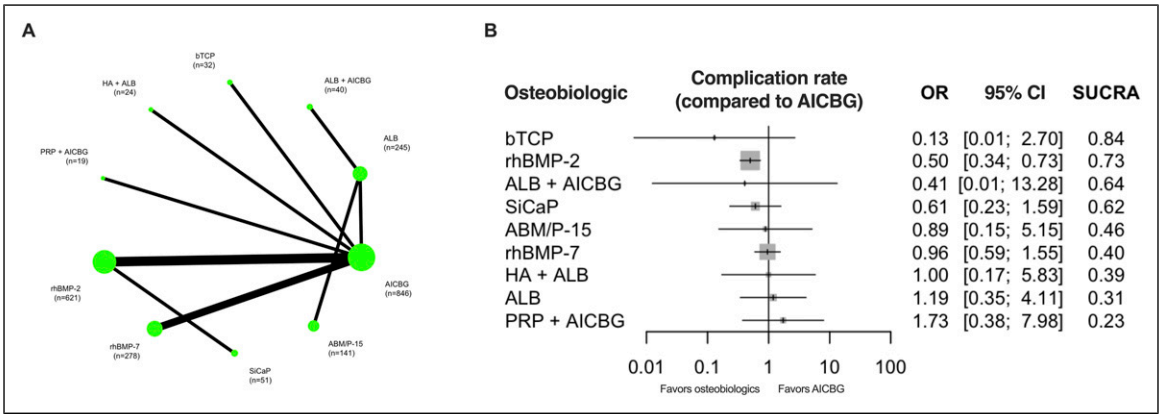


Figure 3. NMA of RCTs investigating complications. (A) Network structure showing treatment comparisons among included studies. Line width corresponds to the number of RCTs comparing each treatment with AICBG, while circle size reflects the total number of patients receiving that treatment, indicated below each circle. (B) Forest plot of complications assessing the effect of included osteobiologics vs. AICBG. The size of each square is inversely proportional to the precision of the effect estimate (i.e., narrower confidence intervals correspond to larger squares). Osteobiologics are ranked from highest to lowest SUCRA score. Abbreviations: ABM/P-15 = anorganic bone matrix/15-amino acid peptide fragment, AICBG = autologous iliac crest bone graft, ALB = autologous local bone, CI = confidence interval, HA = hydroxyapatite, NMA = network meta-analysis, OR = odds ratio, PRP = platelet-rich plasma, RCT = randomized controlled trial, rhBMP = recombinant human bone morphogenetic protein, SiCaP = silicate-substituted calcium phosphate, SUCRA = surface under the cumulative ranking curve

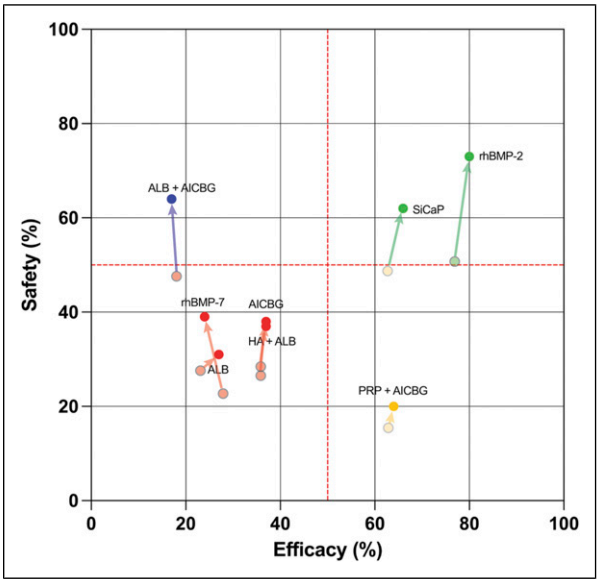


Figure 4. Comparison of SUCRA-based efficacy and safety rankings between pooled and posterior-only NMAs. Scatter plot illustrating changes in SUCRA-based ranking probabilities for fusion efficacy (*x*-axis) and complication safety (*y*-axis) for each osteobiologic when comparing the original pooled NMA[15], which included anterior, lateral, and posterior fusion approaches, with the posterior-only sub-analysis. Each data point represents an osteobiologic, with arrows indicating the directional shift in SUCRA position from the pooled analysis to the posterior-restricted analysis. Dashed reference lines at 50% indicate median ranking probabilities for efficacy and safety. Movements reflect changes in relative ranking rather than absolute treatment effects or statistical significance. Abbreviations: AICBG = autologous iliac crest bone graft, ALB = autologous local bone, HA = hydroxyapatite, NMA = network meta-analysis, PRP = platelet-rich plasma, rhBMP = recombinant human bone morphogenetic protein, SiCaP = silicate-substituted calcium phosphate, SUCRA = surface under the cumulative ranking curve

1391 patients, 9 osteobiologic combinations; Figure 5B), and heterogeneity remained high ($\tau^2 = 4.408$; $I^2 = 74.1\%$ [95% CI 35.7-89.6%]; $P = 0.004$). For operation time (10 studies, 1358 patients, 6 osteobiologic combinations; Figure 5C), ALB (MD −12.0 minutes; 95% CI −21.5 to −2.5; $P = 0.0133$), rhBMP-2 (MD −21.8 minutes; 95% CI −28.0 to −15.7; $P < 0.0001$), and ABM/P-15 (MD −17.0 minutes; 95% CI −32.6 to −1.5; $P = 0.0322$) were associated with significantly shorter procedures compared with AICBG, with no meaningful heterogeneity ($\tau^2 = 0$; $I^2 = 0\%$ [95% CI 0-74.6%]; $P = 0.8371$). Regarding blood loss (9 studies, 1181 patients, 6 different combinations of osteobiologics; Figure 5D), rhBMP-2 demonstrated a significant reduction relative to AICBG (MD −72.6 mL; 95% CI −118.9 to −26.4; $P = 0.002$), and heterogeneity was not significant ($\tau^2 = 960.3$; $I^2 = 44.5\%$ [95% CI 0-79.7%]; $P = 0.13$). The analysis of LOS (6 studies, 846 patients, 4 different combinations of osteobiologics; Figure 5E) revealed no significant differences among treatments, with low heterogeneity ($\tau^2 = 0$; $I^2 = 0\%$ [95% CI 0-84.7%]; $P = 0.61$). No significant publication bias emerged in terms of ODI and operation time among included studies (Supplemental Figure 7A–B).

Discussion

This study presents the results of an NMA on RCTs evaluating osteobiologics used specifically in posterior LSF for degenerative conditions. Consistent with our previously published pooled NMA,[15] rhBMP-2 demonstrated the most robust evidence of improved fusion efficacy compared with AICBG, while also being associated with a lower overall complication risk. Other osteobiologics showed favourable trends in fusion and safety outcomes, and achieved moderate to high SUCRA rankings, but these differences did not reach statistical significance. Collectively, these findings indicate that while several osteobiologics may offer potential advantages, rhBMP-2 remains the only agent supported by consistent, higher-certainty evidence within the current posterior-only RCT literature.

Considering that posterior LSF represents the most commonly performed fusion approach worldwide,[55,56] its biological and mechanical characteristics merit dedicated evaluation. Posterior LSF encompasses PLF fusion as well as posteriorly approached interbody techniques, including PLIF and TLIF, all of which rely on graft incorporation within a distinct local environment. In these procedures, arthrodesis is achieved through a combination of osteobiologic placement within one or more interbody devices, segmental instrumentation, and decortication of posterior elements with additional graft positioning, in conjunction with direct neural decompression, whose extent might, in turn, exert an iatrogenic destabilizing effect.[16] In contrast, anterior and lateral fusion approaches emphasize anterior column load sharing, graft containment within the disc space, and indirect decompression with preservation of the posterior column, thus being associated with different biological demands and approach-specific complication profiles.[56] These differences have been shown to influence fusion biology,[57,58] graft vascularization,[59] and mechanical stability,[60] and may therefore affect the magnitude and detectability of osteobiologic treatment effects reported in comparative analyses.

Within this sub-analysis, restricting the NMA to posterior approaches reduced clinical heterogeneity related to surgical exposure and graft placement, but also resulted in a smaller network and wider CIs for most osteobiologics compared within the pooled analysis. Notably, rhBMP-2 remained the only agent demonstrating statistically significant superiority over AICBG, supporting the robustness of this finding across both pooled and approach-restricted analyses.[15] Interestingly, meta-regression demonstrated that the effect of osteobiologics on both fusion and complication outcomes did not significantly differ between the pooled analyses and models in which surgical technique was included as a covariate. For other

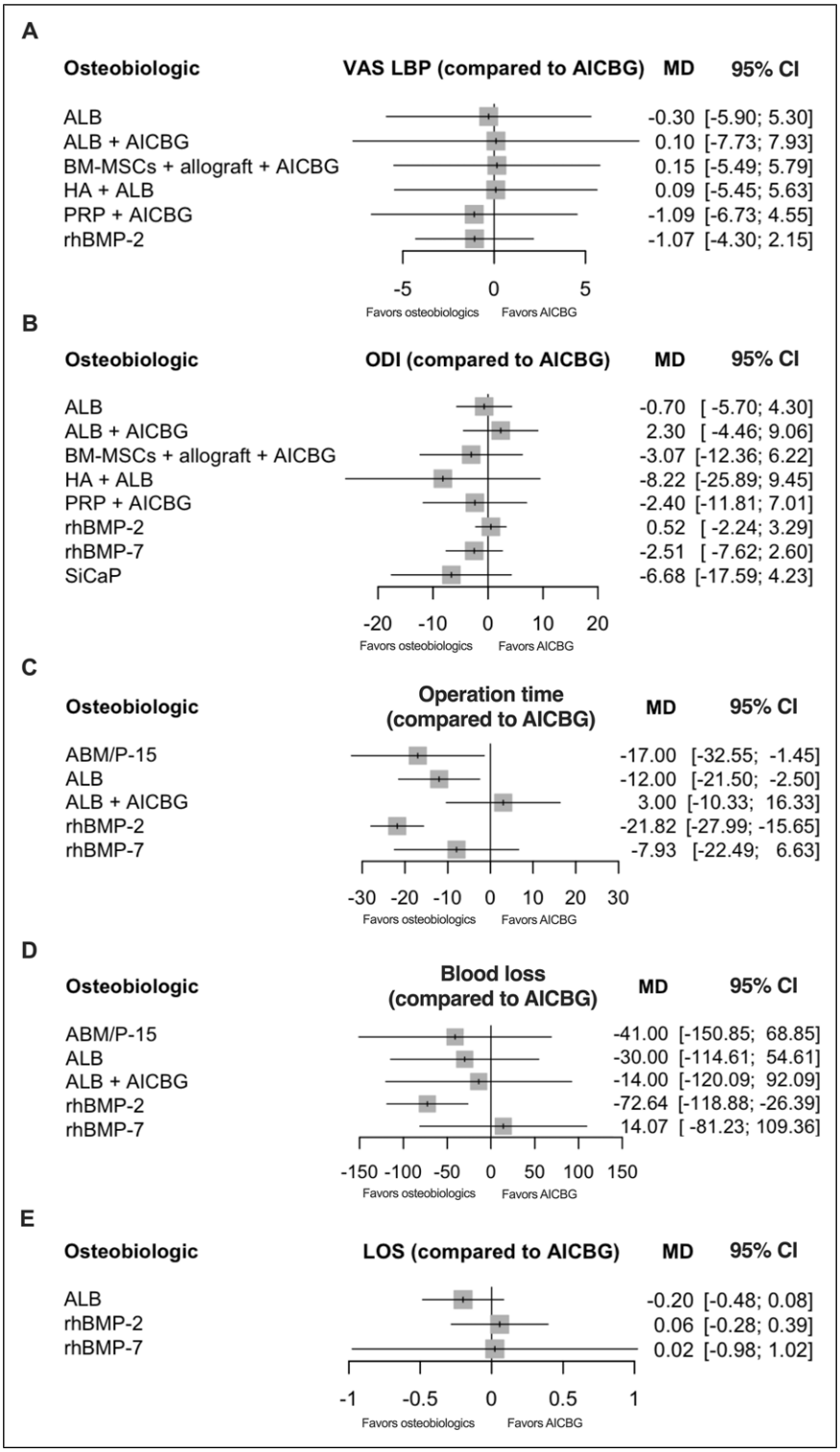


Figure 5. Forest plots of VAS LBP (A), ODI (B), operation time (C), blood loss (D), and LOS (E) assessing the effect of included osteobiologics vs. AICBG. Abbreviations: ABM/P-15 = anorganic bone matrix/15-amino acid peptide fragment, AICBG = autologous iliac crest bone graft, ALB = autologous local bone, BM-MSCs = bone marrow-derived mesenchymal stromal cells, CI = confidence interval, HA = hydroxyapatite, LBP = low back pain, LOS = length of stay, MD = mean difference, ODI = Oswestry Disability Index, PRP = platelet-rich plasma, rhBMP = recombinant human bone morphogenetic protein, SiCaP = silicate-substituted calcium phosphate, VAS = visual analogue scale

osteobiologics, effect estimates generally favored the intervention but did not reach statistical significance, and were considered comparable to AICBG within the limits of the available evidence. When SUCRA-based efficacy and safety rankings from the pooled network were plotted against those derived from the posterior-only analysis, several consistent patterns emerged. All osteobiologics demonstrated higher SUCRA probabilities for safety in the posterior-only network, likely reflecting exclusion of anterior fusion approaches associated with distinct vascular, visceral, and psoas-related risks.[16] Importantly, this shift reflects changes in relative ranking rather than absolute complication rates. For example, the use of rhBMP-2 in ALIF has been historically associated with complications specific to the anterior approach, including retrograde ejaculation, transient renal impairment, and ectopic bone formation in the retroperitoneal space, among others.[61] However, the recent literature suggests that most of these events are more likely attributable to the surgical approach itself rather than to rhBMP-2 (and other osteobiologics), whose direct biological contribution in these cases cannot be conclusively established.[62] Changes in SUCRA efficacy rankings were modest and variable, and given the probabilistic nature of SUCRA metrics and the small magnitude of these shifts,[63] such findings should be interpreted cautiously rather than indicative of approach-specific superiority.

Differences among osteobiologics were more consistently detected for fusion outcomes than for PROMs across both the pooled and posterior-only analyses. This dissociation is well described in the LSF literature and reflects the multifactorial nature of clinical recovery, in which pain and functional improvement are influenced by factors beyond graft biology alone, including adequacy of decompression, fixation stability, alignment, and patient-related characteristics.[64] As a result, improvements in fusion biology may not translate proportionally into superior patient-reported outcomes within the timeframes captured by RCTs.

Consistent with prior studies,[15] rhBMP-2 and ALB were associated with shorter operation times and reduced blood loss compared with AICBG, likely reflecting avoidance of graft harvest rather than intrinsic differences in fusion biology. However, these perioperative efficiencies did not translate into shorter hospital stays, underscoring that LOS is influenced by broader perioperative, local healthcare-related, and institutional factors beyond graft selection.

Taken together, these findings support the value of approach-restricted analyses in refining interpretation of osteobiologic performance and clarify that, within posterior LSF, rhBMP-2 remains the only osteobiologic supported by consistent evidence for improved fusion and safety. This is particularly relevant from a regulatory standpoint, since the rhBMP-2 formulations utilized in the included RCTs are officially approved for ALIF only, with posterior-based LSF approaches considered as off-label applications.[61,65] Therefore, the translation of the reported results into clinical practice should be interpreted with caution. Off-label use may carry specific medico-legal implications, particularly in the absence of explicit regulatory approval, and requires thorough patient counseling and informed consent. Surgeons should therefore balance the strength of the available evidence with local regulations, institutional policies, and individual patient factors when considering the use of these agents. On the other hand, the confirmed efficacy and safety of this osteobiologic in PLIF, TLIF, and PLF may serve as a benchmark for extending official indications beyond ALIF. Such an approval would not only standardize clinical practice and facilitate the development of evidence-based guidelines for PLF, but also reduce medico-legal risk, improve access and insurance coverage for patients, and enable more structured training and research to optimize dosing and safety in these commonly performed procedures. Furthermore, it could promote the broader adoption of rhBMP-2 in countries where its use is currently restricted or not approved, enhancing global access to this therapeutic option.[66] For other agents, current evidence suggests potential benefit but remains limited by imprecision, reinforcing the need for cautious interpretation and further high-quality RCTs.

This study has several limitations. Despite the inclusion of RCTs alone, clinical heterogeneity persisted in terms of surgical technique, graft combinations, and fusion assessment methods.[67] In addition, many osteobiologic comparisons were informed by a limited number of trials, resulting in wide CIs and reduced precision. Functional outcomes were inconsistently reported and likely underpowered. Cost-effectiveness and rare or late adverse events could not be adequately assessed. Potential bias related to industry funding (particularly among trials evaluating rhBMP-2) was not formally explored through sensitivity analyses. However, when comparing industry-funded and nonprivately funded studies in our previous NMA, no significant differences emerged.[15] Moreover, heterogeneity in fusion assessment methods remained present and may have influenced outcome comparability. The definition of "osteobiologic-related complications," while based on a structured and previously adopted framework,[15,68] does not fully account for the multifactorial nature of complications and may introduce overlap with efficacy outcomes (e.g., nonunion). Finally, the exclusion of non-randomized studies may limit generalizability, although necessary to preserve internal validity.

Conclusion

rhBMP-2 was the only osteobiologic to demonstrate consistent superiority over AICBG in both fusion efficacy and safety following posterior LSF. Other osteobiologics were noninferior and did not confer meaningful advantages in pain or functional outcomes. These findings provide an evidence-based framework to guide osteobiologic selection and emphasize that biological augmentation alone is unlikely to overcome the multifactorial determinants of clinical outcome in degenerative LSF.

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Data Availability Statement

The data generated and analyzed during this study will be made available upon reasonable request.

Supplemental Material

Supplemental material for this article is available online.

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