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A commentary by Thomas W. Bauer, MD, PhD, is linked to the online version of this article.

Efficacy and Safety of Osteobiologics for Lumbar Spinal Fusion

A Systematic Review and Network Meta-Analysis

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Background: Lumbar spinal fusion (LSF) is a common surgical procedure for treating lumbar degenerative conditions. The use of osteobiologics to enhance fusion has emerged as a promising alternative to address the limitations of autologous iliac crest bone graft (AICBG), but their comparative efficacy and safety remain unclear. This systematic review and network meta-analysis (NMA) aimed to assess the fusion rates, safety profiles, and clinical outcomes of the use of osteobiologics in LSF.

Methods: PubMed/MEDLINE and Scopus databases were searched for randomized controlled trials (RCTs) comparing different osteobiologics to AICBG in LSF. Data on fusion rates, complications, pain, disability, blood loss, operative time, and length of stay (LOS) were extracted. The risk of bias was evaluated using the Cochrane Risk of Bias-2 tool, and the certainty of evidence was assessed using the GRADE framework. The NMA was performed using a frequentist random-effects model to compare the efficacy and safety of various osteobiologics, along with associated perioperative and clinical outcomes.

Results: Forty-three RCTs including a total of 3,823 patients were identified. The use of rhBMP-2 (recombinant human bone morphogenetic protein-2) significantly improved fusion rates (odds ratio [OR]: 3.71; 95% confidence interval [CI]: 2.59 to 5.32; $p < 0.0001$) and reduced complications (OR: 0.30; 95% CI: 0.13 to 0.68; $p < 0.0001$) compared with AICBG, with moderate certainty of the evidence. Other osteobiologics, including ABM/P-15 (anorganic bone matrix/15-amino acid peptide fragment) and allograft, demonstrated reduced complication rates, although the quality of the evidence was low to very low. No significant differences were observed for pain, disability, or LOS. The use of rhBMP-2, autologous local bone, and silicate-substituted calcium phosphate was associated with decreased operative time, with rhBMP-2 additionally associated with lower intraoperative blood loss.

Conclusions: Use of rhBMP-2 was associated with significantly higher fusion and lower complication rates compared with AICBG, as well as decreased operative time and blood loss. Other osteobiologics may also offer benefits, but the supporting evidence is low-quality and limited by the notable underrepresentation of these materials in the published literature.

Level of Evidence: Therapeutic Level I. See Instructions for Authors for a complete description of levels of evidence.

Lumbar spinal fusion (LSF) is a widely employed surgical technique for treating degenerative conditions of the lumbar spine[1]. Achieving successful spinal fusion poses numerous challenges, including the risk of pseudarthrosis, which occurs in an estimated 5% to 15% of cases[2]. The lack of osseous fusion can result in persistent pain, spinal instability, and hardware loosening or breakage, with increased risks of revision surgery, adjacent segment disease, and considerable socioeconomic burdens[3].

Successful fusion depends on the stabilizing effect of spinal instrumentation and the use of osteobiologics to enhance bone healing[4]. These materials include various grafts and other materials

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with diverse osteoinductive, osteoconductive, and osteogenic properties, which contribute to new bone growth at the fusion site[5]. Traditionally, autologous iliac crest bone graft (AICBG) has been considered the gold standard in LSF, due to its inherent osteoconductive and osteoinductive properties coupled with its prompt availability. Despite its effectiveness, the use of AICBG is limited by donor-site morbidity and restricted availability[3,6]. Additionally, the large market potential of osteobiologics (>$9 billion in 2024[7]) has spurred the development of alternative products designed to mimic or surpass the fusion capabilities of AICBG while minimizing adverse events.

Over the years, numerous osteobiologics, including allografts, recombinant human bone morphogenetic proteins (rhBMPs), cell-based or cell-derived products, and synthetic materials, have been explored for their potential to enhance spinal fusion[8-12]. These alternatives vary remarkably in their biological activity, clinical efficacy, cost, and safety profiles[13]. To date, the safety and efficacy of available osteobiologics have been widely assessed in multiple randomized controlled trials (RCTs). While reporting generally favorable outcomes with most grafts, previous meta-analyses have highlighted notable limitations, such as small sample sizes and low quality among the included studies[1,13,14].

We conducted this systematic review and network meta-analysis (NMA) of RCTs to evaluate fusion rates, safety profiles, and clinical outcomes associated with the use of osteobiologics in LSF. Our objective was to establish a comparative framework to rank these products and their combinations, providing insights into the most effective and safest options for promoting solid fusion.

Materials and Methods

This systematic review was performed following PRISMA (Preferred Items for Systematic Reviews and Meta-Analyses) guidelines[15,16]. The review protocol was registered in the PROSPERO database (CRD42024514566). Complete details regarding the methodology utilized for this study are available in the Appendix eMethods section.

Electronic Literature Search

A systematic search of PubMed/MEDLINE and Scopus databases was performed for literature published up to March 1, 2024. We searched for studies including adult patients affected by lumbar degenerative disorders who underwent LSF augmented with osteobiologics (see Appendix eSupplement 1). Primary outcomes included fusion at the surgically treated segment(s) and osteobiologic-related complications (see Appendix eSupplement 2)[8]. Secondary outcomes included patient-reported outcome measures (PROMs) of pain and disability as well as perioperative outcomes.

Study Selection

Article screening and duplicate detection was performed using the Rayyan platform. Three reviewers (L.A., J.S., and S.T.) independently screened the titles and abstracts of the identified studies. Articles with consensus from at least 2 reviewers advanced to full-text screening. In case of disagreement, the reviewers discussed the inconsistencies until a unanimous decision was reached.

Data Extraction

Extracted data included the study characteristics, patient demographics, diagnoses, types of surgery, osteobiologics employed, and use of postoperative lumbar orthoses. A complete list of the definitions of radiographic fusion reported in the included studies is available in Appendix eTable 1. Perioperative outcomes included complications, blood loss, operative time, and length of stay (LOS). Additionally, PROMs of disability (Oswestry Disability Index [ODI]) and low back pain (LBP) severity (on a numeric rating scale [NRS] or visual analogue scale [VAS]) were extracted.

Risk of Bias and Certainty of the Evidence

The Cochrane Risk of Bias (RoB)-2 tool[17] was utilized to assess the quality of the included studies, and the certainty of the evidence was assessed with the GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework[18].

Statistical Analysis

Odds ratios (ORs) for dichotomous outcomes and mean differences (MDs) for continuous outcomes were calculated with 95% confidence intervals (CIs). Pairwise comparisons were made, and NMA was performed using a frequentist approach[19] and random-effect models. As the gold standard in LSF, AICBG was selected as the reference treatment. For each primary outcome, the treatments were ranked using the surface under the cumulative ranking curve (SUCRA)[20]. For the fusion and complication outcomes, subgroup NMAs were also performed to compare included studies according to funding status. The netmeta package within RStudio (Posit) was used to perform the analyses.

Results

Study Selection

A total of 5,834 articles were identified from the database search, 4,133 remained following duplicate removal, and 4,069 were excluded after title and abstract screening. Subsequently, 64 full-text articles were sought for retrieval; 2 were not found. The remaining 62 full-text articles were screened and 19 were excluded. The remaining 43 articles were included in the review (Fig. 1).

Study Characteristics

The 43 RCTs (42 two-arm[21-62] and 1 three-arm[63]) were published between 2002[23,24,44] and 2024[22] in Denmark[22,43], Egypt[21,63], the U.S.A.[23-25,31,34,35,37-39,45,55,57-61], Germany[26,52-54,62], South Korea[27,42,46,47], Australia[29], the People's Republic of China[30], The Netherlands[32,33], Spain[36], the Czech Republic[40], Canada[41], Sweden[44], Japan[28,50], Brazil[48,51], and Belgium[49,56]. Among these, 4 studies[22,47,58,59] were later follow-ups of previous reports[43,46,57]. Collectively, 3,823 patients with a mean age of 55.7 years, a female proportion of 58%, and a mean body mass index (BMI) of 26.5 kg/m^2 were analyzed. Follow-up ranged from

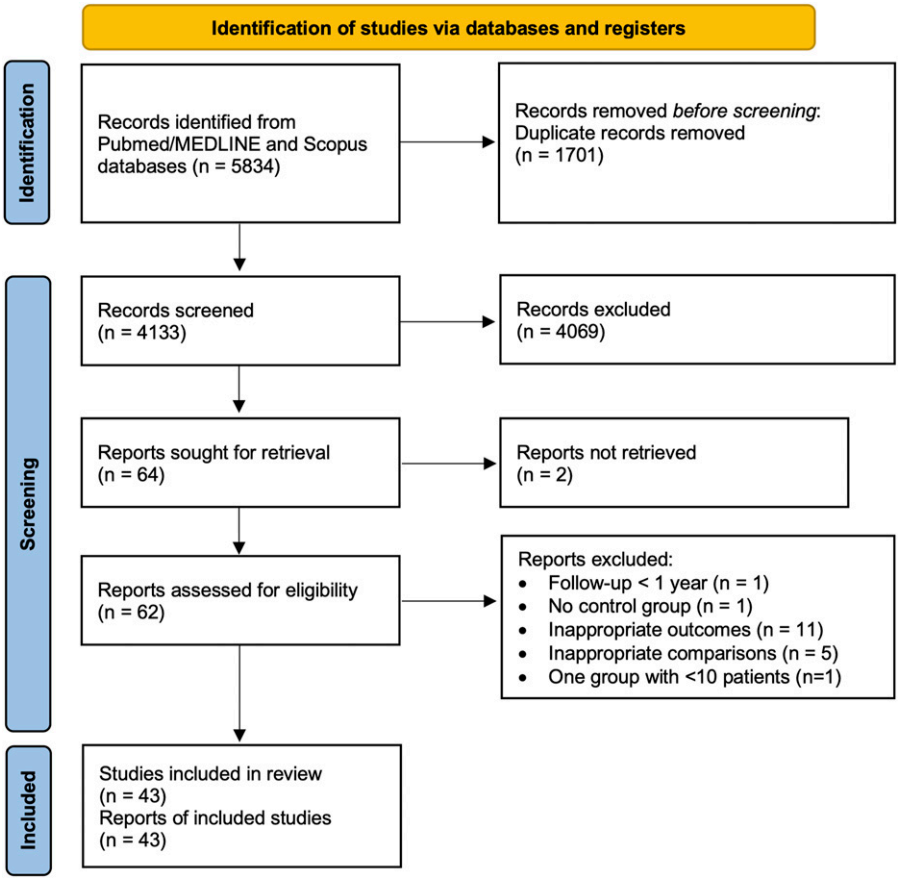


Fig. 1

PRISMA flowchart depicting the article screening process.

12 to 60 months. The surgical techniques performed encompassed transforaminal lumbar interbody fusion (TLIF)[21,36,42,61-63], posterolateral fusion (PLF; either uninstrumented[22,43,44,57-60] or instrumented[27,28,30-35,37,38,40,41,45,50,52,53]), anterior lumbar interbody fusion (ALIF)[23-26,52-55], posterior lumbar interbody fusion (PLIF)[29,39,46,47,49,56], and extreme lateral interbody fusion (XLIF)[48,51]. Osteobiologics included AICBG[21,23-25,27,30-39,41,44,45,48-50,52,53,55-60,62], autologous local bone (ALB)[21,22,28,30,32,33,38,42,43,45-47,50,52,53,61-63], rhBMP-2[23-25,27,29,31,34,35,37-39,41,42,49,51,61], allograft[22,23,25,26,36,40,43,53-55,61], rhBMP-7[32,33,44,57-60], titanium cages[46,47,55], platelet-rich plasma (PRP)[28,56,63], anorganic bone matrix/15-amino acid peptide fragment (ABM/P-15)[22,43], bioglass[46,47], demineralized bone matrix (DBM)[42,45], silicate-substituted calcium phosphate (SiCaP)[29,51], β-tricalcium phosphate (β-TCP)[30], biphasic calcium phosphate (BCP)[41], bone marrow-derived stromal cells (BM-MSC)[36], bone marrow aspirate (BMA)[26], bone marrow concentrate (BMC)[40], ceramic bone graft substitute (CBGS)[48], silica gel matrix (NH-SiO_2)[54], polyetheretherketone (PEEK) cages[61], periosteal cells[52], platelet-rich fibrin (PRF)[63], and hydroxyapatite (HA)[62]. General characteristics of the included studies are summarized in Table I and Appendix eTable 2. Overall, 8 studies (18.6%) had a low risk of bias, 13 (30.2%) had "some concerns," and 22 (51.2%) had a high risk of bias (see Appendix eFigure 1).

Fusion Rate

The NMA for fusion rate included 30 RCTs with a total of 2,671 patients and 18 different combinations of osteobiologics (Fig. 2-A; see also Appendix eTable 3). Compared with AICBG, rhBMP-2 showed a significantly higher fusion rate (OR: 3.71; 95% CI: 2.59 to 5.32; $p < 0.0001$), while all other treatments showed no significant differences (Fig. 3-A), with low inconsistency and heterogeneity (τ^2: 0%; I^2: 0% [95% CI: 0.0% to 53.6%]; $p = 0.73$). No significant publication bias was detected ($p = 0.21$; see Appendix eFigure 2). The importance of individual studies within the network is depicted in Appendix eFigure 3.

When subgrouping studies receiving industry funding (10 studies, 1,281 patients) and those funded by nonprivate, governmental, or institutional sources (6 studies, 463 patients), rhBMP-2 demonstrated greater effectiveness than AICBG in both (OR: 3.80; 95% CI: 2.56 to 5.64; $p < 0.0001$ for industry-funded studies and OR: 3.32; 95% CI: 1.41 to 7.85; $p = 0.01$ for nonindustry-funded studies; see Appendix eFigure 4-A), whereas rhBMP-7 yielded significantly lower fusion rates than AICBG only in the former (OR: 0.41; 95% CI: 0.19 to 0.87; $p = 0.02$). The certainty of the evidence was moderate for rhBMP-2 and low to very low for the other osteobiologics (see Appendix eTable 4).

TABLE I General Characteristics and Patient Demographics of Included Studies*

Study	Country	Funding	Patient Diagnosis	Type of Surgery	Last Follow-up *(mo)*	Treatment Groups	No. of Patients	Age† *(yr)*	Sex, M/F	BMI† *(kg/m²)*	Smokers	Lost to Follow-up
Abou-Madawi 2022[21]	Egypt	None	1-level grade I-II spondylolisthesis not responding to conservative treatment >3 months	TLIF	≥24	ALB	54	47.0 ± 18.0	30/24	24.9 ± 5.3	10	13 total
						AICBG	54	49.0 ± 18.0	27/27	23.5 ± 4.5	8	
Andresen 2024[22]#	Denmark	Cerapedics	LSS with 1- or 2-level DLS	Uninstrumented PLF	60	ABM/P-15 + ALB	43	71.4 ± 6.3	8/35	27.4 ± 4.0	2	7, 22‡
						Allograft + ALB	40	70.1 ± 6.8	8/32	26.9 ± 3.9	0	11, 21‡
Burkus 2002a[23]	U.S.A.	Medtronic	1-level lumbar IDD not responding to conservative treatment >6 months	Standalone ALIF	24	Allograft + rhBMP-2	24	41.5	16/8	NS	8	0
						Allograft + AICBG	22	45.6	10/12	NS	6	2
Burkus 2002b[24]	U.S.A.	NS	1-level lumbar IDD not responding to conservative treatment >6 months	Standalone ALIF	24	rhBMP-2	143	43.3	78/65	NS	47	11
						AICBG	136	42.3	68/68	NS	49	13
Burkus 2005[25]	U.S.A.	Medtronic	1-level lumbar IDD ± grade I DLS not responding to conservative treatment >6 months	Standalone ALIF	24	Allograft + rhBMP-2	79	40.2	32/47	NS	26	3
						Allograft + AICBG	52	43.6	19/33	NS	17	2
Chatterjee 2020[26]	Germany	None	IDD, post-laminectomy syndrome, spondylolisthesis, LSS, failed discectomy, recurrent LDH between L2-L3 and L5-S1	ALIF with plated cage or pedicle screw fixation	12	Allograft	21	59.0 ± 14.6	4/17	25.5 ± 4.4	14	NS
						Allograft + BMA	21	58.3 ± 34.0	10/11	27.4 ± 5.3	15	NS
Cho 2023[27]	South Korea	CGBio/ BioAlpha	1-level LSS, grade 1 DLS or spondylolysis	Instrumented PLF	36	rhBMP-2	32	63.2 ± 8.2	17/15	25.2 ± 3.3	0	4
						AICBG	41	60.8 ± 9.0	18/23	25.9 ± 3.3	1	4
Coughlan 2018[29]	Australia	Baxter Healthcare	1- or 2-level lumbar IDD, spondylolisthesis or LDH not responding to conservative treatment >6 months	PLIF	24	SiCaP	51	50.8 ± 11.4	27/24	26.9 ± 4.3	42	4 total
						rhBMP-2	52	52.3 ± 11.6	28/24	28.6 ± 5.0	41	
Dai 2008[30]	People's Republic of China	Shanghai Natural Science Foundation	1-level LSS	Instrumented PLF	36	β-TCP + ALB	32	48-72	14/18	23-32	5	0
						AICBG + ALB	30	51-73	11/19	20-31	3	0
Dawson 2009[31]	U.S.A.	Medtronic	1- or 2-level lumbar IDD not responding to conservative treatment >6 months	Instrumented PLF	24	rhBMP-2	25	55.9	10/15	NS	6	3
						AICBG	21	56.9	9/12	NS	5	3
Delawi 2010[32]	The Netherlands	Corporate/ industry	1-level grade I-II isthmic or DLS	Instrumented PLF	12	rhBMP-7 + ALB	18	53.0 ± 18.0	10/8	26.0 ± 4.0	8	1
						AICBG + ALB	16	55.0 ± 13.0	6/10	27.0 ± 3.0	4	0
Delawi 2016[33]	The Netherlands	Stryker	1-level DLS or isthmic spondylolisthesis with central or foraminal LSS	Instrumented PLF	12	rhBMP-7 + ALB	60	54.0 ± 14.0	27/33	26.6 ± 4.0	29	3
						AICBG + ALB	59	55.0 ± 13.0	25/34	25.2 ± 5.0	18	3
Dimar 2006[34]	U.S.A.	None	1-level symptomatic lumbar IDD >6 months	Instrumented PLF	24	AICBG	45	52.7	20/25	NS	10	NS
						rhBMP-2	53	50.9	22/31	NS	17	NS
Dimar 2009[35]	U.S.A.	Medtronic	1-level symptomatic lumbar IDD >6 months	Instrumented PLF	24	rhBMP-2	239	53.2 (20-81)	108/131	NS	63	23
						AICBG	224	52.3 (18-86)	95/129	NS	59	33
García de Frutos 2020[36]	Spain	Government funding	Grade I-II DLS ± lumbar 1- or 2-level(s) IDD	TLIF	12	BM-MSCs + allograft + AICBG	34	61.0 ± 14.6	9/25	NS	NS	2
						AICBG	35	60.5 ± 10.3	14/21	NS	NS	2
Glassman 2005[37]	U.S.A.	Cooperate/ industry	1-level lumbar IDD ± grade I DLS not responding to conservative treatment >6 months	Instrumented PLF	12	rhBMP-2	38	53	14/24	NS	8	0
						AICBG	36	53	16/20	NS	8	0

continued

TABLE I (*continued*)

Study	Country	Funding	Patient Diagnosis	Type of Surgery	Last Follow-up *(mo)*	Treatment Groups	No. of Patients	Age† *(yr)*	Sex, M/F	BMI† *(kg/m²)*	Smokers	Lost to Follow-up
Glassman 2008[38]	U.S.A.	Norton Healthcare	IDD, LSS, DLS, deformity, post-decompression revision between L1-S1	Instrumented PLF	24	rhBMP-2 + ALB	50	69.2 ± 5.5	15/35	29.4 ± 5.7	11	3
						AICBG + ALB	52	69.9 ± 5.8	17/35	28.1 ± 6.1	9	3
Haid 2004[39]	U.S.A.	NS	1-level lumbar IDD not responding to conservative treatment >6 months	Standalone PLIF	24	rhBMP-2	34	46.3 (25.8-66.1)	17/17	NS	18	4
						AICBG	33	46.1 (28.5-70.9)	15/18	NS	15	0
Hart 2014[40]	The Czech Republic	NS	Lumbar IDD	Instrumented PLF	24	Allograft	40	62.7 (47-77)	10/30	NS	NS	0
						Allograft + BMC	40	58.5 (42-80)	12/28	NS	NS	0
Hurlbert 2013[41]	Canada	Medtronic	1- or 2-level lumbar IDD	Instrumented PLF	48	rhBMP-2 + BCP	98	53.0	35/63	NS	NS	3
						AIBCG	99	53.0	48/51	NS	NS	6
Hyun 2021[42]	South Korea	Government funding	1- or 2-level IDD between L3-S1	TLIF	12	DBM + rhBMP-2 + ALB	40	64.0 ± 10.3	23/17	24.3 ± 2.7	15	7
						DBM + ALB	36	62.7 ± 9.3	19/17	26.2 ± 4.2	11	3
Jacobsen 2020[43]	Denmark	Orthotech	LSS with 1- or 2-level DLS	Uninstrumented PLF	24	ABM/P-15 + ALB	49	71.4 ± 6.3	14/35	27.4 ± 4.0	NS	0
						Allograft + ALB	49	70.1 ± 6.8	10/39	26.9 ± 3.9	NS	0
Johnsson 2002[44]	Sweden	Cooperate/ industry	Grade I-II isthmic spondylolisthesis	Uninstrumented PLF	12	rhBMP-7	10	42.9 ± 10.8	3/7	NS	4	0
						AICBG	10	40.4 ± 9.6	5/5	NS	3	0
Kang 2012[45]	U.S.A.	Osteotech	1-level DLS with LSS	Instrumented PLF	24	DBM + ALB	28	64.3	10/18	NS	0	2
						AICBG	13	65.3	5/8	NS	0	3
Kubota 2019[28]	Japan	None	LSS with unstable DLS	Instrumented PLF	24	PRP + ALB	25	65.1 ± 2.1	15/10	NS	NS	6
						ALB	25	65.3 ± 2.0	14/11	NS	NS	6
Lee 2016[46]	South Korea	CGBio/ BioAlpha	Severe disc extrusion, LSS, or grade I-II DLS	PLIF	12	Bioglass + ALB	39	61.5 ± 9.4	12/27	NS	4	0
						Titanium cage + ALB	35	61.1 ± 8.3	14/21	NS	2	0
Lee 2020[47],§	South Korea	CGBio/ BioAlpha	Severe disc extrusion, LSS, or grade I-II DLS	PLIF	48	Bioglass + ALB	32	61.5 ± 8.9	8/24	NS	2	7
						Titanium cage + ALB	30	61.1 ± 8.3	12/18	NS	2	5
Menezes 2022[48]	Brazil	Nuvasive	1-level lumbar IDD	XLIF + pedicle screw fixation	24	CBGS	30	57.0 ± 3.8 overall	22/23 overall	26.8 ± 4.1 overall	3 total	2
						AICBG	15					1
Michielsen 2013[49]	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	24	rhBMP-2	19	43.2 ± 8.8	6/13	27.0 ± 3.2	5	0
						AICBG	19	42.2 ± 9.7	10/9	24.6 ± 3.4	10	0
Mohi El din 2021[63]	Egypt	None	1-level isthmic or DLS or IDD not responding to conservative treatment >6 months	TLIF	12	ALB	40	45.1 ± 9.9	17/23	NS	NS	10
						PRF	20	47.4 ± 6.2	10/10	NS	NS	5
						PRP	20	44.1 ± 4.5	9/11	NS	NS	6
Ohtori 2011[50]	Japan	NS	L4-L5 DLS with LSS and chronic LBP >12 months	Instrumented PLF	24	ALB	42	66.0 ± 5.5	22/20	NS	NS	0
						ALB + AICBG	40	67.0 ± 6.0	18/22	NS	NS	0
Pimenta 2013[51]	Brazil	NS	L4-L5 IDD not responding to conservative treatment	Standalone XLIF	36	SiCaP	15	49.1 ± 10.7	4/11	NS	NS	3
						rhBMP-2	15	45.7 ± 11.4	7/8	NS	NS	3
Putzier 2008[52]	Germany	NS	1-level lumbar IDD or grade I-II spondylolisthesis	ALIF + instrumented PLF	12	AICBG + ALB	11	49.3 (34-60)	12/12 overall	NS	NS	1
						Periosteal cells + ALB	13	46.4 (34-58)		NS	NS	2
Putzier 2009[53]	Germany	NS	L4-L5 or L5-S1 lumbar IDD not responding to conservative treatment >6 months	ALIF + instrumented PLF	12	Allograft + ALB	20	45.5 (34-62)	10/10	NS	NS	2
						AICBG + ALB	20	45.4 (26-62)	11/9	NS	NS	2

continued

TABLE I (*continued*)

Study	Country	Funding	Patient Diagnosis	Type of Surgery	Last Follow-up *(mo)*	Treatment Groups	No. of Patients	Age† *(yr)*	Sex, M/F	BMI† *(kg/m²)*	Smokers	Lost to Follow-up
Rickert 2019[54]	Germany	None	L4-L5 or L5-S1 IDD	ALIF with plated cage or ALIF + pedicle screw fixation	12	NH-SiO_2	20	60.6 ± 12.5	6/14	26.4 ± 4.6	NS	1
						Allograft	20	66.1 ± 9.6	4/16	26.5 ± 4.9	NS	3
Sasso 2004[55]	U.S.A.	Cooperate/ industry	1-level symptomatic lumbar IDD >6 months	Standalone ALIF	48	Titanium cage + AICBG	77	41.0 (18-64)	30/47	NS	23	25
						Allograft + AICBG	62	41.2 (27-59)	33/29	NS	20	19
Sys 2011[56]	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	24	PRP + AICBG	19	NS	12/7	27.2 ± 5.0	8	1
						AICBG	19	NS	12/7	25.4 ± 3.6	9	1
Vaccaro 2004[57]	U.S.A.	Cooperate/ industry	Grade I-II DLS with LSS not responding to conservative treatment	Uninstrumented PLF	24	rhBMP-7	24	63.0 ± 11.0	11/13	NS	Excluded	2
						AICBG	12	66.0 ± 7.0	5/7	NS	Excluded	5
Vaccaro 2005[58]§	U.S.A.	Cooperate/ industry	Grade I-II L3-L4 DLS + LSS	Uninstrumented PLF	36	rhBMP-7	24	63.0 ± 11.0	11/13	NS	Excluded	3
						AICBG	12	66.0 ± 7.0	5/7	NS	Excluded	1
Vaccaro 2008a[60]	U.S.A.	None	Grade I-II DLS with LSS not responding to conservative treatment	Uninstrumented PLF	≥36	rhBMP-7	207	68.0 ± 9.8	71/136	NS	NS	63
						AICBG	86	71.0 ± 8.3	26/60	NS	NS	28
Vaccaro 2008b[59]§	U.S.A.	NS	Grade I-II DLS with LSS not responding to conservative treatment	Uninstrumented PLF	48	rhBMP-7	24	63.0 (43-80)	11/13	NS	Excluded	5
						AICBG	12	67.0 (51-79)	5/7	NS	Excluded	4
Villavicencio 2022[61]	U.S.A.	None	Chronic LBP due to IDD with LSS, spondylolisthesis, or recurrent LDH not responding to conservative treatment >6 months	TLIF	24	Allograft + rhBMP-2 + ALB	60	59.9 ± 10.4	31/29	NS	3	3
						PEEK + rhBMP-2 + ALB	61	62.2 ± 10.7	32/29	NS	1	3
vonderHoeh 2017[62]	Germany	Medtronic	1- or 2-level lumbar IDD not responding to conservative treatment >6 months	TLIF	12	ALB + HA	24	64.3 ± 12.6	7/17	NS	1	1
						AICBG	24	65.6 ± 14.4	5/19	NS	0	1

*ABM/P-15 = anorganic bone matrix/15-amino acid peptide fragment, ALB = autologous local bone, AICBG = autologous iliac crest bone graft, ALIF = anterior lumbar interbody fusion, 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, BMI = body mass index, CBGS = ceramic bone graft substitute, 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, NH-SiO_2 = silica gel matrix, 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, TLIF = transforaminal lumbar interbody fusion, XLIF = extreme lateral interbody fusion. †Values are given as the mean, mean ± standard deviation, mean (range), or range. ‡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 + ALB groups, respectively. §Later follow-up report of the preceding study. #Later follow-up report of the study by Jacobsen et al.[43].

Complication Rate

The NMA for complication rates included 29 RCTs with a total of 2,805 patients and 15 different combinations of osteobiologics (Fig. 2-B; see also Appendix eTable 5). The use of rhBMP-2 (OR: 0.30; 95% CI: 0.13 to 0.68; $p < 0.0001$) showed significantly lower complication rates, while all other treatments were not significantly different from AICBG (Fig. 3-B). A high degree of heterogeneity (τ^2: 4.41%; I^2: 74.1% [95% CI: 35.7% to 89.6%]; $p = 0.004$) and no publication bias were detected ($p = 0.15$; see Appendix eFigure 5). The importance of individual studies within the network is depicted in Appendix eFigure 6. The subgroup analysis of industry-funded (12 studies, 1,634 patients) and nonindustry-funded studies (5 studies, 485 patients) revealed that complications rates were significantly lower for rhBMP-2 compared with AICBG in both (OR: 0.28; 95% CI: 0.09 to 0.90; $p = 0.03$ for industry-funded, and OR: 0.41; 95% CI: 0.19 to 0.90; $p = 0.03$ for nonindustry-funded studies) (see Appendix eFigure 4-B). The certainty of the evidence was moderate for rhBMP-2 and low to very low for the other osteobiologics (see Appendix eTable 6).

Head-to-head comparisons for the primary outcomes are shown in Appendix eFigure 7. The SUCRA scores of each osteobiologic with respect to fusion and complications have been interpolated in a cluster ranking plot in Figure 4. The best-performing osteobiologics (>50% safety and >50% efficacy) were ABM/P-15, allograft + BMC, NH-SiO_2, and rhBMP-2. Conversely, rhBMP-7, HA + ALB, ALB + AICBG, CBGS, AICBG, and ALB displayed overall lower performance (<50% safety and <50% efficacy).

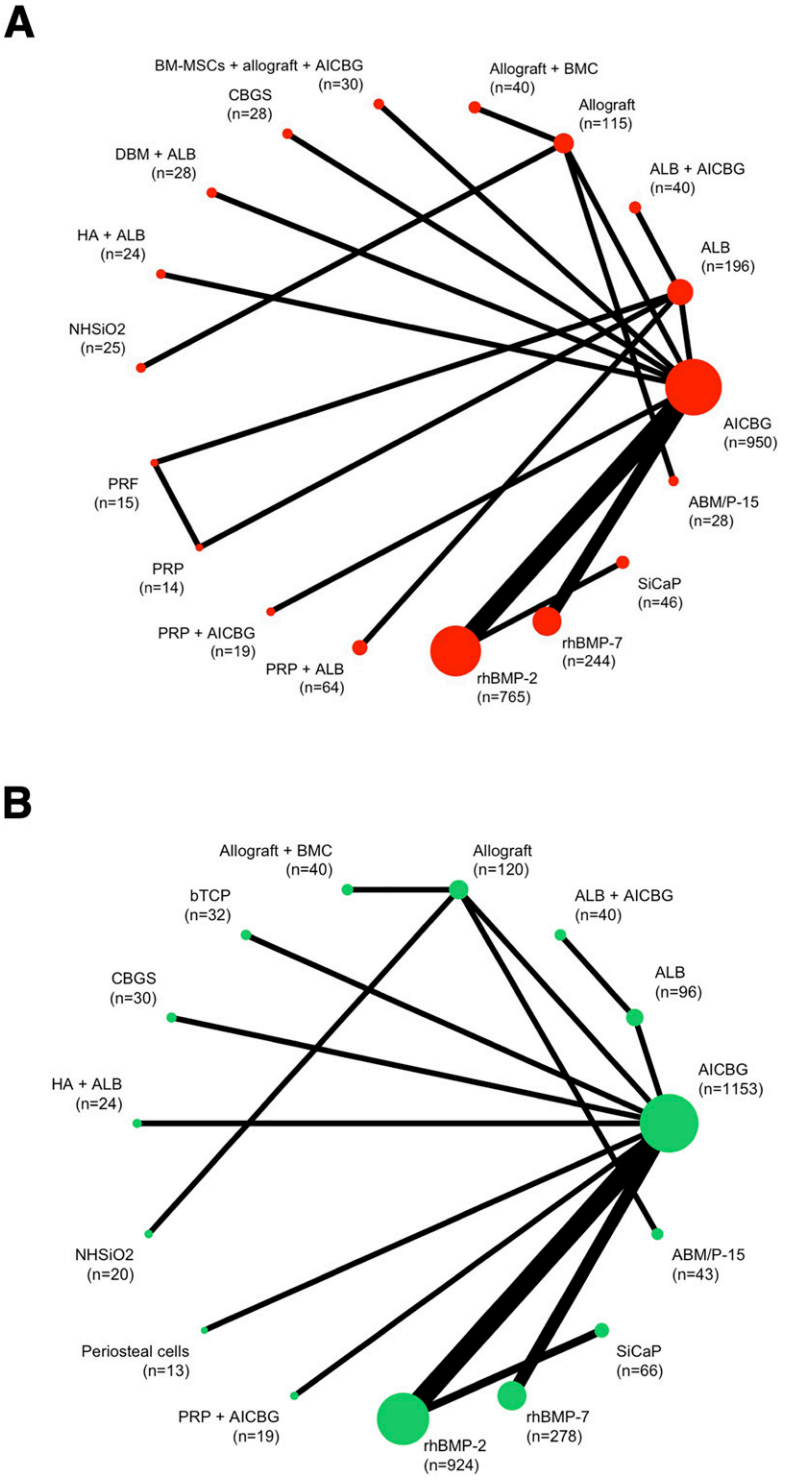


Fig. 2

Network meta-analyses of eligible comparisons for fusion (**Fig. 2-A**) and complication rates (**Fig. 2-B**). Line width is proportional to the number of RCTs comparing each individual treatment vs. AICBG. Circle size is proportional to the number of patients receiving the treatment (which is indicated below the circle). ALB = autologous local bone, AICBG = autologous iliac crest bone graft, ABM/P-15 = anorganic bone matrix/15-amino acid peptide fragment, BM-MSCs = bone marrow-derived mesenchymal stromal cells, BMC = bone marrow concentrate, CBGS = ceramic bone graft substitute, DBM = demineralized bone matrix, HA = hydroxyapatite, NHSiO2 = silica gel matrix, PRF = platelet-rich fibrin, PRP = platelet-rich plasma, rhBMP = recombinant human bone morphogenetic protein, SiCaP = silicate-substituted calcium phosphate.

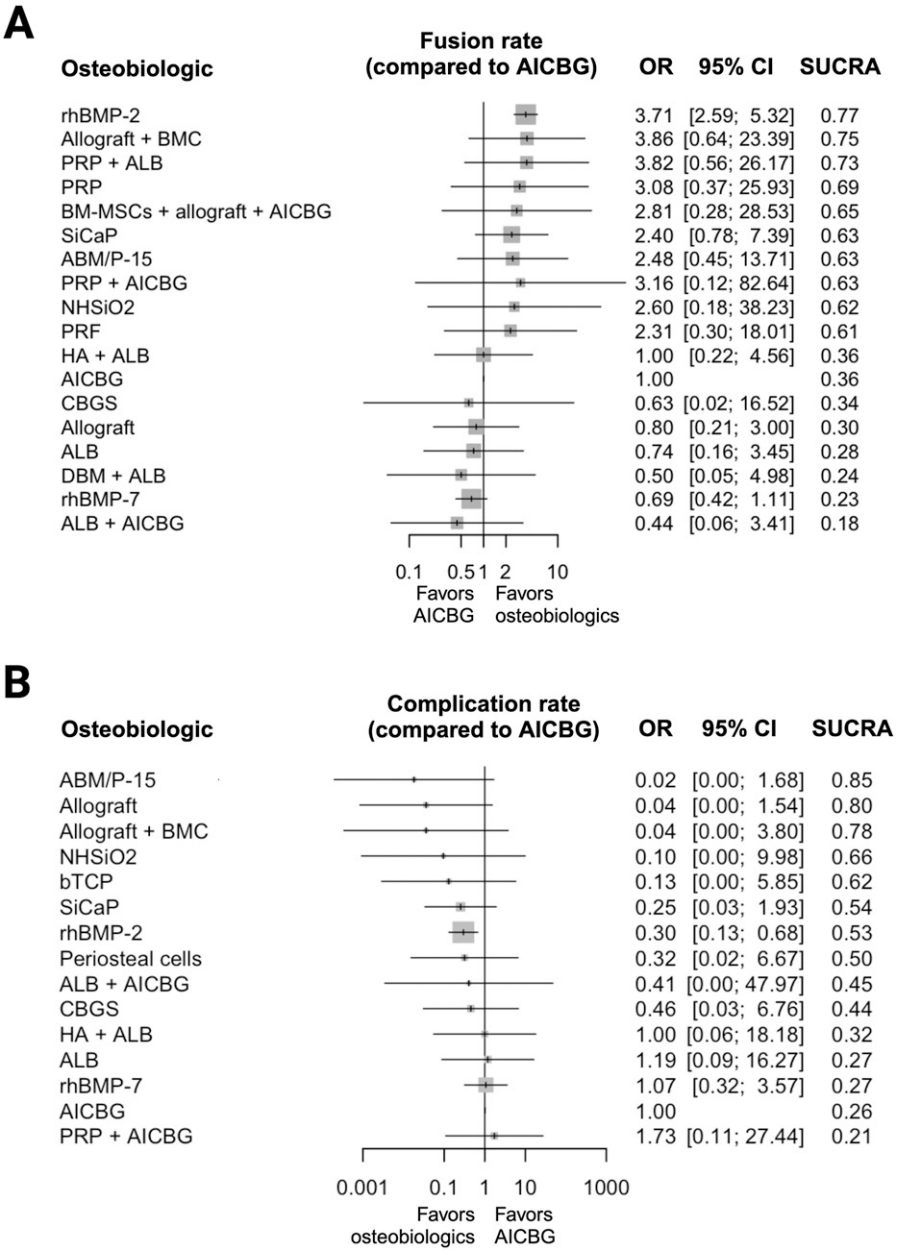


Fig. 3

Forest plots of network meta-analyses of fusion (**Fig. 3-A**) and complication rates (**Fig. 3-B**) of other osteobiologics compared with AICBG. Each square size is inversely proportional to the precision of the effect estimate (i.e., CI width). Osteobiologics are reported from highest to lowest SUCRA score. ALB = autologous local bone, AICBG = autologous iliac crest bone graft, ABM/P-15 = anorganic bone matrix/15-amino acid peptide fragment, bTCP = β-tricalcium phosphate, BM-MSCs = bone marrow-derived mesenchymal stromal cells, BMC = bone marrow concentrate, CBGS = ceramic bone graft substitute, CI = confidence interval, DBM = demineralized bone matrix, HA = hydroxyapatite, $NHSiO_2$ = silica gel matrix, OR = odds ratio, PRF = platelet-rich fibrin, PRP = platelet-rich plasma, rhBMP = recombinant human bone morphogenetic protein, SiCaP = silicate-substituted calcium phosphate, SUCRA = surface under the cumulative ranking curve.

Secondary Outcomes

The NMA for LBP severity included 13 studies with a total of 900 patients and 12 different combinations of osteobiologics (see Appendix eFigure 8-A). No significant differences between the analyzed treatments and AICBG were found, although the NMA showed a high degree of heterogeneity (τ^2: 7.778; I^2: 96.9% [95% CI: 93.6% to 98.5%]; $p < 0.0001$). Similarly, no significant differences were found for the ODI (19 studies, 1,788 patients, 16 different combinations of osteobiologics; see Appendix eFigure 8-B), with a high degree of heterogeneity (τ^2: 4.408; I^2: 74.1% [95% CI: 35.7% to 89.6%]; $p = 0.004$). The NMA for operative time (11 studies, 1,143 patients, 7 different

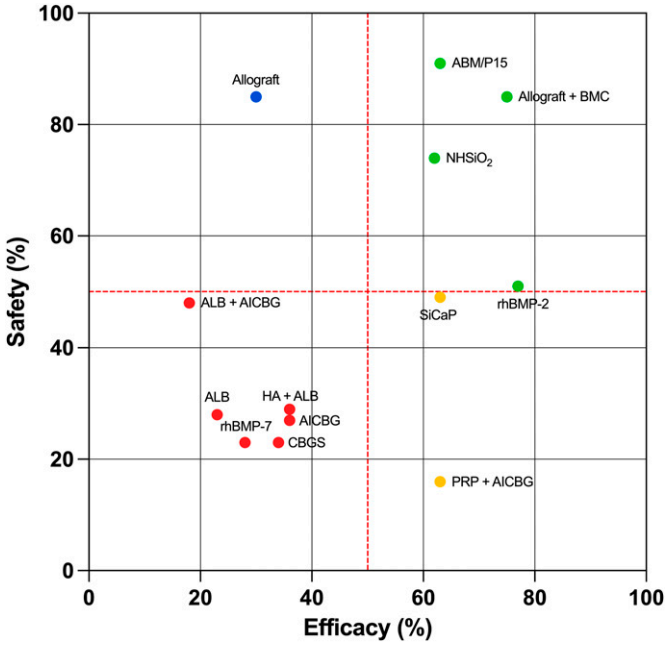


Fig. 4

Cluster ranking plot of osteobiologic efficacy and safety of the included osteobiologics, based on the SUCRA values for fusion and complications. Values closer to 100% indicate an increased spinal fusion rate or a reduced complication rate, respectively. Dot colors are based on the quadrants: green, >50% SUCRA for safety and efficacy; blue, >50% for safety but ≤50% for efficacy; yellow, ≤50% for safety but >50% for efficacy; and orange, ≤50% for both efficacy and safety. ALB = autologous local bone, AICBG = autologous iliac crest bone graft, ABM/P15 = anorganic bone matrix/15-amino acid peptide fragment, BMC = bone marrow concentrate, CBGS = ceramic bone graft substitute, HA = hydroxyapatite, $NHSiO_2$ = silica gel matrix, PRP = platelet-rich plasma, rhBMP = recombinant human bone morphogenetic protein, SiCaP = silicate-substituted calcium phosphate, SUCRA = surface under the cumulative ranking curve.,

combinations of osteobiologics; see Appendix eFigure 8-C) demonstrated that ALB (MD: −12.0 minutes; 95% CI: −21.5 to −2.5 minutes; p = 0.01), SiCaP (MD: −18.4 minutes; 95% CI: −28.6 to −8.3 minutes; p = 0.0004), and rhBMP-2 (MD: −21.8 minutes; 95% CI: −28.0 to −15.7 minutes; p < 0.0001) demonstrated significantly reduced operative times compared with AICBG. No significant heterogeneity was found (τ^2: 0; I^2: 0% [95% CI: 0% to 74.6%]; p = 0.8371). Regarding blood loss (8 studies, 891 patients, 5 different combinations of osteobiologics; see Appendix eFigure 8-D), rhBMP-2 was significantly more effective compared with AICBG (MD: −72.6 mL; 95% CI: −118.9 to −26.4 mL; p = 0.002), with no significant heterogeneity (τ^2: 960.3; I^2: 44.5% [95% CI: 0% to 79.7%]; p = 0.13). The analysis of LOS (7 studies, 891 patients, 5 different combinations of osteobiologics; see Appendix eFigure 8-E) showed no significant differences, with low heterogeneity (τ^2: 0; I^2: 0% [95% CI: 0% to 89.6%]; p = 0.64). No significant publication bias was detected for any of the secondary outcomes (see Appendix eFigures 9-A through 9-E).

Discussion

This study represents the most comprehensive assessment of osteobiologics in LSF to date, revealing critical insights into their efficacy and safety. Among the products analyzed, rhBMP-2 consistently demonstrated the highest fusion rates, significantly outperforming the traditional gold standard, AICBG. These results align with trends in spinal surgery favoring off-the-shelf alternatives due to their availability, reduced operative times, and lower donor-site morbidity[64]. However, the lack of consistency in defining "successful" spinal fusion across studies represents a notable limitation, emphasizing the need for a standardized consensus within the spine community to accurately classify and report fusion success[8]. Additionally, while the enhanced fusion rates observed with certain osteobiologics are promising, their long-term impact on clinical outcomes remains underexplored.

In terms of safety, rhBMP-2 demonstrated significant advantages over AICBG, particularly by abating the risk of donor-site complications. While this product significantly reduced the overall complication rate compared with AICBG, it did not lead to broader improvements in the safety profile of LSF, raising questions about the extent of its clinical benefit beyond fewer complications. It is important to note that our NMA examined overall complication rates, including those considered relevant in the recent AO Spine Guideline for the Use of Osteobiologics (AOGO) Guideline[65]. Not all complications carry the same weight, and a more in-depth analysis of the specific adverse events may be required to fully appraise product safety. Notably, the safety profile of rhBMP-2 has been complicated by controversy in the past, particularly regarding overstating safety outcomes in studies with potential conflicts of interest[66]. Despite the limited number of studies, our analysis revealed significant safety benefits independent of the type of funding source. However, the amount of rhBMP-2 used varied up to 10-fold among studies, which might also have affected the results. Additionally, several osteobiologics have been systematically utilized off-label. For example, rhBMP-2 and ABM/P15 were originally approved for ALIF[67] and anterior cervical interbody fusion only[68], respectively. This raises further concerns regarding safety issues and possible competing interests related to the use of certain products.

Despite enhanced fusion rates, the use of osteobiologics did not translate into significant improvements in PROMs for pain or disability. This lack of effect is not surprising, as the recovery trajectory in patients who have undergone LSF is influenced by multiple factors beyond osteobiologics, such as pre-existing conditions, comorbidities, and variations in surgical techniques[69]. Additionally, data on perioperative outcomes, such as blood loss, LOS, and operative time, were sparse. The available data suggest that rhBMP-2 offered benefits in reducing both operative time and blood loss, potentially improving overall surgical outcomes. Similarly, SiCaP, likely due to its off-the-shelf nature, and ALB, which does not require additional time for harvesting, showed shorter operative times. These findings highlight the need for studies with an improved design integrating perioperative outcomes with long-term clinical results

to ultimately better inform surgical decision-making and optimize patient care.

Our study design allowed us to include more RCTs than previous meta-analyses, such as those by Zhang et al. (analyzing 19 RCTs)[70] and Feng et al. (analyzing 27 RCTs)[71], reflecting the thoroughness of our search strategy. However, our finding that rhBMP-2 improved fusion rates while reducing complication rates contrasts with the latter study[71]. Whereas those authors similarly reported increased fusion rates, they found that rhBMP-2 use was associated with a higher incidence of complications[71]. This discrepancy may be due to their inclusion of a broader range of adverse events, including those not specific to LSF. Additionally, their NMA ranked AICBG higher in terms of safety compared with ours, possibly due to differences in defining complications, such as whether donor-site pain was considered. Moreover, our analysis included a larger number of studies, which could have contributed to the differing results. Notably, products such as SiCaP and NH-SiO_2 ranked relatively high in both safety and efficacy in our analysis, although significance was not reached. Some of our highly ranked products, such as ABM/P15 and allograft + BMC, were not included in the analysis by Feng et al.[71].

The potential advantages of off-the-shelf and non-biologically processed osteobiologics, such as SiCaP, NH-SiO_2, rhBMP-2, and ABM/P15, while requiring further exploration, are promising. Indeed, these products allow for easy scalability and for quality control in specialized environments, and they are not donor-reliant, enabling large-scale production and consistent supply. Over time, this could help reduce costs and expand access to these osteobiologics, making them appealing options for LSF. Although cell-based or cell-derived products, such as allografts, ALB, PRP, and BMC, have demonstrated beneficial outcomes, their effectiveness can be highly dependent on donor quality[72-74]. A particular consideration for such autologous products is that patients undergoing LSF often are elderly or affected by underlying health conditions, which may temper product potency. Alternatively, the addition of cells might be advantageous for recipients whose cellular function is compromised due to age or disease, by potentially enhancing the osteogenesis necessary for successful fusion[75]. However, this area requires further investigation to fully understand its implications.

This NMA has several limitations. Numerous included studies were funded by corporate sponsors. The influence of such funding on the validity, interpretation, and reporting of data remains uncertain, and the results should therefore be interpreted with caution, especially considering the contentious history of rhBMP-2 in cervical and lumbar fusion surgery[66]. Nonetheless, our analysis showed significant and relevant improvements with rhBMP-2 regardless of the funding source, supporting its use for LSF. The heterogeneity in patient populations, surgical techniques, instrumentation, and outcome definitions challenged the assumption of transitivity, which is crucial for valid indirect comparisons in NMAs. Variability in reported data, such as follow-up durations and fusion success criteria, complicated comparisons and might have introduced bias. The general high-to-moderate risk of bias in the included RCTs adds uncertainty to the findings. Additionally, the underrepresentation of several osteobiologics in the current published literature may have skewed the results toward rhBMP-2, AICBG, and other well-represented grafts, thereby potentially limiting the generalizability of our findings in a wider real-world scenario. Furthermore, there is a critical need for more high-quality, publicly funded trials, as current funding sources appear to influence outcomes such as complication rates. Considering the substantial socioeconomic burden of LBP, it is imperative that governments and insurance companies allocate more resources to investigate the cost-effectiveness of these osteobiologics. Additionally, spine professionals must advocate for greater investment in such high-quality studies to ensure evidence-based decision-making.

Conclusions

In this systematic review and NMA, we found that rhBMP-2 use was associated with significantly enhanced fusion, lower complication rates, decreased blood loss, and shorter operative time compared with AICBG. However, the lower complication rates in funded studies suggest potential bias, highlighting the need for cautious interpretation and further investigation. Additionally, the underrepresentation of several osteobiologics in the published literature substantially limits the generalizability of these findings.

Appendix

eA Supporting material provided by the authors is posted with the online version of this article as a data supplement at jbjs.org (http://links.lww.com/JBJS/I741). ■

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