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Biologic Augmentation in Lumbar Spinal Fusion: A Systematic Review of Recombinant Bone Morphogenetic Protein-2, Mesenchymal Stem Cells, and Platelet-Rich Plasma

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Abstract

Achieving solid arthrodesis remains a key challenge in lumbar spinal fusion, particularly in patients at increased risk of pseudarthrosis. Biologic augmentation has been introduced to enhance fusion biology; however, its clinical value remains incompletely defined. To systematically review the clinical evidence on biologic augmentation in adult lumbar spinal fusion, focusing on radiographic fusion, clinical outcomes, and safety. A systematic search of PubMed, the Cochrane Library, and ScienceDirect was conducted in accordance with PRISMA guidelines. Comparative clinical studies evaluating rhBMP-2, mesenchymal stem cells, or platelet-rich plasma in lumbar fusion were included. Data were synthesized qualitatively because of clinical and methodological heterogeneity. Six studies met the inclusion criteria. Biologic augmentation was consistently associated with higher fusion rates or faster radiographic fusion compared with conventional grafting methods. However, improvements in patient-reported outcomes, including pain and functional scores, were generally comparable between the biologic and control groups. Complication rates were also similar, with no consistent safety concerns directly attributable to the biologic agents. The findings suggest that biologic augmentation primarily enhances fusion biology rather than clinical recovery. Differences among biologic agents reflect distinct mechanisms of action and may influence the timing of fusion rather than long-term outcomes. Biologic augmentation improves radiographic fusion in lumbar spinal surgery but does not consistently improve clinical outcomes. Careful patient selection and further high-quality trials are warranted.

Keywords: Lumbar Fusion, Biologic Augmentation, Bone Morphogenetic Protein, Mesenchymal Stem Cells, Platelet-Rich Plasma

INTRODUCTION

Lumbar spinal fusion is a widely performed surgical procedure for degenerative lumbar pathologies that remain symptomatic despite conservative treatment. It is commonly indicated for patients with persistent mechanical back pain, radiculopathy, spinal instability, degenerative disc disease, stenosis, or spondylolisthesis. Over the past decade, both the volume and technical profile of lumbar fusion procedures have continued to evolve, particularly with the increasing use of interbody techniques and advances in spinal instrumentation.(1,2) However, the long-term success of lumbar fusion depends not only on mechanical stabilization but also on the biological processes of bone formation, remodeling, and integration across the fusion bed.

Despite advances in surgical techniques, pseudarthrosis remains an important cause of suboptimal outcomes after lumbar fusion. Nonunion is influenced by multiple patient- and procedure-related factors, including advanced age, smoking, poor bone quality, and multilevel fusion

constructs.(3,4) Clinically, pseudarthrosis may lead to persistent pain, delayed functional recovery, and an increased risk of revision surgery. Its assessment is further complicated by variability in radiographic fusion criteria, imaging modalities, and the timing of evaluation across studies.(3) This heterogeneity makes it difficult to compare fusion success across trials and may obscure the true clinical relevance of biologic interventions.

Autologous iliac crest bone graft (ICBG) has traditionally been regarded as the gold-standard graft material because it provides osteogenic cells, an osteoconductive scaffold, and osteoinductive signaling. Nevertheless, its routine use is limited by donor-site morbidity, postoperative pain, longer operative time, and reduced patient tolerance. Harvest-site pain may persist even when the index spinal procedure is technically successful, thereby affecting early postoperative satisfaction and recovery.(5) These limitations have encouraged the development of biologic augmentation strategies aimed at enhancing fusion biology while reducing dependence on autologous graft harvesting.

Among the available biologic agents, recombinant human bone morphogenetic protein-2 (rhBMP-2) is the most extensively studied osteoinductive adjunct in spinal fusion. Previous evidence suggests that rhBMP-2 may improve radiographic fusion rates compared with ICBG, although concerns remain regarding dose optimization, patient selection, cost, and adverse event profiles.(6,7) Other regenerative approaches, including mesenchymal stem cells (MSCs) and platelet-rich plasma (PRP), have also gained increasing attention. MSC-based products may contribute osteogenic potential and paracrine signaling, whereas PRP provides concentrated platelet-derived growth factors that may support early bone healing. However, their clinical benefits have been demonstrated inconsistently, partly because of variations in preparation methods, surgical techniques, and fusion assessment protocols.(8,9)

Overall, the current evidence regarding biologic augmentation in lumbar fusion remains fragmented across different biologic classes, patient populations, operative techniques, and outcome definitions. Existing reviews frequently focus on a single biologic agent, a specific surgical approach, or broader spinal regions rather than providing a direct synthesis of comparative clinical evidence involving rhBMP-2, MSCs, and PRP in adult lumbar fusion.(6,7,10) Therefore, this systematic review aimed to provide a focused qualitative synthesis of comparative clinical studies evaluating the use of biologic augmentation in adult lumbar spinal fusion, with emphasis on radiographic fusion, patient-reported clinical outcomes, and safety profiles.

METHODS

Study Design and Reporting Guideline

This study was conducted as a systematic review of the literature evaluating biologic augmentation in lumbar spinal fusion. The review methodology and reporting were guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement to ensure transparency, reproducibility, and methodological rigor throughout the study selection and synthesis process. This systematic review was prospectively registered in PROSPERO (CRD420261381949). All stages of the study were conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.

Eligibility Criteria

Studies were considered eligible if they included adult patients undergoing lumbar spinal fusion for degenerative spinal conditions and investigated the use of biologic augmentation strategies, including recombinant human bone

morphogenetic protein-2 (rhBMP-2), mesenchymal stem cells (MSCs), or platelet-rich plasma (PRP). Eligible studies were also required to include a comparative group receiving conventional grafting or fusion without biologic augmentation and to report radiographic fusion outcomes evaluated by computed tomography, plain radiography, or a combination of both.

Randomized controlled trials, randomized phase I–II clinical trials, and comparative cohort studies were included. Studies were excluded if they were systematic reviews, meta-analyses, narrative reviews; case reports; case series without comparators; animal or in vitro studies; conference abstracts without full text; or studies involving cervical or thoracic fusion without separate lumbar data. Studies focusing on non-degenerative indications such as trauma, infection, or tumor were also excluded.

Information Sources and Search Strategy

A comprehensive search of PubMed, Cochrane Library, and ScienceDirect databases was conducted up to December 2025 without language restrictions. The following keyword and Boolean operators were applied in PubMed, Cochrane Library and Science Direct: (″Lumbar spinal fusion" **OR** ″Spinal fusion") **AND** (″Recombinant human bone morphogenetic protein-2" **OR** ″rhBMP-2" **OR** ″Mesenchymal stem cells" **OR** ″MSC" **OR** ″Platelet-rich plasma" **OR** ″PRP")

Study Selection

Two independent reviewers screened all titles and abstracts to identify potentially relevant studies. Full-text versions of shortlisted articles were retrieved for detailed assessment according to the inclusion and exclusion criteria. Discrepancies between reviewers were resolved through discussion and consensus with the third and fourth reviewers. The final selection process and reasons for exclusion were documented and summarized using a PRISMA flow diagram.

Data Extraction

Data extraction was performed using a predefined and standardized table that captured both study characteristics and outcome measures. Extracted data included the author and year of publication, country, study design, patient population and indication, surgical approach and lumbar level involved, type and preparation method of biologic agent, comparator intervention, fusion assessment method, duration of follow-up, radiographic fusion outcomes, patient-reported clinical outcomes, reported complications or adverse events, and the overall findings of each study. Data extraction focused primarily on outcomes reported at the longest available follow-up period for each study.

Risk of Bias Assessment

The methodological quality and risk of bias of included randomized controlled trials were independently assessed by two reviewers using the Cochrane Risk of Bias 2 (RoB 2) tool. The assessment evaluated five domains of potential bias, including bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of the reported results. Each domain was judged as having "low risk," "some concerns," or "high risk" of bias according to the RoB 2 guidelines. Any disagreements between reviewers were resolved through discussion or consultation with a third reviewer. The overall risk-of-bias assessment was incorporated into the data synthesis and presented in tabular form.

Data Synthesis

Given the heterogeneity in study designs, biologic agents, surgical techniques, and outcome assessment methods, a quantitative meta-analysis was not considered appropriate. Instead, a qualitative narrative synthesis was conducted to summarize and compare findings across the included studies. Results were synthesized according to biologic agent class, with particular emphasis on radiographic fusion outcomes, patient-reported clinical outcomes, and safety profiles. Findings were interpreted in the context of study quality, follow-up duration, and the fusion assessment modality.

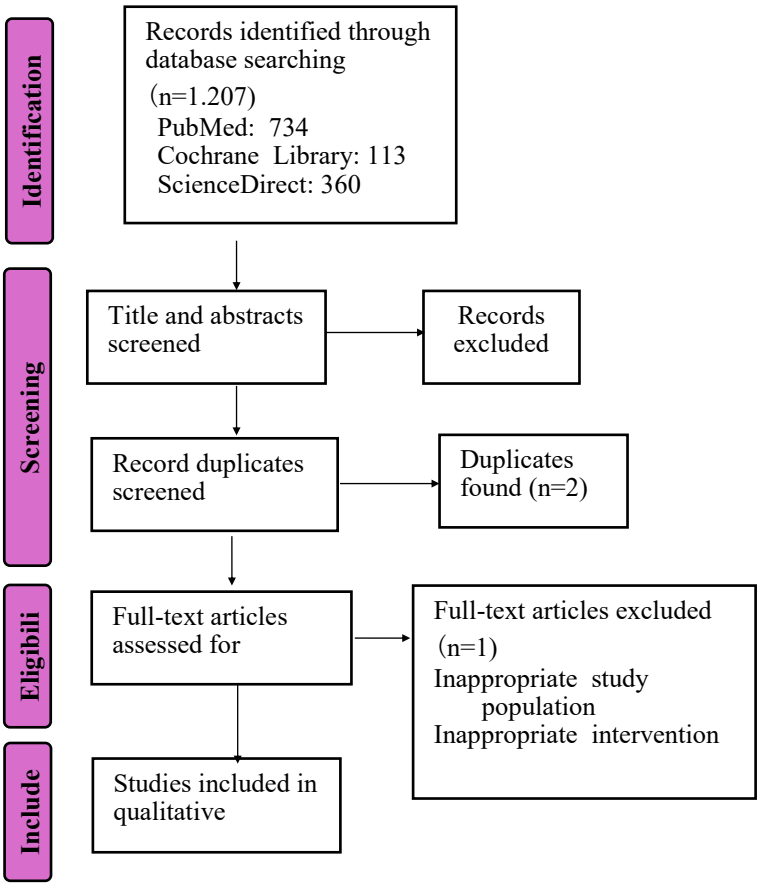

Figure 1. Flow diagram of the literature search strategy for this systematic review

Table 1. Study Characteristics of Included Studies

Author	Country	Study	Population /	Surgical	Biologic Agent	Comparator
Glassman et al. (2008)	USA	Prospective RCT	Adults >60 yrs; instrumented PLF; degenerative conditions (stenosis, spondylolisthesis) (n=102)	Single/ multilevel PLF; ~2 levels average	rhBMP-2/ACS (Infuse) on absorbable collagen sponge; used with local bone and extenders	Iliac crest bone graft (ICBG)
Burkus et al. (2002)	USA (multicenter)	Prospective RCT (non-blinded)	Adults; single-level DDD refractory to ≥6 months conservative therapy (n=279)	Single-level ALIF (L4–L5 or L5–S1) using LT-CAGE titanium interbody cages	rhBMP-2 on collagen sponge (InFUSE); 1.5 mg/mL; ~4.2–8.4 mg/ level; placed inside cages	Autologous iliac crest bone graft in interbody cages
Lee et al. (2010)	USA & South Korea	Retrospective comparative cohort	Adults ≥65 yrs; instrumented PLF for degenerative lumbar disease; subgroup vs <65 yrs (n=127)	Posterolateral lumbar fusion (PLF); single- and multilevel; interbody excluded	rhBMP-2 + allograft; dose-adjusted by level (4.2 mg for 1 level, 8.4 mg for 2 levels, ≥12 mg for ≥3 levels); local bone added	Iliac crest bone graft (autograft)
Kubota et al. (2017)	Japan	Single-center prospective RCT	Adults; lumbar spinal stenosis with spondylolisthesis/ instability; 1–2 levels; prior surgery excluded (n=62)	Posterolateral lumbar fusion (PLF); 1–2 levels; bilateral facet fusion with pedicle screws	Autologous PRP; prepared intraoperatively (~20 mL activated PRP gel + local bone); platelet count ~7.7× baseline; high PDGF/TGF-β	Local autograft (local bone) without PRP
Hurlbert et al. (2013)	Canada (multicenter, 8 centers)	Multicenter prospective RCT	Adults; symptomatic degenerative lumbar disease (DDD ± grade-1 spondylolisthesis); ODI ≥30; instrumented fusion (n=197)	Instrumented PLF; 1–2 levels; no interbody fusion	rhBMP-2 on biphasic calcium phosphate (BCP; 60% HA/40% β-TCP); 42 mg for 1 level, 63 mg for 2 levels; stand-alone graft (local bone discarded)	Iliac crest bone graft (ICBG)
García de Frutos et al. (2020)	Spain (multicenter, 5 hospitals)	Multicenter prospective open-label blinded-reader randomized Phase I–II trial	Adults (18–85 yrs); L4–L5 degenerative spondylolisthesis grade I–II and/or DDD requiring fusion (n=73)	Single-level TLIF (L4–L5); interbody fusion with AICBG in both groups; posterolateral intertransverse space randomized	Expanded autologous bone marrow–derived MSCs + cancellous allograft; ~3×10^5–1×10^6 MSCs/cm^3; posterior graft only	Autologous iliac crest bone graft (AICBG) used posteriorly and anteriorly

Abbreviations: RCT = randomized controlled trial; PLF = posterolateral lumbar fusion; ALIF = anterior lumbar interbody fusion; TLIF = transforaminal lumbar interbody fusion; DDD = degenerative disc disease; rhBMP-2 = recombinant human bone morphogenetic protein-2; PRP = platelet-rich plasma; MSC = mesenchymal stem cell; ICBG = iliac crest bone graft; ACS = absorbable collagen sponge; BCP = biphasic calcium phosphate.

Table 2. Fusion Assessment and Clinical Outcomes

Author (Year)	Fusion Assessment Method	Follow-up	Fusion Rate (%)	Clinical Outcomes (PROMs)
Glassman et al. (2008)	Fine-cut CT (1-mm) at 24 months; 3 blinded reviewers; graded fusion	24 months	86.3% (rhBMP-2/ACS) vs 70.8% (ICBG) on CT	ODI, SF-36 PCS, NRS back/leg pain; both groups improved; no significant between-group difference
Burkus et al. (2002)	Plain radiographs + thin-cut CT at 6, 12, 24 months; blinded radiologists; conservative criteria	24 months	94.5% (rhBMP-2) vs 88.7% (ICBG) at 24 months (CT-based)	ODI, NRS back/leg pain, neurologic status, work status, satisfaction; significant improvement in both groups; no clinically meaningful between-group difference
Lee et al. (2010)	Plain radiographs + dynamic flexion–extension views; CT as secondary; blinded musculoskeletal radiologist	≥24 months (mean ~35–39 months)	≥65 yrs: 82.4% (rhBMP-2+allograft) vs 78.1% (autograft); <65 yrs with rhBMP-2: 94.2%	VAS pain; Kirkaldy–Willis grading; good/excellent: 85.3% (rhBMP-2, ≥65 yrs) vs 73.2% (autograft, ≥65 yrs); difference not statistically significant
Kubota et al. (2017)	CT-based fusion at 12/24 months (bridging bone across transverse processes) + serial plain radiographs q3 months; 3 blinded assessors	24 months	93.7% (PRP) vs 74.2% (control) (segment-based CT); larger fusion area and faster union in PRP group	VAS for low back pain, leg pain, and leg numbness pre-op and at 3, 6, 12, 24 months; both groups improved; no significant between-group difference
Hurlbert et al. (2013)	Plain radiographs (AP, lateral, flex-ext) at 6, 12, 24, 48 months + thin-slice CT at 6, 12, 24 months; two blinded radiologists; strict fusion criteria	Up to 48 months (primary at 24 months)	24 months: ~97% (rhBMP-2) vs 70% (ICBG); 48 months: 94% vs 59–69%; P ≤ 0.007	ODI, SF-36 PCS/MCS, back and leg pain scores; significant improvement in both groups; no significant between-group difference through 4 years
García de Frutos et al. (2020)	Plain X-ray at 3, 6, 12 months (Molinari scale) + CT at 6 and 12 months; independent blinded radiologist; posterior and complete fusion assessed	12 months (extended follow-up ongoing)	CT posterior fusion: 6 months 82.4% vs 45.7% (p=0.0001); 12 months 76.5% vs 65.7% (NS). Complete CT: 6 months 70.6% vs 40.0% (p=0.0038); 12 months 70.6% vs 51.4% (p=0.023)	VAS lumbar/sciatic pain, ODI, SF-36 PCS/MCS at 3, 6, 12 months; significant improvement in both groups; no significant between-group differences

Abbreviations: CT = computed tomography; ODI = Oswestry Disability Index; VAS = visual analog scale; NRS = numeric rating scale; SF-36 PCS/MCS = Short Form-36 Physical/Mental Component Summary; PROMs = patient-reported outcome measures.

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Table 3. Complications, Safety, and Risk of Bias

Author (Year)	Complications / Adverse Events	Summary of Findings	Risk of Bias
Glassman et al. (2008)	Total complications: 8 (rhBMP-2) vs 20 (ICBG); revision for nonunion: 1 vs 5; fewer revisions in rhBMP -2 group	rhBMP-2/ACS achieved higher CT-confirmed fusion, fewer complications, lower revision rate vs ICBG; similar PROM improvement; no increase in 2 -year cost	Low (RCT, blinded CT; minimal attrition; ITT reported)
Burkus et al. (2002)	ICBG: 5.9% harvest-site complications, 32% persistent donor-site pain; rhBMP -2: shorter OR time, less blood loss; no ectopic bone or neurologic compression	rhBMP-2 ALIF achieved higher fusion rates, eliminated donor-site morbidity, and provided comparable clinical improvement to autograft over 2 years	Low–Moderate (RCT, blinded radiographic assessment; surgery not blinded; industry involvement noted)
Lee et al. (2010)	Perioperative complications: 35.3% (rhBMP-2) vs 48.8% (autograft) in ≥65 yrs (NS); revision for pseudarthrosis uncommon and similar between groups	In elderly patients, rhBMP-2+allograft achieved comparable fusion and clinical outcomes to autograft, with trend toward fewer complications; efficacy lower than in younger patients	Moderate (retrospective; non-randomized; blinded radiographic assessment)
Kubota et al. (2017)	No adverse events reported; safety profile comparable between groups	PRP significantly increased CT-confirmed fusion rate, enlarged fusion mass, and shortened time to union (~2 months earlier) vs control; clinical pain outcomes similar	Low (RCT; clear randomization; blinded radiographic assessment; attrition balanced)
Hurlbert et al. (2013)	Overall AEs comparable; donor-site morbidity only in ICBG group; wound complications and infections numerically higher with rhBMP-2 (not statistically significant); revision for nonunion rare (2 per group)	rhBMP-2 significantly increased long-term radiographic fusion rates vs autograft; no superior clinical outcomes; eliminated iliac crest donor-site morbidity	Low–Moderate (RCT, blinded radiographic assessment; surgeons/patients not blinded; industry funding disclosed)
García de Frutos et al. (2020)	TEAEs common; no AEs related to MSC product; serious TEAEs: 14.7% (MSC) vs 8.6% (control); none treatment-related; BM aspiration did not increase complications	MSC+allograft accelerated and increased early posterior fusion and complete radiographic response; similar clinical improvement and safety profile vs AICBG	Low–Moderate (RCT, blinded imaging; open-label surgery; Phase I–II sample size)

Abbreviations: TEAE = treatment-emergent adverse event; BM = bone marrow; AICBG = autologous iliac crest bone graft; NS = not statistically significant; ITT = intention-to-treat; OR = operating room.

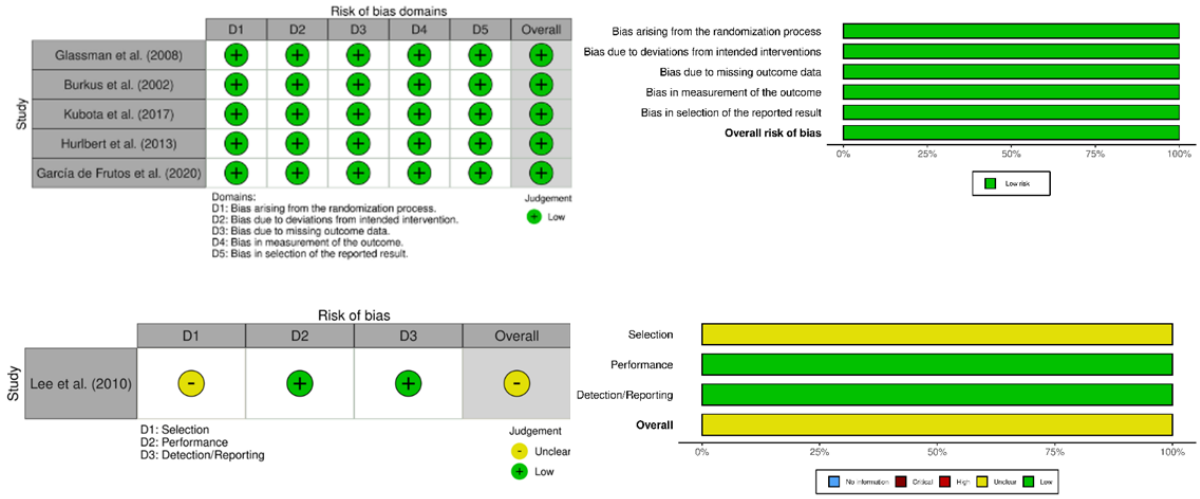

Figure 2. Risk of bias assessment results of the included studies

RESULTS

Study Selection

The comprehensive database search yielded a total of 1,207 records, reflecting a broad initial capture of the literature related to biologic augmentation in lumbar fusion surgery. Of these, 734 records were retrieved from PubMed, 113 from the Cochrane Library, and 360 from ScienceDirect. Following the initial title and abstract screening, 1,199 records were excluded because they did not address lumbar fusion, did not involve biologic augmentation, or were clearly unrelated to the predefined population, intervention, or outcome criteria.

After duplicate screening, nine records proceeded to further evaluation, of which two were identified as duplicates and subsequently removed. This process resulted in seven full-text articles being assessed for eligibility. One full-text article was excluded after detailed review due to the inclusion of an inappropriate study population and an intervention that did not align with the scope of biologic augmentation in lumbar fusion surgery. Ultimately, six studies fulfilled all inclusion criteria and were included in the qualitative synthesis. The full selection process is illustrated in the PRISMA flow diagram (Figure 1), demonstrating a transparent and methodical study identification and selection process.

Characteristics of Included Studies

The six included studies encompassed a heterogeneous but methodologically robust set of clinical investigations, including prospective randomized controlled trials, randomized phase I–II clinical trials, and comparative cohort studies. Collectively, these studies involved a total of 840 patients undergoing lumbar spinal fusion with or without biologic augmentation. Collectively, these studies biologic augmentation strategies in adult patients undergoing lumbar fusion surgery for degenerative spinal conditions, such as degenerative disc disease, lumbar spinal stenosis, and spondylolisthesis.

Three studies primarily assessed recombinant human bone morphogenetic protein-2 (rhBMP-2), evaluating its efficacy relative to iliac crest bone graft or local autograft in both interbody and posterolateral lumbar fusion. One randomized controlled trial evaluated autologous platelet-rich plasma (PRP) as an adjunct to posterolateral lumbar fusion, while one multicenter randomized phase I–II clinical trial investigated expanded autologous bone marrow–derived mesenchymal stem cells (MSCs) combined with allograft material. An additional

comparative cohort study focused on elderly patients undergoing posterolateral lumbar fusion with rhBMP-2 compared with autograft.

Surgical techniques varied among the included studies and included anterior lumbar interbody fusion, transforaminal lumbar interbody fusion, and instrumented posterolateral lumbar fusion, reflecting real -world variability in clinical practice. Follow-up durations ranged from 12 to 48 months, allowing for both early and long-term assessment of fusion outcomes. Radiographic fusion was assessed using computed tomography, plain radiographs with dynamic flexion – extension views, or a combination of both, with several studies employing blinded radiographic evaluators. Detailed characteristics and outcomes of all included studies are summarized in Table 1 -3

Radiographic Fusion Outcomes

Radiographic fusion outcomes consistently favored biologic augmentation across the included studies, although the magnitude and timing of the benefit varied depending on the biologic agent used and the assessment modality. Studies evaluating rhBMP-2 reported higher fusion rates compared with autograft, particularly in posterolateral lumbar fusion, with fusion rates frequently exceeding 90% at medium- to long-term follow-up. These differences were most evident when fusion was assessed using CT-based criteria, which provided a more sensitive assessment of bridging bone formation than plain radiography alone.

In elderly populations, rhBMP-2 achieved fusion rates comparable to autograft, although overall fusion success was lower than that observed in younger cohorts, suggesting an age-related attenuation of the osteoinductive response. Despite this, rhBMP-2 maintained acceptable fusion outcomes and demonstrated a trend toward more rapid fusion compared with autograft in older patients.

The MSC-based randomized trial demonstrated a clear acceleration of early fusion, with significantly higher posterior and complete fusion rates at six months compared with iliac crest bone graft. Although the differences in fusion rates diminished by 12 months, MSC augmentation still resulted in a higher proportion of complete radiographic fusion. This pattern suggests that MSCs may primarily enhance early osteogenesis rather than substantially altering final fusion outcomes.

Similarly, the PRP study demonstrated significantly higher CT-confirmed fusion rates and a larger fusion mass area at 24 months compared with control fusion without PRP. PRP was also associated with a shorter time to radiographic union, suggesting a facilitatory effect on bone healing dynamics.

Clinical Outcomes

Across all included studies, patient-reported clinical outcomes improved substantially following lumbar fusion, regardless of the use of biologic augmentation. Outcome measures such as the Oswestry Disability Index, visual analog scale scores for back and leg pain, and SF-36 physical and mental component scores demonstrated significant postoperative improvement from baseline in both the biologic and control groups

However, despite the radiographic advantages associated with biologic augmentation, no study demonstrated consistent or clinically meaningful superiority in patient-reported outcomes at final follow-up. In studies evaluating rhBMP-2, improvements in pain and functional outcomes were comparable between the rhBMP-2 and autograft groups, even when differences in fusion rates were observed. Similar findings were reported in MSC and PRP studies, in which enhanced or accelerated radiographic fusion did not translate into superior pain relief or functional recovery.

These findings suggest that, while biologic augmentation may influence the

biological process of fusion, clinical improvement following lumbar fusion is likely multifactorial, and radiographic fusion alone may not directly determine patient-perceived outcomes.

Complications and Safety Outcomes

Overall, biologic augmentation was associated with acceptable safety profiles and did not result in an increased incidence of major complications compared with conventional fusion techniques. In rhBMP-2 studies, overall complication rates were similar to those observed with autograft, with the additional benefit of eliminating iliac crest donor-site morbidity. This advantage was particularly relevant in elderly populations, in whom donor-site pain and complications are more prevalent.

The MSC-based trial reported no treatment-related serious adverse events, and bone marrow aspiration for MSC harvesting did not increase perioperative morbidity. Likewise, PRP augmentation was not associated with any treatment-related adverse events, infections, or neurologic complications. Across all included studies, revision surgery for pseudarthrosis was uncommon and occurred at comparable rates between biologic and non-biologic groups.

These findings indicate that biologic augmentation strategies may be applied in lumbar fusion without compromising patient safety when used appropriately and within established clinical indications.

Summary of Evidence

In summary, this synthesis demonstrates that biologic augmentation safely improves and accelerates radiographic fusion in lumbar spinal surgery while eliminating donor-site morbidity associated with autograft harvesting. However, these radiographic advantages do not translate into superior clinical outcomes in terms of pain and functional improvement when compared with conventional grafting techniques.

DISCUSSION

Interpretation of Key Findings

The present systematic review provides a contemporary synthesis of clinical evidence on biologic augmentation in lumbar spinal fusion and demonstrates that biologic agents, specifically rhBMP-2, mesenchymal stem cells, and platelet-rich plasma, consistently enhance radiographic fusion outcomes or accelerate the fusion process compared with conventional grafting strategies. Across heterogeneous surgical approaches and patient populations, biologic augmentation was associated with higher fusion rates or earlier radiographic union, particularly when assessed using computed tomography. These findings support the concept that biologic modulation can meaningfully influence the osteogenic environment of lumbar fusion constructs. However, despite these radiographic advantages, improvements in pain relief, functional recovery, and health-related quality of life were largely comparable between biologic and non-biologic groups, highlighting a persistent disconnect between imaging-based success and patient-perceived outcomes.

Integration With Existing Evidence

The findings of this review are consistent with recent meta-analyses and narrative syntheses reporting that rhBMP-2 achieves higher fusion success rates than iliac crest bone graft in selected lumbar fusion settings, particularly in posterolateral constructs and multilevel procedures.(6,7) Nevertheless, prior reviews have similarly noted that these radiographic benefits do not reliably translate into superior clinical outcomes, a pattern that is reaffirmed by the present synthesis. For PRP, earlier reviews have described heterogeneous results, with some studies demonstrating accelerated early fusion or improved fusion mass quality, but without durable differences in final union rates or functional outcomes.(8,10) The inclusion of newer randomized data on

MSC-based augmentation in this review adds further nuance, suggesting that MSCs may primarily function as biological facilitators of fusion rather than determinants of long-term clinical superiority.

Biological Mechanisms and Differential Effects

The observed differences among biologic agents likely reflect fundamental distinctions in their underlying biological mechanisms. rhBMP-2 functions as a potent osteoinductive signal, directly stimulating osteoblastic differentiation and bone formation, which may explain its robust and reproducible effects on fusion rates across diverse surgical contexts In contrast, MSC-based strategies rely on both osteogenic differentiation and paracrine signaling pathways that modulate inflammation, angiogenesis, and early bone remodeling. This dual mechanism may account for the pronounced early fusion advantages observed in MSC trials without corresponding long-term divergence in clinical outcomes. PRP, by providing a concentrated milieu of platelet-derived growth factors, appears to facilitate the early phases of bone healing and fusion mass maturation, potentially shortening time to union without fundamentally altering ultimate fusion success or patient-reported outcomes.(17,18) These mechanistic differences underscore that biologic augmentation should not be viewed as a monolithic intervention but rather as a spectrum of biologically distinct strategies with differing clinical implications.

Clinical Relevance and Patient Selection

From a clinical standpoint, the results suggest that biologic augmentation may be most appropriately applied in patients at elevated risk of pseudarthrosis, such as older adults, smokers, patients undergoing multilevel fusion, or those in whom iliac crest bone graft harvesting is contraindicated or undesirable. In these contexts, enhancement of the biological milieu may improve fusion reliability and reduce the likelihood of revision surgery, even if short-term patient-reported outcomes remain similar. Importantly, the consistent absence of major safety signals across biologic classes in the included studies supports their judicious use in appropriately selected patients. However, the lack of consistent clinical superiority emphasizes the need for careful patient counseling, as biologic augmentation should be framed as a means to optimize fusion biology rather than as a guarantee of improved pain relief or functional outcomes.(19)

Radiographic Fusion Versus Clinical Outcomes

An important insight reinforced by this review is the imperfect correlation between radiographic fusion and clinical improvement. While solid arthrodesis remains a prerequisite for long-term mechanical stability, pain perception and functional recovery are influenced by a complex interplay of factors, including neural decompression, sagittal alignment, psychosocial variables, and patient expectations. Variability in fusion assessment methods further complicates interpretation, as CT-based criteria may detect differences in fusion quality that are not always clinically apparent.(3) This disconnect underscores the need for future studies to integrate standardized imaging criteria with clinically meaningful outcome measures and to explore whether specific patient subgroups derive greater symptomatic benefit from enhanced fusion biology.

Methodological Limitations and Evidence Gaps

Several limitations inherent to the current evidence base should be acknowledged. The number of high-quality randomized controlled trials remains limited, particularly for MSC-based and PRP-augmented fusion, and existing

studies often have insufficient sample sizes to reliably detect differences in patient-reported outcomes. In addition, substantial heterogeneity in biologic preparation methods, carrier materials, dosing protocols, and surgical techniques further limits cross-study comparability. Most studies also focus primarily on fusion outcomes within a one- to two-year follow-up period, with relatively limited evidence on long-term durability, adjacent segment disease, or cost-effectiveness. Collectively, these limitations highlight persistent gaps in the literature that constrain definitive conclusions regarding the optimal role of biologic augmentation in routine lumbar fusion practice.(20)

Implications for Future Research

Future investigations should focus on rigorously designed, adequately powered randomized controlled trials comparing biologic agents head-to-head within standardized surgical and imaging frameworks. Harmonization of fusion definitions and longer follow-up periods will be critical to determining whether early radiographic advantages translate into durable clinical or economic benefits. In addition, comparative effectiveness and cost-utility analyses are needed to support value-based decision-making, particularly given the substantial costs associated with certain biologic products.(20) As biologic technologies continue to evolve, integrating patient-specific risk stratification with biologic selection may represent a promising direction toward more personalized lumbar fusion strategies.

CONCLUSION

This systematic review demonstrates that biologic augmentation in lumbar spinal fusion—using rhBMP-2, mesenchymal stem cells, or platelet-rich plasma—consistently enhances radiographic fusion outcomes or accelerates the fusion process compared with conventional grafting strategies. However, these radiographic benefits do not reliably translate into superior patient-reported clinical outcomes. Biologic augmentation appears to be safe and may be particularly beneficial in patients at increased risk of pseudarthrosis or in situations in which autologous iliac crest bone graft harvesting is undesirable. Future high-quality comparative studies with standardized fusion assessment methods and longer follow-up periods are required to better define patient selection criteria and to clarify the clinical and economic value of biologic augmentation in lumbar fusion surgery.

REFERENCES

1. Lambrechts MJ, Siegel N, Heard JC, Karamian BA, Dambly J, Baker S, et al. Trends in single-level lumbar fusions over the past decade using a national database.
2. World Neurosurg. 2022 Nov;167:e61–9.
3. Ponkilainen VT, Huttunen TT, Neva MH, Pekkanen L, Repo JP, Mattila VM. National trends in lumbar spine decompression and fusion surgery in Finland, 1997–2018. Acta Orthop. 2021 Apr;92(2):199–203.
4. Yu A, Tiao J, Cai CW, Huang JJ, Mohamed K, Hoang R, et al. Radiographic assessment of successful lumbar spinal fusion: a systematic review of fusion criteria in randomized trials. Global Spine J. 2025 Sep 30;21925682251384662.
5. Boonsirikamchai W, Wilartratsami S, Ruangchainikom M, Korwutthikulrangsri E, Tongsai S, Luksanapruksa P. Pseudarthrosis risk factors in lumbar fusion: a systematic review and meta-analysis. BMC Musculoskelet Disord. 2024 Jun 3;25(1):433.
6. Sheha ED, Meredith DS, Shifflett GD, Bjerke BT, Iyer S, Shue J, et al. Postoperative pain following posterior iliac crest bone graft harvesting in spine surgery: a prospective randomized trial. Spine J. 2018 Jun;18(6):986–92.

7. Malham GM, Louie PK, Brazenor GA, Mobbs RJ, Walsh WR, Sethi RK. Recombinant human bone morphogenetic protein-2 in spine surgery: recommendations for use and alternative bone substitutes—a narrative review. J Spine Surg. 2022 Dec;8(4):477 – 90.
8. Liu S, Wang Y, Liang Z, Zhou M, Chen C. Comparative clinical effectiveness and safety of bone morphogenetic protein versus autologous iliac crest bone graft in lumbar fusion: a meta-analysis and systematic review. Spine (Phila Pa 1976). 2020 Jun 15;45(12):E729 – 41.
9. Kubota G, Kamoda H, Orita S, Yamauchi K, Sakuma Y, Oikawa Y, et al. Platelet-rich plasma enhances bone union in posterolateral lumbar fusion: a prospective randomized controlled trial. Spine J. 2019 Feb;19 (2):e34 – 40.
10. García de Frutos A, González-Tartière P, Coll Bonet R, Ubierna Garcés MT, Del Arco Churruca A, Rivas García A, et al. Randomized clinical trial: expanded autologous bone marrow mesenchymal cells combined with allogeneic bone tissue compared with autologous iliac crest graft in lumbar fusion surgery. Spine J. 2020 Dec;20(12):1899 – 910.
11. Fitzgerald A, McCool R, Carr E, Miller P, Reddish K, Lohr CC, et al. A systematic review of bone graft products used in lumbar interbody fusion procedures for degenerative disc disease. N Am Spine Soc J. 2025 Mar;21:100579.
12. Glassman SD, Carreon LY, Djurasovic M, Campbell MJ, Puno RM, Johnson JR, et al. RhBMP-2 versus iliac crest bone graft for lumbar spine fusion: a randomized controlled trial in patients over sixty years of age. Spine. 2008 Dec;33 (26):2843–9.
13. Burkus JK, Gornet MF, Dickman CA, Zdeblick TA. Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages. J Spinal Disord Tech. 2002;15(5):337–49.
14. Lee KB, Taghavi CE, Hsu MS, Song KJ, Yoo JH, Keorochana G, et al. The efficacy of rhBMP-2 versus autograft for posterolateral lumbar spine fusion in elderly patients. Eur Spine J. 2010 Jun;19(6):924 – 30.
15. RJ, Alexander D, Mahood J, Abraham E, McBroom R. rhBMP-2 for posterolateral instrumented lumbar fusion. 2013.
16. Giannelli A, Forte M, D' Albis G, Cianciotta G, Limongelli L, Stef L, et al. Utilization of platelet-rich plasma in oral surgery: a systematic review of the literature. J Clin Med. 2025 Apr 20;14(8):2844.
17. Bowles-Welch AC, Jimenez AC, Stevens HY, Frey Rubio DA, Kippner LE, Yeago C, et al. Mesenchymal stromal cells for bone trauma, defects, and disease: considerations for manufacturing, clinical translation, and effective treatments. Bone Rep. 2023 Jun;18:101656.
18. Barber SM, Sulhan S, Schwartz L, Konakondla S. Anterior lumbar interbody fusion: patient selection and workup. J Spine Surg. 2024 Dec 20;10(4):706–14.
19. Nunna RS, Gruber MD, Karuparti S, Taylor Z, Genovese S, Jumah F, et al. Cost-effectiveness analyses of bone morphogenetic protein-2 (rhBMP-2) in spinal fusion: a systematic review. Global Spine J. 2025 May;15 (4):2514–35.
20. Chandan Reddy S, Shafi M, Park A, Hughes LP, Khalifeh JM, Azad TD, et al. Long-term outcomes following augmented reality-assisted pedicle screw placement in spinal fusion patients. Acta Neurochir (Wien). 2025 Dec 11;167(1):323.