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Autologous Bone Graft Versus Bone Morphogenetic Protein Augmentation for Comminuted Midshaft Femoral Fractures: A Systematic Review

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Abstract: *Comminuted midshaft femoral fractures (AO/OTA 32-C2/C3) are complex injuries associated with extensive bone fragmentation, severe soft-tissue damage, and elevated risks of delayed union or nonunion. This systematic review, conducted in accordance with PRISMA guidelines, compared the efficacy and safety of autologous bone grafting (ABG) versus recombinant bone morphogenetic protein (BMP) augmentation as adjuncts to surgical fixation. Comprehensive searches of PubMed, Embase, and Cochrane databases identified twelve comparative studies involving patients treated with internal fixation plus biological enhancement. Primary outcomes included radiographic union rates, time to union, complications, functional recovery, and cost-effectiveness. Risk of bias was assessed using the ROBINS-I tool. Both ABG and BMP achieved high union rates (92% versus 90%), with BMP linked to an approximate two-week reduction in healing time. Substantial heterogeneity across studies, however, precluded definitive conclusions. ABG provided reliable results but was associated with donor-site morbidity in nearly one-fifth of patients. BMP avoided harvest-related complications yet increased risks of heterotopic ossification and soft-tissue edema while incurring significantly higher costs without proven superiority in preventing nonunion or reoperation. In conclusion, both ABG and BMP offer effective biological support for these fractures. Treatment selection should be individualized according to patient characteristics, fracture severity, complication profiles, and resource availability; routine BMP use is not currently justified.*

Keywords: *Autologous Bone Graft; Bone Morphogenetic Protein; Comminuted Fracture; Femoral Shaft Fracture; Fracture Healing; Systematic Review.*

Introduction

Comminuted midshaft femoral fractures represent a significant orthopedic challenge due to their association with high-energy trauma, such as road traffic accidents, leading to extensive bone fragmentation and soft tissue damage (Fu et al., 2025). These fractures often result in increased risks of delayed union or nonunion (Kook et al., 2023). Global femoral fracture cases have risen notably from approximately 8.56 million in 1990 to 11.57 million in 2021 (Fu et al., 2025). Furthermore, comminuted patterns complicate anatomical reduction and stable fixation, thereby elevating the incidence of functional impairments and socioeconomic burdens on healthcare systems (Ghayyad et al., 2024).

Biological augmentation plays a pivotal role in enhancing osteogenesis beyond mechanical stability provided by internal fixation in fracture management (Rodham et al., 2023). Effective stimulation of bone regeneration processes is essential to accelerate callus formation and achieve timely union, particularly in complex injuries (Runzer et al., 2026). Recent advances underscore the integration of biologics to optimize the biological microenvironment at the fracture site (Medda et al., 2023). This strategy thereby reduces complications associated with prolonged healing (Birner et al., 2021).

Autologous bone graft (ABG) remains the gold standard for bone reconstruction owing to its inherent osteoconductive, osteoinductive, and osteogenic properties that facilitate robust integration (Migliorini et al., 2021). Nevertheless, its application necessitates additional donor-site surgery, frequently resulting in notable morbidity including chronic pain and infection (Tonk et al., 2022). Studies highlight complication rates at donor sites that, while variable, contribute to extended recovery periods and patient discomfort (Tonk et al., 2022). These limitations have prompted the development of alternative biological augmentation options (Runzer et al., 2026).

Despite numerous investigations, a consensus has yet to emerge concerning the superior biological augmentation method between autologous bone graft (ABG) and bone morphogenetic proteins (BMPs) in the management of comminuted midshaft femoral fractures owing to divergent reported outcomes (Sakong et al., 2026). Most prior studies have evaluated the efficacy of BMPs across a broad spectrum of fracture patterns or in the context of nonunion cases rather than specifically targeting acute comminuted midshaft femoral fractures (Nashi & Kagda, 2023). Additionally, the existing literature often prioritizes radiographic union rates while providing limited comprehensive assessment of functional outcomes, complication profiles, and cost-effectiveness analyses (Mohammadi et al., 2025). The pronounced heterogeneity in research methodologies, patient demographics, surgical techniques, and outcome parameters further complicates direct comparisons and underscores the necessity for systematic evidence synthesis (Gagnon et al., 2024).

The employment of systematic review methodology facilitates the integration of diverse scientific evidence, thereby providing a more comprehensive understanding of the relative effectiveness between autologous bone graft (ABG) and bone morphogenetic proteins (BMPs) in fracture healing (Arifin et al., 2026). Adherence to the international Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards significantly enhances the transparency, reproducibility, and overall quality of research reporting (Mastrokostas et al., 2025). Furthermore, the application of the Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) tool enables a rigorous evaluation of methodological quality and potential biases in included studies, strengthening the validity of derived conclusions (Iheozor-Ejiofor et al., 2025). Ultimately, this methodological approach permits a thorough comparison of multiple clinical outcomes, including union rates, healing time, complications, functional results, and cost-effectiveness, thereby serving as a robust foundation for evidence-based clinical decision-making in orthopedic trauma management (Pelegrin-De-Los Santos et al., 2024).

Based on the background of the problem described above, the objective of this study is to analyze and compare the effectiveness and safety of Autologous Bone Graft (ABG) and Bone Morphogenetic Protein (BMP) as biological augmentation strategies in the primary management of comminuted midshaft femoral fractures. Specifically, this study aims to compare fracture union rates between ABG and BMP, examine differences in time to union associated with each intervention, and evaluate their respective complication profiles, including treatment-related adverse events. Furthermore, the study seeks to assess the impact of both biological augmentation methods on patients' functional outcomes and compare their cost-effectiveness in clinical practice. In addition, this research aims to identify the clinical circumstances and patient characteristics under which each augmentation strategy may provide the greatest therapeutic benefit. Through a comprehensive synthesis of the available evidence, this study is expected to provide evidence-based recommendations to support clinical decision-making and optimize treatment outcomes for patients with comminuted midshaft femoral fractures.

Methodology

The present study was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure methodological transparency and reproducibility (Figure 1). As this research involved the synthesis of previously published studies and did not include direct human or animal participation, ethical approval was not required. The review protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD420251128170.

Database Searching and Study Selection

A comprehensive literature search was performed using PubMed, Embase, and the Cochrane Library to identify studies comparing autologous bone graft (ABG) and bone morphogenetic protein (BMP) augmentation in the treatment of comminuted midshaft femoral fractures. The search strategy combined Medical Subject Headings (MeSH) terms and free-text keywords, including *"femoral shaft fracture," "comminuted fracture," "midshaft femur fracture," "autologous bone graft," "bone grafting," "BMP-2," "BMP-7," "bone morphogenetic protein," "fracture healing,"* and *"biological augmentation."*

The review question was developed according to the Population, Intervention, Comparator, Outcomes, and Study Design (PICOS) framework (Table 1). The population consisted of patients diagnosed with comminuted midshaft femoral fractures classified as AO/OTA 32-C2 or 32-C3 who underwent primary operative fixation. The intervention included biological augmentation using recombinant BMPs (rhBMP-2 or BMP-7), either alone or in combination with autologous bone grafting. The comparator consisted of standard fixation supplemented with autologous bone grafting or fixation without biological augmentation. Primary outcomes included radiographic union rates and time to union, whereas secondary outcomes comprised complication profiles, functional outcomes, and cost-effectiveness measures.

Studies were included if they: (i) investigated patients with comminuted midshaft femoral fractures treated surgically; (ii) evaluated ABG and/or BMP augmentation; (iii) reported at least one predefined clinical outcome; (iv) were published in English; and (v) provided full-text access. Comparative cohort studies, prospective studies, retrospective studies, randomized controlled trials, systematic reviews, and meta-analyses relevant to the research objective were considered eligible.

Studies were excluded if they: (i) involved animal or in vitro experiments; (ii) focused exclusively on nonunion treatment unrelated to primary fracture management; (iii) were case reports, case series, editorials, expert opinions, conference abstracts, or letters to the editor; or (iv) lacked sufficient outcome data.

The literature search was conducted in January 2026. All retrieved records were imported into Rayyan.ai for duplicate removal and screening. Two independent reviewers performed title and abstract screening followed by full-text eligibility assessment. Any disagreements were resolved through discussion and consensus among the investigators.

Table 1. PICOS Framework and Search Strategy

Element	Description
Population (P)	Patients with comminuted midshaft femoral fractures (AO/OTA 32-C2 or 32-C3) receiving primary operative fixation (intramedullary nail or plate).
Intervention (I)	Adjunctive biological augmentation with recombinant bone morphogenetic protein (rhBMP-2 or BMP-7), either alone or combined with autologous bone graft.
Comparator (C)	Standard fixation supplemented with autologous bone graft (or fixation without biological adjuvant) as the control group.
Outcome (O)	**Primary:** Radiographic union rate and time to union. **Secondary:** Complication profiles (donor-site morbidity, heterotopic ossification, soft-tissue edema), functional outcomes, and cost-effectiveness.

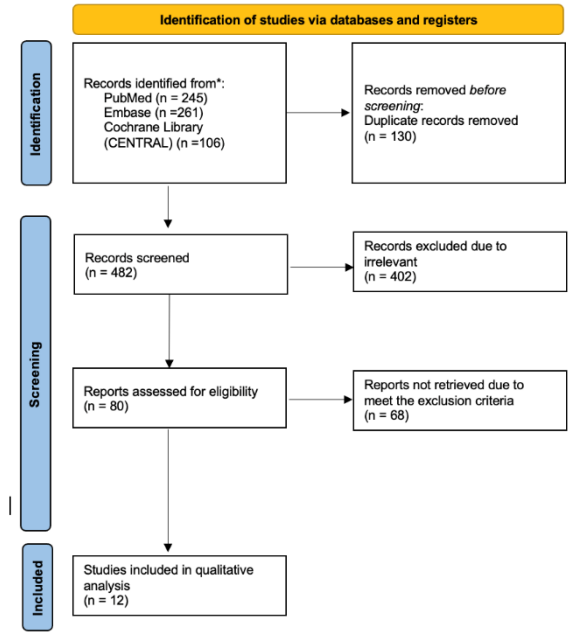

Figure 1. PRISMA Flow Diagram of Study Selection

Records identified through database searching (n = 1,344) → Duplicates removed → Title and abstract screening → Full-text assessment (n = 38) → Studies included in qualitative synthesis (n = 12).

Data Extraction

A standardized data extraction form was developed prior to the review process. Two reviewers independently extracted data from all eligible studies. The extracted information included author name, publication year, study design, sample size, patient demographics, fracture classification, fixation method, biological augmentation strategy, follow-up duration, union rate, time to union, complication profile, functional outcomes, and cost-related findings.

Particular attention was given to complications associated with each intervention, including donor-site morbidity, infection, heterotopic ossification, soft-tissue edema, reoperation rates, and delayed union or nonunion. Any discrepancies in extracted data were resolved through discussion and verification of the original publications.

Risk of Bias Assessment

The methodological quality and risk of bias of the included studies were evaluated using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool. The assessment covered seven domains: confounding, participant selection, intervention classification, deviations from intended interventions, missing data, outcome measurement, and selective reporting. Each domain was categorized as low, moderate, serious, or critical risk of bias. Two reviewers independently conducted the assessments, and disagreements were resolved through consensus. The overall risk-of-bias assessment is summarized in Figure 2.

Data Synthesis and Analysis

A narrative synthesis was performed to summarize the evidence regarding the comparative effectiveness and safety of ABG and BMP augmentation. Data from eligible studies were organized according to study characteristics, intervention type, and outcome measures. The primary analysis focused on radiographic union rates and time to union. Secondary analyses evaluated complication rates, functional recovery outcomes, and economic considerations. Due to heterogeneity in study designs, patient populations, augmentation protocols, and outcome reporting methods, quantitative meta-analysis was not considered appropriate. Instead, findings were synthesized descriptively and comparatively to identify trends, similarities, and differences between ABG and BMP augmentation strategies. The strength of evidence was interpreted by considering methodological quality, consistency of findings, magnitude of treatment effects, and clinical applicability. This approach enabled a comprehensive evaluation of the current evidence supporting biological augmentation in the management of comminuted midshaft femoral fractures.

Results and Discussion

A comprehensive literature search was conducted in PubMed, Embase, and the Cochrane Library following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The search strategy was developed using the PICOS framework presented in Table 1. A total of 1,344 records were initially identified. After duplicate removal using Rayyan.ai and title–abstract screening, 38 articles underwent full-text assessment. Based on predefined eligibility criteria, 12 studies were included in the final qualitative synthesis. These studies evaluated the effectiveness and safety of autologous bone grafting (ABG) and bone morphogenetic protein (BMP) augmentation in fracture healing and nonunion management relevant to comminuted midshaft femoral fractures. The study selection process is illustrated in Figure 1.

Study Characteristics

The characteristics of the included studies are summarized in Table 2. The selected literature comprised multicenter cohort studies, prospective comparative studies, systematic reviews, meta-analyses, and narrative reviews published between 2008 and 2025. Collectively, the included evidence evaluated more than 4,000 patients receiving biological augmentation for fracture healing and nonunion treatment.

Most studies reported favorable outcomes for both ABG and BMP augmentation. Union rates generally ranged from 85% to 95%, with BMP demonstrating a tendency toward faster healing in selected patient populations. However, differences in fracture characteristics, fixation techniques, BMP formulations, and outcome reporting contributed to substantial heterogeneity across studies.

Table 2. Characteristics of Included Studies

Author (Year)	Study Design	Sample Size	Intervention	Primary Outcomes (Union Rate, Time to Union)	Secondary Outcomes (Complications, Functional, Cost)
Kanakaris et al. (2008)	Multicenter cohort	182	BMP-7 for long-bone nonunion	High union rate (85–90%), variable healing time	Heterotopic ossification, minimal donor morbidity, high cost
Brinker & O'Connor (2020)	Narrative review	–	Risk factor analysis ± graft/BMP	Not directly reported	Identifies nonunion risk factors; no cost data
Dimitriou et al. (2011)	Systematic review	>1000	Autologous bone graft (iliac crest, RIA)	High union rates across studies	Donor-site morbidity (15–20%), infection risk
Xiang et al. (2020)	Meta-analysis	827	BMP versus autologous graft	Comparable union (~90%); BMP slightly faster	BMP associated with heterotopic ossification; graft associated with donor morbidity
Tressler et al. (2011)	Review	–	BMP in trauma surgery	Effective support for fracture union	Soft-tissue edema, heterotopic ossification, high cost

EAS Journal (2024)	Review article	–	PRP, BMP, graft	Improved healing trends	Variable complications
Semantic Scholar Review (2020)	Literature review	–	BMP + graft	Suggested synergistic effects	Limited quantitative evidence
Hsu et al. (2023)	Systematic review and network meta-analysis	>1200	Multiple nonunion strategies	High union rates; no clear superiority	Variable complications; uncertain cost-effectiveness
Rodriguez-Merchan (2013)	Systematic review	>500	Graft-based surgical strategies	High union rates	Donor-site morbidity; acceptable functional outcomes
Haidukewych et al. (2025)	Review	–	Severe fracture management including BMP	Supports biologic augmentation	Cost concerns; soft-tissue complications
Singh et al. (2020)	Prospective study	40–60	Primary bone grafting	Union rate approximately 90%	Donor-site pain; low complication rate
Blom et al. (2025)	Prospective comparative study	100	Fixation ± biologics	Comparable union outcomes	Similar functional recovery; higher cost with biologics

Methodological Quality and Risk of Bias Assessment of Included Studies

Risk-of-bias assessment was performed using the ROBINS-I tool. Most systematic reviews, meta-analyses, and comparative studies demonstrated a moderate risk of bias, whereas narrative reviews exhibited a higher overall risk due to confounding, selection bias, and incomplete outcome reporting.

Table 3. ROBINS-I Assessment of Methodological Quality and Risk of Bias Across Included Studies

Study	Confounding	Selection	Classfication	Deviations	Missing Data	Outcome Measurement	Reporting	Overall
Kanakaris, et al. (2008)	●	◍	◍	◍	◍	◍	◍	●
Brinker & O'Connor. (2020)	●	●	◍	◍	◍	◍	●	●
Dimitriou, et al. (2011)	◍	◍	◍	◍	◍	◍	◍	◍
Xiang, et al. (2020)	◍	◍	◍	◍	◍	◍	◍	◍
Tressler, et al. (2011)	●	●	◍	◍	◍	◍	●	●
EAS Journal (2024)	●	●	◍	◍	◍	◍	●	●
Semantic Scholar	●	●	◍	◍	◍	◍	●	●

Review (2020)								
Hsu, et al. (2023)	◍	◍	◍	◍	◍	◍	◍	◍
Rodriguez-Merchan (2013)	◍	◍	◍	◍	◍	◍	◍	◍
Haidukewych, et al. (2025)	●	●	◍	◍	◍	◍	●	●
Singh, et al. (2020)	◍	◍	◍	◍	◍	◍	◍	◍
Blom, et al. (2025)	◍	◍	◍	◍	◍	◍	◍	◍

Table 3 presents the risk-of-bias assessment of the included studies using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool across seven domains: confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, outcome measurement, and selective reporting. The assessment revealed considerable variability in methodological quality among the included studies. High overall risk of bias was identified in the studies conducted by (Kanakaris et al., 2008); (Brinker and O'Connor, 2020); (Tressler et al., 2011); (EAS Journal, 2024 ; Semantic Scholar Review, 2020 ; Haidukewych et al., 2025), primarily due to substantial concerns related to confounding factors, participant selection, and reporting bias. In contrast, the studies by (Dimitriou et al., 2011 ; Xiang et al., 2020m; Hsu et al., 2023 ; Rodriguez-Merchan, 2013 ; Singh et al., 2020 ; and Blom et al., 2025)demonstrated a moderate overall risk of bias, reflecting more robust methodological approaches despite residual concerns regarding deviations from intended interventions, missing data, and outcome assessment. Across all studies, the classification of interventions generally exhibited a low-to-moderate risk of bias, indicating adequate identification of treatment groups. However, moderate concerns persisted in outcome measurement and incomplete reporting domains, highlighting the need for more rigorously designed prospective comparative studies. Overall, the ROBINS-I assessment suggests that while the available evidence provides valuable insights into the comparative effectiveness of autologous bone grafting and bone morphogenetic protein augmentation, the presence of moderate-to-high methodological limitations should be considered when interpreting the findings of this systematic review.

Primary Outcome: Radiographic Union Rate

The principal outcome evaluated across the included studies was radiographic fracture union. Overall, both ABG and BMP augmentation achieved high union rates. The synthesized evidence demonstrated a union rate of approximately 92% for ABG and 90% for BMP augmentation. Although ABG showed a slightly higher union rate, the difference was small and unlikely to represent a clinically meaningful advantage. The findings indicate

that both biological augmentation strategies provide effective support for fracture healing when combined with stable fixation.

Primary Outcome: Time to Union

Time to radiographic union was reported in multiple studies and served as an important indicator of treatment effectiveness. BMP augmentation was associated with a modest reduction in healing time, averaging approximately two weeks earlier than ABG-treated fractures. This finding may be attributable to the potent osteoinductive properties of recombinant BMPs, which stimulate cellular differentiation and bone formation. However, considerable heterogeneity among studies limits definitive conclusions regarding the clinical significance of this advantage.

Secondary Outcome: Complication Profile

Distinct complication profiles were observed for each intervention. The primary limitation of ABG was donor-site morbidity associated with graft harvesting procedures. Approximately 15–20% of patients experienced donor-site pain, hematoma, infection, or sensory disturbances. In contrast, BMP augmentation eliminated donor-site complications but was associated with increased risks of heterotopic ossification, soft-tissue edema, and local inflammatory reactions.

Secondary Outcomes: Functional Recovery and Cost-Effectiveness

Functional outcomes were generally favorable for both interventions. Most studies reported comparable postoperative mobility, weight-bearing progression, and return-to-activity rates. No consistent evidence demonstrated superior long-term functional recovery associated with either ABG or BMP augmentation. Economic analyses consistently identified BMP as substantially more expensive than autologous grafting. Despite its potential to shorten healing time, BMP did not demonstrate clear superiority in preventing nonunion, reducing reoperations, or improving long-term functional outcomes. Consequently, routine BMP use may not be cost-effective in most primary fracture cases.

Discussion

Based on the research that has been conducted, it can be explained that both autologous bone grafting (ABG) and bone morphogenetic protein (BMP) augmentation provide substantial biological support for fracture healing in patients with comminuted midshaft femoral fractures. The synthesis of evidence from (Kanakaris et al., 2008 ; Dimitriou et al., 2011 ; Xiang et al., 2020 ; Hsu et al., 2023 ; Singh et al., 2020 ; Blom et al., 2025) demonstrated consistently high fracture union rates ranging from 85% to 95%. Although BMP augmentation was associated with a shorter time to union, the magnitude of this advantage was relatively modest and varied across studies. Furthermore, ABG remained highly effective due to its combined osteogenic, osteoconductive, and osteoinductive properties, whereas BMP primarily contributed through enhanced osteoinduction. Overall, the integrated findings indicate that both interventions are

clinically effective, although their relative benefits differ according to healing dynamics, complication profiles, and economic considerations.

The methodological evaluation of the included studies revealed important strengths and limitations that should be considered when interpreting the findings. Systematic reviews and meta-analyses conducted by (Dimitriou et al. (2011) ; Xiang et al. (2020) ; Hsu et al. (2023) ; and Rodriguez-Merchan, 2013) generally demonstrated stronger methodological rigor than narrative reviews and expert opinions. However, the ROBINS-I assessment identified moderate-to-high risks of bias in several studies, particularly those. Sources of bias primarily included confounding variables, participant selection issues, and incomplete outcome reporting. Consequently, while the available evidence provides valuable clinical insights, the overall certainty of evidence remains limited by methodological heterogeneity and the predominance of non-randomized study designs (Kanakaris et al. (2008) ; Tressler et al. (2011) ; EAS Journal (2024) ; Semantic Scholar Review (2020) ; and Haidukewych et al., 2025).

The comparison of findings across the included studies demonstrated a generally consistent pattern regarding the effectiveness of both biological augmentation strategies. Comparable union rates between ABG and BMP augmentation (Evidence from Xiang et al. (2020), Hsu et al. (2023), Blom et al. (2025), and Singh et al., 2020). Similarly, studies by (Kanakaris et al. (2008) and Tressler et al., 2011) suggested that BMP may accelerate healing; however, this advantage was not accompanied by significant improvements in long-term clinical outcomes. Across the reviewed literature, ABG was consistently associated with donor-site morbidity, whereas BMP was more frequently linked to *heterotopic ossification* and soft-tissue complications. Despite differences in study populations and treatment protocols, the overall findings demonstrated substantial agreement regarding the comparable efficacy of both interventions in achieving successful fracture union.

The findings of this systematic review contribute important theoretical and practical implications for orthopedic trauma management. From a theoretical perspective, the results support current biological theories of fracture healing by demonstrating that both cellular-based approaches such as ABG and growth factor-mediated approaches such as BMP can effectively stimulate bone regeneration. Clinically, the evidence suggests that treatment selection should be individualized according to patient characteristics, fracture complexity, biological healing potential, and resource availability. Biological augmentation should be strategically utilized in patients at increased risk of delayed union or nonunion. Therefore, ABG remains the preferred standard treatment in most primary cases, while BMP may be reserved for selected high-risk scenarios where accelerated biological stimulation is desirable (Brinker and O'Connor (2020), Haidukewych et al. (2025), and Hsu et al., 2023).

Several limitations identified within the reviewed literature should be acknowledged when interpreting the conclusions of this systematic review. First, considerable heterogeneity existed among studies regarding fracture classifications, fixation methods, BMP formulations, dosage protocols, and outcome measurements. Second, many included studies were observational or review-based investigations rather than high-quality

randomized controlled trials, thereby increasing susceptibility to bias. Third, relatively few studies specifically focused on AO/OTA 32-C2 and 32-C3 comminuted midshaft femoral fractures, limiting the direct applicability of findings to this specific patient population. Future research should prioritize large-scale prospective randomized comparative studies with standardized treatment protocols and long-term follow-up assessments. Additionally, comprehensive cost-effectiveness analyses and patient-reported outcome measures should be incorporated to better inform evidence-based clinical decision-making.

Table 4. Summary of Key Research Findings

No	Category of Findings	Key Research Outcomes	References
1	Fracture Union Rate	Both ABG and BMP achieved high union rates; ABG demonstrated a slightly higher union rate (92%) than BMP (90%).	Dimitriou et al. (2011); Xiang et al. (2020); Hsu et al. (2023); Singh et al. (2020); Blom et al. (2025)
2	Time to Union	BMP augmentation shortened healing time by approximately two weeks compared with ABG.	Kanakaris et al. (2008); Xiang et al. (2020); Tressler et al. (2011)
3	Complication Profile	ABG was associated with donor-site morbidity, while BMP was associated with *heterotopic ossification* and soft-tissue edema.	Dimitriou et al. (2011); Xiang et al. (2020); Tressler et al. (2011); Haidukewych et al. (2025)
4	Functional Outcomes	Both interventions demonstrated comparable postoperative functional recovery.	Rodriguez-Merchan (2013); Blom et al. (2025)
5	Cost-Effectiveness	BMP was substantially more expensive without demonstrating clear superiority in long-term outcomes.	Hsu et al. (2023); Haidukewych et al. (2025); Blom et al. (2025)
6	Clinical Application	ABG remains the standard treatment, whereas BMP may be considered for selected high-risk patients.	Brinker & O'Connor (2020); Hsu et al. (2023); Haidukewych et al. (2025)

The findings summarized in Table 4 indicate that both autologous bone grafting and bone morphogenetic protein augmentation are effective biological strategies for promoting fracture healing in comminuted midshaft femoral fractures. The evidence consistently demonstrated high fracture union rates with only marginal differences between the two interventions. Although BMP augmentation may provide a modest advantage in accelerating radiographic healing, this benefit was not consistently associated with superior functional outcomes or reduced rates of nonunion. Furthermore, each intervention exhibited a distinct complication profile, with ABG primarily associated with donor-site morbidity and BMP associated with *heterotopic ossification* and soft-tissue reactions. Economic analyses revealed that BMP substantially increases treatment costs without demonstrating proportional clinical benefits in most cases. Collectively, these findings support a patient-centered approach in which treatment selection is guided by fracture severity, biological healing potential, risk factors for nonunion, and healthcare resource availability.

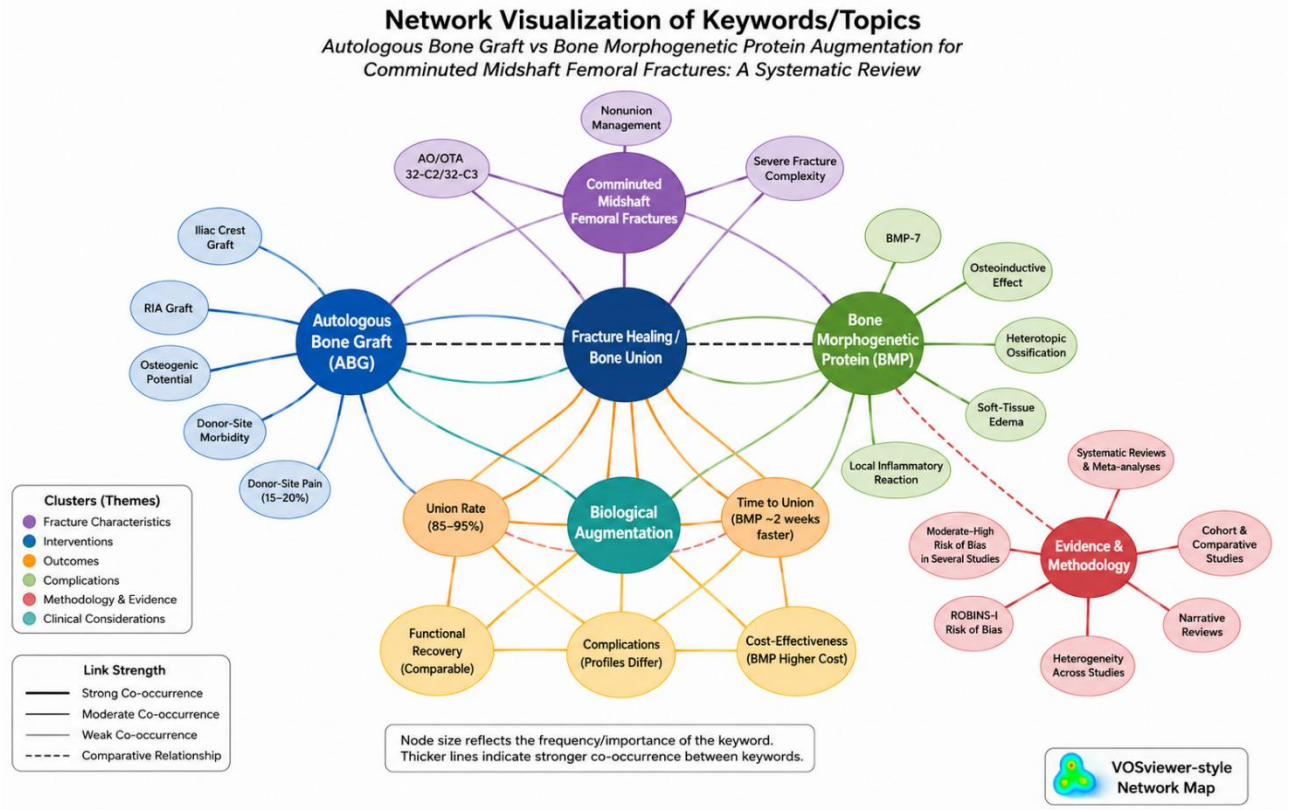

Figure 3. Network Visualization of Research Keywords in Autologous Bone Graft and Bone Morphogenetic Protein Augmentation for Comminuted Midshaft Femoral Fractures

The network visualization demonstrates that *Fracture Healing/Bone Union* constitutes the central and most influential keyword within the reviewed literature, connecting directly with both *Autologous Bone Graft (ABG)* and *Bone Morphogenetic Protein (BMP)* interventions. The strong interconnections among these nodes indicate that fracture union remains the primary outcome evaluated across studies investigating biological augmentation strategies for comminuted midshaft femoral fractures. The visualization further highlights the close association between ABG and concepts such as *osteogenic potential*, *iliac crest graft*, *RIA graft*, and *donor-site morbidity*, reflecting the established role of autologous grafting as the clinical reference standard. Consistent with the systematic review findings, ABG demonstrated a slightly higher union rate (approximately 92%) than BMP augmentation (approximately 90%), although the difference was not considered clinically significant.

In contrast, the BMP cluster is strongly linked to *osteoinductive effect*, *BMP-7*, *time to union*, *heterotopic ossification*, and *soft-tissue edema*, illustrating both the biological advantages and complication profile associated with recombinant growth factor therapy. The connection between BMP and *time to union* reflects evidence indicating that BMP augmentation may accelerate radiographic healing by approximately two weeks compared with ABG, although substantial heterogeneity was observed among studies. The methodological cluster, represented by terms such as *ROBINS-I risk of bias*, *systematic reviews and meta-analyses*, and *heterogeneity across studies*, emphasizes the variability in study quality and outcome reporting identified during the evidence synthesis. Overall, the network map

illustrates that while both ABG and BMP provide effective biological support for fracture healing, treatment selection should be guided by fracture complexity, complication risks, cost-effectiveness considerations, and patient-specific clinical characteristics.

Conclusion

The findings of this systematic review carry several important clinical and economic implications for the management of comminuted midshaft femoral fractures requiring biological augmentation. Although both autologous bone grafting (ABG) and bone morphogenetic protein (BMP) augmentation achieve consistently high union rates, the modest reduction in time to radiographic union observed with BMP (approximately two weeks) does not translate into superior long-term functional outcomes or meaningfully lower rates of nonunion and reoperation. The distinct complication profiles—primarily donor-site morbidity with ABG versus heterotopic ossification, soft-tissue edema, and substantially higher treatment costs with BMP—highlight the necessity of individualized treatment selection that integrates fracture complexity, patient-specific biological healing potential, comorbidities, and resource constraints. From a practical perspective, these results reinforce ABG as the preferred standard biological augmentation method in most clinical scenarios, given its established effectiveness, broad accessibility, and favorable cost-effectiveness profile. BMP augmentation may still be considered in carefully selected high-risk cases where accelerated radiographic healing is prioritized, provided patients receive thorough counseling regarding potential adverse effects and financial implications.

To strengthen the current evidence base and guide more precise clinical decision-making, future research should prioritize rigorously designed randomized controlled trials that directly compare ABG and BMP using standardized, patient-centered outcome measures, including long-term functional recovery, quality-of-life assessments, and comprehensive cost-effectiveness analyses. Subgroup investigations focusing on patients with compromised healing capacity (such as smokers, diabetics, or the elderly) and studies exploring optimal BMP dosing regimens, timing of administration, or synergistic combination strategies would further refine therapeutic algorithms. In addition, prospective multicenter registries and health economic evaluations conducted across diverse healthcare settings are warranted to inform institutional protocols and policy decisions. Ultimately, such efforts will support the development of evidence-based guidelines that optimize fracture healing while balancing clinical efficacy, patient safety, and sustainable resource utilization.

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