Systematic Review

Effectiveness of Intradiscal Regenerative Medicine Therapies for Long-Term Relief of Chronic Low Back Pain: A Systematic Review and Meta-Analysis

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Background: Recent research underscores the potential of intradiscal biologics, such as mesenchymal stem cells (MSCs), platelet-rich plasma (PRP), and alpha-2-macroglobulin, in promoting chondrogenesis within lumbar intervertebral discs as a treatment for discogenic low back pain. Studies indicate significant improvements in pain relief, physical function, and overall quality of life following these interventions.

Objective: This study aims to evaluate the effectiveness of intradiscal injections of MSCs and PRP in managing low back and lower extremity pain. A systematic review and meta-analysis were conducted to assess the outcomes of these treatments.

Study Design: A systematic review and meta-analysis evaluating the efficacy of PRP and MSC injections for discogenic low back and lower extremity pain.

Data Sources: The review included literature from PubMed, Cochrane Library, the U.S. National Guideline Clearinghouse (NGC), prior systematic reviews, and reference lists, covering studies from 1966 to September 2024.

Study Selection: Randomized controlled trials (RCTs), observational studies, and case reports focusing on biologic injections into the disc were included.

Data Extraction and Synthesis: Data were extracted and assessed for methodological quality. Evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria and summarized based on best evidence synthesis principles on a 1-to-5 scale.

Results: The analysis included 8 RCTs (4 evaluating PRP, 5 evaluating MSCs) and 8 observational studies (4 assessing PRP, 4 assessing MSCs) for managing chronic low back pain. Evidence quality was deemed fair (Level III) with limited certainty and moderate recommendation strength based on qualitative and quantitative analyses.

Limitations: Paucity of high-quality studies.

Conclusion: This systematic review and single-arm meta-analysis suggest that intradiscal injections of MSCs and PRP may be effective in managing discogenic low back pain, supported by Level III evidence.

Key words: Chronic low back pain, discogenic pain, regenerative therapy, mesenchymal stem cells, platelet-rich plasma, intradiscal injection

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Chronic low back pain (CLBP) poses a substantial socioeconomic burden worldwide (1-7). According to a global burden of disease report, low back pain ranked as the leading cause of years lived with disability (YLD) out of 395 diseases, injuries, and impairments, accounting for approximately 64 million YLDs or 7.4% of total YLDs in 2019 (5-7). A 2023 report by the Centers for Disease Control and Prevention (CDC) highlighted that 24.3% of U.S. adults experienced chronic pain during the year, with 8.5% reporting high-impact chronic pain. This marks an increase compared to 2021, which estimated chronic pain prevalence at 21% and high-impact chronic pain at 6.9%.

Economic analyses reveal the financial toll of spinal pain management. Dieleman et al (6) reported U.S. expenditures on personal health care and public health for spinal pain at $134.5 billion in 2016, a significant 53.5% increase from $87.6 billion in 2013. Similarly, costs for managing musculoskeletal disorders rose by 43.5%, from $183.5 billion in 2013 to $263.3 billion in 2016.

Pain prevalence varies across spinal regions, with the low back showing the highest prevalence at 43%, followed by the neck at 32%, and the thoracic spine at 13% (8). Annually, the prevalence of low back and neck pain ranges from 22% to 65%, with lifetime prevalence estimates of 84% for low back pain and 67% for neck pain (1–4). Chronic spinal pain persists in approximately 60% of patients for over a year, even after conservative or surgical treatments (1-4).

Chronic spinal conditions are strongly linked to physical disability and mental health issues, including depression, generalized anxiety disorder, and somatization (1-7,10). Additionally, chronic spinal pain in parents is associated with a higher risk of similar conditions in their children as they reach adulthood (11).

While some studies have reported a decline in low back pain prevalence (12), recent evidence indicates rising prevalence across all chronic pain categories, with low back pain being the most predominant (7). This rise parallels increased economic and societal costs, driven by advancements in treatment modalities, including regenerative medicine therapies (1-4,13-30).

Key sources of low back pain include intervertebral discs, zygapophysial (facet) joints, and sacroiliac joints (3,31-36). Discogenic pain accounts for 16.9% to 39% of chronic low back pain cases without radiculopathy (34). Lumbar disc disorders, such as prolapse, protrusion, extrusion, or herniation, have a symptomatic prevalence of approximately 1% to 3% (34,37,38).

While some discogenic pain resolves spontaneously, it becomes chronic in many cases, necessitating extensive treatment. Management options range from conservative approaches, such as physical therapy and pharmacological treatment, to interventional procedures and surgical interventions like fusion or disc replacement (15-23). Interventional techniques, including regenerative medicine therapies, are increasingly employed to address chronic spinal pain (2,3,15-20,24,39-50).

Intervertebral disc degeneration, a major contributor to discogenic pain, mostly due to intervertebral disc degeneration, is driven by neuroinflammation-induced nociceptive fiber innervation in the disc (34,35). The intervertebral disc's unique structure—comprising the nucleus pulposus, annulus fibrosus, and cartilage endplate—offers both structural support and shock absorption. However, degenerative changes disrupt these functions, leading to lumbar spine instability.

Conventional treatments fail to halt the degenerative cascade or promote regeneration (30,34,35,51). Identified mechanisms include the loss of stem and progenitor markers, extracellular matrix imbalance, heightened inflammation, sensory hyperinnervation, vascularization, and dysregulated signaling pathways. In response, regenerative therapies like mesenchymal stem cell (MSC) and platelet-rich plasma (PRP) injections have emerged as promising options (4,13,14,25-30,51-56).

Preclinical and clinical studies provide growing evidence for the efficacy of MSCs and PRP in treating discogenic low back pain. These findings have been evaluated through controlled trials and systematic reviews (57-67).

This systematic review and meta-analysis aim to assess the effectiveness of intradiscal regenerative medicine therapies in managing chronic low back pain.

Methods

A systematic review and meta-analysis were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (68). Methodological approaches from prior reviews and guidelines were also incorporated to enhance rigor and reliability (1-3,15-20,69-71).

Objectives

This review aimed to assess the efficacy and effectiveness of intradiscal mesenchymal stem cells (MSCs), including bone marrow aspirate concentrate (BMAC) and other

sources, as well as platelet-rich plasma (PRP) injections, in treating low back and lower extremity pain.

Eligibility Criteria

Studies were included if they:

- Were randomized controlled trials (RCTs) or observational studies with at least six months of follow-up.
- Included at least 25 patients (for observational studies).
- Diagnosed discogenic low back pain through discograms, imaging, or clinical criteria.

Information Sources

A comprehensive literature search was conducted to identify RCTs and observational studies on intradiscal injections of BMAC and PRP, encompassing publications from all countries and languages without restrictions.

1. PubMed from 1966 https://pubmed.ncbi.nlm.nih.gov/
2. Cochrane Library https://www.cochranelibrary. com/
3. Google Scholar https://scholar.google.com/
4. U.S. National Guideline Clearinghouse (NGC) https://www.ahrq.gov/gam/index.html
5. Clinical Trials https://www.clinicaltrials.gov/
6. Previous systematic reviews and cross-references
7. All other sources including nonindexed journals and abstracts

The literature search covered publications from 1966 to September 2024.

Search Strategy

The search strategy included all intradiscal injections of regenerative medicine solutions in the treatment of low back and lower extremity pain. The search terms included: ((((((spinal pain, chronic low back pain) OR chronic lumbosacral pain) OR lumbar discogenic pain OR disc degeneration OR disc herniation OR internal disc disruption) OR nerve root compression) OR lumbosciatic pain) OR postlaminectomy) OR lumbar surgery syndrome) OR radicular pain) AND ((((((((((epidural injection) OR platelet rich plasma injection or stem cell injection) OR epidural perineural injection) OR stem cells) OR platelet rich plasma OR stem cells) OR intradiscal injections or PRP or stem cells AND ((metaanalysis (pt) OR randomized controlled trial (pt) OR controlled clinical trial (pt) OR randomized controlled trials (mh) OR random allocation (mh) OR double-blind method (mh) OR single-blind method (mh) OR clinical trial (pt) OR clinical trials (mh) OR ("clinical trial" (tw)) OR ((singl* (tw) OR doubl* (tw) OR trebl* (tw) OR tripl* (tw)) AND (mask* (tw) OR blind* (tw))) OR (placebos (mh) OR placebo* (tw) OR random* (tw) OR research design (mh:noexp))))

Data Selection

Two independent reviewers (LM and MRS) developed the search criteria, performed the literature search, and extracted relevant data. Disagreements were resolved by a third reviewer (ADK). In cases of potential conflicts of interest among the reviewers, disputes were assigned to additional reviewers.

Study of Risk of Bias and Methodological Quality Assessment

The quality of RCTs and observational studies was assessed using several tools:

- **Cochrane Review Criteria:** Trials scoring ≥ 9 out of 13 were deemed high quality, while scores of 5-8 indicated moderate quality (Appendix Table 1) (71).
- **Interventional Pain Management Techniques – Quality Appraisal of Reliability and Risk of Bias Assessment (IPM-QRB):** Scores of 32-48 indicated high quality, 16–31 moderate quality, and < 16 low quality (Appendix Table 2) (72). Low-quality studies were excluded.
- **Newcastle-Ottawa Quality Assessment Scale:** Studies scoring ≥ 6 were considered high quality, scores of 3-5 were moderate quality, and scores < 3 were low quality and excluded (Appendix Table 3 and 4) (73).
- **IPM-QRB for Nonrandomized Studies (IPM-QRBNR):** Studies scoring 32-48 were high quality, 16-31 moderate quality, and < 16 low quality and excluded (Appendix Table 5) (74).

Only studies meeting the inclusion criteria and achieving moderate to high-quality ratings based on these assessments were included in the analysis.

Assessment Utilizing GRADE Criteria

The evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) system (75,76), which evaluates the quality of evidence based on five factors: 1) methodological limitations, 2) consistency, 3) indirectness, 4) imprecision, and 5) publication bias. The evidence was graded as high, moderate, low, or very low. Adjustments were made to the grade based on the study's methodological quality, with the possibility of downgrading or upgrading the grade.

Two authors (LM and MRS) independently conducted the methodological quality assessment and GRADE evaluation in an unblinded manner. Any discrepancies were resolved by involving a third reviewer (ADK). In cases of potential conflicts of interest (e.g., authorship), the involved authors were excluded from reviewing those studies for quality assessment.

Outcome Measures

An outcome was considered clinically significant if there was a reduction of at least 2 points on the Visual Analog Scale (VAS) or Numeric Rating Scale (NRS), or a minimum 50% reduction in pain, coupled with improvement in functional status. A study was deemed clinically significant and effective if the primary outcome achieved statistical significance (*P*-value ≤ 0.05).

Analysis of Evidence

The evidence was synthesized qualitatively and quantitatively. Quantitative synthesis included conventional meta-analysis and single-arm meta-analysis. At least 2 review authors (LM and MRS) independently analyzed the evidence in a standardized manner. Any disagreements between reviewers were resolved by a third author (ADK), and consensus was reached. If conflicts of interest arose (e.g., authorship), the involved reviewers were excluded from assessment and analysis.

Qualitative Analysis

Qualitative analysis was performed using best-evidence synthesis, incorporating multiple criteria, including the Cochrane Review criteria and the U.S. Preventive Services Task Force (USPSTF) criteria (Table 1) (77). The evidence was rated on a scale from strong to opinion- or consensus-based, with five levels of evidence. Table 2 outlines the strength of recommendations as developed by the National Guideline Clearinghouse Extent Adherence to Trustworthy Standards (NEATS) instrument (78), as modified by the guideline panel (1,70).

Meta-Analysis

Dual-Arm Meta-Analysis

The Review Manager (version 5.4, Cochrane Collaboration, 2020) software was used for dual-arm meta-analysis. For pain and functional improvement data, studies were reported as standardized mean differences (SMD) with 95% confidence intervals (CI). Treatment effects were evaluated using random-effects models, with heterogeneity assessed through I^2 statistics.

Single-Arm Meta-Analysis

For single-arm meta-analysis, Comprehensive Meta-Analysis software (version 3.0, Biostat Inc., Englewood, NJ) was used. Pain and functional improvement data were reported as mean differences with 95% CI, and treatment effects were plotted using forest plots. Heterogeneity was also interpreted using I^2 statistics.

Results

Study Selection

Figure 1, based on the 2020 PRISMA guidance (68), presents a flow diagram of the study selection process.

Following the search criteria, 35 publications were identified for potential inclusion (79-113), consisting of 9 randomized controlled trials (RCTs) (79-87), with 8 trials meeting the inclusion criteria (79-83,85-87). Additionally, 26 observational studies were identified (88-113), with 8 studies meeting the inclusion criteria (88,92,95,96,105,106,108,109). The remaining observa-

Table 1. *Qualitative modified approach to grading of evidence of therapeutic effectiveness studies.*

Level I	Strong	Evidence obtained from multiple relevant high-quality randomized controlled trials
Level II	Moderate	Evidence obtained from at least one relevant high-quality randomized controlled trial or multiple relevant moderate or low-quality randomized controlled trials
Level III	Fair	Evidence obtained from at least one relevant moderate or low-quality randomized trial or Evidence obtained from at least one relevant high-quality non-randomized trial or observational study with multiple moderate or low-quality observational studies
Level IV	Limited	Evidence obtained from multiple moderate or low-quality relevant observational studies
Level V	Consensus based	Opinion or consensus of large group of clinicians and/or scientists

Modified from: Manchikanti L, et al. A modified approach to grading of evidence. *Pain Physician* 2014; 17:E319-E325 (77).

Table 2. *Guide for strength of recommendations as modified for American Society of Interventional Pain Physicians (ASIPP) guidelines.*

Rating for Strength of Recommendation	
Strong	There is high confidence that the recommendation reflects best practice. This is based on: a) strong evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, with no or minor exceptions; c) minor or no concerns about study quality; and/or d) the extent the panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation. ASIPP Adaptation: Consensus was achieved that there is high certainty that the net benefit is substantial providing strong recommendation. Recommendation: Strong
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on: a) good evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, with minor and/or few exceptions; c) minor and/or few concerns about study quality; and/or d) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation. ASIPP Adaptation: Consensus was achieved that there is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial. Recommendation: Moderate
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on: a) limited evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, but with important exceptions; c) concerns about study quality; and/or d) the extent of panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation. ASIPP Adaptation: The consensus achieved that there is potential improvement in certain individuals or groups of patients based on individual professional judgement and shared decision making. Recommendation: Weak

Adapted and modified from: National Guideline Clearinghouse Extent Adherence to Trustworthy Standards (NEATS) instrument (1,70,78).

tional studies were excluded for not meeting the inclusion criteria.

Methodologic Quality and Risk of Bias Assessment

Trials that met the inclusion criteria and scored at least 9 out of 13 using the Cochrane review criteria (71) were classified as high quality, while trials scoring 5-8 were considered moderate quality.

Tables 3 and 4 provide methodological quality assessment and risk of bias for the 8 RCTs (79-86,85-87) using the Cochrane review criteria (71) and the IPM-QRB criteria (72). Assessment using the Cochrane review criteria categorized all trials as high quality, each scoring at least 9 of 13 (79-83,85-87). According to the IPM-QRB instrument, all trials (79-83,85-87) were rated as high quality, with scores above 32 out of 48.

Table 5 shows the assessment of methodological quality using the Newcastle-Ottawa Quality Assessment Scale for cohort studies, with all 8 studies

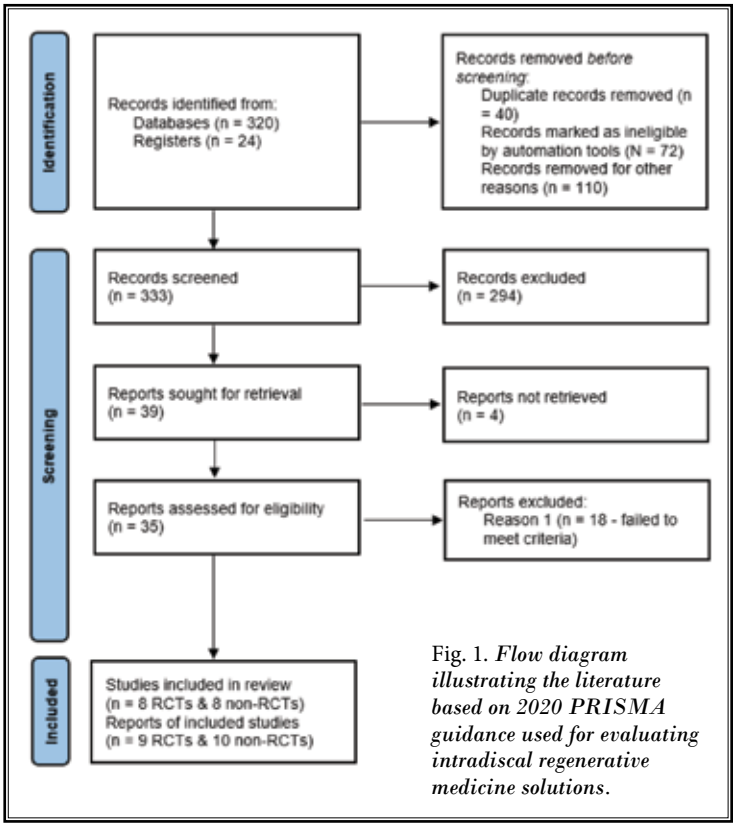


Fig. 1. *Flow diagram illustrating the literature based on 2020 PRISMA guidance used for evaluating intradiscal regenerative medicine solutions.*

Table 3. *Methodological quality assessment of randomized trials of intradiscal biologics utilizing Cochrane review criteria.*

	Tuakli-Wosornu et al, 2016 (79)	Noriega et al, 2017 (80)	Amirdelfan et al, 2021 (82)	Navani et al, 2024 (83)	Goyal et al, 2022 (85)	Akeda et al, 2022 (86)	Gornet et al, 2024 (81)	Pers et al, 2024 (87)
Randomization adequate	Y	Y	Y	Y	Y	Y	Y	Y
Concealed treatment allocation	Y	Y	Y	Y	Y	Y	Y	Y
Patient blinded	Y	Y	Y	Y	Y	Y	Y	N
Care provider blinded	Y	N	Y	Y	N	Y	N	N
Outcome assessor blinded	Y	Y	Y	Y	Y	Y	Y	N
Drop-out rate described	Y	Y	Y	Y	Y	Y	Y	Y
All randomized participants analyzed in the group	Y	Y	Y	Y	Y	Y	Y	Y
Reports of the study free of suggestion of selective outcome reporting	Y	Y	Y	Y	Y	Y	Y	Y
Groups similar at baseline regarding most important prognostic indicators	Y	Y	Y	Y	Y	Y	Y	Y
Co-intervention avoided or similar in all groups	Y	Y	Y	Y	Y	Y	Y	Y
Compliance acceptable in all groups	Y	Y	Y	Y	Y	Y	Y	Y
Time of outcome assessment in all groups similar	Y	Y	Y	Y	Y	Y	Y	Y
Are other sources of potential bias not likely	U	N	Y	N	Y	Y	N	Y
SCORE	12/13	11/13	___13/13	12/13	12/13	13/13	11/13	10/13

Y = yes; N = no; U = unclear

Source: Furlan AD, et al; Editorial Board of the Cochrane Back, Neck Group. 2015 Updated Method Guideline for Systematic Reviews in the Cochrane Back and Neck Group. *Spine (Phila Pa 1976)* 2015; 40:1660-1673 (71).

Table 4. *Methodologic quality assessment of randomized trials of intradiscal biologics utilizing IPM-QRB criteria.*

		Tuakli-Wosornu et al, 2016 (79)	Noriega et al, 2017 (80)	Amirdelfan et al, 2021 (82)	Navani et al, 2024 (83)	Goyal et al, 2022 (85)	Akeda et al, 2022 (86)	Gornet et al, 2024 (81)	Pers et al, 2024 (87)
I.	TRIAL DESIGN AND GUIDANCE REPORTING								
1.	CONSORT or SPIRIT	2	2	2	2	1	1	2	3
II.	DESIGN FACTORS								
2.	Type and Design of Trial	3	3	3	3	2	2	2	3
3.	Setting/Physician	3	1	3	3	3	3	3	3

Table 4. *Methodologic quality assessment of randomized trials of intradiscal biologics utilizing IPM-QRB criteria.*

		Tuakli-Wosornu et al, 2016 (79)	Noriega et al, 2017 (80)	Amirdelfan et al, 2021 (82)	Navani et al, 2024 (83)	Goyal et al, 2022 (85)	Akeda et al, 2022 (86)	Gornet et al, 2024 (81)	Pers et al, 2024 (87)
4.	Imaging	3	3	3	3	3	3	3	3
5.	Sample Size	2	2	3	3	2	2	3	3
6.	Statistical Methodology	1	1	1	1	1	1	1	1
III.	PATIENT FACTORS								
7.	Inclusiveness of Population	2	2	2	2	2	2	1	2
	• For discogenic pain								
8.	Duration of Pain	2	2	2	2	2	2	2	2
9.	Previous Treatments	2	2	2	2	2	2	2	2
10.	Duration of Follow-up with Appropriate Interventions	2	2	2	2	2	2	3	3
IV.	OUTCOMES								
11.	Outcomes Assessment Criteria for Significant Improvement	2	4	4	4	4	4	4	4
12.	Analysis of all Randomized Participants in the Groups	2	2	2	2	2	2	2	2
13.	Description of Drop Out Rate	1	1	2	2	2	2	2	2
14.	Similarity of Groups at Baseline for Important Prognostic Indicators	2	2	2	2	2	2	2	2
15.	Role of Co-Interventions	1	1	1	1	1	1	1	1
V.	RANDOMIZATION								
16.	Method of Randomization	2	2	2	2	2	2	2	2
VI.	ALLOCATION CONCEALMENT								
17.	Concealed Treatment Allocation	2	2	2	2	2	2	2	2
VII.	BLINDING								
18.	Patient Blinding	1	1	1	1	1	1	1	0
19.	Care Provider Blinding	1	0	1	1	0	1	0	0
20.	Outcome Assessor Blinding	1	0	1	1	1	1	1	0
VIII.	CONFLICTS OF INTEREST								
21.	Funding and Sponsorship	0	-3	-3	-3	0	0	-3	2
22.	Conflicts of Interest	0	0	-2	0	0	0	-2	2
TOTAL		37/48	32/48	36/48	38/48	37/48	38/48	34/48	44/48

Modified from: Manchikanti L, et al. Assessment of methodologic quality of randomized trials of interventional techniques: Development of an interventional pain management specific instrument. *Pain Physician* 2014; 17:E263-E290 (72).

Table 5. *Newcastle-Ottawa quality assessment scale for cohort studies of intradiscal biologics.*

	Pettine et al, 2015 (92)	Haines et al, 2022 (95)	Kirchner & Anitua, 2016 (106)	Atluri et al, 2022 (88)	Lewandrowski et al, 2023 (96)	Monfett et al, 2016 (105)	Jain et al, 2020 (108)	Machado et al, 2022 (109)
SELECTION								
1. Representativeness of the exposed cohort	Y	Y	Y	Y	Y	Y	Y	Y
2. Selection of the non exposed cohort	Y	Y	Y	Y	Y	Y	Y	Y
3. Ascertainment of exposure	Y	Y	Y	Y	Y	Y	Y	Y
4. Demonstration that outcome of interest was not present at start of study	Y	Y	Y	Y	Y	Y	Y	Y
COMPARABILITY								
1. Comparability of cohorts on the basis of the design or analysis	N	N	N	Y	N	N	N	N
OUTCOME								
1. Assessment of outcome	Y	Y	Y	Y	Y	Y	Y	Y
2. Was follow-up long enough for outcomes to occur	Y	Y	Y	Y	Y	Y	Y	Y
3. Adequacy of follow up of cohorts	N	N	N	Y	N	N	N	N
TOTAL	6/8	6/8	6/8	8/8	6/8	6/8	6/8	6/8

Source: Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. Accessed 7/09/2024. www.ohri.ca/programs/clinical_epidemiology/oxford.asp (73).

(88,92,95,96,105,106,108,109) scoring 6 or higher, indicating high quality.

Table 6 presents the methodological quality assessment for the 8 observational studies (88,92,95,96,105,106,108,109) based on the IPM-QRBNR criteria (74). One study (88) was classified as high quality with a score above 32, while the other 7 studies (92,95,96,105,106,108,109) were rated as moderate quality.

Study Characteristics

Tables 7 and 8 summarize the characteristics and outcomes of the studies that met the inclusion criteria. Among the RCTs, 4 trials evaluated PRP (79,83,85,86), and 5 trials (80-83,87) evaluated MSCs. One trial by Navani et al (83) compared intradiscal PRP and MSCs against a placebo control. Among the observational studies, 4 studies assessed the role of PRP (105,106,108,109), while 4 studies evaluated MSCs (88,92,95,96).

Quantitative and Qualitative Analysis

Both quantitative and qualitative analyses were conducted for the studies that met the inclusion criteria.

Quantitative Analysis

Pain – Conventional Dual-Arm Analysis

Five studies (81-83,87,88), including 2 with different doses, involving 396 patients compared BM/MSC versus control in a dual-arm meta-analysis at 1 month. The results showed no statistically significant difference in pain levels between the 2 groups [SMD -0.26 (-0.79, 0.27), $P = 0.33$] (Fig. 2A).

Five studies (80-82,87,88), including 2 with different doses, involving 420 patients compared BM/MSC versus control in a dual-arm meta-analysis at 3 months. The results showed no statistically significant difference in pain levels between the 2 groups [SMD 0.03 (-0.17, 0.23), $P = 0.75$] (Fig. 2B).

Five studies (80-82,87,88), including 2 with different doses, involving 402 patients compared BM/MSC versus control in a dual-arm meta-analysis at 6 months. The results showed no statistically significant difference in pain levels between the 2 groups [SMD 0.05 (-0.16, 0.25), p = 0.65] (Fig. 2C).

Five studies (80-82,87,88), including 2 with different doses, involving 446 patients compared BM/MSC versus control in a dual-arm meta-analysis at 12

Table 6. *Assessment of nonrandomized or observational studies of intradiscal biologics utilizing IPM-QRBNR.*

		Pettine et al, 2015 (92)	Haines et al, 2022 (95)	Kirchner & Anitua, 2016 (106)	Atluri et al, 2022 (88)	Lewandrowski et al, 2023 (96)	Monfett et al, 2016 (105)	Jain et al, 2020 (108)	Machado et al, 2022 (109)
I.	STUDY DESIGN AND GUIDANCE REPORTING								
1.	STROBE or TREND GUIDANCE	3	2	2	3	2	1	2	3
II.	DESIGN FACTORS								
2.	Study Design and Type	2	2	2	4	2	1	2	2
3.	Setting/Physician	2	2	2	2	2	2	2	2
4.	Imaging	3	3	3	3	3	3	3	3
5.	Sample Size	0	0	1	2	1	0	0	0
6.	Statistical Methodology	2	2	2	2	2	0	2	2
III.	PATIENT FACTORS								
7.	Inclusiveness of Population	4	4	2	3	2	4	4	2
	• For discogenic pain								
8.	Duration of Pain	2	2	2	2	2	2	2	2
9.	Previous Treatments	2	2	2	2	2	2	2	2
10.	Duration of Follow-up with Appropriate Interventions	4	3	3	3	3	4	1	1
IV.	OUTCOMES								
11.	Outcomes Assessment Criteria for Significant Improvement	2	2	2	4	4	0	2	2
12.	Description of Drop Out Rate	2	2	2	2	2	2	2	2
13.	Similarity of Groups at Baseline for Important Prognostic Indicators	0	0	0	2	2	0	0	0
14.	Role of Co-Interventions	2	2	2	2	2	2	2	2
V.	ASSIGNMENT								
15.	Method of Assignment of Participants	0	0	0	0	0	0	0	0
VI.	CONFLICTS OF INTEREST								
16.	Funding and Sponsorship	0	0	0	0	0	0	0	0
TOTAL		30/48	28/48	27/48	36/48	31/48	23/48	26/48	25/48

Modified from: Manchikanti L, et al. Development of an interventional pain management specific instrument for methodologic quality assessment of nonrandomized studies of interventional techniques. *Pain Physician* 2014; 17:E291-E317 (74).

Table 7. *Study characteristics of randomized controlled trials assessing intradiscal biologics.*

Study Study Characteristic Methodological Quality Scoring	Number of Patients and Interventions	Intervention Group	Comparator	Outcome Measures and Time of Measurement	Results	Strengths	Weaknesses	Conclusions
PLATELET-RICH PLASMA								
Tuakli-Wosornu et al, 2016 (79) RA, PC, DB Single center Quality Scores: Cochrane = 12/13 IPM-QRB = 37/48	n = 47 Lumbar discogenic pain Selection Criteria: Clinical Evaluation: Imaging and provocation discography Biologic Used: PRP	n = 29 patients in the treatment group Injection of disc levels that elicited concordant pain with evidence of incomplete annular disruption with < 2 mL were injected with 1-2 mL of PRP	n = 18 Injection of disc levels that elicited concordant pain with evidence of incompetent annular disruption with less than 2 mL were injection with 1-2 mL of contrast	FRI & NRS for pain, pain and physical function domains of the SF-36, and the modified NASS Outcome Questionnaire 1, 4, & 8 weeks, 6 months, 1 year	Follow-up rate: 92% 8-week follow up: Significant improvement in pain ($P = 0.02$, function p = 0.3) Patient satisfaction ($P = 0.01$) PRP Group: Worst pain decreased from baseline of 7.98 to 5.82. Comparator: 7.72 at baseline and 6.83 One-year follow-up: Significant improvements from baseline to one-year were observed NRS worst pain 2.12-point change ($P < 0.01$) Significant improvement in FRI scores was maintained through one-year from baseline	Well designed, randomized, double-blind control design with a rigorous participation selection process and high follow-up rate and long-term data of at least one-year in the majority of the treatment group Satisfactory results at 8 weeks, 6 months, and one-year	The relief patterns were significant; however, authors have not calculated 50% or greater proportion of patients with the 50% or greater pain relief Data collection in the control group was performed only up to 8 weeks	Positive trial Intradiscal injections of PRP x 1 showed significant improvement at 8-week follow-up with maintained improvement compared to controls at 1-year follow-up
Navani et al, 2024 (83) RA, PC, DB Multicenter Quality Scores: Cochrane = 12/13 IPM-QRB = 38/48	43 patients were randomized into 3 groups: Placebo = 12 PRP = 15 BMC = 16 Selection Criteria: Imaging, clinical assessment Biologic Used: Intradiscal PRP Intradiscal BMC	Intradiscal PRP injection, 1-2 mL, into the painful disc(s) until resistance to further injection was felt by the operator in the PRP group (n = 15) In the BMC group, 1-2 mL of BMC was injected intradiscally until resistance to further injection was felt by the operator (N = 16)	Patients in the placebo group receive deep trigger point injections with normal saline into the muscle (n = 12)	NRS, patient satisfaction, ODI 1, 3, 6, and 12 months	Significant improvement was seen in PRP and BMC groups at 6- and 12-month follow-up compared to baseline There was no significant difference between PRP and BMC over a 12-month period ($P = 0.094$) ODI was significantly reduced ($P = 0.001$) for both biologic groups Changes in pain scores over 12 months were significant ($P = 0.0043$) ODI scores significantly improved in the crossover group also ($P = 0.0137$)	Multicenter, randomized, controlled trials with crossover design Overall, good results compared to overall appropriate results compared to placebo There were no differences between PRP and BMC group	Placebo group was intramuscular injection with short-term follow-up, randomization blinding	Positive trial Comparative analysis of intradiscal PRP and BMC compared to intramuscular injection of muscle saline injection into the muscle showed significant improvement in biologic treatment groups There was no difference in PRP or BMC

Table 7 cont. *Study characteristics of randomized controlled trials assessing intradiscal biologics.*

Study Study Characteristic Methodological Quality Scoring	Number of Patients and Interventions	Intervention Group	Comparator	Outcome Measures and Time of Measurement	Results	Strengths	Weaknesses	Conclusions
Pers et al, 2024 (87) RA, PC, DB Multicenter Quality Scores: Cochrane = 10/13 IPM-QRB = 44/48	Randomized patients = 114 BM-MSC group (n =58) Sham placebo group (n = 56) Biologic Used: Intradiscal BM-MSC	Intradiscal injection of 2 mL of 20 million BM-MSCs in injectable-grade Plasma-lyte using a 22G spinal needle	Sham injection without intradiscal puncture consisted of subcutaneous injection in the back of the patient of 2 mL of sterile saline in similar conditions in the surgical theatre	Primary endpoint: Rate of responders defined by improvement of VAS for pain of at least 20% and 20 mm, or improvement of ODI of 20% between baseline and month 12 The secondary structural co-primary endpoint: Change in the disc fluid content measured by quantitative T2 MRI Secondary endpoints: Pain VAS, ODI, SF-36 MCID in all time points of 1, 3, 6, 12 and 24 months	At 12-month follow-up, the study did not demonstrate clinical and imaging benefits and co-primary endpoint was not reached However, at 12-months, the percentage of responders was 74% of patients in the experimental group vs. 68.8% in the placebo group The change in disc fluid content suggestive of disc regeneration between baseline and month 12 was an average of 41.7% in the placebo group vs. 37.9% in the treatment group VAS improved at all points in both groups The proportion of patients reaching MCID in VAS pain score with 30% improvement between baseline and 1, 3, 6, 12 and 24 months were slightly elevated in BM-MSC group but not statistically significant The same result was seen in the proportion of patients reaching the MCID in ODI scores with 10-point improvement No serious adverse effects related to the intervention occurred	The first of its nature DB, RA, multicenter PC trial of allogenic bone marrow-derived mesenchymal stromal cell-based therapy in patients with strict inclusion criteria Data shows procedure is safe This trial provides valuable insights into the complexities of MSC therapy in challenging clinical context	There was no significant difference between treatment group and placebo group	Negative trial Comparative analysis of allogenic bone marrow-derived mesenchymal stromal cell-based therapy for patients with chronic low back pain showed that the procedure is safe. However, at 12 months, the study did not demonstrate clinical and imaging benefits as study endpoints did not reach significance There were non-significant improvements in endpoints, VAS, and ODI

Table 7 cont. *Study characteristics of randomized controlled trials assessing intradiscal biologics.*

Study Study Characteristic Methodological Quality Scoring	Number of Patients and Interventions	Intervention Group	Comparator	Outcome Measures and Time of Measurement	Results	Strengths	Weaknesses	Conclusions
Navani et al, 2024 (83) RA, PC, DB Multicenter Quality Scores: Cochrane = 12/13 IPM-QRB = 38/48	43 patients were randomized into 3 groups: Placebo = 12 PRP = 15 BMC = 16 Selection Criteria: Imaging, clinical assessment Biologic Used: Intradiscal PRP Intradiscal BMC	Intradiscal PRP injection, 1-2 mL into the painful disc(s) until resistance to further injection was felt by the operator in the PRP group (n = 15) In the BMC group, 1-2 mL of BMC was injected intradiscally until resistance to further injection was felt by the operator (n = 16)	Patients in the placebo group receive deep trigger point injections with normal saline into the muscle (n = 12)	NRS, patient satisfaction, ODI 1, 3, 6, and 12 months	Significant improvement was seen in PRP and BMC groups at 6- and 12-month follow-up compared to baseline There was no significant difference between PRP and BMC over a 12-month period ($P = 0.094$) The ODI was significantly reduced ($P = 0.001$) for both biologic groups The changes in pain scores over 12 months were significant ($P = 0.0043$) The ODI scores significantly improved in the crossover group also ($P = 0.0137$)	Multicenter, randomized, controlled trials with crossover design. Overall, good results compared to overall appropriate results compared to placebo There were no differences between PRP and BMC group	Placebo group was intramuscular injection with short-term follow-up, randomization blinding	Positive trial Comparative analysis of intradiscal PRP and BMC compared to intramuscular injection of muscle saline injection into the muscle showed significant improvement in biologic treatment groups There was no difference in PRP or BMC
Noriega et al, 2017 (80) RA, PC, DB Quality Scores: Cochrane = 11/13 IPM-QRB = 32/48	24 patients with chronic low back pain with lumbar disc degeneration and unresponsive to conservative treatments. Selection Criteria: Clinical and imaging selection criteria Biologic Used: allogeneic bone marrow MSCs	n = 12 The intervention group received allogeneic bone marrow MSCs by intradiscal injection of 25 x 10, 6 cells per segment under local anesthesia	n = 12 A sham infiltration of paravertebral musculature with anesthetic	VAS, ODI, MRI, SF-12 Follow-up = 12 months	MSC-treated patients displayed a quick and significant improvement in all algofunctional indices versus the controls Both lumbar pain and disability were significantly reduced at 3 months and improvement was maintained at 6 and 12 months. Overall, there was an average 28% improvement in pain and disability 1 year after the intervention Only 5 of the 12 outcomes in patients (40%) receiving MSCs were described as perfect treatment with 100% improvement	Well performed RCT with multiple parameters. 100% improvement was seen in 40% of the patients Average improvement was only 28% in pain and disability one year after the intervention	Overall improvement was on average 28% for pain and disability one year after the intervention	Positive trial 40% of patients with perfect results 28% improvement in all patients Degeneration improved in MSC treated patients and worsened in the controls. Feasibility and safety were confirmed in this preliminary study

Table 7 cont. *Study characteristics of randomized controlled trials assessing intradiscal biologics.*

Study Study Characteristic Methodological Quality Scoring	Number of Patients and Interventions	Intervention Group	Comparator	Outcome Measures and Time of Measurement	Results	Strengths	Weaknesses	Conclusions
Amirdelfan et al, 2021 (82) RA, PC, DB Multicenter Quality Scores: Cochrane = 13/13 IPM-QRB = 36/48	100 participants with chronic low back pain were divided into 3:3:2:2 ratio Selection Criteria: Clinical and imaging assessment Biologic Used: Allogeneic, MPCs from bone marrow from a healthy donor	Allogeneic expanded STRO-3+ MPCs from iliac crest, 2cc per injection 2 groups: 18 million mesenchymal precursor cells + hyaluronic acid (n = 30) 6 million mesenchymal precursor cells + hyaluronic acid (n = 30) hyaluronic acid control (n = 20), or Saline control (n = 20)	2 Groups: Injection of 2 cc hyaluronic acid (n = 20) Injection of saline (n = 20)	VAS, ODI, SF-36	There were significant differences between the control and MPC groups for improvement in VAS and ODI. All study groups showed improvements from baseline at all time points 6 million MPC showed significant mean VAS score improvement compared with saline at 12, 24, and 36 months ($P = 0.018$, $P = 0.005$, and $P = 0.047$) and was significant compared with hyaluronic acid at 3 and 6 months ($P = 0.005$ and $P = 0.0032$) 18 million MPC group was superior to saline at 12, 24, and 36 months ($P = 0.024$, $P = 0.028$, and $P = 0.006$) and was significant compared with hyaluronic acid at 3 months ($P = 0.012$) Disability Scores: MPC groups have greater proportion of subjects at most thresholds. Both MPC groups, both 6 million and 18 million MPC groups were superior at 12, 24, and 36 months to saline SF-36 Results: MPC groups were superior to saline and hyaluronic acid. There were no radiographic results, no significant changes	Multicenter, randomized, placebo-controlled, long-term safety and efficacy study	Complicated design and presentation of results making it difficult for replication.	Positive trial Positive results with safety and efficacy in a randomized, multi-site trial with multiple variables; however, there were no significant radiographic improvements in any of the groups

Table 7 cont. *Study characteristics of randomized controlled trials assessing intradiscal biologics.*

Study Study Characteristic Methodological Quality Scoring	Number of Patients and Interventions	Intervention Group	Comparator	Outcome Measures and Time of Measurement	Results	Strengths	Weaknesses	Conclusions
Gornet et al, 2024 (81) RA, PC, DB Multicenter Quality Scores: Cochrane = 11/13 IPM-QRB = 34/48	n = 60 Selection Criteria: Clinical evaluation, imaging Biologic Used: Allogeneic disc progenitor cells	Intradiscal biologics Low dose cells n = 20 High dose cells n = 20 Single intradiscal injection of 1 mL into a single symptomatic lumbar intervertebral disc	Vehicle alone (n = 10) Placebo (n = 10) Single intradiscal injection of 1 mL into a single symptomatic lumbar intervertebral disc.	VAS pain improvement > 30% at 12 weeks, ODI, EQ-5D Health Index	At week 52: High dose group had a mean VAS percentage decrease from baseline (62.8%, *P* = 0.0005), achieving the endpoint of back pain improvement greater than 30%. At week 104: The clinical improvement was maintained in the high dose group. The vehicle group had a smaller significant decrease in VAS (-52.8, *P* = 0.044) Low dose and placebo group showed non-significant improvements Overall, only the high dose group had a significant change in disc volume at 52 and 104 weeks	This appears to be the first approved biologic therapy, randomized, clinical trial using allogeneic disc progenitor cells to show improvement in pain, disability, and quality of life, along with along with increase in disc volume in patients with lumbar disc degeneration	Small number of patients even though sample size calculations were performed. Further, significant adverse events surprisingly in vehicle or placebo groups.	Positive allogeneic disc progenitor cells trial Significant effectiveness of high-dose allogeneic disc progenitor cells with clinically meaningful improvement in back pain and disc volume at one-year and 2 years

AC = active controlled; BMC = bone marrow concentrate; BM-MSC = bone marrow mesenchymal stromal cell; DB = double-blind; EQ-5D-5L = EuroQol 5 Dimension; FRI = Functional Rating Index; IPM-QRB = Interventional Pain Management techniques–Quality Appraisal of reliability and Risk of Bias Assessment; JOA = Japanese Orthopedic Association; MCID = minimal clinically important difference; MPC = mesenchymal precursor cells; MRI = magnetic resonance imaging; MSCs = mesenchymal stem cells; NASS = North American Spine Society; NRS = Numeric Rating Scale; ODI = Oswestry Disability Index; P = prospective; PC = placebo controlled; PIRF = percutaneous intradiscal radiofrequency; PRP = platelet-rich plasma; PRPr = platelet-rich plasma releasate; RA = randomized; RCT = randomized controlled trial; RMDQ = Roland Morris Disability Questionnaire; SF-12 = 12-Item Short Form Health Survey; SF-36 = 36-item Short Form Health Survey; STRO-3 = stromal precursor antigen-3; VAS = Visual Analog Scale

Table 8. *Study characteristics of non-randomized and observational studies assessing intradiscal biologics.*

Study Study Characteristic Methodological Quality Scoring	Number of Patients and Interventions	Intervention Group	Comparator	Outcome Measures and Time of Measurement	Results	Strengths	Weaknesses	Conclusions
PLATELET-RICH PLASMA								
Jain et al, 2020 (108) R Single center Quality Scores: Newcastle-Ottawa = 6/8 IPM-QRBNR = 26/48	25 patients Discogenic pain Selection Criteria: Clinical evaluation, imaging, provocative discography Biologic Used: PRP	PRP injection at a single or multiple disc levels	None	NRS, ODI	At 6-month follow up proportion of patients showing > 50% reduction in NRS was 55%, ODI was 65%. Correlation coefficient between platelet concentration and reduction in NRS and ODI. NRS at 6-months ($P = 0.0002$) and ODI ($P = 0.0006$)	Appropriate selection criteria NRS and ODI scores appear to have been significantly reduced Authors carefully evaluated correlation coefficients between platelet concentration (PRP) and reduction in NRS and ODI at different time periods. Further, they also evaluated proportion of patients with greater than 50% reduction in NRS and ODI scores	Relatively small with only 80% of patients being followed.	Positive study 65% of the patients reported greater than 50% reduction in pain scores with significant reduction in ODI scores ($P = 0.0006$)
Kirchner & Anitua, 2016 (106) O, R, pilot study Quality Scores: Newcastle-Ottawa = 6/8 IPM-QRBNR = 27/48	n = 86 Lumbar disc degeneration Selection Criteria: Clinical evaluation, imaging Biologic Used: PRGF-Endoret	One intradiscal, one intraarticular facet, and one transforaminal epidural injection	None	VAS over time 1 month, 3 months, 6 months	Pain reduction after PRGF- Endoret injections showed statistically significant drop from 8.4 ± 1.1 before the treatment to 0.8 ± 1.7 at 6-month follow-up At the end of 6 months, 91% of patients showed an excellent score, with 8.1% showing moderate improvement, and 1.2% were inefficient score group	Reasonably large sample of 86 patients	Only a 6 month follow up The injection was into the disc plus intraarticular and transforaminal epidural injections. Consequently, specificity may have been lost	Positive study Fluoroscopy-guided infiltrations of intervertebral discs and facet joints with PRGF in patients with chronic LBP resulted in significant pain reduction assessed by VAS The results showed reduction of the VAS over time. The study ended at 6 months with 91% of the patients showing an excellent score, 8.1% showing moderate improvement, and 1.2% showing lack of response

Table 8 cont. *Study characteristics of non-randomized and observational studies assessing intradiscal biologics.*

Study Study Characteristic Methodological Quality Scoring	Number of Patients and Interventions	Intervention Group	Comparator	Outcome Measures and Time of Measurement	Results	Strengths	Weaknesses	Conclusions
Machado et al, 2022 (109) P, case series Quality Scores: Newcastle-Ottawa = 6/8 IPM-QRBNR = 25/48	n = 46 Chronic low back pain Selection Criteria: Clinical evaluation, imaging Biologic Used: PRP	1 mL of PRP into each disc. In addition, majority of the patients also received 2 mL for transforaminal injection per site, 5 mL for caudal injection, 2 mL for each facet joint and capsule, and 2 mL for each site of paravertebral muscles	None	VAS, RMDQ	Significant lower scores of RMDQ and pain VAS at weeks 12, 26, 52 in comparison to baseline (P = 0.001) Mean VAS pain scores decreased by approximately 35%, RMDQ decreased by 40% at 52 weeks. Opioid consumption was significantly reduced at 52 weeks	Injections of PRP in a prospective case series of multitargets for low back pain	There is no specific structure causing the pain; it was multitargeted and multiple injections with no definitive diagnostic process	Positive study Significant improvement in pain, function, and opioid consumption
Monfett et al, 2016 (105) P Single center Quality Scores: Newcastle-Ottawa = 6/8 IPM-QRBNR = 23/48	n = 29 Lumbar discogenic pain, lumbar disc degeneration Selection Criteria: Discogenic Pain Biologic Used: PRP	Injection of PRP	None	Pain relief, functional status 2 years	Statistically and clinically significant improvements in pain and function through 2 years of follow-up	None	A small retrospective evaluation	Positive study Intradiscal PRP injections show continued safety and improvements in pain and function at 2 years post-procedure
MESENCHYMAL STEM CELLS								
Pettine et al, 2015 (92) P, open-label, NR, 2-arm study Quality Scores: Newcastle-Ottawa = 6/8 IPM-QRBNR = 30/48	26 patients Selection Criteria: Symptomatic moderate to severe discogenic low back pain Patient age (yrs)= 18–61 years (median 40) Biologic Used: BMC	Autologous bone marrow concentration (nonexpanded) 2–3 mL of BMC was injected in lumbar disc (1.66_106/mL)	None	ODI, VAS, and MRI 3 years	The average ODI and VAS scores were reduced to 22.8 and 24.4 at 3 months After 36 months, 6 patients proceeded to surgery. • After 36 months, 20 of the 26 patients reported average ODI and VAS improvement to 17.5 ± 32 and 21.9 ± 4.4 respectively One year MRI indicated 40% of patients improved one modified Pfirrmann Grade and no patient worsened radiographically	A first prospective evaluation assessing the effectiveness of intradiscal bone marrow publishing long-term follow-up of 36 months. 20 of 26 patients reported improvement	Nonrandomized prospective evaluation without comparative groups Weak data at 3-month follow-up	Positive study At 36-month follow-up, 6 of 26 patients progressed to surgery. The remaining 20 patients (77%) reported significant ODI and VAS improvements Authors concluded that there were no adverse effects, and the study provided evidence of safety and feasibility of intradiscal BMC therapy

Table 8 cont. *Study characteristics of non-randomized and observational studies assessing intradiscal biologics.*

Study Study Characteristic Methodological Quality Scoring	Number of Patients and Interventions	Intervention Group	Comparator	Outcome Measures and Time of Measurement	Results	Strengths	Weaknesses	Conclusions
Haines et al, 2022 (95) P, cohort study Single center Quality Scores: Newcastle-Ottawa = 6/8 IPM-QRBNR = 28/48	32 patients Selection Criteria: Provocative discography Biologic Used: BMAC	Intradiscal injection with 1-6 mL BMAC per disc based on acceptance of the volume by the disc	None	VAS back pain, VAS leg pain, ODI, EQ-5D-5L	32 patients were treated with 92 levels VAS back pain decreased by 2.4 points ($P = < 0.001$) from 3 to one-year post procedure VAS leg pain scores decreased by 1.5 points ($P = < 0.005$) ODI scores decreased by 12.4 points ($P = < 0.001$) MCID: VAS back pain 59.4% VAS leg pain 43.8% ODI 56.3% No complications were reported. Three patients went on to have fusion surgery.	Strict selection criteria and methodology with appropriate statistical analysis	Non-randomized, prospective evaluation without control groups.	Positive study Improvement was seen in established MCID values, with 59.4% improvement in VAS back pain scores, 43.8% in VAS leg pain scores, and 56.3% in ODI scores Authors concluded that intradiscal injection of autologous BMAC significantly improved low back pain, disability, and quality of life at one-year
Atluri et al, 2022 (88) Open label, P, NR, 2-arm exploratory study Single center Quality Scores: Newcastle-Ottawa = 8/8 IPM-QRBNR = 36/48	n = 80 Selection Criteria: Clinical evaluation, imaging Biologic Used: BMAC	Intradiscal injection of BMC 2 mL, epidural space 2 mL, facet joints 0.5 mL, and sacroiliac joint 1 mL	Conservative management	NRS, ODI, EQ-5D-5L, PROMIS global physical and mental health Follow up 3, 6, and 12 months	Significant improvement at 12-month follow-up with 67% of patients in the study group achieving MCID utilizing ODI, compared to 8% in the control group Greater than 2-point pain reduction was seen in 56% of the patients at 12 months Opioid use decreased in the interventional group	Even though it was an observational, open-label study, it was a prospective controlled study with multiple parameters and outcomes criteria with one-year follow up	All the patients were self-pay, thus, only the patients who could afford the treatment were included Injection was not specifically intradiscal, it was intradiscal intra-facet, epidural, and sacroiliac joint	Positive study Positive study with significant improvement shown overall at 12 months in 67% of the patients

Table 8 cont. *Study characteristics of non-randomized and observational studies assessing intradiscal biologics.*

Study Characteristic Methodological Quality Scoring	Number of Patients and Interventions	Intervention Group	Comparator	Outcome Measures and Time of Measurement	Results	Strengths	Weaknesses	Conclusions
Lewandrowski et al, 2023 (96) R, O, cohort study Single center Quality Scores: Newcastle-Ottawa = 6/8 IPM-QRBNR = 31/48	n = 33 Degenerative disc disease diagnosed by imaging Selection Criteria: Clinical evaluation, imaging Biologic Used: Biologic allogeneic polyclonal MSC	Intradiscal injection of approximately 5 million allogeneic polyclonal MSCs and 1% hyaluronic acid derived from immunoselected umbilical cord stem cells	None	VAS, ODI, modified Macnab criteria	2-year follow-up, the average VAS low back pain reduction and ODI reductions were significant Macnab outcomes were excellent in 11 patients (33.3%), good in 19 (57.6%), and fair in 39.1% Imaging - Pfirrmann grading was 4.05 ± 0.72 and improved to 3.65 ± 0.81 at final follow-up	Observational study with long-term follow-up Overall, VAS score reduction at 2-year follow-up was 6.565 ± 1.619 ($P < 0.001$). ODI reduction at 2-year follow-up was 38.333 ± 14.865 ($P < 0.001$)	Observational study with a small sample size	Positive study Favorable outcomes at 2-year follow up

BMC = bone marrow concentrate; BMAC = bone marrow aspirate concentrate; EQ-5D-5L = EuroQol 5 Dimension; IPM-QRBNR = Interventional Pain Management Techniques – Quality Appraisal of Reliability and Risk of Bias Assessment for Nonrandomized Studies; LBP = low back pain; MCID = Minimal Clinically Important Difference; MRI = magnetic resonance imaging; NR =- nonrandomized; NRS = Numeric Rating Scale; O = observational; ODI = Oswestry Disability Index; P = prospective; PROMIS = Patient Reported Outcomes Measurement and Information System; PRP = platelet-rich plasma; PRGF = plasma rich in growth factor; R = retrospective; RMDQ = Roland-Morris Disability Questionnaire; VAS = Visual Analog Scale

months. The results showed no statistically significant difference in pain levels between the 2 groups [SMD -0.39 (-0.82, 0.04), P = 0.07] (Fig. 2D).

Three trials (81,82,87), including 2 with different doses, involving 330 patients compared BM/MSC versus control in a dual-arm meta-analysis at 24 months. The results showed a statistically significant difference in pain levels between the 2 groups [SMD -0.41 (-0.72, 0.10), P = 0.009] (Fig. 2E).

Functionality – Conventional Dual-Arm Analysis

Four studies (82,83,87,88), including one with 2 groups, involving 424 patients compared BM/MSC versus control functionality in a dual-arm meta-analysis at one month. Results showed a borderline statistically significant difference in functionality levels between the 2 groups [SMD -0.35 (-0.70, 0.00), P = 0.05] (Fig. 3A).

Five studies (80,82,83,87,88), including one with 2 groups, involving 441 patients compared BM/MSC versus control functionality in a dual-arm meta-analysis at 3 months. The results showed a statistically significant difference in functionality levels between the 2 groups [SMD -0.61 (-1.08, -0.14), P = 0.01] (Fig. 3B).

Four studies (80,82,87,88), including one with 2 groups, involving 408 patients compared BM/MSC versus control functionality in a dual-arm meta-analysis at 6 months. The results showed a statistically significant difference in functionality levels between the 2 groups [SMD -0.63 (-1.13, -0.13), P = 0.01] (Fig. 3C).

Four studies (80,82,87,88), including one with 2 groups, involving 386 patients compared BM/MSC versus control functionality in a dual-arm meta-analysis at 12 months. The results showed a statistically significant difference in functionality levels between the 2 groups [SMD -0.68 (-1.13, -0.22), P = 0.003] (Fig. 3D).

Pain – Single-Arm Meta-Analysis

Figure 4A presents the results of a single-arm meta-analysis utilizing PRP. Four studies

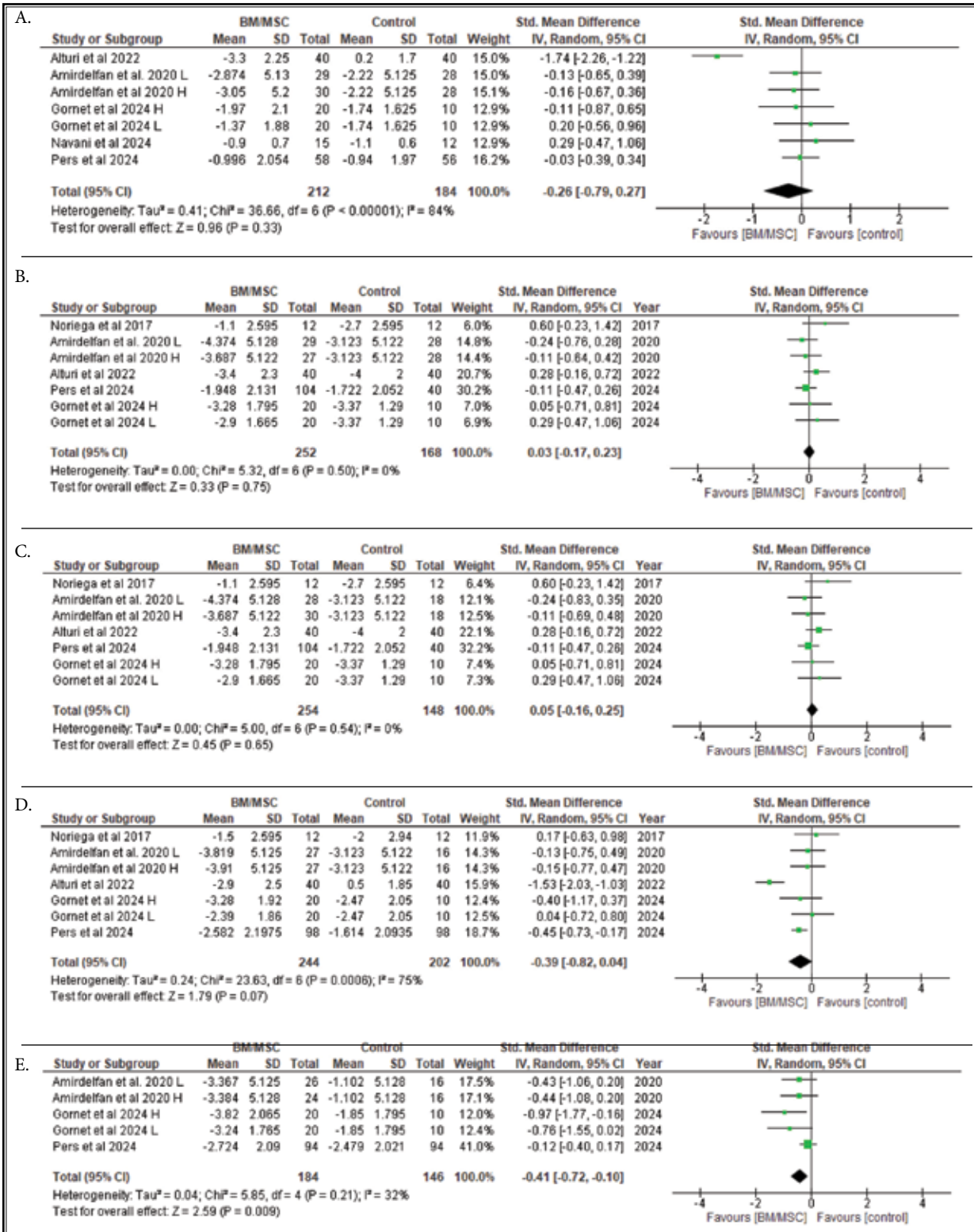


Fig. 2. *A. 1 Month NRS BM/MSC vs Control. B. 3 Months NRS BM/MSC vs Control. C. 6 Month NRS BM/MSC vs Control. D. 12 Months NRS BM/MSC vs Control. E. 24 Months NRS BM/MSC vs Control.*

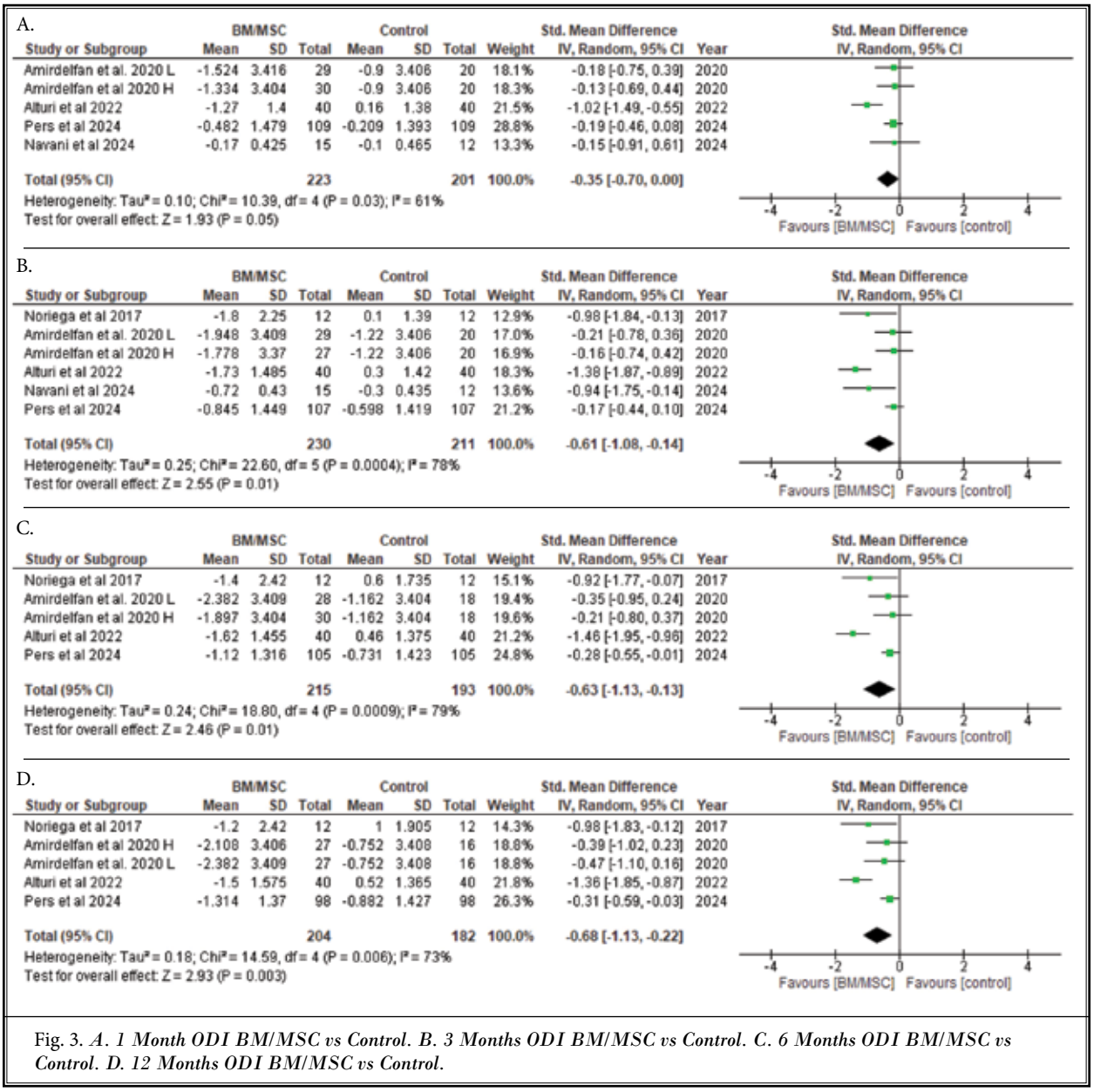


Fig. 3. *A. 1 Month ODI BM/MSC vs Control. B. 3 Months ODI BM/MSC vs Control. C. 6 Months ODI BM/MSC vs Control. D. 12 Months ODI BM/MSC vs Control.*

(79,83,105,106) were included to assess pain scores at one month using the NRS. As shown in Fig. 4A, the pooled mean difference in pain scores from baseline to the one month follow-up was a decrease of 1.754 points (95% CI: -3.627 to 0.120, $P < 0.0001$).

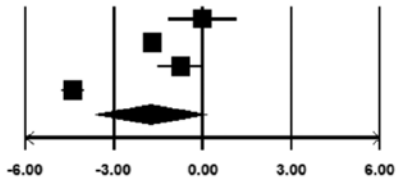
Figure 4B shows the results of a single-arm meta-analysis utilizing PRP. Three studies (83,106,108) were used to assess pain scores at 3 months using the NRS. As shown in Fig. 4B, the pooled mean difference in pain scores from baseline to the 3-month follow-up was a decrease of 3.435 points (95% CI: -6.710 to -0.160, $P < 0.0001$).

Figure 4C shows the results of a single-arm meta-analysis utilizing PRP. Four studies (83,105,106,108) were included to assess pain scores at 6 months using the NRS. As shown in Fig. 4C, the pooled mean difference in pain scores from baseline to the 6-month follow-up was a decrease of 3.686 points (95% CI: -6.555 to -0.817, $P < 0.0001$).

Figure 4D presents the results of a single-arm meta-analysis utilizing BM/MSC. Six studies (81-83,87,88,96), 2 of which had 2 groups, were used to assess pain scores at one month using the NRS. As shown in Fig. 4D, the

A.

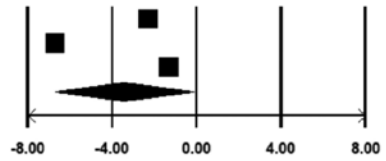
Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Tukali-Wosornu et al 2016	0.000	0.590	0.348	-1.156	1.156	0.000	1.000
Navani et al 2024	-1.700	0.165	0.027	-2.023	-1.377	-10.303	0.000
Monfett et al 2016	-0.740	0.410	0.168	-1.544	0.064	-1.805	0.071
Kirchner et al 2016	-4.400	0.199	0.040	-4.790	-4.010	-22.111	0.000
Pooled	-1.754	0.956	0.914	-3.627	0.120	-1.835	0.067
Prediction Interval	-1.754			-10.808	7.300		



Between-study		Other heterogeneity statistics			
Tau	TauSq	Q-value	df (Q)	P-value	I-squared
1.875	3.514	151.036	3	0.000	98.014

B.

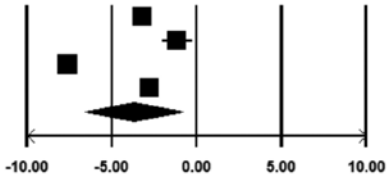
Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Navani et al 2024	-2.300	0.176	0.031	-2.645	-1.955	-13.068	0.000
Kirchner et al 2016	-6.700	0.183	0.033	-7.059	-6.341	-36.612	0.000
Jain et al 2020	-1.300	0.234	0.055	-1.759	-0.841	-5.556	0.000
Pooled	-3.435	1.671	2.792	-6.710	-0.160	-2.056	0.040
Prediction Interval	-3.435			-45.821	38.951		



Between-study		Other heterogeneity statistics			
Tau	TauSq	Q-value	df (Q)	P-value	I-squared
2.887	8.336	437.210	2	0.000	99.543

C.

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Navani et al 2024	-3.200	0.164	0.027	-3.521	-2.879	-19.512	0.000
Monfett et al 2016	-1.140	0.444	0.197	-2.010	-0.270	-2.568	0.010
Kirchner et al 2016	-7.600	0.150	0.023	-7.894	-7.306	-50.667	0.000
Jain et al 2020	-2.750	0.245	0.060	-3.230	-2.270	-11.224	0.000
Pooled	-3.686	1.464	2.143	-6.555	-0.817	-2.518	0.012
Prediction Interval	-3.686			-17.720	10.347		



Between-study		Other heterogeneity statistics			
Tau	TauSq	Q-value	df (Q)	P-value	I-squared
2.915	8.495	580.140	3	0.000	99.483

Fig. 4. *A. Single-arm PRP meta-analysis on NRS at 1 month. B. Single-arm PRP meta-analysis on NRS at 3 months. C. Single-arm PRP meta-analysis on NRS at 6 months.*

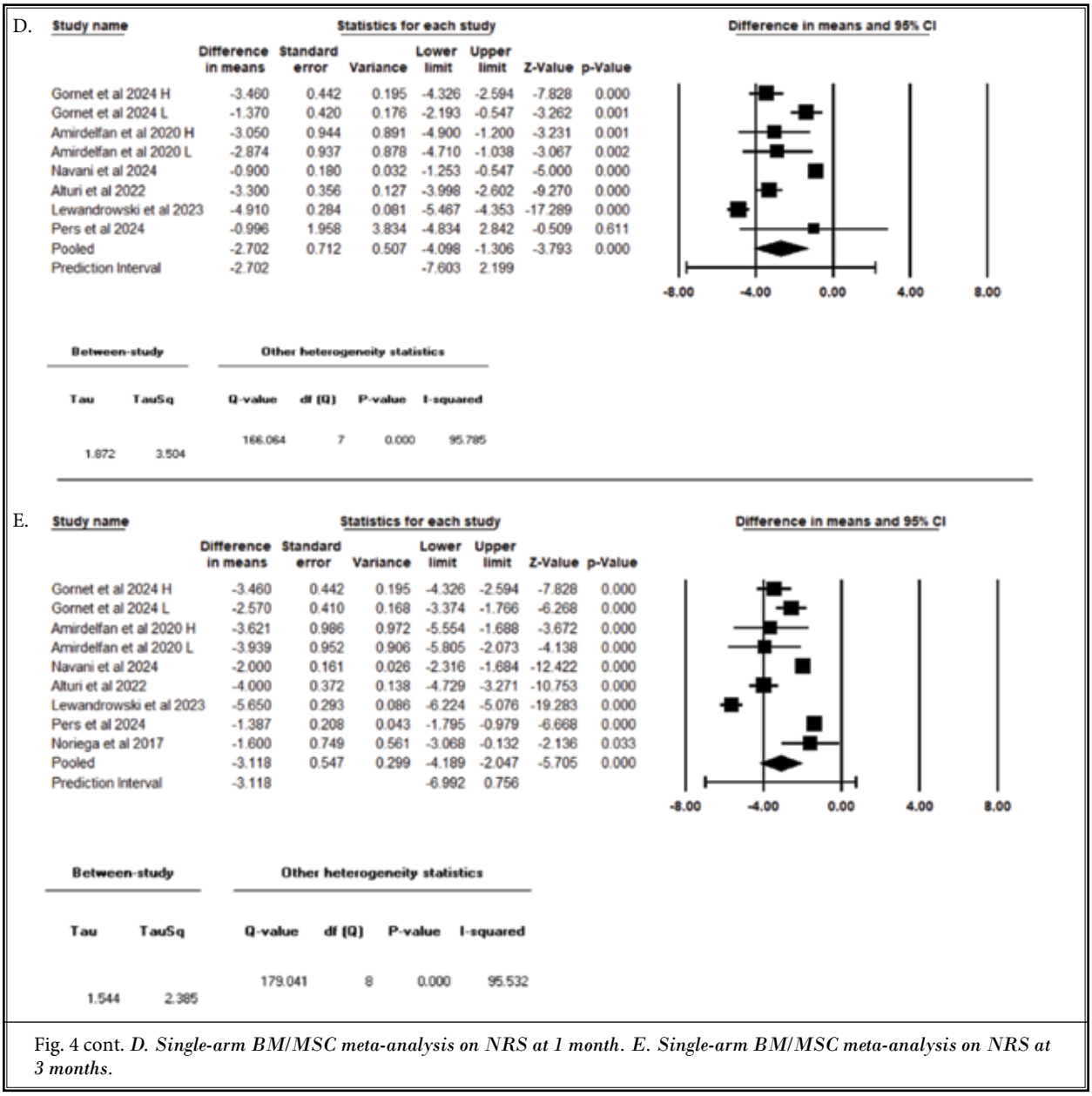


Fig. 4 cont. *D. Single-arm BM/MSC meta-analysis on NRS at 1 month. E. Single-arm BM/MSC meta-analysis on NRS at 3 months.*

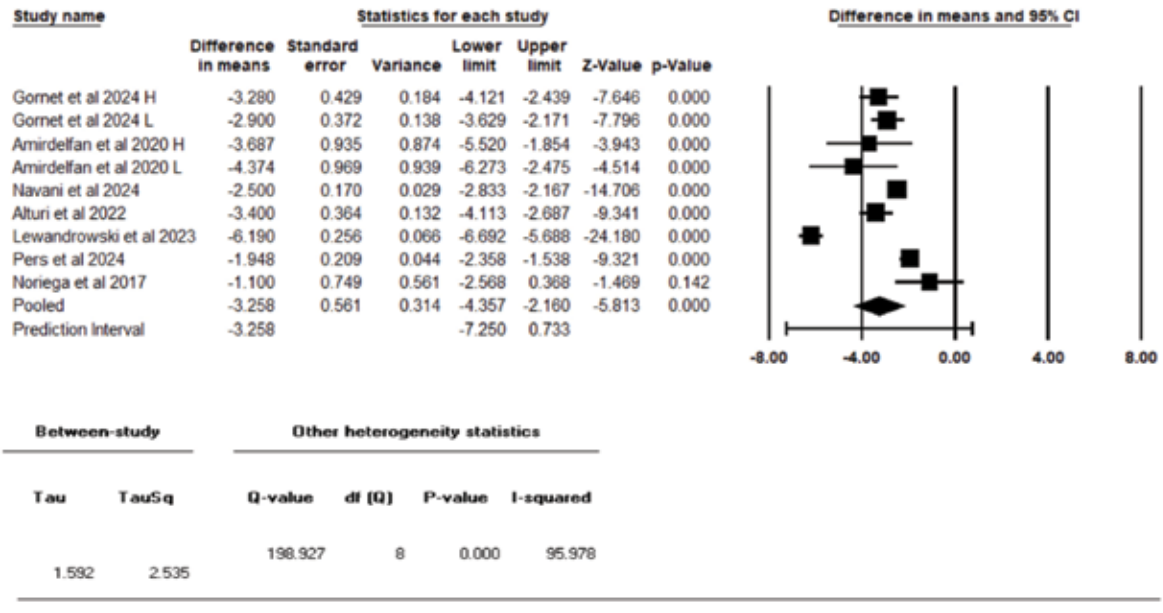
pooled mean difference in pain scores from baseline to the one month follow-up was a decrease of 2.702 points (95% CI: -4.098 to -1.306, $P < 0.0001$).

Figure 4E shows the results of a single-arm meta-analysis utilizing BM/MSC. Seven studies (80-83,87,88,96), 2 of which had 2 groups, were included to assess pain scores at 3 months using the NRS. As shown in Fig. 4E, the pooled mean difference in pain scores from baseline to the 3-month follow-up was a decrease of 3.118 points (95% CI: -4.189 to -2.047, $P < 0.0001$).

Figure 4F presents the results of a single-arm meta-analysis utilizing BM/MSC. Seven studies (80-83,87,88,96), 2 of which had 2 groups, were used to assess pain scores at 6 months using the NRS. As shown in Fig. 4F, the pooled mean difference in pain scores from baseline to the 6-month follow-up was a decrease of 3.258 points (95% CI: -4.357 to -2.160, $P < 0.0001$).

Figure 4G shows the results of a single-arm meta-analysis utilizing BM/MSC. Eight studies (80-83,87,88,95,96), 2 of which had 2 groups, were included to assess pain scores at 12 months using the NRS. As shown in Fig. 4G, the pooled mean difference in pain

F.



G.

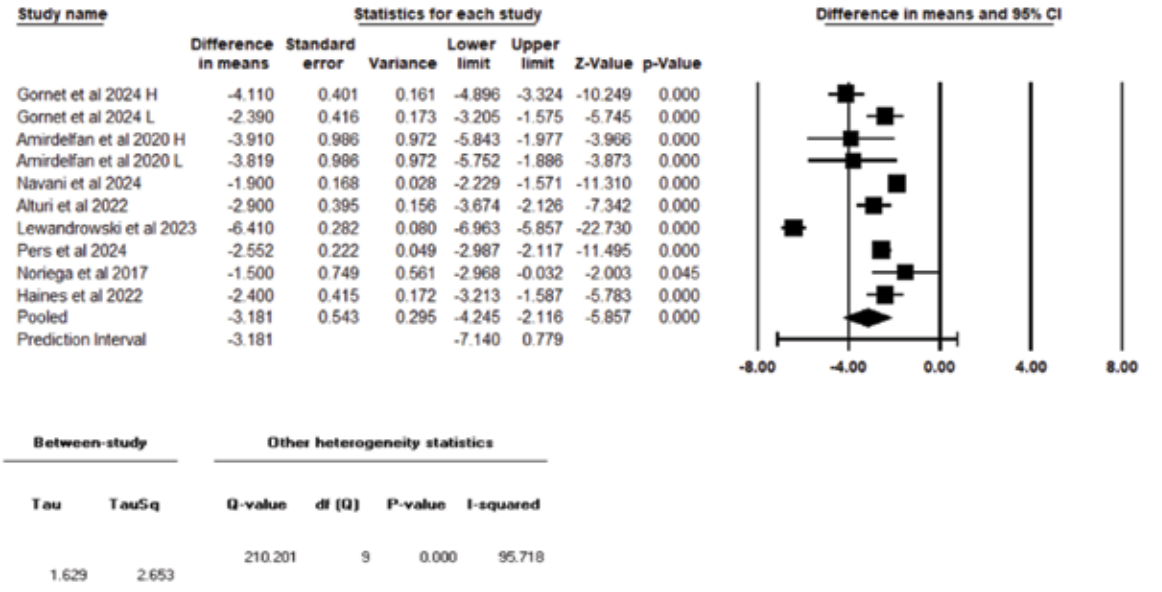


Fig. 4 cont. *F. Single-arm BM/MSC meta-analysis on NRS at 6 months. G. Single-arm BM/MSC meta-analysis on NRS at 12 months.*

scores from baseline to the 12-month follow-up was a decrease of 3.181 points (95% CI: -4.245 to -2.116, $P < 0.0001$).

Figure 4H presents the results of a single-arm meta-analysis utilizing BM/MSC. Four studies (81,82,87,96), 2 of which had 2 groups, were used to assess pain scores at 24 months using the NRS. As shown in Fig. 4H, the pooled mean difference in pain scores from baseline to the 24-month follow-up was a decrease of 3.904 points (95% CI: -5.438 to -2.369, $P < 0.0001$).

Functionality – Single Arm Meta-Analysis

Figure 5A shows the results of a single-arm meta-analysis utilizing BM/MSC. Five studies (82,83,87,88,96), one of which had 2 groups, were used to assess functionality scores at one month using the Oswestry Dis-

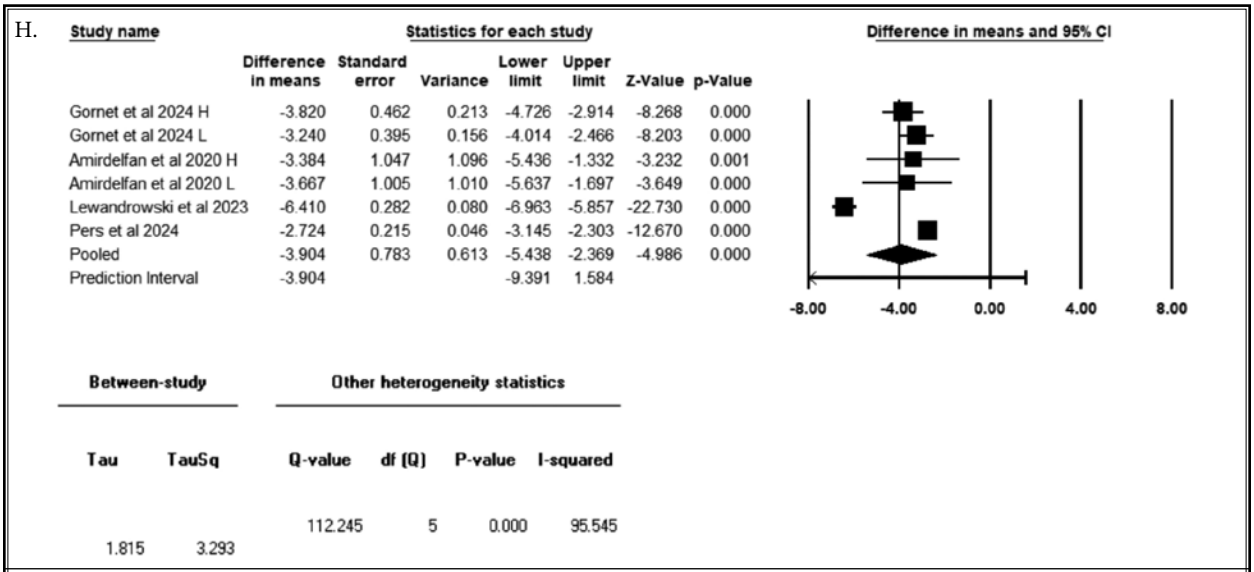


Fig. 4 cont. *H. Single-arm BM/MSC meta-analysis on NRS at 24 months.*

ability Index (ODI). As shown in Fig. 5A, the pooled mean difference in functionality scores from baseline to the one month follow-up was a decrease of 12.386 points (95% CI: -20.721 to -4.051, $P < 0.0001$).

Figure 5B presents the results of a single-arm meta-analysis utilizing BM/MSC. Six studies (80,82,83,87,88,96), one of which had 2 groups, were used to assess functionality scores at 3 months using the ODI. As shown in Fig. 5B, the pooled mean difference in functionality scores from baseline to the 3-month follow-up was a decrease of 17.115 points (95% CI: -23.753 to -10.476, $P < 0.0001$).

Figure 5C shows the results of a single-arm meta-analysis utilizing BM/MSC. Six studies (80,82,83,87,88,96), one of which had 2 groups, were used to assess functionality scores at 6 months using the ODI. As shown in Fig. 5C, the pooled mean difference in functionality scores from baseline to the 6-month follow-up was a decrease of 17.997 points (95% CI: -23.989 to -12.005, $P < 0.0001$).

Figure 5D presents the results of a single-arm meta-analysis utilizing BM/MSC. Six studies (80,82,83,87,88,96), one of which had 2 groups, were used to assess functionality scores at 12 months using the ODI. As shown in Fig. 5D, the pooled mean difference in functionality scores from baseline to the 12-month follow-up was a decrease of 16.687 points (95% CI: -22.628 to -10.746, $P < 0.0001$).

Figure 5E shows the results of a single-arm meta-analysis utilizing BM/MSC. Three studies (82,87,96), one of which had 2 groups, were included to assess functionality scores at 24 months using the ODI. As shown in Fig. 5E, the pooled mean difference in functionality scores from baseline to the 24-month follow-up was a decrease of 22.772 points (95% CI: -35.537 to -10.008, $P < 0.0001$).

In summary, conventional meta-analysis revealed significant pain relief at 24 months and functional improvement at 3-, 6-, and 12-month follow-ups. However, single-arm meta-analysis demonstrated significant improvements from baseline to follow-up at all assessed time points, ranging from one month to 24 months.

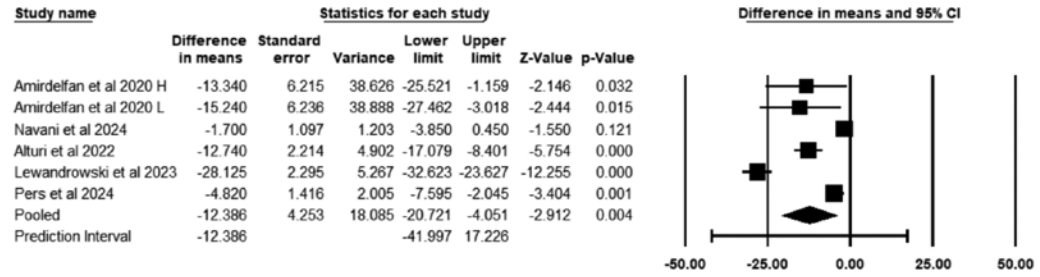
Qualitative Analysis

The qualitative analysis, based on the systematic review of studies and outcomes, is summarized in Tables 3-6. The qualitative evidence is moderate, or Level II, based on the following findings: Among the 4 studies on PRP, 3 RCTs (79,83,86) were positive, and 4 out of 4 nonrandomized studies (105,106,108,109) were positive. Similarly, for MSCs, 4 out of 5 RCTs (80-83,87) were positive, and 4 out of 4 nonrandomized studies (88,92,95,96) were positive. Therefore, the overall qualitative evidence is moderate or Level II.

Assessment Utilizing GRADE Criteria

The GRADE criteria were applied to assess the certainty of evidence from RCTs evaluating PRP and MSC interventions for the same outcomes, as shown in Table

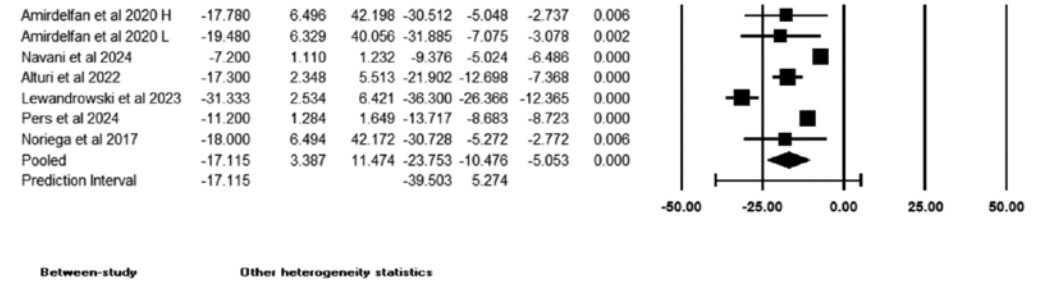
A.



Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Amirdelfan et al 2020 H	-13.340	6.215	38.626	-25.521	-1.159	-2.146	0.032
Amirdelfan et al 2020 L	-15.240	6.236	38.888	-27.462	-3.018	-2.444	0.015
Navani et al 2024	-1.700	1.097	1.203	-3.850	0.450	-1.550	0.121
Alturi et al 2022	-12.740	2.214	4.902	-17.079	-8.401	-5.754	0.000
Lewandrowski et al 2023	-28.125	2.295	5.267	-32.623	-23.627	-12.255	0.000
Pers et al 2024	-4.820	1.416	2.005	-7.595	-2.045	-3.404	0.001
Pooled	-12.386	4.253	18.085	-20.721	-4.051	-2.912	0.004
Prediction Interval	-12.386			-41.997	17.226		

Between-study		Other heterogeneity statistics			
Tau	TauSq	Q-value	df (Q)	P-value	I-squared
9.781	95.663	119.946	5	0.000	95.831

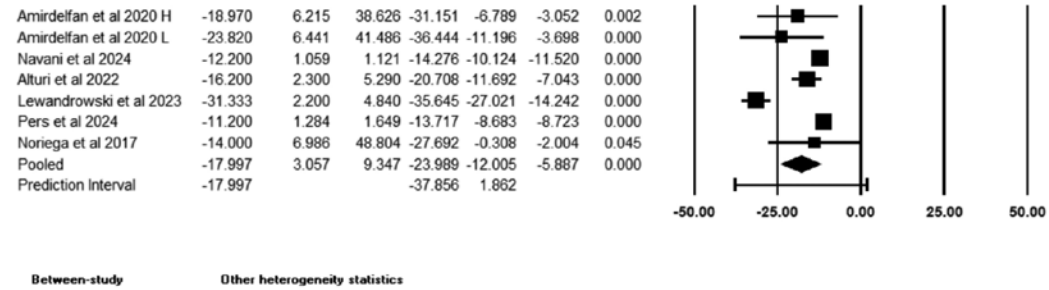
B.



Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Amirdelfan et al 2020 H	-17.780	6.496	42.198	-30.512	-5.048	-2.737	0.006
Amirdelfan et al 2020 L	-19.480	6.329	40.056	-31.885	-7.075	-3.078	0.002
Navani et al 2024	-7.200	1.110	1.232	-9.376	-5.024	-6.486	0.000
Alturi et al 2022	-17.300	2.348	5.513	-21.902	-12.698	-7.368	0.000
Lewandrowski et al 2023	-31.333	2.534	6.421	-36.300	-26.366	-12.365	0.000
Pers et al 2024	-11.200	1.284	1.649	-13.717	-8.683	-8.723	0.000
Noriega et al 2017	-18.000	6.494	42.172	-30.728	-5.272	-2.772	0.006
Pooled	-17.115	3.387	11.474	-23.753	-10.476	-5.053	0.000
Prediction Interval	-17.115			-39.503	5.274		

Between-study		Other heterogeneity statistics			
Tau	TauSq	Q-value	df (Q)	P-value	I-squared
8.024	64.384	85.432	6	0.000	92.977

C.

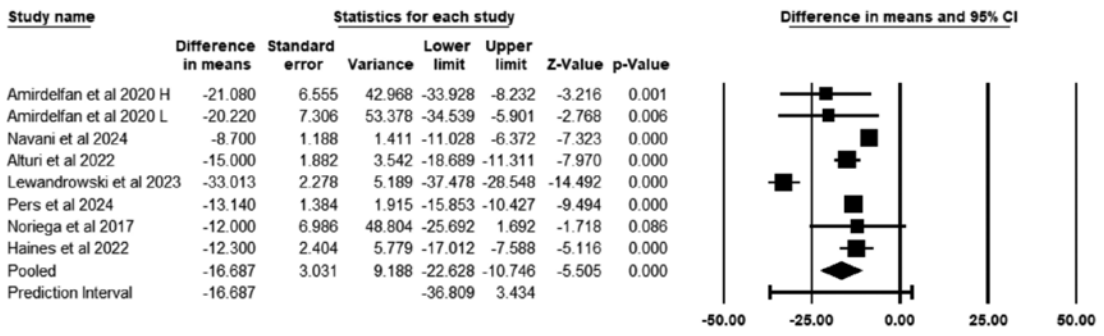


Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Amirdelfan et al 2020 H	-18.970	6.215	38.626	-31.151	-6.789	-3.052	0.002
Amirdelfan et al 2020 L	-23.820	6.441	41.486	-36.444	-11.196	-3.698	0.000
Navani et al 2024	-12.200	1.059	1.121	-14.276	-10.124	-11.520	0.000
Alturi et al 2022	-16.200	2.300	5.290	-20.708	-11.692	-7.043	0.000
Lewandrowski et al 2023	-31.333	2.200	4.840	-35.645	-27.021	-14.242	0.000
Pers et al 2024	-11.200	1.284	1.649	-13.717	-8.683	-8.723	0.000
Noriega et al 2017	-14.000	6.986	48.804	-27.692	-0.308	-2.004	0.045
Pooled	-17.997	3.057	9.347	-23.989	-12.005	-5.887	0.000
Prediction Interval	-17.997			-37.856	1.862		

Between-study		Other heterogeneity statistics			
Tau	TauSq	Q-value	df (Q)	P-value	I-squared
7.095	50.337	73.025	6	0.000	91.784

Fig. 5. *A. Single-arm meta-analysis on functionality at 1 month. B. Single-arm meta-analysis on functionality at 3 months. C. Single-arm meta-analysis on functionality at 6 months.*

D.



E.

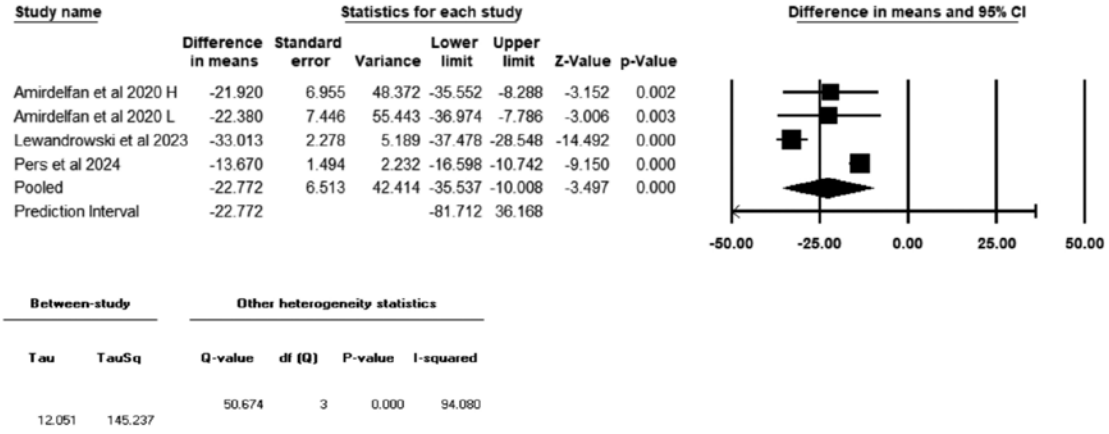


Fig. 5 cont. *D. Single-arm meta-analysis on functionality at 12 months. E. Single-arm meta-analysis on functionality at 24 months.*

9. The assessment considered study design, risk of bias, inconsistency, indirectness, imprecision, and publication bias.

For PRP, 3 out of 4 trials showed positive results (79,83,86). Tuakli-Wosornu et al (79) conducted a trial with 47 patients (29 in the PRP group and 18 in the control group), which yielded positive results. However, due to the small sample size, the certainty of the findings is low, and the impact on practice is uncertain. In Navani et al (83), 43 patients were studied, with 15 in the PRP group, 12 in the placebo group, and 16 in the BMC group. This trial showed positive results with no significant difference between PRP and BMC, with a low to moderate risk of bias. Despite the positive results, the small sample size led to low certainty and uncertain impact on practice.

Goyal et al (85) found negative results in a trial with 48 patients (12 received PRP and 12 received percutaneous intradiscal radiofrequency), resulting in low impact and very low certainty due to the negative findings and the moderate risk of bias.

Akeda et al (86) studied 16 patients, 8 of whom received intradiscal PRP injections, with positive results. However, the very small sample size resulted in low certainty about the impact.

For MSCs, Pers et al (87) conducted a high-quality trial with negative results. While there was nonsignificant improvement in the MSC groups, there was no

Table 9. *Evidence profile using randomized controlled trials of interventions for the same outcome and similar certainty of evidence.*

CERTAINTY ASSESSMENT							Number of Patients	Impact	Certainty
Study	**Study Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**			
PLATELET-RICH PLASMA									
Tuakli-Wosornu et al, 2016 (79)	RA, PC, DB	Low	NS	NS	NS	Low	47 PRP = 29 Comparator = 18	Positive trial Intradiscal injections of PRP x 1 showed significant improvement at 8-week follow-up with maintained improvement compared to controls at 1-year follow-up.	Low
Navani et al, 2024 (83)	RA, PC, DB	Low/ Moderate	NS	NS	NS	Low	43 Placebo = 12 PRP = 15 BMC = 16	Positive trial Comparative analysis of intradiscal PRP and BMC compared to intramuscular injection of muscle saline injection into the muscle showed significant improvement in biologic treatment groups There was no difference in PRP or BMC	Low
Goyal et al, 2022 (85)	RA, AC	Low/ Moderate	NS	NS	NS	Low	48 PRP = 24 PIRF = 24	Negative trial for PRP The response to intradiscal injection of PRP showed poor response with 4 of 26 patients responding at 3 months and 11 of 26 patients responding at 6 months	Very low
Akeda et al, 2022 (86)	RA, AC, DB	Low	NS	NS	NS	Low	16 PRPr = 8 Comparator = 8	Positive PRP trial Significant improvement at 60 weeks in PRPr group compared to baseline data; however, even though it was different, it did not reach statistical significance in comparison with the steroid group	Low

Table 9 cont. *Evidence profile using randomized controlled trials of interventions for the same outcome and similar certainty of evidence.*

CERTAINTY ASSESSMENT							Number of Patients	Impact	Certainty
Study	**Study Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**			
MESENCHYMAL STEM CELLS									
Pers et al, 2024 (87)	RA, PC, DB	Low	NS	NS	NS	Low	114 BM-MSC = 58 Sham placebo group = 56	Negative trial A large multicenter, RA, PC, trial in degenerative disc disease using a single intradiscal injection of allogenic MSCs, showed no clinical and imaging benefits at 12-month follow-up There were only non-significant improvements in various parameters including disc fluid content, VAS, ODI, with BM-MSC scoring better	Low
Navani et al, 2024 (83)	RA, PC, DB	Low/ Moderate	NS	NS	NS	Low	43 Placebo = 12 PRP = 15 BMC = 16	Positive trial Comparative analysis of intradiscal PRP and BMC compared to intramuscular injection of muscle saline injection into the muscle showed significant improvement in biologic treatment groups There was no difference in PRP or BMC	Low
Noriega et al, 2017 (80)	RA, PC, DB	Low/ Moderate	NS	NS	NS	Low	24 MSC = 12 Comparator = 12	Positive trial 40% of patients with perfect results 28% improvement in all patients Degeneration improved in MSC treated patients and worsened in the controls. Feasibility and safety were confirmed in this preliminary trial	Low

Table 9 cont. *Evidence profile using randomized controlled trials of interventions for the same outcome and similar certainty of evidence.*

CERTAINTY ASSESSMENT							Number of Patients	Impact	Certainty
Study	**Study Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**			
Amirdelfan et al, 2021 (82)	RA, PC, DB	Low/ Moderate	NS	NS	NS	Low	100 Allogeneic expanded STRO-3+ MPCs from iliac crest, 2cc per injection 2 Groups: 18 million mesenchymal precursor cells + hyaluronic acid (n = 30) 6 million mesenchymal precursor cells + hyaluronic acid (n = 30) hyaluronic acid control (n = 20), or Saline control (n = 20) 2 Groups: Injection of 2 cc hyaluronic acid (n = 20) Injection of saline (n = 20)	Positive trial Positive results with safety and efficacy in a randomized, multi-site trial with multiple variables; however, there were no significant radiographic improvements in any of the groups	Low
Gornet et al, 2024 (81)	RA, PC, DB, AC	Low	NS	NS	NS	Low	60 Intradiscal biologics Low dose cells (n = 20) High dose cells (n = 20) Single intradiscal injection of 1 mL into a single symptomatic lumbar intervertebral disc Vehicle alone (n = 10) Placebo n = 10 Single intradiscal injection of 1 mL into a single symptomatic lumbar intervertebral disc	Positive allogeneic disc progenitor cells trial Significant effectiveness of high-dose allogeneic disc progenitor cells with clinically meaningful improvement in back pain and disc volume at one-year and 2 years.	Low

AC = active controlled; BMC = bone marrow concentrate; BM-MSC = bone marrow mesenchymal stromal cell; DB = double-blind; MSC = mesenchymal stem cells; NS = Not serious; PC = placebo controlled; PRP = platelet-rich plasma; PIRF = percutaneous intradiscal radiofrequency; PRPr = platelet-rich plasma releasate; RA = randomized; STRO-3 = stromal precursor antigen-3

difference between groups, leading to low impact and certainty.

Navani et al (83) again studied 16 patients who received BMC with positive results, but due to the small sample size, the impact and certainty remained low.

Noriega et al (80) studied 24 patients, with 12 in the active group, showing positive results. However, due to the risk of bias and small sample size, the certainty and impact were low.

Amirdelfan et al (82) included 100 patients but had a complex study design involving multiple treatment groups and confounding factors. The trial showed significant improvements in MSC groups over hyaluronic acid, with 6 million mesenchymal precursor cells outperforming 18 million, but the complexity of the design and confounding results led to low certainty.

Gornet et al (81) studied 60 patients, with 40 receiving intradiscal biologics (20 with low-dose and 20 with high-dose cells), yielding positive results, but due to low sample size and modest improvement (30%), the impact was borderline, and certainty was low.

Therefore, the GRADE assessment indicates low certainty for both PRP and MSCs.

Summary of Evidence

As previously stated, qualitative evidence is moderate, or Level II.

Quantitative evidence from conventional meta-analysis showed positive results, with significant differences in pain levels at the 24-month follow-up across 3 studies.

Conventional meta-analysis also demonstrated significant improvements in functionality at 3-, 6-, and 12-month follow-ups. In contrast, the single-arm meta-analysis showed significant improvements in both pain and functionality from baseline at all follow-up periods from one month to 24 months. Based on the meta-analysis, which mainly relies on single-arm analysis, the evidence is classified as Level III to II, indicating fair to moderate quality.

Finally, based on the GRADE assessment, the certainty of evidence is low.

Consequently, the overall evidence is fair, with low confidence but moderate recommendations.

Discussion

This systematic review and meta-analysis evaluate the effectiveness of intradiscal regenerative medicine therapies for long-term relief of chronic low back pain. The analysis includes a range of systematic reviews, randomized controlled trials (RCTs), and observational studies.

Eight RCTs (79-83,85-87) and eight nonrandomized or observational studies (88,92,95,96,105,106,108,109) were identified. Among these, four RCTs focused on platelet-rich plasma (PRP) injections (79,83,85,86) and five trials on mesenchymal stem cell (MSC) injections (80-83,87). Three trials used allogeneic MSCs (80-82), one used homologous bone marrow concentrate (BMC) (83), and one used allogeneic bone marrow-derived MSCs (87). After applying the GRADE methodology for qualitative and quantitative analysis, the evidence was downgraded to Level III or fair, indicating low certainty and moderate recommendation.

This review parallels several systematic reviews published in previous years but incorporates a substantial number of recent studies on PRP, allogeneic MSCs, and homologous BMC. Methodological quality was assessed using well-established tools, including Cochrane Review criteria, IPM-QRB for RCTs, and Newcastle Ottawa Scale and IPM-QRBNR for observational studies. The study quality was rated as high based on Cochrane and Newcastle Ottawa criteria, but moderate to high when using IPM-QRBNR. Meta-analysis, both conventional and single-arm, demonstrated significant improvements in various parameters during long-term follow-up. The evidence was ultimately downgraded to Level II to III with low certainty, supporting moderate recommendations for clinical utility.

The first randomized controlled trial (RCT) of its kind was conducted by Tuakli-Wosornu et al (2016) with a cohort of 47 patients, including 29 in the treatment group and 18 in the control group. The study included an initial 8-week follow-up, followed by a one-year follow-up. This prospective, double-blind, randomized trial investigated the effects of lumbar intradiscal PRP injections. A rigorous participant selection process was employed, and the study had a high follow-up rate, with most patients completing the one-year follow-up. The results demonstrated statistically significant improvements for those receiving intradiscal PRP injections in terms of pain (P = 0.02), function (P= 0.3), and patient satisfaction (P = 0.01) compared to the control group. Importantly, there were no reported adverse events, including disc infection, neurological injury, or progressive herniation. While the findings are clinically significant, further studies are needed. The main limitation of this trial was its small sample size of 29 patients, which resulted in low certainty based on the GRADE criteria.

Navani et al (83) in 2024 conducted a multicenter, prospective, crossover randomized controlled trial (RCT) with a 12-month follow-up. This double-blind, placebo-controlled study showed that both PRP and BMC treatments resulted in statistically significant improvements in pain and function compared to the placebo, with no significant difference between BMC and PRP. The study's design and criteria were appropriate, but the trial had some limitations. The total sample size was small, comprising only 43 patients: 12 in the placebo group, 15 in the PRP group, and 16 in the BMC group. Although the results were positive, the small sample size led to low certainty in the findings, as assessed by the GRADE criteria.

Additionally, 2 RCTs by Goyal et al (85) and Akeda et al (86) utilized a double-blind randomized control design with an active control comparison, either comparing PRP injections to intradiscal radiofrequency ablation or corticosteroid injections. Goyal et al (85) compared intradiscal radiofrequency ablation with PRP injections, demonstrating superior results with PRP at the 6-month follow-up. Similarly, Akeda et al (86) compared PRP to intradiscal corticosteroid injections, showing significantly better improvements with PRP. Both studies, however, had important limitations. Goyal et al (85) found negative results when comparing PRP to intradiscal radiofrequency ablation, leading to low certainty in the findings. Akeda et al (86) included only 16 patients, with 8 in the treatment group and 8 in the control group, resulting in low certainty of evidence.

A recent study by Pers et al (87) was a large multicenter, randomized, placebo-controlled trial focused on degenerative disc disease, using a single intradiscal injection of allogenic mesenchymal stem cells (MSCs). The study was well-conducted, incorporating multiple outcome assessments. The sample size was adequate, with 58 patients in the bone marrow-derived MSC group and 56 in the sham placebo group. While the procedure was found to be safe at the 12-month follow-up, the study did not demonstrate clinical or imaging benefits, as it failed to meet the co-primary endpoint. Both groups showed only nonsignificant improvements from baseline, with a slight improvement observed in the treatment group receiving bone marrow-derived MSC injections.

Finally, Zelinski et al (84) conducted a study that did not meet the inclusion criteria, with only a 3-month follow-up and a sample size of 26 patients, which demonstrated a lack of effectiveness of PRP.

In this analysis, we included 8 RCTs (79-83,85-87), consisting of 6 placebo-controlled trials (79-83,87) and 2 trials with an active control design (85,86). Among the observational studies, we included 4 PRP studies (105,106,108,109), one study on allogeneic MSCs (96), and 3 studies on bone marrow (88,92,95). Notable studies include a series by Pettine et al (92-94), which examined 26 patients receiving autologous bone marrow concentrate (BMC) injections and followed them for 3 years in the first prospective study. Another significant study was by Atluri et al (88), an open-label, single-center trial with 80 patients. This study, along with several others, not only injected the discs but also targeted facet joints, sacroiliac joints, and provided epidural injections based on the theory of the three-joint complex. All studies showed positive results, suggesting the potential need to address multiple components in treatment.

Sanapati et al (29) reviewed the existing literature at the time, including 2 reviews on the effectiveness of intradiscal biologics in clinical settings (27,28), as well as studies related to animal trials (25) and spinal conditions such as spinal cord injury, intervertebral disc repair, and spinal fusion (26). Basso et al (27), in their systematic review of clinical evidence, focused on 7 articles that collectively studied a population of just 104 patients.

Wu et al (28), in a systematic review and single-arm meta-analysis of 6 studies on cell-based therapies for lumbar discogenic pain, concluded that these therapies were associated with improvements in both pain and disability scores. Later, Sanapati et al (29), in a 2018 publication, identified 6 studies - one RCT and five observational studies - of which 2 RCTs (79,80) and 2 observational studies (105,106) were included in the present analysis. The results of a single-arm meta-analysis showed significant improvement at the 6-month follow-up, with high heterogeneity across the studies, and a reduction in pain scores from baseline of 40.631 ± 14 points (95% CI: -68.07 to -13.19, $P < 0.0001$, $I^2 = 97.8$). At the 12-month follow-up, significant improvements were also observed with a pooled sample size of 57 patients. Sanapati et al (29) identified a total of 9 publications studying cell-based therapies for lumbar discogenic low back pain. Among these, there was one RCT (80) and 3 publications reporting a single study (92-94), but the studies had a small sample size and did not meet the criteria for inclusion in the present analysis. A single-arm analysis of 6 available studies, including one RCT and a pooled sample size of 71, showed a reduction in pain scores from baseline to 12 months of 36.943

points (95% CI: -49.855 to -24.030, $P < 0.001$), with high heterogeneity across the studies ($I^2 = 86\%$). Additionally, significant improvement in functional status was noted at 12 months, with a 26.342-point decrease in disability scores (95% CI: -32.359 to -20.325, $P < 0.001$), with moderate heterogeneity ($I^2 = 55\%$).

Yolcu et al (58), in a 2020 systematic review on the use of MSCs or BMC, included 6 studies with a total of 93 patients. The review found pain improvement in 38.8% of patients at 3 months, 40.8% at 6 months, and 44.1% at 12 months. The average improvement in ODI scores at 3-, 6-, and 12-month follow-ups were 24, 26.5, and 25.7, respectively. The authors concluded that the analysis suggested a potential positive impact based on these preliminary results. However, the systematic review was based on small sample sizes, with most studies being nonrandomized and lacking quality assessment or meta-analysis. Furthermore, the review noted that the 50% success rate for pain improvement was not achieved at any point during the study period, although disability scores showed significantly greater improvement than pain scores.

Her et al (59) published a systematic review in 2022 on the use of intradiscal injections of BMAC and culture-expanded bone marrow mesenchymal stromal cells (BM-MSCs) for discogenic pain. With significant progress in the field by 2022, the authors included 16 studies with a total of 607 patients in their qualitative synthesis, without pooling the data. The included studies consisted of 3 RCTs, 9 prospective cohort studies, 3 case series, and 1 retrospective study. Studies with fewer than 25 patients or less than 6 months of follow-up were excluded from the present analysis. Consequently, only 3 studies (80,82,92) were included in the current review. Her et al (59) found that, generally, intradiscal autologous or allogeneic BMAC and culture-expanded BM-MSCs led to improvements in discogenic pain compared to baseline. Additionally, intradiscal injection was associated with improved physical functioning and positive anatomical changes observed on spine MRI, although anatomical findings were inconsistent across studies. The authors also noted that the overall GRADE score for this study was very low due to high heterogeneity and poor generalizability. No meta-analysis was performed.

Soufi et al (63) published a systematic review on the potential role of stem cell regenerative therapy in degenerative disc disease and low back pain, though without performing a meta-analysis. They identified 11 clinical studies, including one RCT that met the inclusion criteria, with a total of 119 patients. In their review, the authors concluded that there was no evidence to support the use of stem cell therapy in humans for these conditions.

Schneider et al (61) published a systematic review in 2022 on the effectiveness of intradiscal biologic treatments, including PRP and MSCs, without performing a meta-analysis. They included 12 studies in their review and found that the quality of evidence for the effectiveness of intradiscal biologics was very low. One RCT evaluating PRP reported positive outcomes, but it had significant methodological flaws. Additionally, a single trial evaluating MSCs showed negative results. The overall success rate for PRP injections was 54.8%, while for MSCs, the success rate at 6 months was 53.5%, which decreased to 40.7% in a worst-case analysis. Functional improvement of more than 30% was achieved in 74.3% of patients at 6 months, but this decreased to 44.1% when applying the worst-case analysis. The authors concluded that limited observational data supports the use of intradiscal biologic agents for treating discogenic low back pain. However, they noted that according to the GRADE criteria, the evidence supporting the use of intradiscal MSCs and PRP was of very low quality.

Kawabata et al (64) published a systematic review in 2023 on advances in PRP treatment for spinal diseases. They concluded that basic research highlighted the promising regenerative potential of PRP, while clinical studies have shown the safety and efficacy of PRP therapy for treating various spinal diseases, including degenerative disc disease.

Machado et al (65) published a systematic review in 2023 on the use of PRP for low back pain. The review included 13 RCTs and 27 nonrandomized studies or case reports. Of the 13 RCTs, 11 found favorable results in comparison to the control group in terms of pain and disability, while one showed no superiority over the control group, and another was discontinued due to a lack of therapeutic effect at the 8-week evaluation. The studies included various types of injections, such as epidurals, facet joint injections, and sacroiliac joint injections. Overall, the authors concluded that PRP was generally an effective and safe treatment for degenerative low back pain, with positive results found in most studies and a small number of adverse events. They rated the quality of evidence supporting PRP for low back pain as Level II. However, the review had multiple deficiencies, including a lack of methodological quality assessment of the studies and a GRADE assessment.

Zhang et al (66) published a 2024 study on the clinical efficacy of PRP injection therapy compared to different control groups for chronic low back pain, including a network meta-analysis of RCTs. The analysis identified 4 articles with 154 cases; however, only 2 studies focused on intradiscal injections. The results indicated better short-term improvement in chronic low back pain with corticosteroids after 4 weeks. Additionally, PRP and radiofrequency ablation showed similar improvement effects, but at a 6-month follow-up, PRP demonstrated a greater advantage in improving disability indices. However, due to the inclusion of very few studies on intradiscal therapy, the value of this network meta-analysis may be limited.

In contrast to the studies mentioned above, Peng et al (67) focused on the efficacy of intradiscal PRP injection in the treatment of discogenic low back pain, conducting a single-arm meta-analysis in 2023. They included 6 trials, consisting of 3 RCTs and 3 prospective single-arm trials, with 2 of these studies (79,108) being included in our analysis. The meta-analysis showed that 51.9% of patients experienced a 50% reduction in pain scores from baseline after 6 months of treatment. Pain scores significantly decreased by 1.42 points (P = 0.0008) after 6 months. No significant adverse reactions were reported in any of the 6 included studies. The authors concluded that there was no significant change in pain at one-, 2-, and 6-months post-treatment and that intradiscal PRP injection was both effective and safe.

Yum et al (13) published a review in 2024 discussing the existing gaps in the use of PRP treatment for the lumbar spine. They emphasized that all clinical studies evaluating PRP as a treatment should include full transparency and detailed information on the methods used for PRP preparation and injection. Additionally, they proposed that future double-blind, randomized trials could address existing gaps by evaluating the effects of platelet concentration and dose on clinical outcomes, as well as establishing a timeline for expected clinical improvement after PRP injections. It is important to note that this publication is neither a systematic review nor a meta-analysis.

Akeda et al (114), in a critical review published in 2019, examined the potential of PRP in the management of chronic low back pain. They extensively discussed how PRP can stimulate cell proliferation and enhance the metabolic activity of intervertebral cells both in vitro and in vivo. The review highlighted several animal studies that demonstrated the effectiveness of PRP injections in degenerated intervertebral discs, noting improvements in structural changes (such as intervertebral disc height) and matrix integrity, as assessed by MRI and histology. While clinical evidence for tissue repair in intervertebral discs through PRP treatment is currently lacking, they concluded that PRP holds a significant promise as a potential intradiscal therapy for treating degenerative disc diseases.

In 2024, Lorio et al (56) provided a perspective on intradiscal therapies for lumbar discogenic pain, addressing various aspects such as the current state of the field, existing knowledge gaps, and the importance of clinical adoption. They identified mesenchymal stromal cells, PRP, nucleus pulposus structural allograft, and other cell-based compositions as viable candidate products to date. The review emphasized that the goals of these therapies include repairing, supplementing, and restoring damaged intervertebral discs, as well as preventing further degeneration. Additionally, the authors discussed the U.S. Food and Drug Administration (FDA) guidance on interpreting the minimal manipulation and homologous use criteria, which are crucial for classifying these treatments as tissue, drug/device, or biologic. Finally, they outlined key evidence and knowledge gaps related to intradiscal therapies, proposed imperatives for evaluating the effectiveness of these treatments, and highlighted emerging technologies in the field.

Zhang et al (66) conducted a meta-analysis to assess the clinical efficacy of PRP injection therapy compared to various control groups for chronic low back pain, with outcomes reported up to 6 months. They identified four articles for inclusion in the meta-analysis, which showed that corticosteroids provided better short-term improvement in chronic low back pain after 4 weeks. However, PRP was found to be more advantageous in improving disability indices at the 6-month follow-up.

Bhujel et al (55) published a 2022 review on the role of MSC-derived exosomes in intervertebral disc regeneration. They highlighted recent findings suggesting that the pleiotropic effects of MSCs are not related to their differentiation capacity but rather are mediated through the secretion of soluble paracrine factors. Early studies have demonstrated that MSC-derived exosomes possess therapeutic potential for treating intervertebral disc degeneration by promoting cell proliferation, tissue regeneration, modulating the inflammatory response, and reducing apoptosis. Similarly, in 2019, Akeda et al (114) published a critical review on the role of PRP in managing chronic low back pain of discogenic

origin. They discussed evidence showing that PRP has significant potential to stimulate cell proliferation and metabolic activity of intervertebral cells in vitro. Based on several animal studies, they found that injecting PRP into degenerated intervertebral discs effectively restored structural changes (such as intervertebral disc height) and improved matrix integrity, as evaluated by MRI and histology. These findings suggest that PRP has a significant biological effect on tissue repair, potentially counteracting intervertebral disc degeneration.

This systematic review and meta-analysis offer several advantages over existing studies, as it is the largest of its kind to date. A thorough evaluation was conducted, focusing on the methodological quality of the included studies, which were selected based on strict inclusion criteria. Both qualitative and quantitative analyses were performed, and the GRADE assessment was applied, adjusting the grading of the studies based on various factors.

This review has several limitations. Despite comprehensive search criteria and the inclusion of multiple databases and trials, only 16 studies met our inclusion criteria and were included in this systematic review, with some incorporated into the meta-analysis. Additionally, half of these studies were observational studies and case reports with considerable heterogeneity. The studies generally involved small sample sizes. Other drawbacks include the lack of valid or reliable patient selection criteria for those with discogenic pain. Moreover, there is a lack of detailed information regarding the quality and composition of the injectate, as well as technical complications associated with discography, and the diffusion or bulk flow of the injectate to the site of inflammation. Finally, while some studies provided statistically significant results, there is limited data on clinically meaningful outcomes.

Conclusion

The results of this systematic review and single-arm meta-analysis suggest that MSCs and PRP may be effective in treating discogenic low back pain, though the evidence is of variable strength. The overall evidence quality is rated as Level III (fair). Additional studies are needed to further clarify the role of MSCs and PRP in mediating or modulating beneficial outcomes for low back pain.

Author Contributions

The study was designed by EK, NK, and LM.

Statistical analysis was performed by EK and NK.

All authors contributed to the preparation of this study, reviewed, and approved the content with the final version.

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Appendix Table 1. *Sources of risk of bias and Cochrane Review rating system.*

Bias Domain	**Source of Bias**		**Possible Answers**
Selection	(1) Was the method of randomization adequate?	A random (unpredictable) assignment sequence. Examples of adequate methods are coin toss (for studies with 2 groups), rolling a dice (for studies with 2 or more groups), drawing of balls of different colors, drawing of ballots with the study group labels from a dark bag, computer-generated random sequence, preordered sealed envelopes, sequentially-ordered vials, telephone call to a central office, and preordered list of treatment assignments.	Yes/No/Unsure
		Examples of inadequate methods are: alternation, birth date, social insurance/security number, date in which they are invited to participate in the study, and hospital registration number.	
Selection	(2) Was the treatment allocation concealed?	Assignment generated by an independent person not responsible for determining the eligibility of the patients. This person has no information about the persons included in the trial and has no influence on the assignment sequence or on the decision about eligibility of the patient.	Yes/No/Unsure
Performance	(3) Was the patient blinded to the intervention?	Index and control groups are indistinguishable for the patients or if the success of blinding was tested among the patients and it was successful.	Yes/No/Unsure
Performance	(4) Was the care provider blinded to the intervention?	Index and control groups are indistinguishable for the care providers or if the success of blinding was tested among the care providers and it was successful.	Yes/No/Unsure
Detection	(5) Was the outcome assessor blinded to the intervention?	Adequacy of blinding should be assessed for each primary outcome separately. This item should be scored "yes" if the success of blinding was tested among the outcome assessors and it was successful or:	Yes/No/Unsure
		• for patient-reported outcomes in which the patient is the outcome assessor (e.g., pain, disability): the blinding procedure is adequate for outcome assessors if participant blinding is scored "yes"	
		• for outcome criteria assessed during scheduled visit and that supposes a contact between participants and outcome assessors (e.g., clinical examination): the blinding procedure is adequate if patients are blinded, and the treatment or adverse effects of the treatment cannot be noticed during clinical examination	
		• for outcome criteria that do not suppose a contact with participants (e.g., radiography, magnetic resonance imaging): the blinding procedure is adequate if the treatment or adverse effects of the treatment cannot be noticed when assessing the main outcome	
		• for outcome criteria that are clinical or therapeutic events that will be determined by the interaction between patients and care providers (e.g., cointerventions, hospitalization length, treatment failure), in which the care provider is the outcome assessor: the blinding procedure is adequate for outcome assessors if item "4" (caregivers) is scored "yes"	
		• for outcome criteria that are assessed from data of the medical forms: the blinding procedure is adequate if the treatment or adverse effects of the treatment cannot be noticed on the extracted data	
Attrition	(6) Was the drop-out rate described and acceptable?	The number of participants who were included in the study but did not complete the observation period or were not included in the analysis must be described and reasons given. If the percentage of withdrawals and drop-outs does not exceed 20% for short-term follow-up and 30% for long-term follow-up and does not lead to substantial bias a "yes" is scored (N.B. these percentages are arbitrary, not supported by literature).	Yes/No/Unsure
Attrition	(7) Were all randomized participants analyzed in the group to which they were allocated?	All randomized patients are reported/analyzed in the group they were allocated to by randomization for the most important moments of effect measurement (minus missing values) irrespective of noncompliance and cointerventions.	Yes/No/Unsure
Reporting	(8) Are reports of the study free of suggestion of selective outcome reporting?	All the results from all prespecified outcomes have been adequately reported in the published report of the trial. This information is either obtained by comparing the protocol and the report, or in the absence of the protocol, assessing that the published report includes enough information to make this judgment.	Yes/No/Unsure

Appendix Table 1 cont. *Sources of risk of bias and Cochrane Review rating system.*

Bias Domain	**Source of Bias**		**Possible Answers**
Selection	(9) Were the groups similar at baseline regarding the most important prognostic indicators?	Groups have to be similar at baseline regarding demographic factors, duration and severity of complaints, percentage of patients with neurological symptoms, and value of main outcome measure(s).	Yes/No/Unsure
Performance	(10) Were cointerventions avoided or similar?	If there were no cointerventions or they were similar between the index and control groups.	Yes/No/Unsure
Performance	(11) Was the compliance acceptable in all groups?	The reviewer determines if the compliance with the interventions is acceptable, based on the reported intensity, duration, number and frequency of sessions for both the index intervention and control intervention(s). For example, physiotherapy treatment is usually administered for several sessions; therefore it is necessary to assess how many sessions each patient attended. For single-session interventions (e.g., surgery), this item is irrelevant.	Yes/No/Unsure
Detection	(12) Was the timing of the outcome assessment similar in all groups?	Timing of outcome assessment should be identical for all intervention groups and for all primary outcome measures.	Yes/No/Unsure
Other	(13) Are other sources of potential bias unlikely?	Other types of biases. For example: • When the outcome measures were not valid. There should be evidence from a previous or present scientific study that the primary outcome can be considered valid in the context of the present. • Industry-sponsored trials. The conflict of interest (COI) statement should explicitly state that the researchers have had full possession of the trial process from planning to reporting without funders with potential COI having any possibility to interfere in the process. If, for example, the statistical analyses have been done by a funder with a potential COI, usually "unsure" is scored.	Yes/No/Unsure

Adapted and modified from: Furlan AD, et al; Editorial Board of the Cochrane Back, Neck Group. 2015 Updated method guideline for systematic reviews in the Cochrane Back and Neck Group. *Spine (Phila Pa 1976)* 2015; 40:1660-1673 (71).

Appendix Table 2. *Item checklist for assessment of randomized controlled trials of IPM techniques utilizing IPM-QRB.*

		Scoring
I.	TRIAL DESIGN AND GUIDANCE REPORTING	
1.	CONSORT or SPIRIT	
	Trial designed and reported without any guidance	0
	Trial designed and reported utilizing minimum criteria other than CONSORT or SPIRIT criteria or trial was conducted prior to 2005	1
	Trial implies it was based on CONSORT or SPIRIT without clear description with moderately significant criteria for randomized trials or the trial was conducted before 2005	2
	Explicit use of CONSORT or SPIRIT with identification of criteria or trial conducted with high level reporting and criteria or conducted before 2005	3
II.	DESIGN FACTORS	
2.	Type and Design of Trial	
	Poorly designed control group (quasi selection, convenient sampling)	0
	Proper active-control or sham procedure with injection of active agent	2
	Proper placebo control (no active solutions into active structures)	3
3.	Setting/Physician	
	General setting with no specialty affiliation and general physician	0
	Specialty of anesthesia/PMR/neurology/radiology/ortho, etc.	1
	Interventional pain management with interventional pain management physician	2
4.	Imaging	
	Blind procedures	0
	Ultrasound	1
	CT	2
	Fluoro	3
5.	Sample Size	
	Less than 50 participants in the study without appropriate sample size determination	0
	Sample size calculation with less than 25 patients in each group	1
	Appropriate sample size calculation with at least 25 patients in each group	2
	Appropriate sample size calculation with 50 patients in each group	3
6.	Statistical Methodology	
	None or inappropriate	0
	Appropriate	1
III.	PATIENT FACTORS	
7.	Inclusiveness of Population	
7a.	For discogenic pain:	
	Poorly identified mixed population	0
	Clearly identified mixed population	1
	Disorders specific trials (i.e. well defined discogenic pain)	2
8.	Duration of Pain	
	Less than 3 months	0
	3 to 6 months	1
	> 6 months	2
9.	Previous Treatments	
	Conservative management including drug therapy, exercise therapy, physical therapy, etc.	
	Were not utilized	0
	Were utilized sporadically in some patients	1

Appendix Table 2 cont. *Item checklist for assessment of randomized controlled trials of IPM techniques utilizing IPM-QRB.*

		Scoring
	Were utilized in all patients	2
10.	Duration of Follow-up with Appropriate Interventions	
	Less than 3 months or 12 weeks for epidural, facet joint or sacroiliac joint procedures, etc. and 6 months for intradiscal procedures and implantables	0
	3 to 6 months for intradiscal injections, epidural, facet joint or sacroiliac joint procedures, etc., or 1 year for intradiscal procedures or implantables	1
	6 months to 12 months for intradiscal injections, epidurals, facet joint or sacroiliac joint procedures, etc., and 2 years or longer for intradiscal procedures and implantables	2
	18 months or longer for intradiscal injections, epidurals, facet joint or sacroiliac joint procedures, etc., or 5 years or longer for intradiscal procedures and implantables	3
IV.	OUTCOMES	
11.	Outcomes Assessment Criteria for Significant Improvement	
	No descriptions of outcomes OR < 20% change in pain rating or functional status	0
	Pain rating with a decrease of 2 or more points or more than 20% reduction OR functional status improvement of more than 20%	1
	Pain rating with decrease of ≥ 2 points AND ≥ 20% change or functional status improvement of ≥ 20%	2
	Pain rating with a decrease of 3 or more points or more than 50% reduction OR functional status improvement with a 50% or 40% reduction in disability score	3
	Significant improvement with pain and function ≥ 50% or 3 points and 40% reduction in disability scores	4
12.	Analysis of all Randomized Participants in the Groups	
	Not performed	0
	Performed without intent-to-treat analysis without inclusion of all randomized participants	1
	All participants included with or without intent-to-treat analysis	2
13.	Description of Drop Out Rate	
	No description of dropouts, despite reporting of incomplete data or ≥ 20% withdrawal	0
	Less than 20% withdrawal in one year in any group	1
	Less than 30% withdrawal at 2 years in any group	2
14.	Similarity of Groups at Baseline for Important Prognostic Indicators	
	Groups dissimilar with significant influence on outcomes with or without appropriate randomization and allocation	0
	Groups dissimilar without influence on outcomes despite appropriate randomization and allocation	1
	Groups similar with appropriate randomization and allocation	2
15.	Role of Co-Interventions	
	Co-interventions were provided but were not similar in the majority of participants	0
	No co-interventions or similar co-interventions were provided in the majority of the participants	1
V.	RANDOMIZATION	
16.	Method of Randomization	
	Quasi randomized or poorly randomized or not described	0
	Adequate randomization (coin toss, drawing of balls of different colors, drawing of ballots)	1
	High quality randomization (Computer generated random sequence, pre-ordered sealed envelopes, sequentially ordered vials, telephone call, pre-ordered list of treatment assignments, etc.)	2
VI.	ALLOCATION CONCEALMENT	
17.	Concealed Treatment Allocation	

Appendix Table 2 cont. ***Item checklist for assessment of randomized controlled trials of IPM techniques utilizing IPM-QRB.***

		Scoring
	Poor concealment of allocation (open enrollment) or inadequate description of concealment	0
	Concealment of allocation with borderline or good description of the process with probability of failure of concealment	1
	High quality concealment with strict controls (independent assignment without influence on the assignment sequence)	2
VII.	BLINDING	
18.	Patient Blinding	
	Patients not blinded	0
	Patients blinded adequately	1
19.	Care Provider Blinding	
	Care provider not blinded	0
	Care provider blinded adequately	1
20.	Outcome Assessor Blinding	
	Outcome assessor not blinded or was able to identify the groups	0
	Performed by a blinded independent assessor with inability to identify the assignment-based provider intervention (i.e., subcutaneous injection, intramuscular distant injection, difference in preparation or equipment use, numbness and weakness, etc.)	1
VIII.	CONFLICTS OF INTEREST	
21.	Funding and Sponsorship	
	Trial included industry employees	-3
	Industry employees involved; high levels of funding with remunerations by industry or an organization funded with conflicts	-3
	Industry or organizational funding with reimbursement of expenses with some involvement	0
	Industry or organization funding of expenses without involvement	1
	Funding by internal resources only with supporting entity unrelated to industry	2
	Governmental funding without conflict such as NIH, NHS, AHRQ	3
22.	Conflicts of Interest	
	None disclosed with potential implied conflict	0
	Marginally disclosed with potential conflict	1
	Well disclosed with minor conflicts	2
	Well disclosed with no conflicts	3
	Hidden conflicts with poor disclosure	–1
	Misleading disclosure with conflicts	–2
	Major impact related to conflicts	–3
TOTAL		48

Modified from: Manchikanti L, et al. Assessment of methodologic quality of randomized trials of interventional techniques: Development of an interventional pain management specific instrument. *Pain Physician* 2014; 17:E263-E290 (72).

Appendix Table 3. ***Newcastle-Ottawa quality assessment scale for case control studies.***

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?
   a) yes, with independent validation ✸
   b) yes, eg record linkage or based on self reports
   c) no description

2) Representativeness of the cases
   a) consecutive or obviously representative series of cases ✸
   b) potential for selection biases or not stated

3) Selection of Controls
   a) community controls ✸
   b) hospital controls
   c) no description

3) Definition of Controls
   a) no history of disease (endpoint) ✸
   b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for _____ (Select the most important factor.)
   b) study controls for any additional factor ¯ (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure
   a) secure record (eg surgical records) ✸
   b) structured interview where blind to case/control status ✸
   c) interview not blinded to case/control status
   d) written self report or medical record only
   e) no description

2) Same method of ascertainment for cases and controls
   a) yes ✸
   b) no

3) Non-Response rate
   a) same rate for both groups ✸
   b) non respondents described
   c) rate different and no designation

Source: Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. Accessed 7/09/2024. www.ohri.ca/programs/clinical_epidemiology/oxford.asp (73)

Appendix Table 4. ***Newcastle-Ottawa quality assessment scale cohort studies.***

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average _____ (describe) in the community ✸
   b) somewhat representative of the average _____ in the community ✸
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort ✸
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
   a) secure record (eg surgical records) ✸
   b) structured interview ✸
   c) written self report
   d) no description

4) Demonstration that outcome of interest was not present at start of study
   a) yes ✸
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for _____ (select the most important factor) ✸
   b) study controls for any additional factor ✸ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
   a) independent blind assessment ✸
   b) record linkage ✸
   c) self report
   d) no description

2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow up period for outcome of interest) ✸
   b) no

3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for ✸
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ✸
   c) follow up rate < ____% (select an adequate %) and no description of those lost
   d) no statement

Source: Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. Accessed 7/09/2024. www.ohri.ca/programs/clinical_epidemiology/oxford.asp (73)

Appendix Table 5. *Item checklist for assessment of nonrandomized or observational studies of IPM techniques utilizing IPM-QRBNR.*

I.	STUDY DESIGN AND GUIDANCE REPORTING	Scoring
1.	STROBE or TREND Guidance	
	Case Report/Case Series	0
	Study designed without any guidance	1
	Study designed with minimal criteria and reporting with or without guidance	2
	Study designed with moderately significant criteria or implies it was based on STROBE or TREND without clear description or the study was conducted before 2011 or similar criteria utilized with study conducted before 2011	3
	Designed with high level criteria or explicitly uses STROBE or TREND with identification of criteria or conducted prior to 2011	4
II.	DESIGN FACTORS	
2.	Study Design and Type	
	Case report or series (uncontrolled – longitudinal)	0
	Retrospective cohort or cross-sectional study	1
	Prospective cohort case-control study	2
	Prospective case control study	3
	Prospective, controlled, nonrandomized	4
3.	Setting/Physician	
	General setting with no specialty affiliation and general physician	0
	Specialty of anesthesia/PMR/neurology, etc.	1
	Interventional pain management with interventional pain management physician	2
4.	Imaging	
	Blind procedures	0
	Ultrasound	1
	CT	2
	Fluoro	3
5.	Sample Size	
	Less than 100 participants without appropriate sample size determination	0
	At least 100 participants in the study without appropriate sample size determination	1
	Sample size calculation with less than 50 patients in each group	2
	Appropriate sample size calculation with at least 50 patients in each group	3
	Appropriate sample size calculation with 100 patients in each group	4
6.	Statistical Methodology	
	None	0
	Some statistics	1
	Appropriate	2
III.	PATIENT FACTORS	
7.	Inclusiveness of Population	
7a.	For discogenic pain:	
	Poorly identified mixed population	1
	Poorly identified mixed population with large sample (≥ 200)	2
	Clearly identified mixed population	3
	Disorders specific trials (i.e. well defined discogenic pain)	4
8.	Duration of Pain	
	Less than 3 months	0
	3 to 6 months	1

Appendix Table 5 cont. ***Item checklist for assessment of nonrandomized or observational studies of IPM techniques utilizing IPM-QRBNR.***

I.	STUDY DESIGN AND GUIDANCE REPORTING	Scoring
	> 6 months	2
9.	Previous Treatments	
	Conservative management including drug therapy, exercise therapy, physical therapy, etc.	
	Were not utilized	0
	Were utilized sporadically in some patients	1
	Were utilized in all patients	2
10.	Duration of Follow-up with Appropriate Interventions	
	Less than 3 months or 12 weeks for epidural, facet joint or sacroiliac joint procedures, etc. and 6 months for intradiscal procedures and implantables	1
	3 to 6 months for intradiscal injections, epidural, facet joint or sacroiliac joint procedures, etc., or 1 year for intradiscal procedures or implantables	2
	6 months to 12 months for intradiscal injections, epidurals, facet joint or sacroiliac joint procedures, etc., and 2 years or longer for intradiscal procedures and implantables	3
	18 months or longer for intradiscal injections, epidurals, facet joint or sacroiliac joint procedures, etc., or 5 years or longer for intradiscal procedures and implantables	4
IV.	OUTCOMES	
11.	Outcomes Assessment Criteria for Significant Improvement	
	No descriptions of outcomes OR < 20% change in pain rating or functional status	0
	Pain rating with a decrease of 2 or more points or more than 20% reduction OR functional status improvement of more than 20%	1
	Pain rating with decrease of ≥ 2 points AND ≥ 20% change or functional status improvement of ≥ 20%	2
	Pain rating with a decrease of 3 or more points or more than 50% reduction OR functional status improvement with a 50% or 40% reduction in disability score	3
	Significant improvement with pain and function ≥ 50% or 3 points and 40% reduction in disability scores	4
12.	Description of Drop Out Rate	
	No description despite reporting of incomplete data or more than 30% withdrawal	0
	Less than 30% withdrawal in one year in any group	1
	Less than 40% withdrawal at 2 years in any group	2
13.	Similarity of Groups at Baseline for Important Prognostic Indicators	
	No groups or groups dissimilar with significant influence on outcomes	0
	Groups dissimilar without significant influence on outcomes	1
	Groups similar	2
14.	Role of Co-Interventions	
	Dissimilar co-interventions or similar co-interventions in some of the participants	1
	No co-interventions or similar co-interventions in majority of the participants	2
V.	ASSIGNMENT	
15.	Method of Assignment of Participants	
	Case report/case series or selective assignment based on outcomes or retrospective evaluation based on clinical criteria	1
	Prospective study with inclusion without specific criteria	2
	Retrospective method with inclusion of all participants or random selection of retrospective data	3
	Prospective, well-defined assignment of methodology and inclusion criteria (quasi randomization, matching, stratification, etc.)	4

Appendix Table 5 cont. ***Item checklist for assessment of nonrandomized or observational studies of IPM techniques utilizing IPM-QRBNR.***

I.	STUDY DESIGN AND GUIDANCE REPORTING	Scoring
VI.	CONFLICTS OF INTEREST	
16.	Funding and Sponsorship	
	Trial included industry employees with or without proper disclosure	-3
	Industry employees involved; high levels of funding with remunerations by industry or an organization funded with conflicts	-3
	Industry or organizational funding with reimbursement of expenses with some involvement or no information available	0
	Industry or organization funding of expenses without involvement	1
	Funding by internal resources only	2
	Governmental funding without conflict such as NIH, NHS, AHRQ	3
TOTAL MAXIMUM		48

Modified from: Manchikanti L, et al. Development of an interventional pain management specific instrument for methodologic quality assessment of nonrandomized studies of interventional techniques. *Pain Physician* 2014; 17:E291-E317 (74).