

Applications and Advances of Regenerative Medicine in Surgery: A Systematic Review (Prisma)

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ABSTRACT

Background: Regenerative medicine aims to repair, regenerate, or replace human cells, tissues, and organs in order to restore normal function, offering innovative solutions to surgical challenges through cell therapy, biomaterials, bioprinting, and tissue engineering.

Objective: To assess the applications and advances of regenerative medicine in surgery.

Methods: A systematic review was conducted following the PRISMA guidelines. A literature search was performed in PubMed, ClinicalKey, ISI Web of Science, ScienceDirect, and Google Scholar for studies published between 2022 and 2026. Articles reporting clinical studies involving human surgical patients were included. After applying the inclusion and exclusion criteria, 26 articles were selected for analysis.

Results: In cardiovascular surgery, decellularized homografts showed excellent 5-year outcomes, with a mortality rate of 2.5% and a reintervention rate of 6.5%, while mesenchymal stem cells (MSCs) modulated the post-infarction inflammatory response. In ophthalmology, cell transplantation restored the ocular surface and improved visual outcomes. In trauma and orthopedic surgery, MSC-based tissue engineering showed outcomes equivalent to autologous bone grafting for the treatment of nonunion. In vascular surgery, acellular tissue-engineered vessels (ATEVs) demonstrated high patency rates and absence of rejection. Platelet-rich plasma (PRP) enhanced the healing of chronic wounds. In plastic surgery, autologous skin substitutes demonstrated stability at 5 years.

Discussion: Current evidence supports the safety of regenerative therapies; however, their efficacy varies according to the underlying condition and clinical context. Multimodal approaches combining cells, growth factors, and scaffolds appear to outperform monotherapies, particularly in chronic wound healing and bone regeneration.

Conclusion: Regenerative medicine offers a broad and promising therapeutic armamentarium with favorable safety profiles. Personalized combinations of therapeutic modalities guided by individual patient characteristics may represent the pathway toward transforming these strategies into established treatments.

KEYWORDS: Regenerative medicine; surgery; stem cells; bioprinting; tissue engineering.

ARTICLE DETAILS

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INTRODUCTION

Regenerative medicine focuses on the repair, regeneration, and/or replacement of human cells, tissues, or organs to restore their normal function. Current approaches include cell-based therapies, particularly stem cells, biomaterials, bioprinting, and the implantation of cell-seeded scaffolds

through tissue engineering. Within the field of surgery, regenerative medicine provides innovative solutions to surgical challenges with the aim of improving clinical outcomes.¹

Regenerative medicine seeks to facilitate the repair of damaged tissues, replace damaged cells, and restore impaired

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organ systems using bioengineered tissues. Major advances in this field include tissue engineering, stem cell technologies, organoid biology, and gene editing.²

Cell therapy is based on the ability of cells to differentiate into other cell types. This approach involves introducing new, healthy cells—either differentiated cells or undifferentiated stem cells—into diseased or damaged tissues. Biomaterials, which may be enriched with growth factors and cytokines, often function as extracellular matrices and play an important role in gene expression, cell survival and death, proliferation, migration, and differentiation. The implantation of cell-seeded scaffolds combines these two strategies and may be used, for example, in the development of a bioartificial liver.³ Furthermore, exosomes—nanoscale extracellular vesicles produced by stem cells during regenerative processes—may contribute to the treatment of surgical conditions and potentially provide therapeutic alternatives for diseases that have traditionally been considered difficult or impossible to cure. However, limited information is currently available regarding their medium- and long-term use. Therefore, further research is required to establish their long-term safety and effectiveness.⁴

METHODOLOGY

The objective of this systematic review was to assess the applications and advances of regenerative medicine in surgery. General surgery should be recognized as one of the most comprehensive surgical specialties, encompassing a broad spectrum of diseases involving systems ranging from the gastrointestinal tract to the breast and endocrine system.⁵ This literature review followed a systematic approach based on the PRISMA (Preferred Reporting Items for Systematic

Reviews and Meta-Analyses) guidelines to ensure comprehensive identification and assessment of relevant studies addressing the applications and advances of regenerative medicine in surgery.

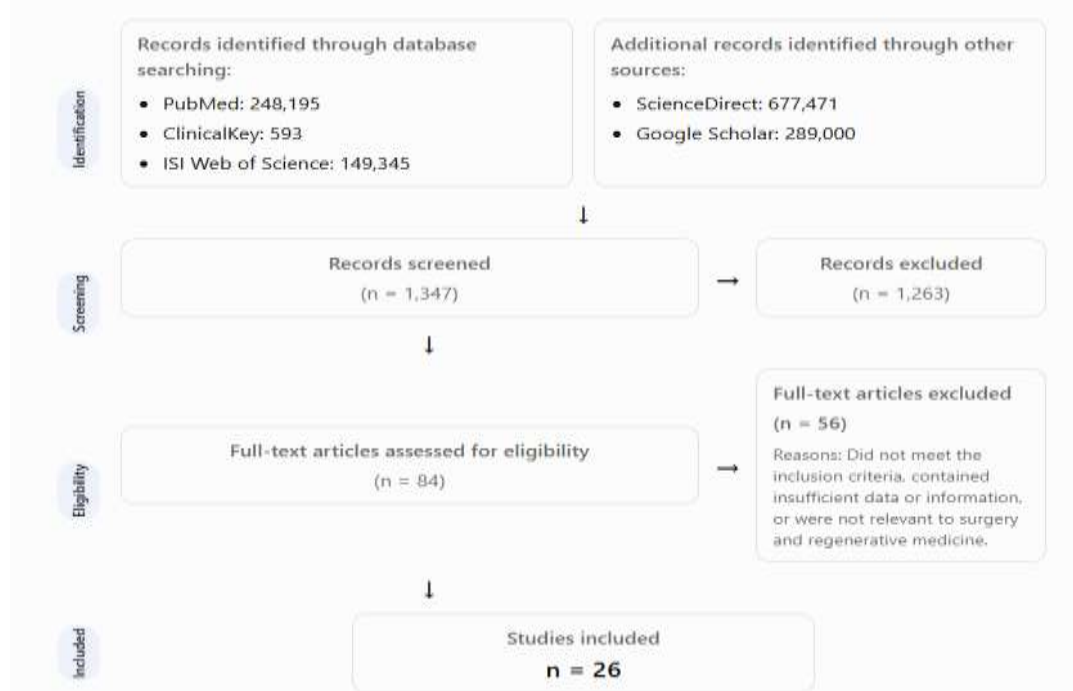
A systematic literature search was conducted in PubMed, ClinicalKey, ISI Web of Science, ScienceDirect, and Google Scholar. The combination of search terms that yielded the most relevant results across the databases was as follows: (((((Regenerative Medicine) AND (General Surgery)) AND (Stem Cells)) OR (Bioprinting)) OR (Tissue Engineering))).

The initial search retrieved 248,195 articles from PubMed, 593 from ClinicalKey, 149,345 from ISI Web of Science, 677,471 from ScienceDirect, and 289,000 from Google Scholar. The following inclusion criteria were applied: scientific articles published between 2022 and 2026; articles related to surgery or general surgery; publications in scientific journals; articles published in either Spanish or English; and freely accessible full-text articles.

The following exclusion criteria were applied: study protocols, systematic reviews, books, manuals, guidelines, and meta-analyses; studies conducted using animal models; studies with keywords unrelated to those specified in the search strategy; and restricted-access documents.

After applying these criteria, 431 articles were identified in PubMed, 19 in ClinicalKey, 43 in ISI Web of Science, 268 in ScienceDirect, and 606 in Google Scholar, yielding a total of 1,347 articles. Following title screening, 84 articles were considered potentially eligible. Their abstracts and keywords were subsequently reviewed. Based on this assessment, 58 articles were excluded because they fell outside the scope of the present systematic review. Finally, 26 articles met the selection criteria and were included in the systematic review.

FLOW DIAGRAM



RESULTS

CARDIOVASCULAR SURGERY

Table 1 summarizes the main findings regarding the applications of regenerative medicine in cardiovascular surgery.

Table 1. Regenerative Medicine in Cardiovascular Surgery

Study	Sample	Methodology	Results
Bayes-Genis, A., et al. (2024) ⁶	12 patients (7 intervention, 5 control)	Phase I clinical trial of PeriCord implantation (decellularized pericardial matrix + Wharton's jelly mesenchymal stromal cells).	Adequate safety profile. Modulation of circulating monocytes toward classical macrophages (inflammatory resolution), reduction in monocyte chemoattractants, and an increase in a plasma factor with a post-treatment prognosis similar to that of meteorin.
Horke, A., et al. (2026) ⁷	144 patients	Evaluation of decellularized aortic homografts (HAD) not cryopreserved for aortic valve replacement.	HAD is safe. At 5 years: freedom from death (97.5%), reintervention (93.5%), endocarditis (96.4%), hemorrhage (99.2%), and thromboembolism (99.3%). Excellent hemodynamic performance.
Gallego-Navarro, C., et al. (2025) ⁸	95 children with hypoplastic left heart syndrome and variants	Efficacy study of intracardiac injections of autologous umbilical cord blood mononuclear cells (UCB-MNC) during stage II palliative surgery.	Treatment did not improve cardiac function in patients with hypoplastic left heart syndrome.
Bobylev, D., et al. (2022) ⁹	121 patients (analysis at 5 years of the ESPOIR trial)	Mid-term performance analysis of decellularized pulmonary homografts (DPH) for pulmonary valve replacement.	Incidence of myocarditis: 0.15% per patient-year. Lower structural degeneration. Excellent DPH performance and low rates of adverse events.
Eildermann, K., et al. (2024) ¹⁰	21 explanted patches (7 bovine, 7 equine, 7 autologous human tissue-engineered patches)	Histological study. Comparison of patch types according to origin (bovine, equine, or autologous human).	Superior biocompatibility of autologous human patches compared with bovine and equine patches.
Fukuda, S., et al. (2023) ¹¹	5 patients with limb ischemia	Clinical trial of autologous mesenchymal stromal cells cultured from bone marrow + platelet-rich plasma.	Improvement in clinical severity. Significant increase in 6-minute walking distance, dorsal foot perfusion pressure, transcutaneous partial pressure of oxygen at the ankle, and ankle-brachial index.

OPHTHALMOLOGY

Table 2 summarizes the main findings regarding the applications of regenerative medicine in ophthalmic surgery.

Study	Sample	Methodology	Results
Tandon, R., et al. (2024) ¹²	50 patients (25 in the COMET group, 25 in the autologous conjunctival cell group)	Comparative clinical trial of cell transplantation (cultivated oral mucosal epithelial transplantation [COMET] vs. autologous conjunctival cells cultured on human amniotic membrane using ex vivo tissue engineering).	Both cell types were effective in restoring ocular surface integrity. COMET treatment was shown to be safe and effective, with improvement in corrected visual acuity, increased corneal transparency, reduced vascularization, and prevention of recurrent symblepharon.
Soma, T., et al. (2024) ¹³	4 patients with limbal stem cell deficiency	Case study involving transplantation of corneal epithelial cell sheets derived from human induced pluripotent stem cells (iPSCs).	Improvement of the condition was observed in all patients. Visual acuity increased and corneal opacity decreased in all treated eyes. This was the first reported use of iPSCs for this indication.

Table 2. Regenerative Medicine in Ophthalmic Surgery.

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TRAUMA AND ORTHOPEDIC SURGERY

Table 3 summarizes the findings regarding the applications of regenerative medicine in trauma and orthopedic surgery.

Study	Sample	Methodology	Results
Widodo, W., et al. (2026)¹⁴	15 patients with total brachial plexus injury (group distribution not specified)	Randomized clinical trial involving intercostal-to-median nerve transfer combined with local injection of umbilical cord-derived mesenchymal stem cells vs. secretome.	Implantation of umbilical cord-derived mesenchymal stem cells or secretome combined with nerve transfer may provide clinical improvement. However, additional conditioning is required to achieve histological improvement.
Park, E-K., et al. (2024)¹⁵	7 patients (9 hips) with osteonecrosis of the femoral head (ONFH)	Study of osteoblasts expanded ex vivo from bone marrow-derived mesenchymal stem cells combined with calcium metaphosphate scaffolds (tissue engineering).	The size of the necrotic lesion decreased in 4 hips. No significant changes were observed in VAS, JIC classification, or HHS between the preoperative assessment and the final follow-up. The therapy showed promising results for precollapse and early-collapse ONFH with medium-to-large lesions in weight-bearing areas.
Chiaverni, D., et al. (2024)¹⁶	20 patients (10 with iliac crest autograft, 10 with tissue-engineered product)	Cohort study comparing standard iliac crest autograft treatment vs. a tissue-engineered product containing mesenchymal stem cells.	No significant differences were observed between the experimental and standard treatments. The tissue-engineered product represents a viable alternative when autograft is unavailable or contraindicated. No adverse events were reported.
Noorpi, NHB.M., et al. (2025)¹⁷	7 patients with diabetic ulcers and traumatic injuries	Experimental study involving the application of autologous PRP skin cells ("skin cell droplets").	A significant reduction in ulcer size was observed at 21, 35, 49, and 77 days of treatment ($p < 0.05$). The "skin cell droplet" method appears to be safe and effective for the treatment of ulcers.

Table 3. Regenerative Medicine in Trauma and Orthopedic Surgery.

GYNECOLOGY AND OBSTETRICS

Table 4 summarizes the findings regarding the applications of regenerative medicine in gynecology and obstetrics.

Study	Sample	Methodology	Results
Farmer, D.L., et al. (2026)¹⁸	6 pregnant women with a diagnosis of fetal myelomeningocele	Study evaluating the topical application of a dose of live allogeneic human mesenchymal stem cells seeded onto an extracellular matrix during intrauterine repair of myelomeningocele.	At birth, the infants had an intact repair site with no evidence of cerebrospinal fluid leakage, infection, or abnormal tissue growth. Magnetic resonance imaging showed reversal of hindbrain herniation and absence of tumor formation. No adverse events were reported.
Wang, H., et al. (2025)¹⁹	195 participants (98 in the collagen scaffold group, 97 in the intrauterine device [IUD] group)	Comparative clinical trial of preventive devices (collagen scaffold vs. intrauterine device [IUD]) following hysteroscopic adhesiolysis for intrauterine adhesions (IUAs).	The adhesion recurrence-free rate was higher in the collagen scaffold group than in the IUD group. The collagen scaffold was superior to the IUD in preventing adhesion recurrence.

Table 4. Regenerative Medicine in Gynecologic and Obstetric Surgery.

VASCULAR SURGERY/ANGIOLOGY

Table 5 summarizes the findings regarding the applications of regenerative medicine in vascular surgery.

Study	Sample	Methodology	Results
Costela-Ruiz, V.J., et al. (2026)²⁰	20 patients (10 in the control group, 10 in the intervention group) with venous leg ulcers (VLUs)	Ongoing clinical trial involving the local application of four doses of bioengineered artificial mesenchymal stem cell sheets (BAMS), administered once weekly, vs. conventional treatment.	Ongoing study. The authors expect BAMS therapy to reduce healing time and complications, improve quality of life through its regenerative and analgesic properties, and reduce healthcare costs.

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Parikh, S., et al. (2025)²¹	19 patients with peripheral vascular trauma in combat settings (2 withdrawals: 1 due to thrombosis and 1 due to ATEV damage from residual fragments)	Observational study evaluating the use of an acellular tissue-engineered vessel (ATEV) for vascular repair.	At 18 months: vessel patency was 87.1%, infection rate was 0%, limb salvage was 100%, and patient survival was 100%. ATEVs were well tolerated, with no cases of immunologic rejection.
Moore, E.E., et al. (2025)²²	76 patients with arterial injuries (without an available autologous vein and with risk factors for infection), from 2 clinical studies	Evaluation of ATEV performance in the repair of arterial injuries.	Results from the 2 studies: primary patency, 84.3% and 93.8%; secondary patency, 90.2% and 93.8%; amputation, 9.8% and 0%; infection, 2% and 0%; and mortality, 5.9% and 0%, respectively.

Table 5. Regenerative Medicine in Vascular Surgery.

PLASTIC SURGERY

Table 6 summarizes the findings regarding the applications of regenerative medicine in the field of plastic surgery.

Study	Sample	Methodology	Results
Kaiser, B., et al. (2024)²³	5 women with nasal septal perforations (NSP) measuring 0.5–2 cm in diameter	Phase I clinical trial evaluating the use of tissue-engineered cartilage from autologous nasal chondrocytes (N-TEC) for NSP repair.	Autologous treatment is feasible and supports the need for further clinical trials. The lesions closed, and the mucosa healed completely in three patients.
Schiestl, C., et al. (2025)²⁴	10 pediatric patients with large skin defects (7 completed the study)	Five-year follow-up study evaluating the use of a cultured autologous dermoepidermal skin substitute.	The skin substitutes were safe, remained stable, and showed no changes. No signs of fragility or tumor formation were observed. Scar quality was similar to that of normal skin.
Velasquillo, C., et al. (2024)²⁵	Sample not specified	Experimental study evaluating the use of a 3D poly-ε-caprolactone (3D-PCL) structure bio-printed with human chondrocytes derived from residual microtia tissue.	The combination of 3D-PCL auricular structures and residual autologous microtia tissue generated an auricular framework suitable for reconstruction.
Lv, Y., et al. (2024)²⁶	16 patients with refractory wounds (8 with PRP + AD, 8 with AD without PRP)	Comparative clinical study of artificial dermis (AD) with vs. without autologous platelet-rich plasma (PRP).	Thirteen patients achieved complete wound healing (7 in the PRP + AD group). The PRP + AD group showed shorter times to epithelialization, better infection control and vascularization, and shorter hospitalization.
Farhat ul Ain Tayyaba, et al. (2022)²⁷	50 patients with partial-thickness skin grafts (30 with PRP, 20 controls)	Experimental study evaluating the application of platelet-rich plasma (PRP) collected by apheresis and applied immediately.	Graft take was achieved in 100% of patients receiving PRP therapy, compared with only 9 patients in the control group.
Fulchignoni, C., et al. (2022)²⁸	27 fingers with fingertip tissue loss (15 treated with Matriderm, 12 with skin grafts)	Comparative study evaluating the use of a dermal substitute (Matriderm) vs. skin grafting.	Similar mean scores were observed in both groups: Vancouver Scar Scale, 2.3; Quick Disabilities of the Arm, Shoulder and Hand score, 13.3; and two-point discrimination, 7.7 mm. Matriderm may be considered a treatment option.

Table 6. Regenerative Medicine in Plastic Surgery.

UROLOGY

Karapanos, L., et al. conducted a study in 2023 to compare the surgical success and morbidity of urethroplasty using a tissue-engineered autologous oral mucosal graft (MukoCell) versus a native oral mucosal graft (NOMG). The study included 153 patients, 77 of whom received the tissue-engineered graft. MukoCell was associated with a lower

success rate; however, it reduced operative time and oral morbidity and improved patients' quality of life²⁹

NEUROSURGERY

Saini, R., et al. published a phase I clinical trial in 2022 evaluating the safety and feasibility of intramedullary injection of bone marrow-derived mesenchymal stem cells (BM-MSCs) in patients with acute complete spinal cord

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injury. The study included 13 patients, of whom 7 were assigned to the stem cell group and 6 to the control (placebo) group. Five patients in the control group died, compared with three patients in the stem cell group. The authors concluded that intramedullary injection of bone marrow-derived mesenchymal stem cells is safe and feasible³⁰

DISCUSSION

The use of regenerative medicine in surgery represents a major advancement, as demonstrated by the growing body of clinical trials and studies presented in this review. Mesenchymal stem cells (MSCs) have demonstrated a favorable safety profile as well as immunomodulatory properties (6, 18, 30). In the cardiovascular field, PeriCord implantation demonstrated modulation of monocytes toward non-classical macrophages involved in the resolution of inflammation, together with a reduction in chemoattractants and an increase in meteorin-like protein as a prognostic marker (6). These findings suggest that its therapeutic effect may involve an immunomodulatory mechanism that could promote myocardial repair.

Decellularized homografts represent a promising alternative in cardiovascular surgery. Decellularized aortic homografts (DAHs) used for aortic valve replacement have shown excellent 5-year outcomes, with a 97.5% freedom-from-death rate (7). Similarly, decellularized pulmonary homografts (DPHs) have demonstrated favorable performance, with an incidence of myocarditis of only 0.15% per patient-year (9). These findings suggest that decellularization preserves the structural integrity of the extracellular matrix while removing immunogenic components, thereby reducing rejection and potentially increasing graft durability. This hypothesis is further supported by the study by Eildermann et al. (2024) (10), which demonstrated superior biocompatibility of autologous human patches compared with bovine- and equine-derived patches.

However, not all clinical trials have demonstrated positive outcomes. Gallego-Navarro et al. (2025) (6) failed to demonstrate an improvement in cardiac function in patients with hypoplastic left heart syndrome treated with umbilical cord blood mononuclear cells. This finding could be attributed to the severity of the underlying condition, the administered dose, or the possibility that these cells do not possess the same regenerative potential in a hypoplastic heart. These findings emphasize the need for further clinical trials to determine their potential clinical application.

In ophthalmology, epithelial cell transplantation has demonstrated efficacy in ocular surface reconstruction. Tandon, R., et al. (2024) (12) found that both COMET and autologous conjunctival cells restored ocular surface integrity, with improvements in visual acuity and corneal transparency and a reduction in vascularization. Furthermore, the first reported use of induced pluripotent stem cells (iPSCs) for limbal stem cell deficiency resulted in

improvement in all treated patients (13), positioning iPSCs as a promising therapeutic option for this condition.

In trauma and orthopedic surgery, Widodo, W., et al. (2026) (14) demonstrated that umbilical cord-derived MSCs or secretome combined with nerve transfer provided clinical improvement in patients with brachial plexus injuries, although additional conditioning was required to achieve histological improvement. Park, E-K., et al. (2024) (15) reported promising results in patients with osteonecrosis of the femoral head treated with expanded osteoblasts and calcium metaphosphate scaffolds, with a reduction in lesion size in 4 of 9 hips, although no significant changes were observed in clinical scores.

Chaverri, D., et al. (2024) (16) demonstrated that an MSC-based tissue-engineered product showed no significant differences compared with iliac crest autografting for the treatment of atrophic nonunion, suggesting that it may represent a viable alternative when autologous grafts are unavailable.

In vascular surgery and angiology, acellular tissue-engineered vessels (ATEVs) have demonstrated favorable outcomes in the treatment of peripheral vascular trauma, with primary patency rates of 84.3% and 93.8% (21, 22). It should be considered that these patients lacked an available autologous vein and had risk factors for infection.

Combined therapy with platelet-rich plasma (PRP) has shown promising results in chronic wound healing. Noorpi, NHBM., et al. (2025) (17) observed a reduction in diabetic ulcer size following treatment with autologous “skin cell droplets” combined with PRP. Lv, Y., et al. (2024) (26) reported that adding PRP to artificial dermis shortened healing time and improved infection control and vascularization. Farhat ul Ain Tayyaba, et al. (2022) (27) reported 100% graft take among patients treated with PRP, highlighting the potential role of platelet-derived factors in tissue regeneration.

In plastic surgery, Schiestl, C., et al. (2025) (24) demonstrated that cultured autologous skin substitutes in pediatric patients were safe and stable at 5 years, with no signs of fragility or tumor formation and with scar quality comparable to normal skin. Velasquillo, C., et al. (2024) (25) investigated 3D-PCL auricular structures bioprinted with chondrocytes derived from residual microtia tissue, generating a suitable framework for autologous auricular reconstruction. Kaiser, B., et al. (2024) (23) demonstrated that tissue-engineered cartilage derived from nasal chondrocytes (N-TEC) was useful for nasal septal perforations, achieving complete closure in three of five patients.

In urology, Karapanos, L., et al. (2023) (29) found that MukoCell used in urethroplasty was associated with a lower success rate but provided advantages in terms of reduced oral morbidity and improved quality of life.

The safety of regenerative approaches has been consistently demonstrated across several studies. Farmer, D.L., et al. (2026) (18) reported intrauterine repair of myelomeningocele using live allogeneic MSCs, with intact surgical repair sites

at birth, reversal of hindbrain herniation, and no evidence of tumor formation. Saini, R., et al. (2022) (30) also demonstrated the safety and feasibility of intramedullary MSC injection in patients with spinal cord injury.

LIMITATIONS AND FUTURE RESEARCH

The small sample sizes of several included studies may introduce bias and limit the generalizability of the findings. The absence of control groups in some studies may also increase the risk of systematic error. Furthermore, the long-term stability and durability of regenerated tissues have not been thoroughly investigated. The lack of standardized protocols for PRP and biomaterials also limits the reproducibility and comparability of results across studies. Future research should focus on randomized, multicenter clinical trials with larger sample sizes and longer follow-up periods. The combination of cells, growth factors, scaffolds, and physical stimulation appears to represent one of the most promising approaches for optimizing regenerative outcomes and ultimately improving patients' quality of life.

CONCLUSION

This systematic review of the literature demonstrates that regenerative medicine has successfully evolved from the experimental stage toward established clinical applications in surgery. Mesenchymal stem cells, decellularized homografts, biomaterials, platelet-rich plasma, and bioprinting constitute a broad therapeutic armamentarium with favorable safety profiles and variable efficacy depending on the underlying condition and clinical context.

Multimodal approaches integrating cells, growth factors, and scaffolds have demonstrated superior outcomes compared with monotherapies, particularly in chronic wound healing and bone regeneration. Conversely, therapeutic failures in highly complex conditions highlight the need for appropriate patient selection and standardized treatment protocols.

Personalized combinations of different therapeutic modalities, guided by individual patient characteristics, represent the most promising pathway for transforming these strategies into established treatments capable of achieving significant and sustained improvements in patients' quality of life.

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