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REVIEW ARTICLE

Advances in Peripheral Nerve Regeneration Study Methods: A Systematic Literature Review

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ABSTRACT:

Introduction: Peripheral nerve injuries are a common condition seen in healthcare facilities; it has been discovered that almost one-third of peripheral nerve injury cases show insufficient recovery of nerve function. There are a number of contributory variables that delay the restoration of nerve function, such as insufficient molecular-level support, aging-related factors and regeneration. Considering the complexity of the process and the effects of peripheral nerve injury, this study aims to review the current literature on peripheral nerve regeneration, with a focus on research models, intervention strategies, evaluation parameters, and reported outcomes. **Methods:** Several databases, including PubMed, Google Scholar, Research Gate, and Web of Science, were used for the literature search. This systematic literature review was carried out using PRISMA guidelines as a basis for analysis. The articles were evaluated according to the year, type of injury, animal model, study intervention, and regeneration outcome. **Result:** Five rodent-based studies and human peripheral nerve injury published within the past 15 years. These studies involved either nerve compression or transection models and interventions such as aerobic exercise, electrical stimulation, and stem cell therapy. Regeneration was evaluated through histomorphology, immunohistochemistry, gait analysis, and electrophysiological tests, are characteristics that indicate satisfactory regeneration findings across all studies. **Conclusion:** This review highlights the diversity of experimental models and therapeutic approaches used in peripheral nerve regeneration research, proves essential for accurately determining regeneration outcomes. These findings support the continued development of integrated strategies to enhance and evaluate peripheral nerve repair in future studies.

KEYWORDS: Peripheral nerve injury, nerve regeneration, outcome of regeneration.

INTRODUCTION:

Peripheral nerve injuries are a frequently observed condition in health care facilities as a result of the extensive distribution of the peripheral nervous system throughout the human body^{1,2}. Based on World Health Organization (WHO) in 2010, there has been a consistent upward trend in disability rates over time. According to available data, an estimated range of 785million (15.6%) to 975 million (19.4%) individuals aged 15 and above encountered disabilities. Among this population, approximately 2-4% had a notable deterioration in their overall quality of life^{1,3}. It has been found that approximately one-third (33%) of cases involving peripheral nerve injury exhibit inadequate recovery of nerve function, due to inadequate molecular-level support from the microenvironment, the rate of axonal regeneration is relatively slow, with a rate of approximately 1mm per day and age-related factors can further exacerbate the issue by causing a decline in both the speed and intensity of regeneration^{4,5,6}.

The processes observed in peripheral nerve injuries encompasses demyelination at the site of injury, axonal destruction, and complete disintegration of neural tissue^{7,8}. During the early phases of injury, the cell membrane of the axon undergoes destruction at the site of injury, resulting in the entry of calcium ions (Ca²⁺) into the cell and triggers a retrograde signaling^{7,9}. Consequently, this cascade leads to the disruption of the cytoskeletal structure within the neuron. Schwann cells undergo substantial alterations via reprogramming, leading to a transformation in phenotype that is favorable for the regeneration mechanism^{9,10}.

The objective of this Systematic Literature Review is to comprehensively synthesize contemporary literature pertaining to the field of peripheral nerve regeneration research. The studies discussed in this context explore various approaches to peripheral nerve injury, the therapies utilized, and the regeneration outcomes reported in each respective study. The primary objective of this comprehensive review is to function as a scholarly resource in the domain of nerve regeneration, while also providing practical guidance for clinical implementations.

METHODS:

Information Sources:

The present study adheres to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria, as outlined by Page MJ et al. (2021), in order to provide a structured framework for reporting the systematic literature review¹¹. The literature search was performed by utilizing various databases, such as PubMed, Google Scholar, ResearchGate, and Web of Science. The objective of the search was to discover pertinent publications that have been published in the English language over the course of the last decade.

Search Strategy:

The search query "peripheral nerve injury" was initially inputted. Following that, further pertinent keywords were merged using Boolean operators (namely OR), then input the additional keyword "regeneration" using AND operator to combine the search results in order to broaden the scope of the search. The search terms and tactics can be provided upon request. All of the reviewed studies were selected based on inclusion and exclusion criteria. Each search procedure was carried out independently by two authors, and the screening and verifying processes were done alternately by both authors. Any disagreements arose pertaining to the selection of articles between them were settled by the discussion that held 2-3 times a weeks, and consensus was achieved through deliberation and mutual accord. The researchers applied the following inclusion criteria will explained in the next section.

Selection Process:

This study focuses on articles that present findings from original experimental research. The focus of this study is on articles that have been published in the English language. Inclusion criteria of these study are: (1) Studies that employed living models, (2) studies that incorporated an intervention within the experimental design, and (3) studies that reported measurable OUTCOMES RELATED TO NERVE REGENERATION. This review omitted articles that did not fit the specified criteria or were not accessible in their entirety. The required information or data will collected from included articles which are the primary characteristics in this study, including Type of injury, Type of animal model, intervention provided in the study and Outcome of regeneration.

Quality Assessment:

The assessment of article quality was conducted using The Cambridge Quality Checklist, a well-established instrument for evaluating the quality of various study designs, particularly for experimental research in order to reach conclusions regarding correlations, risk factors, and causal risk factors¹². The scoring of each item is determined by pre-established quality criteria, wherein scores range from 0 to 5. The articles that received the highest scores were given priority for inclusion in this review.

The redesigned techniques section offers enhanced elaboration and precision pertaining to the search strategy, selection process, and criteria for quality assessment. Enhancing transparency facilitates a more comprehensive comprehension of the applied process in the systematic literature review, hence enabling readers to gain a deeper understanding.

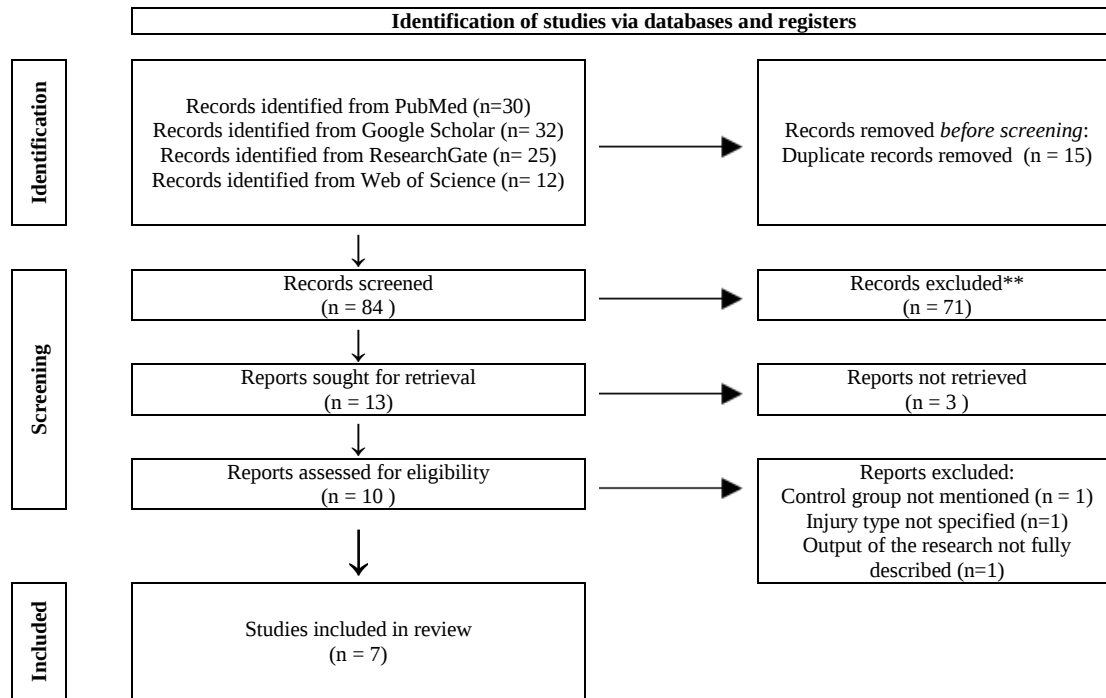


Figure 1. Flow Diagram of the Systematic Literature Review

Table 2. Quality Evaluation of Each Included Studies¹²

Authors	Year of Publication	Adequate Sampling Methode (score 0-1)	Adequate Response Rate (score 0-1)	Adequate Sample Size (score 0-1)	Good Measure of Correlate (score 0-1)	Good Measure of Outcome (score 0-1)
Ria Margiana, et al	2021	1 (random sampling)	1 (Response rate were above 70%)	1 (18 rats were used in this experiment)	1 (2 statistical methode to evaluate correlation, One-way ANOVA and paired t-test)	1 (6 sources of information were used to evaluate the results)
Ria Margiana, Khoirul Ima, Rizni Fitriana, Kamila Alawiyah	2021	1 (random sampling)	1 (Response rate were above 70%)	1 (3 groups of samples)	0 (One-way ANOVA)	1 (4 sources of information were used to evaluate the results)
Jinghui Huang, et al	2013	1 (random sampling)	1 (Response rate were above 70%)	1 (192 rats were used in this experiment)	1 (One-Way ANOVA with Tukey's post hoc test for analyzing pair-wise comparisons)	1 (7 sources of information were used to evaluate the results)
Joseph Roh, et al	2023	1 (random sampling)	1 (Response rate were above 70%)	1 (39 rats were used in this experiment)	1 (Two-Way ANOVA with Tukey's multiple compatisons test within each group)	1 (5 sources of information were used to evaluate the results)
Ria Margiana	2017	1 (random sampling)	1 (Response rate were above 70%)	1 (36 rats were used in this experiment)	1 (2 statistical methode to evaluate correlation, One-way ANOVA and Spearman test for analyzing correlation between each variable)	1 (7 sources of information were used to evaluate the results)
Wahyu Widodo, et al	2024	1 (random sampling)	1 (Response rate were above 70%)	1 (15 patients were used in this study)	1 (2 statistical methode to evaluate correlation, One-way ANOVA and Spearman test for analyzing correlation between each variable)	1 (4 sources of information were used to evaluate the results)
Seung Yeol Lee, et al	2024	1 (random sampling)	1 (Response rate were above 70%)	1 (120 patients were used in this study)	0 (Independent t-test)	1 (6 sources of information were used to evaluate the results)

RESULTS:

Study Selection:

The initial literature search resulted in the identification of 99 articles retrieved from multiple search engines. After the elimination of 15 duplicate articles, the remaining number of articles available for further screening amounted to 84. The screening method involved the evaluation of titles and abstracts, also the inclusion requirements. As a result, a total of ten publications were evaluated to determine their suitability for inclusion in the study. Among the articles considered, one was excluded from the analysis due to the absence of a control group, while one others were eliminated because they did not clearly specify the type of injury under investigation. Additionally, one article was removed from the study due to insufficient detailed descriptions of the regeneration parameters and outcomes resulting from the interventions provided.

Study Characteristics:

Studies published between 2013 and 2024 included both animal and human models of peripheral nerve injury. Preclinical studies used rat models with sciatic or tibial nerve compression or transection, while clinical studies involved patients with chronic brachial plexus injury or burn-related hand nerve injury. Interventions comprised low-intensity aerobic exercise, electrical stimulation, human umbilical cord mesenchymal stem cell-derived conditioned medium, and extracorporeal shock wave therapy. Together, these studies represent a diverse range of experimental and clinical approaches for evaluating peripheral nerve regeneration and functional recovery.

Quality Evaluation of Included Studies:

The results of the quality evaluation of the included studies show almost similar scores (Table 2). All studies received a score of 1 for the assessment of an adequate sampling method due to randomized sampling was employed to pick the subjects for the study samples in each study. The second assessment is adequate response rate, all studies have a value of 1, where the response level of experimental animals after being treated either by compression or transection shows significant changes in disability in the limbs innervated by the injured nerve. All studies provided information on the number of experimental animals that would be comprised the research sample in the sufficient sample size section, and they included an acknowledgment that the research sample had received an appropriate ethical committee's approval. The assessment of correlation measurements in 7 studies showed a value of 1, due to the use of statistical analysis to assess the correlation between variables having more than 1 statistical method, except in two study which used only 1 statistical method in defining the correlation. Hence, all studies show a value of 1 in measuring the outcome of the study, because there are more than 1 parameter measuring the results of peripheral nerve regeneration.

Results of Distinct Studies:

Animal studies demonstrated that physical, electrical, and biological interventions consistently promoted peripheral nerve regeneration. In a sciatic nerve compression model, 3-minute compression followed by low-intensity aerobic exercise increased Schwann cell numbers and myelin sheath thickness, as shown by hematoxylin and eosin staining. These histological improvements were supported by positive S100 and GAP-43 expression on day 42, indicating enhanced Schwann cell activity and axonal regeneration¹³. Following sciatic nerve transection, electrical stimulation (ES) applied to the proximal nerve stump for 20 minutes resulted in significant histomorphological changes. Toluidine blue staining showed increased axon diameter, number of regenerating axons, and myelin thickness at weeks 4, 12, and 24¹⁵. Retrograde labeling demonstrated increased motor and sensory neuron cell bodies, indicating effective axonal sprouting toward distal targets. ES treatment also induced a twofold increase in brain-derived neurotrophic factor (BDNF) expression and increased gastrocnemius muscle wet weight, suggesting reduced denervation-related muscle atrophy^{15,16}. In a tibial nerve transection model, ES applied for 10 or 60 minutes promoted ordered axonal sprouting by day 14. Shorter stimulation duration produced greater GFP-positive axonal extension, indicating more efficient regeneration¹⁶.

Biological intervention using conditioned medium derived from human umbilical cord mesenchymal stem cells (hUC-MSC) also enhanced regeneration. Treated groups showed increased myelin abundance, larger myelin sheath diameter, and higher proportions of S100-positive Schwann cells at days 7 and 70. Reduced CD34 expression at later stages suggested maturation of regenerated nerve tissue¹⁷. Functional recovery in animal models was confirmed by gait analysis and electrophysiological testing. Aerobic exercise improved Sciatic Functional Index (SFI) and Toe-Out Angle (TOA) values following nerve compression^{13,14}. ES significantly increased

compound muscle action potential (CMAP) amplitude and nerve conduction velocity (NCV) at weeks 4, 12, and 24¹⁵. Improvements in Tibial Functional Index (TFI) and Peroneal Functional Index (PFI) further supported enhanced functional recovery¹⁶. hUC-MSC–treated animals showed earlier gait recovery and sustained functional improvement compared with untreated controls¹⁷.

Human clinical studies reinforced the translational relevance of these findings. In patients with chronic total brachial plexus injury, intercostal-to-median nerve neurotization resulted in significant improvement in Flexor Digitorum Superficialis (FDS) muscle strength, DASH score, and SF-36 quality-of-life measures, while histological analysis demonstrated regenerative tissue changes, although functional recovery was more pronounced. In another clinical study involving burn-related hand nerve injuries with hypertrophic scarring, ESWT significantly reduced pain and improved hand function, grip strength, and fine motor dexterity after 12 weeks. Ultrasound imaging revealed reduced scar thickness and improved skin characteristics. These results indicate that ESWT promotes functional recovery through neuromodulation and scar remodeling, even without direct surgical nerve repair.

Collectively, these studies demonstrate that peripheral nerve regeneration is best evaluated using a multimodal outcome approach, integrating histological, molecular, electrophysiological, and functional measures. The alignment of findings across animal and human studies highlights the strong translational value of these regenerative strategies.

Table 3. Summary of all the included studies and key elements used in this systematic literature review

Authors	Year of Publication	Type of Model	Nerve	Type of Injury	Intervention	Outcome of Regeneration
Ria Margiana, et al (13)	2021	Male Sprague-Dawley rats (age 2-3 months old)	Sciatic nerve	The left sciatic nerve was clamped for about 3 minutes with surgical clamp.	Low intensity aerobic exercise (Treadmill for rats)	Schwann cells, perineum and nerve fibers made up of axons and myelin sheets are identified with HE staining. S100 and GAP43 are expressed at levels that are typical in the sciatic nerve are identified with IHC. Analysis of gait function are using Sciatic Functional Index.
Ria Margiana, Khoirul Ima, Rizni Fitriana, Kamila Alawiyah (14)	2021	Male Sprague-Dawley rats (age 2-3 months old)	Sciatic nerve	The left sciatic nerve was pinched for about 4 minutes with Castroviejo needle holder.	Low intensity aerobic exercise (Treadmill for rats)	Gait functional analysis using Tibial Functional Index (TFI), Peroneal Functional Index (PFI), Toe Out Angel (TOA) and Q1-Q4 angles.
Jinghui Huang, et al (15)	2013	Young adult male Sprague-Dawley rats (weight 200 – 220 g)	Sciatic nerve	Transection of the left sciatic nerve, causing the development of a neuroma between the proximal and distal stumps.	Electrical stimulation (ES) on the proximal nerve stump for about 20 minutes	Analysis of compound muscle action potentials (CMAPs), including peak amplitude, latency of onset, and nerve conduction velocity using electrophysiological tools. Measure the total number of myelinated axons, diameter of nerve fibers, and myelin thickness using toluidine blue staining. Identify sprouting axons across nerve injury are using retrograde labeling and identify the muscle fiber with photographs metode and measure the muscle fiber are using the Leica software. BDNF and ChAT expression in the spinal cord were analyzed with IHC.
Joseph Roh, et al (16)	2023	Adult male Lewis and Thy1-GFP male rats (age 7-10 weeks old)	Tibial nerve	Transection of the right tibial nerve, then the epineural repair is performed.	Electrical stimulation (ES) on the tibial nerve 2 mm proximal from the distal stump for about 10 or 60 minutes	Analysis of endogenous GFP axon expression in the injury site are using IHC, calculated the nerve fibers, size of neural tissue and the thickness of myelin sheath with toluidine blue staining. Walking gait analysis to identify the tibial functional index (TFI).

Ria Margiana, et al (17)	2019	Young Sprague-Dawley rats (age 2-3 months old)	Sciatic nerve (0,5 cm proximal to the bifurcation of sciatic nerve to tibial and peroneal nerve)	Transection of the sciatic nerve, followed by nerve repair with end-to-end suture metode.	Day 3 of the conditioned medium cultured from human umbilical cord mesenchymal stem cell were applied around location of the injury after suturing the transected nerve	Analysis of the nerve proliferation are using Hematoxylin-eosin staining for calculate the total number of neuron, analysis myelination process using IHC by identify expression of S100, and assessment of neovascularization are using IHC by identify CD34 for calculate the total number of vessels. Gait functional analysis by measuring SFI, TFI, PFI and Q1-Q4 angles.
Wahyu Widodo, et al (18)	2024	Human clinical peripheral nerve injury	Brachial plexus injury	Chronic/neglected brachial plexus injury (6 to <18 months)	Neurotization (3rd–5th intercostal nerves to median nerve)	This clinical trial assessed peripheral nerve regeneration using a combination of functional clinical outcomes , including muscle strength of the FDS, SF-36 quality-of-life scores, and DASH disability scores and histologic parameters from biopsies evaluating inflammation, regeneration, and fibrosis at the neuromuscular junction. While functional outcomes improved significantly post-operatively, histologic measures did not show significant changes.
Seung Yeol Lee, et al (19)	2024	Human clinical peripheral nerve injury	Superficial radial nerve, branches of median and ulnar nerves	Hand with burn injury	Non-invasive therapeutic modality, extracorporeal shock wave therapy (ESWT)	Outcomes included pain intensity measured by a 10-point visual analog scale, hand function assessed using the Jebsen–Taylor Hand Function Test, grip strength evaluation, fine motor dexterity measured by the Purdue Pegboard Test, ultrasound-based scar thickness assessment, and evaluation of skin characteristics before and immediately after the 12-week intervention.

DISCUSSION:

The result findings reported in the chosen papers offer useful insights into the intricate process of nerve regeneration following various interventions and therapies. The ramifications of these discoveries are significant in terms of comprehending the mechanisms involved in nerve healing and developing viable ways to enhance nerve regeneration in different clinical contexts.

1. Histomorphological evaluations:

The majority of the included studies used histomorphological assessment, specifically by HE and toluidine blue staining, as one of the outcome parameters of nerve regeneration outcomes. As mentioned in each study in this research, the very easy-to-use stains HE and toluidine blue are capable of creating precise images of the peripheral nerve components nerve fibers, Schwann cells, and myelin sheath thickness^{20,21}.

The observed continuous improvement in histomorphological assessments serves as a hopeful indicator of the efficacy of the treatments. The augmentation of Schwann cell population, the enhancement of myelin sheath thickness, and the facilitation of axon regeneration are pivotal elements in the process of nerve regeneration^{22,23}. The observed histological alterations indicate that many interventions, including low-intensity aerobic exercise, ES, and conditioned media derived from mesenchymal stem cells, have the potential to exert a beneficial impact on the structural components of nerve regeneration.

2. Immunohistochemistry (IHC) is a widely used technique in the field of pathology and biomedical research²¹.

The utilization of markers like as S100, GAP43, and BDNF offers significant contributions towards understanding the molecular pathways that underlie the process of neuron regeneration. The proteins S100 and GAP43 have been found to be closely linked to the processes of axon growth and regeneration. Additionally, the heightened optical density of BDNF indicates its potential involvement in facilitating nerve healing. The aforementioned results underscore the intricate characteristics of nerve regeneration, encompassing both structural and molecular constituents^{24,25}.

3. Functional assessments are a method used to evaluate an individual's ability to perform tasks and activities in several domains of life. These assessments aim to assess the function of the related nerves (example: SFI specifically evaluates the functional condition of the sciatic (ischiodic) nerve, whereas the Tibial Functional Index (TFI) assesses tibial nerve function. In addition, functional assessments can measure the angular motion of the foot by evaluating the Toe Out Angle (TOA) and angles Q1–Q4. These parameters serve as indicators of motor recovery following peripheral nerve injury. The TOA is defined as the angle formed between the direction of walking and the long axis of the rat's hind paw during gait analysis. It reflects the degree of external rotation of the paw and is used to assess motor coordination and functional restoration after nerve damage. Meanwhile, angles Q1–Q4 represent four sequential angular positions recorded throughout one gait cycle, corresponding to the phases of initial contact, mid-stance, propulsion, and swing, which collectively describe limb movement and gait pattern. Improvements in these parameters indicate enhanced motor function and gait recovery during nerve regeneration. The enhanced functional outcomes found in the groups who received treatment, as evidenced by the SFI, TFI, PFI, and measures such as TOA and Q1-Q4, hold significant therapeutic importance²⁶. The restoration of motor function and gait pattern is a fundamental objective in individuals who have sustained nerve damage. The observed expedited recuperation of ambulatory capability and toe splay in the experimental cohorts suggests the potential advantages of therapies aimed at reinstating functional capacity.

In the reviewed clinical study, Flexor Digitorum Superficialis (FDS) muscle strength served as an objective marker of successful motor reinnervation following median nerve reconstruction, reflecting effective axonal regeneration, neuromuscular junction reformation, and restoration of voluntary motor control. This measure is particularly relevant in chronic nerve injuries, where prolonged denervation increases the risk of irreversible muscle atrophy. Complementing this, the Disabilities of the Arm, Shoulder, and Hand (DASH) score provided a patient-centered evaluation of upper limb function by capturing the ability to perform daily activities that require strength, coordination, and fine motor control. Improvements in DASH scores therefore reflect functional recovery that extends beyond isolated muscle performance. Together, FDS muscle strength and DASH score offer a robust and clinically meaningful functional assessment framework that links nerve regeneration mechanisms to real-world functional outcomes, thereby enhancing the translational relevance of human peripheral nerve regeneration studies.

4. Electrophysiological assessments:

The electrophysiological results, which involve an increase in compound muscle action potential (CMAP) amplitudes and nerve conduction velocity (NCV), suggest improved nerve conduction and functionality following interventions like ES. The objective assessments presented in this study provide support for the histological and functional changes reported in the groups who received treatment. These findings further justify the potential usefulness of the therapies being investigated^{27,28,29}.

Importance of New Findings:

1. The novel findings at Q1, Q2, Q3, and Q4 are significant for many reasons:

These parameters represent functional outcomes, which are important for patients with nerve injuries. Functional restoration, including the restoration of walking ability and gait patterns, is the primary objective of investigations on nerve regeneration.

Using multiple parameters (Q1, Q2, Q3, and Q4) allows for a more thorough evaluation of functional alterations. It enables researchers to evaluate various aspects of motor function and gait, thereby providing a more comprehensive picture of recovery.

2. Clinical Significance:

These parameter improvements have direct clinical significance. Enhanced walking ability and gait patterns can have a significant impact on the quality of life of patients with nerve injuries, allowing them to regain mobility and independence.

3. Outcome Evaluation:

In this context, measuring the outcome requires evaluating the variables Q1, Q2, Q3, and Q4 as described above. Typically, these measurements are collected via gait analysis, motion capture systems, or manual evaluations by trained evaluators.

LIMITATION AND FUTURE PLANS:

The limitations of the study and proposes potential avenues for future research.

1. The presence of heterogeneity in experimental protocols poses a significant challenge in directly comparing results due to variances in damage models, treatment durations, and evaluation timepoints across different

research. The implementation of standardized experimental techniques would enhance the reliability and validity of comparative analyses.

2. The availability of limited long-term data poses a challenge in comprehending the durability of the observed enhancements and evaluating the probable occurrence of late-stage problems or adverse reactions.
3. Several studies included in the analysis exhibited relatively limited sample sizes, thereby compromising the extent to which their conclusions can be applied to the broader population. Subsequent investigations with higher sample sizes have the potential to augment the statistical robustness of the findings.
4. Despite the fact that the novel findings related to Q1, Q2, Q3, and Q4 are encouraging, it is essential to consider the following limitations:
 - a. Standardization: The provided text does not include the precise definitions and measurement methodologies for Q1, Q2, Q3, and Q4. Future research should strive for standardized measurement protocols in order to facilitate comparisons between diverse research efforts.
 - b. The clinical applicability of these findings should be investigated in greater depth. There is a need for clinical trials and longitudinal studies to determine whether improvements in these parameters translate to meaningful patient benefits.

Incorporate a conclusion and an acknowledgment into this text:

In summary, several studies employ experimental animal models, particularly mice, and majority of studies used nerve injury procedures by encompassing the compression and the transection of the involved nerves. Various therapeutic interventions have been carried out, such as in the studies described in this paper, with the objective of evaluating the effectiveness of treatment on injured nerves. Following these therapeutic interventions, several kinds of measurements are now forth to assess the regeneration outcome, such as histomorphology, IHC, retrograde labelling which combined with functional assessment such as gait analysis and electrophysiology as indicators of successful regeneration.

Low-intensity aerobic exercise, ES, and mesenchymal stem cell-derived conditioned media may improve nerve regeneration. These interventions appear to improve nerve repair structure and function. To overcome restrictions and implement these results therapeutically, more research is needed. Nerve regeneration is complicated, thus interdisciplinary collaboration and creative treatment research are needed to improve nerve damage results. Novel results on Q1, Q2, Q3, and Q4 are critical to nerve injury and regeneration functional recovery. These results demonstrate the potential benefits of the therapies and the importance of full functional assessments in nerve regeneration research. Standardized testing and clinical confirmation are needed to fully understand these findings for nerve injury patients.

CONFLICT OF INTEREST:

There are no conflicts of interest in this study since there is no evidence that the researcher has any financial or personal interests that would influence their research or publishing.

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REVIEW ARTICLE

Advances in Peripheral Nerve Regeneration Study Methods: A Systematic Literature Review

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ABSTRACT:

Introduction: Peripheral nerve injuries are a common condition seen in healthcare facilities; it has been discovered that almost one-third of peripheral nerve injury cases show insufficient recovery of nerve function. There are a number of contributory variables that delay the restoration of nerve function, such as insufficient molecular-level support, aging-related factors and regeneration. Considering the complexity of the process and the effects of peripheral nerve injury, this study aims to review the current literature on peripheral nerve regeneration, with a focus on research models, intervention strategies, evaluation parameters, and reported outcomes. **Methods:** Several databases, including PubMed, Google Scholar, Research Gate, and Web of Science, were used for the literature search. This systematic literature review was carried out using PRISMA guidelines as a basis for analysis. The articles were evaluated according to the year, type of injury, animal model, study intervention, and regeneration outcome. **Result:** Five rodent-based studies and human peripheral nerve injury published within the past 15 years. These studies involved either nerve compression or transection models and interventions such as aerobic exercise, electrical stimulation, and stem cell therapy. Regeneration was evaluated through histomorphology, immunohistochemistry, gait analysis, and electrophysiological tests, are characteristics that indicate satisfactory regeneration findings across all studies. **Conclusion:** This review highlights the diversity of experimental models and therapeutic approaches used in peripheral nerve regeneration research, proves essential for accurately determining regeneration outcomes. These findings support the continued development of integrated strategies to enhance and evaluate peripheral nerve repair in future studies.

KEYWORDS: Peripheral nerve injury, nerve regeneration, outcome of regeneration.

INTRODUCTION:

Peripheral nerve injuries are a frequently observed condition in health care facilities as a result of the extensive distribution of the peripheral nervous system throughout the human body^{1,2}. Based on World Health Organization (WHO) in 2010, there has been a consistent upward trend in disability rates over time. According to available data, an estimated range of 785million (15.6%) to 975 million (19.4%) individuals aged 15 and above encountered disabilities. Among this population, approximately 2-4% had a notable deterioration in their overall quality of life^{1,3}. It has been found that approximately one-third (33%) of cases involving peripheral nerve injury exhibit inadequate recovery of nerve function, due to inadequate molecular-level support from the microenvironment, the rate of axonal regeneration is relatively slow, with a rate of approximately 1mm per day and age-related factors can further exacerbate the issue by causing a decline in both the speed and intensity of regeneration^{4,5,6}.

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The processes observed in peripheral nerve injuries encompasses demyelination at the site of injury, axonal destruction, and complete disintegration of neural tissue^{7,8}. During the early phases of injury, the cell membrane of the axon undergoes destruction at the site of injury, resulting in the entry of calcium ions (Ca²⁺) into the cell and triggers a retrograde signaling^{7,9}. Consequently, this cascade leads to the disruption of the cytoskeletal structure within the neuron. Schwann cells undergo substantial alterations via reprogramming, leading to a transformation in phenotype that is favorable for the regeneration mechanism^{9,10}.

The objective of this Systematic Literature Review is to comprehensively synthesize contemporary literature pertaining to the field of peripheral nerve regeneration research. The studies discussed in this context explore various approaches to peripheral nerve injury, the therapies utilized, and the regeneration outcomes reported in each respective study. The primary objective of this comprehensive review is to function as a scholarly resource in the domain of nerve regeneration, while also providing practical guidance for clinical implementations.

METHODS:

Information Sources:

The present study adheres to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria, as outlined by Page MJ et al. (2021), in order to provide a structured framework for reporting the systematic literature review¹¹. The literature search was performed by utilizing various databases, such as PubMed, Google Scholar, ResearchGate, and Web of Science. The objective of the search was to discover pertinent publications that have been published in the English language over the course of the last decade.

Search Strategy:

The search query "peripheral nerve injury" was initially inputted. Following that, further pertinent keywords were merged using Boolean operators (namely OR), then input the additional keyword "regeneration" using AND operator to combine the search results in order to broaden the scope of the search. The search terms and tactics can be provided upon request. All of the reviewed studies were selected based on inclusion and exclusion criteria. Each search procedure was carried out independently by two authors, and the screening and verifying processes were done alternately by both authors. Any disagreements arose pertaining to the selection of articles between them were settled by the discussion that held 2-3 times a weeks, and consensus was achieved through deliberation and mutual accord. The researchers applied the following inclusion criteria will explained in the next section.

Selection Process:

This study focuses on articles that present findings from original experimental research. The focus of this study is on articles that have been published in the English language. Inclusion criteria of these study are: (1) Studies that employed living models, (2) studies that incorporated an intervention within the experimental design, and (3) studies that reported measurable OUTCOMES RELATED TO NERVE REGENERATION. This review omitted articles that did not fit the specified criteria or were not accessible in their entirety. The required information or data will collected from included articles which are the primary characteristics in this study, including Type of injury, Type of animal model, intervention provided in the study and Outcome of regeneration.

Quality Assessment:

The assessment of article quality was conducted using The Cambridge Quality Checklist, a well-established instrument for evaluating the quality of various study designs, particularly for experimental research in order to reach conclusions regarding correlations, risk factors, and causal risk factors¹². The scoring of each item is determined by pre-established quality criteria, wherein scores range from 0 to 5. The articles that received the highest scores were given priority for inclusion in this review.

The redesigned techniques section offers enhanced elaboration and precision pertaining to the search strategy, selection process, and criteria for quality assessment. Enhancing transparency facilitates a more comprehensive comprehension of the applied process in the systematic literature review, hence enabling readers to gain a deeper understanding.

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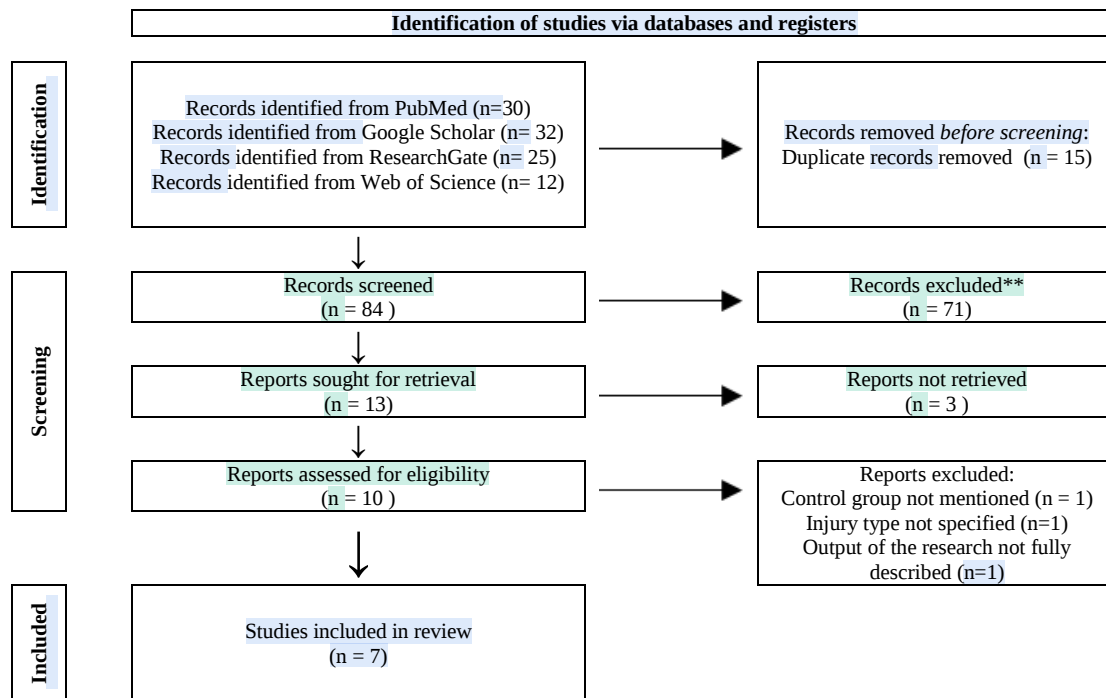


Figure 1. Flow Diagram of the Systematic Literature Review

Table 2. Quality Evaluation of Each Included Studies¹²

Authors	Year of Publication	Adequate Sampling Methode (score 0-1)	Adequate Response Rate (score 0-1)	Adequate Sample Size (score 0-1)	Good Measure of Correlate (score 0-1)	Good Measure of Outcome (score 0-1)
Ria Margiana, et al	2021	1 (random sampling)	1 (Response rate were above 70%)	1 (18 rats were used in this experiment)	1 (2 statistical methode to evaluate correlation, One-way ANOVA and paired t-test)	1 (6 sources of information were used to evaluate the results)
Ria Margiana, Khoirul Ima, Rizni Fitriana, Kamila Alawiyah	2021	1 (random sampling)	1 (Response rate were above 70%)	1 (3 groups of samples)	0 (One-way ANOVA)	1 (4 sources of information were used to evaluate the results)
Jinghui Huang, et al	2013	1 (random sampling)	1 (Response rate were above 70%)	1 (192 rats were used in this experiment)	1 (One-Way ANOVA with Tukey's post hoc test for analyzing pair-wise comparisons)	1 (7 sources of information were used to evaluate the results)
Joseph Roh, et al	2023	1 (random sampling)	1 (Response rate were above 70%)	1 (39 rats were used in this experiment)	1 (Two-Way ANOVA with Tukey's multiple compatisons test within each group)	1 (5 sources of information were used to evaluate the results)
Ria Margiana	2017	1 (random sampling)	1 (Response rate were above 70%)	1 (36 rats were used in this experiment)	1 (2 statistical methode to evaluate correlation, One-way ANOVA and Spearman test for analyzing correlation between each variable)	1 (7 sources of information were used to evaluate the results)
Wahyu Widodo, et al	2024	1 (random sampling)	1 (Response rate were above 70%)	1 (15 patients were used in this study)	1 (2 statistical methode to evaluate correlation, One-way ANOVA and Spearman test for analyzing correlation between each variable)	1 (4 sources of information were used to evaluate the results)
Seung Yeol Lee, et al	2024	1 (random sampling)	1 (Response rate were above 70%)	1 (120 patients were used in this study)	0 (Independent t-test)	1 (6 sources of information were used to evaluate the results)

RESULTS:

Study Selection:

The initial literature search resulted in the identification of 99 articles retrieved from multiple search engines. After the elimination of 15 duplicate articles, the remaining number of articles available for further screening amounted to 84. The screening method involved the evaluation of titles and abstracts, also the inclusion requirements. As a result, a total of ten publications were evaluated to determine their suitability for inclusion in the study. Among the articles considered, one was excluded from the analysis due to the absence of a control group, while one others were eliminated because they did not clearly specify the type of injury under investigation. Additionally, one article was removed from the study due to insufficient detailed descriptions of the regeneration parameters and outcomes resulting from the interventions provided.

Study Characteristics:

Studies published between 2013 and 2024 included both animal and human models of peripheral nerve injury. Preclinical studies used rat models with sciatic or tibial nerve compression or transection, while clinical studies involved patients with chronic brachial plexus injury or burn-related hand nerve injury. Interventions comprised low-intensity aerobic exercise, electrical stimulation, human umbilical cord mesenchymal stem cell-derived conditioned medium, and extracorporeal shock wave therapy. Together, these studies represent a diverse range of experimental and clinical approaches for evaluating peripheral nerve regeneration and functional recovery.

Quality Evaluation of Included Studies:

The results of the quality evaluation of the included studies show almost similar scores (Table 2). All studies received a score of 1 for the assessment of an adequate sampling method due to randomized sampling was employed to pick the subjects for the study samples in each study. The second assessment is adequate response rate, all studies have a value of 1, where the response level of experimental animals after being treated either by compression or transection shows significant changes in disability in the limbs innervated by the injured nerve. All studies provided information on the number of experimental animals that would be comprised the research sample in the sufficient sample size section, and they included an acknowledgment that the research sample had received an appropriate ethical committee's approval. The assessment of correlation measurements in 7 studies showed a value of 1, due to the use of statistical analysis to assess the correlation between variables having more than 1 statistical method, except in two study which used only 1 statistical method in defining the correlation. Hence, all studies show a value of 1 in measuring the outcome of the study, because there are more than 1 parameter measuring the results of peripheral nerve regeneration.

Results of Distinct Studies:

Animal studies demonstrated that physical, electrical, and biological interventions consistently promoted peripheral nerve regeneration. In a sciatic nerve compression model, 3-minute compression followed by low-intensity aerobic exercise increased Schwann cell numbers and myelin sheath thickness, as shown by hematoxylin and eosin staining. These histological improvements were supported by positive S100 and GAP-43 expression on day 42, indicating enhanced Schwann cell activity and axonal regeneration¹³. Following sciatic nerve transection, electrical stimulation (ES) applied to the proximal nerve stump for 20 minutes resulted in significant histomorphological changes. Toluidine blue staining showed increased axon diameter, number of regenerating axons, and myelin thickness at weeks 4, 12, and 24¹⁵. Retrograde labeling demonstrated increased motor and sensory neuron cell bodies, indicating effective axonal sprouting toward distal targets. ES treatment also induced a twofold increase in brain-derived neurotrophic factor (BDNF) expression and increased gastrocnemius muscle wet weight, suggesting reduced denervation-related muscle atrophy^{15,16}. In a tibial nerve transection model, ES applied for 10 or 60 minutes promoted ordered axonal sprouting by day 14. Shorter stimulation duration produced greater GFP-positive axonal extension, indicating more efficient regeneration¹⁶.

Biological intervention using conditioned medium derived from human umbilical cord mesenchymal stem cells (hUC-MSC) also enhanced regeneration. Treated groups showed increased myelin abundance, larger myelin sheath diameter, and higher proportions of S100-positive Schwann cells at days 7 and 70. Reduced CD34 expression at later stages suggested maturation of regenerated nerve tissue¹⁷. Functional recovery in animal models was confirmed by gait analysis and electrophysiological testing. Aerobic exercise improved Sciatic Functional Index (SFI) and Toe-Out Angle (TOA) values following nerve compression^{13,14}. ES significantly increased

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compound muscle action potential (CMAP) amplitude and nerve conduction velocity (NCV) at weeks 4, 12, and 24¹⁵. Improvements in Tibial Functional Index (TFI) and Peroneal Functional Index (PFI) further supported enhanced functional recovery¹⁶. hUC-MSC-treated animals showed earlier gait recovery and sustained functional improvement compared with untreated controls¹⁷.

Human clinical studies reinforced the translational relevance of these findings. In patients with chronic total brachial plexus injury, intercostal-to-median nerve neurotization resulted in significant improvement in Flexor Digitorum Superficialis (FDS) muscle strength, DASH score, and SF-36 quality-of-life measures, while histological analysis demonstrated regenerative tissue changes, although functional recovery was more pronounced. In another clinical study involving burn-related hand nerve injuries with hypertrophic scarring, ESWT significantly reduced pain and improved hand function, grip strength, and fine motor dexterity after 12 weeks. Ultrasound imaging revealed reduced scar thickness and improved skin characteristics. These results indicate that ESWT promotes functional recovery through neuromodulation and scar remodeling, even without direct surgical nerve repair.

Collectively, these studies demonstrate that peripheral nerve regeneration is best evaluated using a multimodal outcome approach, integrating histological, molecular, electrophysiological, and functional measures. The alignment of findings across animal and human studies highlights the strong translational value of these regenerative strategies.

Table 3. Summary of all the included studies and key elements used in this systematic literature review

Authors	Year of Publication	Type of Model	Nerve	Type of Injury	Intervention	Outcome of Regeneration
Ria Margiana, et al (13)	2021	Male Sprague-Dawley rats (age 2-3 months old)	Sciatic nerve	The left sciatic nerve was clamped for about 3 minutes with surgical clamp.	Low intensity aerobic exercise (Treadmill for rats)	Schwann cells, perineum and nerve fibers made up of axons and myelin sheets are identified with HE staining. S100 and GAP43 are expressed at levels that are typical in the sciatic nerve are identified with IHC. Analysis of gait function are using Sciatic Functional Index.
Ria Margiana, Khoirul Ima, Rizni Fitriana, Kamila Alawiyah (14)	2021	Male Sprague-Dawley rats (age 2-3 months old)	Sciatic nerve	The left sciatic nerve was pinched for about 4 minutes with Castroviejo needle holder.	Low intensity aerobic exercise (Treadmill for rats)	Gait functional analysis using Tibial Functional Index (TFI), Peroneal Functional Index (PFI), Toe Out Angel (TOA) and Q1-Q4 angles.
Jinghui Huang, et al (15)	2013	Young adult male Sprague-Dawley rats (weight 200 – 220 g)	Sciatic nerve	Transection of the left sciatic nerve, causing the development of a neuroma between the proximal and distal stumps.	Electrical stimulation (ES) on the proximal nerve stump for about 20 minutes	Analysis of compound muscle action potentials (CMAPs), including peak amplitude, latency of onset, and nerve conduction velocity using electrophysiological tools. Measure the total number of myelinated axons, diameter of nerve fibers, and myelin thickness using toluidine blue staining. Identify sprouting axons across nerve injury are using retrograde labeling and identify the muscle fiber with photographs metode and measure the muscle fiber are using the Leica software. BDNF and ChAT expression in the spinal cord were analyzed with IHC.
Joseph Roh, et al (16)	2023	Adult male Lewis and Thy1-GFP male rats (age 7-10 weeks old)	Tibial nerve	Transection of the right tibial nerve, then the epineural repair is performed.	Electrical stimulation (ES) on the tibial nerve 2 mm proximal from the distal stump for about 10 or 60 minutes	Analysis of endogenous GFP axon expression in the injury site are using IHC, calculated the nerve fibers, size of neural tissue and the thickness of myelin sheath with toluidine blue staining. Walking gait analysis to identify the tibial functional index (TFI).

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Ria Margiana, et al (17)	2019	Young Sprague-Dawley rats (age 2-3 months old)	Sciatic nerve (0,5 cm proximal to the bifurcation of sciatic nerve to tibial and peroneal nerve)	Transection of the sciatic nerve, followed by nerve repair with end-to-end suture metode.	Day 3 of the conditioned medium cultured from human umbilical cord mesenchymal stem cell were applied around location of the injury after suturing the transected nerve	Analysis of the nerve proliferation are using Hematoxylin-eosin staining for calculate the total number of neuron, analysis myelination process using IHC by identify expression of S100, and assessment of neovascularization are using IHC by identify CD34 for calculate the total number of vessels. Gait functional analysis by measuring SFI, TFI, PFI and Q1-Q4 angles.
Wahyu Widodo, et al (18)	2024	Human clinical peripheral nerve injury	Brachial plexus injury	Chronic/neglected brachial plexus injury (6 to <18 months)	Neurotization (3rd-5th intercostal nerves to median nerve)	This clinical trial assessed peripheral nerve regeneration using a combination of functional clinical outcomes , including muscle strength of the FDS, SF-36 quality-of-life scores, and DASH disability scores and histologic parameters from biopsies evaluating inflammation, regeneration, and fibrosis at the neuromuscular junction. While functional outcomes improved significantly post-operatively, histologic measures did not show significant changes.
Seung Yeol Lee, et al (19)	2024	Human clinical peripheral nerve injury	Superficial radial nerve, branches of median and ulnar nerves	Hand with burn injury	Non-invasive therapeutic modality, extracorporeal shock wave therapy (ESWT)	Outcomes included pain intensity measured by a 10-point visual analog scale, hand function assessed using the Jebsen-Taylor Hand Function Test, grip strength evaluation, fine motor dexterity measured by the Purdue Pegboard Test, ultrasound-based scar thickness assessment, and evaluation of skin characteristics before and immediately after the 12-week intervention.

DISCUSSION:

The result findings reported in the chosen papers offer useful insights into the intricate process of nerve regeneration following various interventions and therapies. The ramifications of these discoveries are significant in terms of comprehending the mechanisms involved in nerve healing and developing viable ways to enhance nerve regeneration in different clinical contexts.

1. Histomorphological evaluations:

The majority of the included studies used histomorphological assessment, specifically by HE and toluidine blue staining, as one of the outcome parameters of nerve regeneration outcomes. As mentioned in each study in this research, the very easy-to-use stains HE and toluidine blue are capable of creating precise images of the peripheral nerve components nerve fibers, Schwann cells, and myelin sheath thickness^{20,21}.

The observed continuous improvement in histomorphological assessments serves as a hopeful indicator of the efficacy of the treatments. The augmentation of Schwann cell population, the enhancement of myelin sheath thickness, and the facilitation of axon regeneration are pivotal elements in the process of nerve regeneration^{22,23}. The observed histological alterations indicate that many interventions, including low-intensity aerobic exercise, ES, and conditioned media derived from mesenchymal stem cells, have the potential to exert a beneficial impact on the structural components of nerve regeneration.

2. Immunohistochemistry (IHC) is a widely used technique in the field of pathology and biomedical research²¹.

The utilization of markers like as S100, GAP43, and BDNF offers significant contributions towards understanding the molecular pathways that underlie the process of neuron regeneration. The proteins S100 and GAP43 have been found to be closely linked to the processes of axon growth and regeneration. Additionally, the heightened optical density of BDNF indicates its potential involvement in facilitating nerve healing. The aforementioned results underscore the intricate characteristics of nerve regeneration, encompassing both structural and molecular constituents^{24,25}.

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3. Functional assessments are a method used to evaluate an individual's ability to perform tasks and activities in several domains of life. These assessments aim to assess the function of the related nerves (example: SFI specifically evaluates the functional condition of the sciatic (ischadicus) nerve, whereas the Tibial Functional Index (TFI) assesses tibial nerve function. In addition, functional assessments can measure the angular motion of the foot by evaluating the Toe Out Angle (TOA) and angles Q1–Q4. These parameters serve as indicators of motor recovery following peripheral nerve injury. The TOA is defined as the angle formed between the direction of walking and the long axis of the rat's hind paw during gait analysis. It reflects the degree of external rotation of the paw and is used to assess motor coordination and functional restoration after nerve damage. Meanwhile, angles Q1–Q4 represent four sequential angular positions recorded throughout one gait cycle, corresponding to the phases of initial contact, mid-stance, propulsion, and swing, which collectively describe limb movement and gait pattern. Improvements in these parameters indicate enhanced motor function and gait recovery during nerve regeneration. The enhanced functional outcomes found in the groups who received treatment, as evidenced by the SFI, TFI, PFI, and measures such as TOA and Q1-Q4, hold significant therapeutic importance²⁶. The restoration of motor function and gait pattern is a fundamental objective in individuals who have sustained nerve damage. The observed expedited recuperation of ambulatory capability and toe splay in the experimental cohorts suggests the potential advantages of therapies aimed at reinstating functional capacity.

In the reviewed clinical study, Flexor Digitorum Superficialis (FDS) muscle strength served as an objective marker of successful motor reinnervation following median nerve reconstruction, reflecting effective axonal regeneration, neuromuscular junction reformation, and restoration of voluntary motor control. This measure is particularly relevant in chronic nerve injuries, where prolonged denervation increases the risk of irreversible muscle atrophy. Complementing this, the Disabilities of the Arm, Shoulder, and Hand (DASH) score provided a patient-centered evaluation of upper limb function by capturing the ability to perform daily activities that require strength, coordination, and fine motor control. Improvements in DASH scores therefore reflect functional recovery that extends beyond isolated muscle performance. Together, FDS muscle strength and DASH score offer a robust and clinically meaningful functional assessment framework that links nerve regeneration mechanisms to real-world functional outcomes, thereby enhancing the translational relevance of human peripheral nerve regeneration studies.

4. Electrophysiological assessments:

The electrophysiological results, which involve an increase in compound muscle action potential (CMAP) amplitudes and nerve conduction velocity (NCV), suggest improved nerve conduction and functionality following interventions like ES. The objective assessments presented in this study provide support for the histological and functional changes reported in the groups who received treatment. These findings further justify the potential usefulness of the therapies being investigated^{27,28,29}.

Importance of New Findings:

1. The novel findings at Q1, Q2, Q3, and Q4 are significant for many reasons:

These parameters represent functional outcomes, which are important for patients with nerve injuries. Functional restoration, including the restoration of walking ability and gait patterns, is the primary objective of investigations on nerve regeneration.

Using multiple parameters (Q1, Q2, Q3, and Q4) allows for a more thorough evaluation of functional alterations. It enables researchers to evaluate various aspects of motor function and gait, thereby providing a more comprehensive picture of recovery.

2. Clinical Significance:

These parameter improvements have direct clinical significance. Enhanced walking ability and gait patterns can have a significant impact on the quality of life of patients with nerve injuries, allowing them to regain mobility and independence.

3. Outcome Evaluation:

In this context, measuring the outcome requires evaluating the variables Q1, Q2, Q3, and Q4 as described above. Typically, these measurements are collected via gait analysis, motion capture systems, or manual evaluations by trained evaluators.

LIMITATION AND FUTURE PLANS:

The limitations of the study and proposes potential avenues for future research.

1. The presence of heterogeneity in experimental protocols poses a significant challenge in directly comparing results due to variances in damage models, treatment durations, and evaluation timepoints across different

research. The implementation of standardized experimental techniques would enhance the reliability and validity of comparative analyses.

2. The availability of limited long-term data poses a challenge in comprehending the durability of the observed enhancements and evaluating the probable occurrence of late-stage problems or adverse reactions.
3. Several studies included in the analysis exhibited relatively limited sample sizes, thereby compromising the extent to which their conclusions can be applied to the broader population. Subsequent investigations with higher sample sizes have the potential to augment the statistical robustness of the findings.
4. Despite the fact that the novel findings related to Q1, Q2, Q3, and Q4 are encouraging, it is essential to consider the following limitations:
 - a. Standardization: The provided text does not include the precise definitions and measurement methodologies for Q1, Q2, Q3, and Q4. Future research should strive for standardized measurement protocols in order to facilitate comparisons between diverse research efforts.
 - b. The clinical applicability of these findings should be investigated in greater depth. There is a need for clinical trials and longitudinal studies to determine whether improvements in these parameters translate to meaningful patient benefits.

Incorporate a conclusion and an acknowledgment into this text:

In summary, several studies employ experimental animal models, particularly mice, and majority of studies used nerve injury procedures by encompassing the compression and the transection of the involved nerves. Various therapeutic interventions have been carried out, such as in the studies described in this paper, with the objective of evaluating the effectiveness of treatment on injured nerves. Following these therapeutic interventions, several kinds of measurements are now forth to assess the regeneration outcome, such as histomorphology, IHC, retrograde labelling which combined with functional assessment such as gait analysis and electrophysiology as indicators of successful regeneration.

Low-intensity aerobic exercise, ES, and mesenchymal stem cell-derived conditioned media may improve nerve regeneration. These interventions appear to improve nerve repair structure and function. To overcome restrictions and implement these results therapeutically, more research is needed. Nerve regeneration is complicated, thus interdisciplinary collaboration and creative treatment research are needed to improve nerve damage results. Novel results on Q1, Q2, Q3, and Q4 are critical to nerve injury and regeneration functional recovery. These results demonstrate the potential benefits of the therapies and the importance of full functional assessments in nerve regeneration research. Standardized testing and clinical confirmation are needed to fully understand these findings for nerve injury patients.

CONFLICT OF INTEREST:

There are no conflicts of interest in this study since there is no evidence that the researcher has any financial or personal interests that would influence their research or publishing.

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