JOURNAL OF INNOVATIONS IN MEDICAL RESEARCH

ISSN 2788-7022 JUN. 2026 VOL. 5, NO. 2

CONTENTS

Paradigm Academic Press
Journal of Innovations in Medical Research
ISSN 2788-7022
JUN. 2026 VOL.5, NO.2

From Remission and Regression of Diseases to Controlled Normal Life Activity

Evgeniy Bryndin[1]

[1] Interdisciplinary Researcher of the International Academy of Education, Technological Platform Medicine of the Future, Novosibirsk, Russia

Correspondence: Evgeniy Bryndin, Interdisciplinary Researcher of the International Academy of Education, Technological Platform Medicine of the Future, Novosibirsk, Russia.

doi:10.63593/JIMR.2788-7022.2026.06.001

Abstract

Remission and regression are concepts related to disease dynamics, particularly in oncology, but also used in other areas of medicine. They describe the reduction or disappearance of symptoms and signs of a disease, which can lead to the restoration of normal life. However, it is important to understand that remission does not always mean a complete cure, while regression indicates a stable improvement in a patient's condition. Upon achieving remission or regression, a patient can gradually return to their normal life, engage in professional activities, interact with different people, and maintain physical activity. Remission and regression are important stages in disease treatment. Modern technologies for disease remission and regression are actively developing in several areas, including cancer, autoimmune, and rheumatic diseases. These include both established methods and innovative approaches based on advances in genetic engineering, immunotherapy, and other technologies. Research into disease remission and regression is an active area of research aimed at improving patient outcomes and developing more effective therapeutic strategies. Research into disease remission and regression spans various fields of medicine, including oncology and endocrinology. Studies show that early and long-term remission improves functional outcomes. Efforts to standardize remission and regression across various fields of medicine are ongoing to improve diagnosis, functional status, and comparison of research results.

Keywords: remission and regression of diseases, rehabilitation, controlled normal life activity

1. Introduction

Disease remission ensures a state of stability:

* Disease remission is often the result of treatment: medication, psychotherapy, and lifestyle changes.

* During remission, it is important to continue to be monitored by a doctor and follow their recommendations to ensure that discontinuing therapy does not lead to a relapse.

* The duration of remission varies from person to person and depends on the type of disease, its stage, the treatment received, the individual's individual characteristics, and other factors.

During remission, a person can:

* Return to work and other activities that brought them joy before the illness;

* Restore or improve relationships with loved ones;

* Reduce medication doses (sometimes completely discontinue them under a doctor's supervision);

* Feel in control of their life.

With many chronic diseases (mental, somatic, oncological), remission allows a person to lead a full life: study,

work, build relationships, and pursue hobbies. However, it is important to understand that this does not guarantee a full recovery, and continued medical monitoring is necessary.

Disease regression can be either a natural or induced process, which in some cases allows for a return to normal life. However, this is not a universal phenomenon, and its success depends on the type of disease, the timeliness of treatment, and rehabilitation. In cases where regression is associated with psychological mechanisms, additional support may be required to adapt to life after illness.

Returning to normal life after illness often requires rehabilitation — a set of measures aimed at restoring a person's physical, mental, and social well-being. Rehabilitation may include:

Medical care: medication therapy, physiotherapy, orthopedic support.

Physical rehabilitation: exercises, breathing exercises (e.g., after pneumonia).

Psychological support: mental correction and psychotherapeutic methods to restore mental and emotional well-being.

Social and vocational adaptation: assistance with employment, training in new skills.

Remission and regression of diseases return patients to controlled normal life activities.

2. Disease Remission

Remission is a period of the disease course when symptoms significantly diminish or disappear completely. However, the risk of relapse — a return of the disease — remains. The term is applied to various diseases: mental, infectious, genetic, autoimmune, oncological, and others.

2.1 Types of Remission

(1) By degree of symptom reduction:

Complete. Symptoms are completely absent, and examination results (tests, instrumental studies) are normal or close to normal. This is considered the most favorable outcome of the disease. However, even with complete remission, the risk of relapse remains, as pathological cells may remain in the body.

Incomplete (partial). The patient's condition is stable, but objective indicators (laboratory or instrumental study data) are abnormal. For example, in oncological diseases, this may be a fragmentary tumor removal, leaving a portion of it in the body.

Clinical. Subjective improvement in well-being: pain subsides, temperature and blood pressure return to normal, etc. However, objective signs of the disease may persist. This condition often causes concern among physicians, as patients may discontinue treatment, and the disease may progress unnoticed.

(2) By duration:

Persistent. Can last for years or decades. The person returns to their normal life, but if the immune system is weakened, the disease may return. In oncology, a five-year disease-free period is often considered a benchmark; however, this period is arbitrary and depends on the type of disease, stage, and treatment.

Unstable. Short-term relief, during which the disease can quickly return. This is often indicated by unstable test results.

(3) Other types:

Spontaneous. Disappearance or significant reduction in disease manifestations without specific treatment. Rare and poorly studied.

Molecular (in oncology). Using ultra-sensitive methods, specific genetic defects characteristic of the patient's tumor cannot be detected in the patient's blood.

2.2 Remission in Various Diseases

Oncological Diseases. Remission means that the tumor is responding to therapy and its progression can be controlled. Surgery, chemotherapy, radiation therapy, targeted therapy, and immunotherapy are used to achieve remission (Kelly A. Turner, 2014). Even with complete remission, the risk of relapse remains, so the patient requires regular monitoring by an oncologist.

Mental Disorders (depression, bipolar disorder, anxiety disorders, etc.). Remission allows the patient to return to work, social activities, and hobbies. With mild depression, remission can occur within 2-4 weeks of starting treatment; with more severe conditions, it can take several months to a year.

Autoimmune diseases (multiple sclerosis, type 1 diabetes, Hashimoto's thyroiditis, etc.). Remission can occur when inflammation subsides or stress is relieved. The likelihood of remission is influenced by the rate of target tissue regeneration and the activity of the immune system (Chiara Tani, Roberta Vagelli & Chiara Stagnaro,

2018; Elkoshi Z., 2025).

Infectious arthritis. For example, the virus remains in the body, but its activity is suppressed by the immune system. When the immune system is weakened, a relapse may occur. In such situations, remission of infectious arthritis is used (Iona Donnelly, 2018; Marina G. Birck et al., 2025).

2.3 Recommendations During Remission

* Follow the treatment plan: continue taking prescribed medications and visit your doctor regularly.

* Avoid emotional stress and overwork.

* Maintain a healthy lifestyle: quit bad habits, sleep at least 7-8 hours a day, and spend more time outdoors.

* If new or unusual symptoms appear (weight loss, weakness, pain, bleeding, etc.), consult a doctor for further examination.

It's important to remember that remission does not equate to a full recovery. Only a doctor can assess your condition and provide recommendations for further monitoring and treatment.

3. Disease Regression

In medicine, regression is a stage in the course of a disease during which clinical manifestations gradually disappear, followed by restoration of the patient's health. The term is used in various fields of medicine, with some differences in meaning (Castillo H, et al., 2008; Worley G. et al., 2015; Ghaziuddin N. et al., 2017; Mircher C. et al., 2017; Ernest Yeboah Boateng & Daniel A. Abaye, 2019; Santoro S. L. et al., 2020; Rosso M. et al., 2020; Ton J. Cleophas & Aeilko H. Zwinderman, 2021; Santoro J. D. et al., 2022; Santoro J. D. et al., 2022; Bonne S et al., 2023; Wang, T., 2026).

3.1 Main Types of Regression

(1) Tumor Regression (in Oncology)

Complete regression — the absence of viable tumor tissue based on examination data and signs of metastasis.

Partial regression — a reduction in tumor size or volume by more than 50% in the absence of new metastases.

Spontaneous regression — a rare phenomenon in which a malignant tumor disappears without specific antitumor treatment or with inadequate therapy (Evgeny Bryndin, 2025a). More common in:

* Melanoma;

* Renal cell carcinoma;

* Neuroblastoma;

* Certain types of blood cancer.

The mechanisms of spontaneous regression are not fully understood. Possible causes include:

* Activation of the immune system against tumor antigens;

* Hormonal changes;

* Tumor necrosis;

* Cell apoptosis;

* Infections, etc.

(2) Histological regression — a decrease in the number of neoplastic (tumor) cells within the tumor or their complete disappearance. For example, in melanoma, this may be accompanied by fibrosis, the appearance of new vessels, and inflammation.

(3) Caudal regression syndrome — a rare congenital malformation characterized by abnormalities of the lower spine and often damage to the lower extremities and internal organs. The term is used here not to describe the course of the disease, but as a name for the disorder itself. Causes may include genetic mutations (for example, in the VANGL1 gene) and environmental factors.

(4) Regression in psychiatry is not an improvement in a patient's condition, but a defense mechanism of the psyche: a return to less mature behavior patterns under stress (moody, tearfulness, etc.).

(5) Regression to the mean (in medical statistics) is a statistical phenomenon whereby extreme values (for example, very high blood pressure) naturally return to the mean without any treatment.

3.2 Difference Between Regression and Remission

While both terms describe an improvement in a patient's condition, there are differences between them:

Regression most often refers to a reduction or disappearance of a pathological lesion (e.g., a tumor) and can lead

to a full recovery. In oncology, this term is often used synonymously with positive dynamics during treatment.

Remission is a period of decreased disease activity, when symptoms diminish or disappear, but the risk of relapse remains. Remission does not always mean that the pathological process has completely stopped.

3.3 Transition from Remission to Regression

The transition from remission to regression can occur for several reasons:

Persistence of individual tumor cells. Even during remission, isolated malignant cells may remain in the body, which after a while begin to actively divide.

Decreased immunity. If the immune system weakens, this can trigger the growth of remaining pathological cells.

Cellular adaptation to treatment. Cancer cells can develop resistance to chemotherapy drugs by changing their genetic programming.

Stress and other external factors. These can negatively impact overall health and contribute to disease progression.

Failure to comply with doctor's recommendations. For example, refusal of maintenance therapy or poor diet.

Regression assessment should be based not only on the patient's well-being but also on objective examination data (tests, biopsies, imaging, etc.).

4. Innovations in Disease Regression and Remission

Innovations in disease regression and remission involve the application of modern data analysis technologies, personalized medicine, and the development of new treatments and disease management methods. Particular attention is paid to machine learning, genetic research, and combination therapeutic approaches.

4.1 Machine Learning and Remission Prediction

Machine learning (ML) methods enable the analysis of large volumes of clinical, laboratory, and genetic data to predict remission and treatment response. For example, algorithms such as lasso regression, ridge regression, support vector machines (SVM), random forests, XGBoost, and SHAP (Shapley Additive Explainer) have been used in rheumatoid arthritis (RA) research. These methods helped identify key clinical variables associated with remission with different biologic agents (e.g., age for adalimumab, rheumatoid factor for etanercept, and erythrocyte sedimentation rate for infliximab and golimumab).

In the case of psoriatic arthritis, XGBoost and logistic regression were used to predict 12-month remission based on the DAPSA index. Machine learning algorithms are also used to predict hospitalization and outpatient corticosteroid use in patients with inflammatory bowel disease (IBD).

4.2 Genetic and Molecular Research

Finding genetic determinants of diseases using machine learning and systems biology opens new possibilities for personalized medicine. For example, models predicting the risk of IBD based on single nucleotide polymorphisms (SNPs) were built using data from the Immunochip project. Research in genetics and immunology helps identify biomarkers that may indicate the likelihood of remission or disease progression.

4.3 Managing Regression of Pathological Processes

In some cases, it is possible to manage the natural process of disease regression. For example, with herniated discs, spontaneous resorption (reduction or disappearance of the herniation) is observed in approximately 36% of cases. Doctors can accelerate this process with a combination of drug therapy (aimed at relieving pain and treating the underlying cause) and physical therapy (magnetic therapy, laser therapy, shockwave therapy, etc.) — the so-called modulated resorption method.

4.4 Combination Therapy Approaches

In oncology, combination treatments (for example, chemotherapy combined with radiation therapy) sometimes lead to complete regression even in advanced cancers. For example, a case of ten-year complete remission in disseminated small cell lung cancer with central nervous system involvement after six cycles of chemotherapy is described.

4.5 Personalized Medicine

A personalized approach involves dividing patients into groups based on the type and severity of the disease, the likelihood of its progression, and its response to treatment. This is achieved through the analysis of clinical, laboratory, genetic, and other data. Personalized medicine enables the selection of the most effective treatment regimens to achieve remission and minimize side effects.

4.6 Challenges and Prospects

Despite progress, the implementation of machine learning and personalized medicine methods in clinical practice faces a number of challenges:

* The need for large volumes of data to train models;

* Ethical issues related to sharing patient data;

* The need to standardize the development and presentation of algorithms;

* The difficulty of integrating new methods into existing medical information systems.

Technological advances promise further advances in disease prognosis, improved treatment outcomes, and prolongation of remission.

Thus, innovations in the field of disease regression and remission encompass both technological (machine learning, big data analysis), as well as organizational, infrastructural, methodological and other areas, which opens up new prospects for medicine (Evgeny Bryndin, 2025b; 2025c; 2026a).

5. Monitoring Normal Lifestyle

Maintaining normal life during remission or regression includes:

Medical monitoring. Regular medical check-ups, laboratory and instrumental examinations (CT, MRI, PET-CT, blood tests, etc.) to promptly detect relapse or disease progression.

Maintenance therapy. Prescribing medications to maintain the achieved state (e.g., hormonal therapy for hormone-dependent tumors, targeted or immunotherapy drugs).

Lifestyle modification. A balanced diet (e.g., a Mediterranean diet with plenty of vegetables, fruits, fish, and olive oil), quitting smoking and alcohol, moderate physical activity (e.g., walking).

Weight control. Excess fat tissue can provoke the growth of cancer cells.

Psychological support. Dealing with anxiety and fear of relapse, possibly with the participation of a psychologist or Psycho-oncologist.

Avoiding risk factors. For example, excessive sun exposure in some types of cancer.

5.1 Factors Affecting the Risk of Recurrence

Disease biology. Some tumor types (e.g., testicular cancer, some lymphomas) tend to have long-term remission, while others (pancreatic cancer, triple-negative breast cancer) tend to relapse early.

Disease stage. Early detection and treatment increase the chances of long-term remission.

Treatment effectiveness. Incomplete tumor removal during surgery and cell resistance to therapy increase the risk of recurrence.

Immune system status. A strong immune system more effectively suppresses remaining pathological cells.

Following doctor’s recommendations. Irregular monitoring, poor diet, and unhealthy habits can increase the risk of recurrence.

5.2 Important Recommendations

* Continue treatment and monitoring even if you feel better.

* If new symptoms appear (weight loss, weakness, pain, lumps, etc.), consult a doctor immediately.

* Discuss any lifestyle changes (pregnancy, job change, relocation) with your doctor.

* Avoid self-medication and taking dietary supplements without consulting a specialist.

Approaches to managing the condition depend on the type of disease, its stage, the treatment received, and the individual characteristics of the patient.

6. Conclusion

To maintain a normal condition after treatment and maintain an active lifestyle, we recommend:

Regularly see a doctor. Scheduled visits to a specialist (oncologist, internist, or other specialist doctor) allow for timely detection of changes and adjustments to treatment.

Follow treatment recommendations. This may include taking medications and supportive therapy (hormonal, targeted, and immunotherapy).

Lead healthy lifestyle. Eat a balanced diet, quit smoking and drinking alcohol, control your weight, and manage stress (Evgeny Bryndin, 2023).

Maintain physical activity. Moderate exercise (walking, swimming, and exercise therapy) improves overall

well-being, reduces the risk of complications, and improves quality of life.

Monitor your emotional state. Get psychological support, stress management techniques, and, if necessary, individual or group therapy.

Avoid risk factors. For example, hypothermia, excessive exertion, and exposure to infections.

Approaches to disease management depend on the type of disease, its stage, the treatment received, and the individual characteristics of the patient. All decisions should be made in consultation with the treating physician.

The key goals of remission and regression strategies (weakening and neutralizing diseases) are the implementation of advanced medical technologies (Bryndin E.G. & Bryndina I.E., 2018; Evgeny Bryndin, 2025d; 2025e; 2026b; 2025f).

Potential modern medical approaches to achieving a disease-free life:

(1) Genetic engineering and CRISPR. CRISPR technology allows for highly precise DNA editing. Scientists are exploring the possibility of modifying genes responsible for aging, lengthening telomeres, and eliminating genetic diseases that increase vulnerability to age-related diseases.

(2) Regenerative medicine and stem cells. Stem cell therapy can restore damaged organs and tissues. 3D bioprinting of living tissues and organs is also developing, potentially allowing for the replacement of worn-out or diseased organs.

(3) Nanotechnology and nanobots. Miniature robots may be used in the future to find and fix problems in the body: destroy cancer cells, bacteria, and repair damaged tissue.

(4) Fighting inflammaging. Scientist Claudio Franceschi believes that the main cause of age-related diseases is low-grade chronic inflammation (inflammaging), not associated with infections. Developing methods to control this process can slow down and reduce the risk of age-related diseases.

(5) Optimization of lysosome function. Lysosomes are membrane sacs in cells that break down unnecessary components. Research has shown that activating lysosomes can help remove toxic proteins and rejuvenate cells.

(6) Digital correction of consciousness. Correction of an individual's consciousness in the digital form of a biological body. The technology is being improved towards the safe correction of damaged consciousness (Evgeny Bryndin, 2021; 2026c).

Innovations in the field of disease regression and remission encompass technological, organizational, infrastructural, methodological, and other areas, opening up new prospects for the development of medicine and healthcare.

References

Bonne S, Iftimovici A, Mircher C, Conte M, Louveau C, Legrand A, Danset-Alexandre C, Cannarsa C, Debril A, Consoli A, Krebs M-O, Ellul P and Chaumette B. (2023). Down syndrome regression disorder, a case series: Clinical characterization and therapeutic approaches. *Front. Neurosci., 17*, 1126973. doi: 10.3389/fnins.2023.1126973

Bryndin E.G., Bryndina I.E. (2018). Healthy lifestyle as an innovative basis for healthcare. *Prenosology and Healthy Lifestyle, 2*(23), 73-78.

Castillo H, Patterson B, Hickey F, et al. (2008). Difference in age at regression in children with autism with and without Down syndrome. *J Dev Behav Pediatr, 29*(2), 89–93. 10.1097/DBP.0b013e318165c78d

Chiara Tani, Roberta Vagelli, Chiara Stagnaro. (2018). Remission and low disease activity in systemic lupus erythematosus: An achievable goal even with fewer steroids? Real-life data from a monocentric cohort. *Lupus Science & Medicine, 5*(1). DOI: 10.1136/lupus-2017-000234

Elkoshi Z. (2025). New insights into the phenomenon of remissions and relapses in autoimmune diseases and the puzzle of benign autoantibodies in healthy individuals. *Front. Immunol., 16*, 1522356. doi: 10.3389/fimmu.2025.1522356

Ernest Yeboah Boateng, Daniel A. Abaye. (2019). A Review of the Logistic Regression Model with Emphasis on Medical Research. *Journal of Data Analysis and Information Processing, 7*(4), 190-207. DOI:10.4236/jdaip.2019.74012

Evgeniy Brindin. (2026a). Swarm Artificial Intelligence in Healthcare and Medicine. *Far East Journal of Experimental and Theoretical Artificial Intelligence, 8*(1), In press.

Evgeniy Brindin. (2026b). Maintaining Body's Hormonal-Genetic Synergy Prolongs Human Life. *International Journal of Current Microbiology and Applied Sciences, 15*(1). 112-120. https://doi.org/10.20546/ijcmas.2026.1501.013

Evgeniy Bryndin. (2025e). Maintaining the Health of Organism at Molecular Level Based on Informative Genomics. *International Journal of Biochemistry, Biophysics & Molecular Biology, 10*(2) 53-60. https://doi.org/10.11648/j.ijbbmb.20251002.13

Evgeny Bryndin. (2021). Professional Training of Intellectual Disabled Person by Holographic Image of Competent Healthy Specialist. *International Journal of Psychological and Brain Sciences, 6*(3), 44-51. DOI:10.11648/j.ijpbs.20210603.12

Evgeny Bryndin. (2023). Healthy Lifestyle Education in Educational Institutions. All-Russian Scientific and Practical Conference with International Participation “Hygiene and Health Protection of Children and Adolescents: History and Modernity, a Look into the Future.” St. Petersburg: Publishing House of the Federal State Budgetary Educational Institution of Higher Education North-Western State Medical University named after I.I. Mechnikov, Ministry of Health of the Russian Federation, 29–32.

Evgeny Bryndin. (2025a). Spontaneous Regression of Oncological Necrotic Tissue. *Clinical Research and Studies, 4*(4). DOI:10.31579/2835-2882/088.

Evgeny Bryndin. (2025b). Detection of Initial Donozology Stage Using Virtual Cell with AI. *International Journal of Current Microbiology and Applied Sciences, 14*(2), 217-225.

Evgeny Bryndin. (2025c). Intelligent Digital Clinic of Interacting Multimodal AI Assistants. *Research in Medical & Engineering Sciences, 11*(4), 1237-1241.

Evgeny Bryndin. (2025d). International Translational Medicine in World Healthcare. *Pathology and Laboratory Medicine, 9*(1), 32-37. https://doi.org/10.11648/j.plm.20250901.13

Evgeny Bryndin. (2025f). Elimination of Cancerous Tumors of Different Organs by Intelligent Cell Therapy and Spontaneous Regression. *Cancer Research and Cellular Therapeutics, 9*(5). DOI:10.31579/2640-1053/247

Evgeny Bryndin. (2026c). Spatial Generative Multimodal Dynamic AGI as Model of Consciousness. *American Journal of Robotics and Intelligent Systems, 1*(1), 1-9. DOI:10.11648/j.ajris.20260101.11

Ghaziuddin N., Miles J., Nassiri A. (2015). Catatonia in down syndrome; a treatable cause of regression. *Neuropsychiatr. Dis. Treat.*, 11941–949. 10.2147/NDT.S77307

Iona Donnelly. (2018). Novel methodology to discern predictors of remission and patterns of disease activity over time using rheumatoid arthritis clinical trials data. https://www.academia.edu/98569906/Novel_methodology_to_discern_predictors_of_remission_and_patterns_of_disease_activity_over_time_using_rheumatoid_arthritis_clinical_trials_data

Kelly A. Turner. (2014). Radical Remission: Surviving Cancer Against All Odds. *HarperOne*, 320.

Marina G. Birck, Jessica Boivin, Laura Yan, Nathalie Carrier, Cristiano S. Moura, Walter P. Maksymowych, Gilles Boire, Denis Choquette, Luck Lukusa, Michael Mallinson, Linda Wilhelm, Autumn Neville, Sasha Bernatsky. (2025). Disease remission and sustained remission after etanercept biosimilar or originator initiation in rheumatoid arthritis: an interim real-world analysis. *Arthritis Research & Therapy*, 1-7. https://doi.org/10.1186/s13075-025-03607-7

Mircher C., Cieuta-Walti C., Marey I., Rebillat A.-S., Cretu L., Milenko E. et al. (2017). Acute regression in young people with down syndrome. *Brain Sci., 7*, 57. 10.3390/brainsci7060057

Rosso M., Fremion E., Santoro S. L., Oreskovic N. M., Chitnis T., Skotko B. G. et al. (2020). Down syndrome disintegrative disorder: a clinical regression syndrome of increasing importance. *Pediatrics, 145*, e20192939. 10.1542/peds.2019-2939

Santoro J. D., Partridge R., Tanna R., Pagarkar D., Khoshnood M., Rehmani M. et al. (2022). Evidence of neuroinflammation and immunotherapy responsiveness in individuals with down syndrome regression disorder. *J. Neurodev. Disord., 14*, 35. 10.1186/s11689-022-09446-w

Santoro J. D., Patel L., Kammeyer R., Filipink R. A., Gombolay G. Y., Cardinale K. M. et al. (2022). Assessment and diagnosis of down syndrome regression disorder: international expert consensus. *Front. Neurol., 13*, 940175. 10.3389/fneur.2022.940175

Santoro S. L., Cannon S., Capone G., Franklin C., Hart S. J., Hobensack V. et al. (2020). Unexplained regression in down syndrome: 35 cases from an international down syndrome database. *Genet. Med.*, 22767–776. 10.1038/s41436-019-0706-8

Ton J. Cleophas, Aeilko H. Zwinderman. (2021). Quantile Regression in Clinical Research. Textbook.

Wang, T. (2026). Moving Beyond Mean: Harnessing Big Data for Health Insights by Quantile Regression. In: Zhao, Y., Chen, DG. (eds) *Big Data Analytics in Biostatistics and Bioinformatics*. ICSA Book Series in Statistics. Springer, Cham. https://doi.org/10.1007/978-3-032-06649-7_3

Worley G., Crissman B. G., Cadogan E., Milleson C., Adkins D. W., Kishnani P. S. (2015). Down syndrome disintegrative disorder: new-onset autistic regression, dementia, and insomnia in older children and adolescents with down syndrome. *J. Child Neurol.*, 301147–1152. 10.1177/0883073814554654

Paradigm Academic Press
Journal of Innovations in Medical Research
ISSN 2788-7022
JUN. 2026 VOL.5, NO.2

A Review of the Physiological Effects of Foam Rolling on Skeletal Muscle

Mingyang Wei[1]

[1] AnnpoBio Pharmaceuticals (Guangdong) Co., Ltd., Guangzhou 510515, China

Correspondence: Mingyang Wei, AnnpoBio Pharmaceuticals (Guangdong) Co., Ltd., Guangzhou 510515, China.

doi:10.63593/JIMR.2788-7022.2026.06.002

Abstract

As a commonly employed modality for self-myofascial release, foam rolling is widely used in sports rehabilitation and physical training. This article analyzes the physiological effects of foam rolling on skeletal muscle and explores its potential mechanisms. After retrieving PubMed, Cochrane, ScienceDirect, and Embase, and manually screening references, a total of 16 randomized controlled trials, 4 systematic reviews or mechanism reviews, 2 survey studies, and 3 other primary studies were finally included. Available evidence suggests that acute foam rolling is generally associated with improved joint range of motion, whereas muscle strength and explosive performance generally show acute inhibitory trends, consistent with a transient neurophysiological response. Foam rolling appears to have limited direct effects on muscle activation, although it may support recovery-related neuromuscular function in specific settings. It may also alleviate delayed-onset muscle soreness and improve pain-related or hemodynamic responses, but these effects appear to be context-dependent. Its mechanisms involve multifactorial interactions, including myofascial release, mechanoreceptor activation, and hemodynamic regulation. Limitations of existing studies include small sample sizes, heterogeneous intervention protocols, and short follow-up periods. Future research should adopt large-sample, long-term designs to determine optimal intervention parameters and confirm efficacy in clinical populations.

Keywords: foam rolling, self-myofascial release, muscle performance

1. Introduction

Foam rolling is a common tool for self-myofascial release, which is frequently used in sports rehabilitation and training. Its main function is to relieve muscle pain caused by exercise, improve joint mobility, and help exercise recovery to a certain extent (Bartsch K et al., 2025; Ikutomo H et al., 2025; Niazi S et al., 2025). However, the specific mechanism of foam rolling is still unclear. Previous studies and mechanistic reviews suggest that foam rolling may influence soft tissue mechanics, pain perception, and hemodynamic responses, possibly through interactions involving fascial loading, mechanoreceptor stimulation, and neural modulation. (Gao Y & Gao D., 2026; Dębski P et al., 2025; Clijsen R et al., 2025)

In recent years, clinical and sports scientific research has paid more attention to the application effect of foam rolling, but there are obvious differences in experimental design, intervention intensity, action site, measurement indicators, etc. (Amiri B & Zemková E., 2025; Aragão-Santos JC et al., 2025; Bartik P & Pacholek M., 2025; Bartsch K et al., 2025; Sezik AÇ et al., 2024; Gao Y & Gao D., 2026; Heinke L et al., 2025; Hosseini SM et al., 2026; Ikutomo H et al., 2025; Monteiro ER et al., 2025; Niazi S et al., 2025; Ormeno L & Driller M., 2025; Park S & Kim B., 2025; Patti A et al., 2025; Posch D et al., 2026; Rodoplu C et al., 2025; Siegel SD et al., 2026; Szajkowski S et al., 2025; Yeşilyaprak SS & Özden F., 2025; Wu CW et al., 2026; Wilke J et al., 2020). In addition, relevant studies focus on the acute improvement effect of foam rolling on joint mobility (Bartik P & Pacholek M., 2025; Hosseini SM et al., 2026; Patti A et al., 2025; Wilke J et al., 2020); relevant studies focus on

the impact of foam rolling on the recovery effect, specifically focusing on delayed muscle soreness or fatigue after exercise (Park S & Kim B., 2025; Szajkowski S et al., 2025; Wu CW et al., 2026). Recent studies have demonstrated potential benefits of the foam roller in specific clinical populations (e.g., knee osteoarthritis (Ikutomo H et al., 2025), Parkinson's disease (Kaşlı K et al., 2025), and upper cross syndrome (Kalantariyan M et al., 2026)), although its efficacy exhibits situational dependence. This heterogeneity between studies makes it difficult to integrate the physiological effects of foam rolling systematically. To address this heterogeneity, this review proposes an "initial state dependence" framework as an organizing perspective: the effects of foam rolling differ systematically depending on whether the muscle is in a normal resting state versus a state of fatigue or injury. This framework is developed and supported throughout the Discussion.

Based on this, this article systematically sorts out the existing literature, analyzes the impact of foam rolling on muscle performance, muscle activation, muscle pain and recovery after exercise, and vascular and hemodynamic function, and explores its potential mechanism to provide reference for clinical rehabilitation and exercise training.

2. Methods

In order to fully understand the physiological effect of foam rolling on muscles, this article first searches in four databases: PubMed, Cochrane, ScienceDirect and Embase. The keywords use "foam roller" and "muscle". The title and abstract use the combination of Boolean logic "AND". After deduplication and preliminary screening, 25 relevant articles were ultimately included.

Inclusion criteria: 1) randomized controlled trials; 2) systematic reviews; 3) narrative or mechanism-based reviews; 4) survey studies examining practitioner beliefs or usage patterns; 5) observational or correlational studies providing mechanistic context.

Exclusion criteria: 1) case reports or small sample cohorts; 2) research that focuses on technology development; 3) articles without accessible full text or non-English publications. Considering the rapid development of this field, priority was given to studies published within the past three years; however, one earlier high-quality systematic review was retained to support background synthesis.

Ultimately, 25 studies were included, comprising 16 randomized controlled trials (Amiri B & Zemková E., 2025; Aragão-Santos JC et al., 2025; Bartik P & Pacholek M., 2025; Heinke L et al., 2025; Hosseini SM et al., 2026; Ikutomo H et al., 2025; Niazi S et al., 2025; Ormeno L & Driller M., 2025; Patti A et al., 2025; Posch D et al., 2026; Rodoplu C et al., 2025; Szajkowski S et al., 2025; Yeşilyaprak SS & Özden F., 2025; Wu CW et al., 2026; Kaşlı K et al., 2025; Kalantariyan M et al., 2026), 4 systematic reviews or mechanism reviews (Gao Y & Gao D., 2026; Monteiro ER et al., 2025; Park S & Kim B., 2025; Wilke J et al., 2020), 2 survey studies (Bartsch K et al., 2025; Siegel SD et al., 2026), and 3 other primary studies (including correlation and observational studies) (Sezik AÇ et al., 2024; Dębski P et al., 2025; Clijsen R et al., 2025).

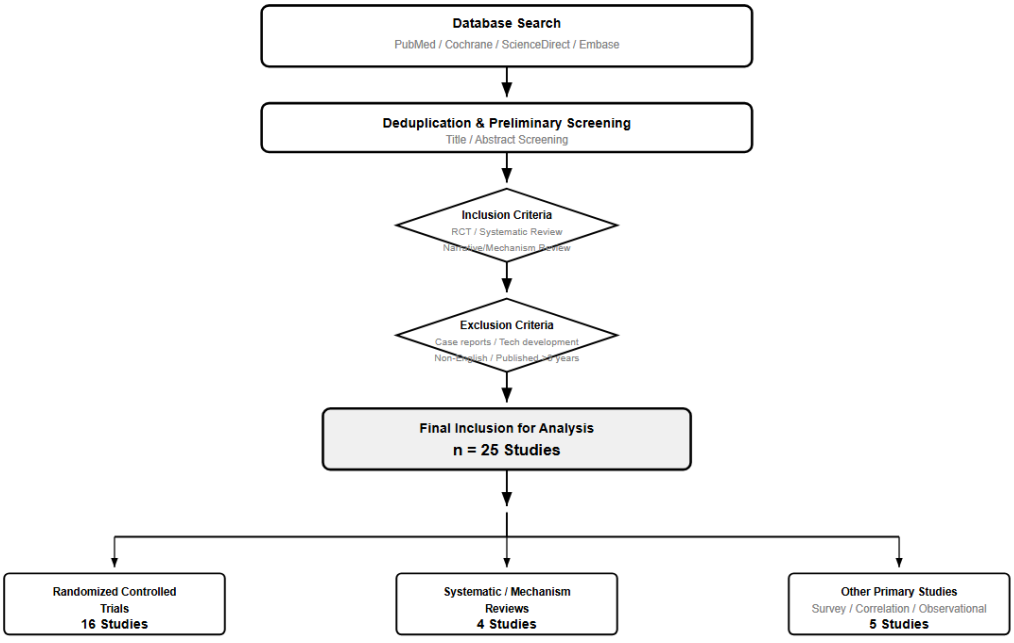

Figure 1. Literature search and screening algorithm

Quality evaluation uses the Cochrane bias risk assessment tool to evaluate the methodological quality of 16 randomized controlled trials. Evaluation points include random sequence generation, distribution hiding, subject and researcher blind method, outcome evaluation blind method, incomplete data, selective reports, and other biased sources. Most studies clearly describe random sequence generation. However, due to the operation limitations of foam rolling itself, it is difficult for the subjects and the researchers who carry out the intervention to be completely blind, which is a common limitation in methodology. Generally speaking, the quality included in the research is at a medium to high level, with the basis for systematic analysis.

3. Results

According to the research purpose, results and conclusions, the analysis of the 25 included studies shows that the physiological effects of foam rolling on skeletal muscle are mainly divided into four directions: Muscle Performance, Muscle Activation, Muscle Soreness and Recovery, and Vascular and Hemodynamic Function.

3.1 Muscle Performance

Acute foam rolling improves joint flexibility but may transiently reduce strength or explosive power (Amiri B & Zemková E., 2025; Aragão-Santos JC et al., 2025; Bartik P & Pacholek M., 2025; Hosseini SM et al., 2026; Patti A et al., 2025; Rodoplu C et al., 2025; Wilke J et al., 2020). Long-term effects on lower limb muscle groups and ROM appear positive, yet adaptive changes in metabolism or mechanical power are limited (Park S & Kim B., 2025; Posch D et al., 2026).

3.2 Muscle Activation

Direct evidence regarding the acute effects of foam rolling on muscle activation-related outcomes remains limited. Existing experimental evidence suggests no substantial immediate change in upper-extremity sensorimotor function following a single bout of foam rolling (Yeşilyaprak SS & Özden F., 2025), whereas findings from specific patient populations or multimodal corrective interventions should be interpreted cautiously (Niazi S et al., 2025; Kalantariyan M et al., 2026). Mechanistic reviews have proposed possible neurophysiological effects of myofascial release interventions, but these mechanisms remain to be confirmed by direct experimental studies (Gao Y & Gao D., 2026).

3.3 Muscle Soreness and Recovery

Foam rolling alleviates delayed-onset muscle soreness, increases pressure pain threshold, and aids flexibility recovery. Both vibration and non-vibration rolling improve post-exercise recovery compared with static stretching (Park S & Kim B., 2025; Rodoplu C et al., 2025; Szajkowski S et al., 2025; Wu CW et al., 2026).

3.4 Vascular and Hemodynamic Function

Evidence related to the vascular and hemodynamic effects of foam rolling remains limited. Existing reviews suggest that foam rolling may influence selected hemodynamic or autonomic responses (Monteiro ER et al., 2025). In clinical populations, foam rolling has also been associated with improvements in pain or functional outcomes in conditions such as hip osteoarthritis and Parkinson's disease, although these findings should not be interpreted as direct evidence of vascular effects (Ikutomo H et al., 2025;)[22]. Studies on soft tissue biomechanical responses (Dębski P et al., 2025) and adjacent percussive modalities (Clijsen R et al., 2025) may offer indirect mechanistic context, but they do not directly confirm foam rolling-specific vascular effects.

4. Discussion

This review systematically analyzes 25 studies and summarizes the physiological effects of foam rolling on skeletal muscle into four areas. Improved blood flow and autonomic regulation provide the physiological basis for muscle recovery and soreness relief, while muscle activation and coordination influence strength and performance. Enhanced flexibility improves fascial gliding and movement efficiency. These four dimensions interact to form a comprehensive mechanistic network, with effects that are condition-dependent, offering a theoretical foundation for training and rehabilitation.

4.1 Effects of Foam Rolling on Flexibility and Its Underlying Mechanisms

In the included studies, foam rolling was generally associated with short-term improvements in joint mobility. Regardless of the intervention site (thoraco-lumbar fascia (Amiri B & Zemková E., 2025), hip joint (Ikutomo H et al., 2025), knee joint (Rodoplu C et al., 2025), or ankle joint (Patti A et al., 2025)) and measurement methods (sitting forward flexion, passive joint mobility, etc.), the vast majority of studies found significant results. Wilke et al. (2020) conducted a systematic review with multilevel meta-analysis and confirmed the acute effects of foam rolling on range of motion in healthy adults. Long-term intervention research focuses on lower limb muscle groups and joint flexibility (Park S & Kim B., 2025; Posch D et al., 2026). However, Posch et al. (2026) suggested that long-term adaptive effects may be limited, and there may be a discrepancy between objective measurements and subjective feelings. The only study that showed no significant effect (Bartik P & Pacholek

M., 2025) had a short intervention duration and involved young male athletes. This suggests that intervention dose and subject characteristics are critical. If the single session is too short or tissue characteristics differ, the effects may also differ.

Currently, there are three main explanations for the mechanism of flexibility improvement. The first is the myofascial mechanical response hypothesis. The pressure and friction of foam rolling can influence the fascial matrix, allowing smoother fascial gliding and more efficient force transmission (Gao Y & Gao D., 2026; Wilke J et al., 2020). Gao and Gao (2026) comprehensively reviewed the mechanisms of myofascial release, noting that direct histological evidence for structural changes following a single intervention remains insufficient. The second is the activation of mechanoreceptors. Foam rolling compresses Ruffini corpuscles and Pacinian corpuscles in the muscles and fascia. These signals are transmitted to the spinal cord and higher nerve centers, reducing muscle spindle sensitivity, soothing muscle tension, and expanding joint range of motion (Gao Y & Gao D., 2026; Dębski P et al., 2025). The third is altered perception and pain modulation. Dębski et al. (2025) found a relationship between attitude toward pain and the effects of foam rolling on soft tissue biomechanical parameters. Clijsen et al. (2025) observed physiological effects following local percussion massage, suggesting that foam rolling may activate descending inhibitory pathways, making individuals more tolerant of stretch and pain. These three mechanisms may work together rather than exclude each other.

4.2 Acute Inhibitory Effects of Foam Rolling on Strength and Power

The study of acute force or explosive force generally showed an inhibitory trend after foam rolling intervention, although the magnitude and consistency of this effect varied across studies. (Aragão-Santos JC et al., 2025; Heinke L et al., 2025; Ormeno L & Driller M., 2025). This pattern has been reported in several acute studies and may reflect a short-term neurophysiological response, although findings remain context-dependent. Aragão-Santos et al. (2025) found that foam rolling and massage ball with or without vibration affected the squat load-velocity profile, with some conditions showing decreased performance. Heinke et al. (2025) observed that jump height decreased following foam rolling, and this effect was correlated with pain intensity. Ormeno and Driller (2025) reported that foam roller use during a warm-up had limited effects on performance in trained athletes. Nerve inhibition means that the central nervous system actively downregulates the excitability of α-motor neurons, reducing muscle output. From the perspective of adaptation and protection, this may be beneficial: deep pressure is interpreted by the central system as a signal of tissue pressure or possible damage, which automatically triggers protective mechanisms and limits force output to avoid injury.

Gao and Gao (2026) discussed that this effect is based on neural circuits. It is worth noting that the decline in strength is not a decline in the intrinsic capacity of the muscle itself (e.g., cross-bridge ability or energy metabolism). It is more likely a temporary adjustment of neural drive strategy. This is consistent with the pain gate control theory and the neurophysiological model of manual treatment (Gao Y & Gao D., 2026; Dębski P et al., 2025). These results show that foam rolling has no significant positive impact on strength and power in the short term, and sometimes even has a short-term inhibitory effect. From a practical point of view, foam rolling needs to be used carefully before training dominated by strength or explosive power, such as weightlifting, sprinting, or jumping.

In addition, in terms of strength and power recovery, most studies have found that the use of foam rolling after exercise can promote subjective recovery (Rodoplu C et al., 2025; Szajkowski S et al., 2025; Wu CW et al., 2026), but Rodoplu et al. (2025) did not observe significant changes in functional muscle parameters. These results show that foam rolling can be used as an auxiliary tool in recovery training, which is especially suitable for relieving pain and restoring flexibility. However, if the goal is high-intensity strength training or the pursuit of extreme performance, it is better to cooperate with other training methods.

4.3 The Role of Foam Rolling in Post-Exercise Recovery

Contrary to the force inhibition effect observed during acute use, foam rolling shows a positive and extensive recovery effect in the state of fatigue or injury induced by exercise. Most studies have found that foam rolling can significantly relieve delayed-onset muscle soreness (Park S & Kim B., 2025; Rodoplu C et al., 2025; Szajkowski S et al., 2025; Wu CW et al., 2026), and also shows advantages in subjective recovery. Park and Kim (2025) confirmed the positive effects of vibration foam rolling on pain and fatigue in individuals with muscle fatigue. This seemingly contradictory two-way effect (inhibiting strength in normal muscles while promoting recovery in fatigued muscles) can be explained by “initial state dependence.”

In the exercise-induced fatigue state, metabolic waste accumulates inside the muscles, stimulating acid-sensitive channels and nociceptors, resulting in fatigue and pain. There is also slight damage and inflammation of muscle fibers. Against this background, foam rolling plays a recovery role through several pathways.

The first is improvement of hemodynamics and autonomic responses. Monteiro et al. (2025) conducted a scoping review suggesting that foam rolling may influence heart rate and blood pressure regulation. The second

is promotion of lymphatic return and reduction of edema. Foam rolling applies pressure, encouraging tissue fluid flow toward lymphatics, relieving local swelling and pressure. The third is pain modulation at the neurological level. By activating descending inhibitory pathways in the spinal cord and releasing endogenous opioids and serotonin, pain is reduced (Gao Y & Gao D., 2026; Dębski P et al., 2025; Clijsen R et al., 2025). Dębski et al. (2025) highlighted the role of pain attitude in modulating foam rolling effects. Pain relief makes exercise more comfortable and allows for a faster return to normal movement patterns, reducing secondary injuries caused by compensation.

In normal muscles, the pathological state that needs "repair" does not exist, and foam rolling mainly manifests as neural inhibition. This also explains why the same tool has completely different effects in different scenarios. However, Amiri and Zemková (2025) found that trunk stability and breathing exercises were superior to foam rolling for restoring postural stability after core muscle fatigue, suggesting that foam rolling may not be the optimal choice in certain recovery contexts.

4.4 Muscle Activation and Agonist-Antagonist Balance

This review finds that the acute effect of foam rolling on muscle activation is limited. Yeşilyaprak and Özden (2025) found that a single foam rolling intervention had no significant effect on muscle activation and was not sufficient to change central nervous system regulation.

What is worth paying attention to is the agonist-antagonist balance. Gao and Gao (2026) discussed that when foam rolling targets the quadriceps, the activation of the antagonist hamstring muscles may decrease through reciprocal inhibition, potentially affecting overall exercise performance. From a neurophysiological perspective, this effect comes from the principle of reciprocal inhibition: agonist muscle Ia fibers are stimulated by pressure, and the excitatory signal downregulates the output of antagonist muscle α-motor neurons through inhibitory interneurons in the spinal cord. Foam rolling may trigger this mechanism.

This discovery has significant clinical and training implications. Kalantariyan et al. (2026) demonstrated the importance of agonist-antagonist balance in the rehabilitation of upper crossed syndrome. In practice, when relieving tension or soreness in a muscle group, it should be considered to also roll the antagonist muscle to maintain agonist-antagonist balance. For example, after rolling the quadriceps, the hamstrings should also be rolled; after rolling the biceps, the triceps should also be rolled. This "agonist-antagonist balance" principle can be used as a guideline for foam rolling, especially for knee and shoulder joint stability training and rehabilitation.

4.5 The Knowledge-Practice Gap

A notable finding of this review is the persistent gap between practitioner beliefs and the available scientific evidence. Two international survey studies included in this review (Bartsch K et al., 2025; Siegel SD et al., 2026) collectively reveal that sports and rehabilitation professionals commonly hold beliefs about foam rolling—such as its ability to directly increase muscle flexibility or improve performance—that are not fully supported by current evidence. Bartsch et al. (2025) found that many practitioners were unaware of documented contraindications and adverse events, while Siegel et al. (2026) confirmed that practitioner beliefs often exceed what the evidence supports. This gap may lead to suboptimal application—for instance, using foam rolling immediately before strength-dominant activities despite evidence of acute inhibitory effects, or over-attributing recovery benefits to foam rolling alone. Bridging this gap requires better dissemination of evidence-based guidelines, particularly regarding optimal application parameters and context-dependent indications.

4.6 Limitations of the Study

There are some limitations in this review. First, the sample sizes of the included studies are generally small (Sezik AÇ et al., 2024; Posch D et al., 2026; Wilke J et al., 2020), limiting statistical power and generalizability. Second, the foam rolling intervention parameters vary significantly: rolling speed differs; pressure magnitude varies; single session duration ranges from 30 seconds to several minutes; frequency is not uniform; intervention cycles are inconsistent (acute vs. several weeks), making it difficult to conduct dose-effect analyses (Bartsch K et al., 2025; Siegel SD et al., 2026). Third, most studies only observe acute effects and lack long-term follow-up data (Amiri B & Zemková E., 2025; Bartik P & Pacholek M., 2025; Heinke L et al., 2025; Ormeno L & Driller M., 2025). Fourth, the nature of the intervention makes it difficult to achieve blinding, and there may be implementation bias. Fifth, Bartsch et al. (2025) and Siegel et al. (2026) highlighted a significant gap between practitioner beliefs and scientific evidence, which may affect the translation of research findings into clinical practice. Sixth, most study subjects are healthy young individuals, and caution should be exercised when generalizing results to clinical populations (such as those with chronic pain or post-operative recovery), although preliminary evidence exists for osteoarthritis (Ikutomo H et al., 2025) and Parkinson's disease (Kaşlı K et al., 2025). In general, these limitations remind us to be cautious when interpreting the results and suggest that future research can be further improved in terms of sample size, intervention standardization, long-term follow-up, and application to different populations.

5. Conclusion

Based on the existing literature, the physiological effects of foam rolling on skeletal muscle can be summarized as follows:

First, under normal muscle state, foam rolling intervention can significantly improve joint flexibility, which is relatively stable in acute use and limited long-term intervention. However, strength and explosive power tend to decrease slightly in the short term, which may be due to neural inhibition. Therefore, before strength- or power-based training, the timing of foam rolling needs to be carefully arranged.

Second, during muscle fatigue or mild injury after exercise, foam rolling plays a positive role. Most studies show that it can relieve delayed-onset muscle soreness, raise the pressure pain threshold, and promote subjective recovery. This mainly depends on several pathways: improving hemodynamic responses, promoting lymphatic return, and activating descending pain suppression pathways.

Third, the acute effect of foam rolling on muscle activation is limited, but it may improve neuromuscular function during the recovery period in specific contexts. It is worth noting that when rolling on the agonist muscle group, the activation level of the antagonist muscle may be reduced through reciprocal inhibition, affecting joint stability. Therefore, in training and rehabilitation, it is necessary to arrange the order of agonist-antagonist muscle groups and adopt the “agonist-antagonist balance” principle.

Fourth, foam rolling may accelerate muscle recovery and improve training adaptability by improving blood flow and possible neural regulation. Preliminary evidence also supports the application of foam rolling in specific clinical populations, including hip osteoarthritis and Parkinson’s disease.

Fifth, a significant gap exists between practitioners’ beliefs and current scientific evidence regarding foam rolling applications. Survey studies indicate that many professionals hold views about foam rolling’s benefits that exceed what the evidence supports, underscoring the need for improved knowledge translation and clearer evidence-based practice guidelines.

Future research can further clarify the optimal parameters of foam rolling intervention, such as intervention site, rolling speed, pressure, single session duration, frequency, and total cycle (dose-effect relationship), while exploring synergistic application protocols for agonist-antagonist muscles. In addition, large-sample, multi-center, and long-term follow-up studies should be conducted, including clinical populations such as those with chronic pain or post-operative recovery, combining objective physiological indicators and subjective feelings to comprehensively evaluate the effects of foam rolling in different movement states and rehabilitation scenarios.

References

Amiri B, Zemková E. (2025). Trunk stability and breathing exercises superior to foam rolling for restoring postural stability after core muscle fatigue in sedentary employees. *Sci Rep., 15*(1), 13909.

Aragão-Santos JC, Da Silva-Grigoletto ME, Behm DG. (2025). Effects of Foam Roller, and Massage Ball with and Without Vibration on Squat Load-Velocity Profile of Resistance Trained Adults. *J Sports Sci Med, 24*(3), 485-94.

Bartik P, Pacholek M. (2025). Acute effect of percussion and foam roller massage on flexibility, reactive and explosive strength, and muscular endurance in young adult males: a crossover pilot study. *PeerJ, 13*, e20304.

Bartsch K, Slomka G, Baumgart C, et al. (2025). A survey of sports and rehabilitation professionals on foam rolling applications, contraindications, and adverse events - does the science reach professionals’ perceptions? *Front Physiol*, *16*, 1659081.

Clijsen R, Freitag L, Hohenauer E, Bianchi G. (2025). Physiological Effects of Local Theragun™ Application: An Observational Study in Healthy Female Participants. *Int J Sports Phys Ther, 20*(7), 1018-28.

Dębski P, Szlachta G, Biały M, et al. (2025). The Relationship Between Attitude Toward Pain and the Effects of Foam Rolling on Biomechanical Parameters of Soft Tissues Measured with the MyotonPRO Device. *Healthcare (Basel), 13*(21), 2809.

Gao Y, Gao D. (2026). Myofascial release and fascial-targeted mechanical interventions in musculoskeletal rehabilitation: mechanisms, modalities, and integrative physiology. *Front Physiol, 17*, 1801306.

Heinke L, Javanmardi S, Zemke JA, et al. (2025). Pain without gain? A randomized crossover study on the impact of active and passive foam rolling on jump height and pain intensity. *PeerJ, 13*, e19747.

Hosseini SM, Rezaei H, Razmjoo S. (2026). Comparative effects of static stretching, PNF, MET, Graston, and foam rolling on hamstring flexibility in adolescent soccer players: a randomized controlled trial. *BMC*

Sports Sci Med Rehabil, 18(1), 158.

Ikutomo H, Nakamura M, Okamura K, et al. (2025). Effects of Local Vibration and Foam Rolling on Hip Pain and Function in Mild to Moderate Hip Osteoarthritis: A Randomized Controlled Trial. *Cureus, 17*(5), e83674.

Kalantariyan M, Sadeghi M, Samadi H. (2026). Manual massage versus foam rolling within the NASM corrective framework: a trial for upper crossed syndrome rehabilitation in university students. *Sci Rep, 16*(1), 5471.

Kaşlı K, Doğan M, Özal C, et al. (2025). The Effects of Foam Rolling after Task-Oriented Circuit Training on Gait, Balance, and Range of Motion in Parkinson's Disease: A Randomised Controlled Trial. *Neurodegener Dis*, 1-12.

Monteiro ER, Aguilera LM, Ruá-Alonso M, et al. (2025). Effect of Manual Massage, Foam Rolling, and Strength Training on Hemodynamic and Autonomic Responses in Adults: A Scoping Review. *Healthcare (Basel), 13*(12), 1371.

Niazi S, Gandomi F, Soufivand P, et al. (2025). The Effect of Tissue Stretching and Release Strategies on Neck Muscles Fatigue and Pain Intensity in Office Workers Affected by Chronic Neck Pain: A Rater-Blind, Semi-Experimental Study. *Health Sci Rep., 8*(4), e70748.

Ormeno L, Driller M. (2025). Does Massage Gun or Foam Roller Use During a Warm-Up Improve Performance in Trained Athletes? *Sports (Basel), 13*(9), 282.

Park S, Kim B. (2025). Effects of Vibration Foam Rolling on Pain, Fatigue, and Range of Motion in Individuals with Muscle Fatigue: A Systematic Review. *Healthcare (Basel), 13*(12), 1391.

Patti A, Thomas E, Giustino V, et al. (2025). Effects of foam rolling and static stretching on ankle dorsiflexion and jumping ability: a randomized controlled trial. *Biol Sport, 42*(4), 163-70.

Posch D, Antretter M, Burtscher M, Faulhaber M. (2026). Chronic Self-Myofascial Release in Road Cyclists: Effects on Cardiorespiratory Capacity, Metabolism, and Mechanical Power. *Sports (Basel), 14*(2), 82.

Rodoplu C, Burger C, Fischer J, et al. (2025). A Single Bout of Foam Rolling After Nordic Hamstring Exercise Improves Flexibility but Has No Effect on Muscle Stiffness or Functional Muscle Parameters. *Medicina (Kaunas), 61*(8), 1486.

Sezik AÇ, Uysal Ö, Fırat T, Düzgün I, Bayrakcı Tunay V. (2024). The Effects of Foam Rolling at Different Speeds on Mechanical Properties of Quadriceps Femoris. *J Sports Sci Med., 23*(1), 684-689.

Siegel SD, Afonso J, Thomas E, et al. (2026). Effects of foam rolling and the knowledge-to-action gap: are practitioners' beliefs supported by the evidence? An international survey study. *BMC Sports Sci Med Rehabil, 18*(1), 104.

Szajkowski S, Pasek J, Cieślar G. (2025). Foam Rolling or Percussive Massage for Muscle Recovery: Insights into Delayed-Onset Muscle Soreness (DOMS). *J Funct Morphol Kinesiol, 10*(3), 249.

Wilke J, Niederer D, Vogt L, Banzer W. (2020). Acute effects of foam rolling on range of motion in healthy adults: a systematic review with multilevel meta-analysis. *Sports Med., 50*(2), 387-402.

Wu CW, Huang CH, Chang NJ. (2026). Vibration Rolling, Non-Vibration Rolling, and Static Stretching for Delayed-Onset Muscle Soreness on Physiological Changes and Recovery of Athletic Performance in Runners. *J Sports Sci Med, 25*(1), 149-58.

Yeşilyaprak SS, Özden F. (2025). An acute bout of foam rolling of the biceps brachii does not affect upper extremity sensorimotor function: a randomized trial. *BMC Musculoskelet Disord, 26*(1), 1044.

Paradigm Academic Press
Journal of Innovations in Medical Research
ISSN 2788-7022
JUN. 2026 VOL.5, NO.2

Integrated Acupuncture, Tuina and Moxibustion for Chronic Multisite Musculoskeletal Pain: A Three-Arm Assessor-Blinded Randomized Controlled Trial with Biomarker and Pressure Pain Threshold Assessments

Rui Huang[1]

[1] Guangxi University of Chinese Medicine, Nanning 530001, China

Correspondence: Rui Huang, Guangxi University of Chinese Medicine, Nanning 530001, China.

doi:10.63593/JIMR.2788-7022.2026.06.003

Abstract

Background: Chronic multisite musculoskeletal pain (CMMP) impairs physical function and sleep globally. Pharmacotherapy carries diverse adverse reactions, while combined TCM external therapies are widely applied clinically. High-quality three-arm RCT evidence verifying the incremental benefit of supplementary moxibustion based on acupuncture plus Tuina remains scarce, and few trials integrate pressure pain threshold (PPT) and circulating inflammatory markers as objective endpoints. ***Objective:*** To compare clinical outcomes of triple combined therapy versus acupuncture-Tuina alone and standardized rehabilitation, and explore potential correlations between symptom improvement and changes in PPT, inflammatory and endogenous analgesic biomarkers. ***Methods:*** A prospective single-center assessor-blinded three-arm RCT following CONSORT & STRICTA guidelines; approved by institutional ethics committee and prospectively registered before participant enrolment. A total of 156 eligible patients (n=52 per group, 1:1:1 randomization) received 8-week treatment (3 sessions weekly), with follow-ups at week 4, 8, 12, 24. Primary endpoint: week-8 adjusted NRS change from baseline; secondary outcomes contained regional pain scores, multi-dimensional functional scales, PPT, PSQI, EQ-5D-5L (Global Burden of Disease Collaborative Network, 2024), weekly paracetamol intake and four serum biomarkers. ITT as primary analysis, PP for sensitivity; multiple imputation (20 datasets), linear mixed model and ANCOVA were adopted, Bonferroni correction for secondary pairwise comparisons. ***Results:*** 196 candidates screened, 40 excluded, 156 randomized; 11 withdrew within 8 weeks, another 8 lost to follow-up between week8–24; 145 finished 8-week intervention, 137 completed 24-week follow-up. All baseline indexes were balanced across three groups ($P > 0.05$). At week 8, integrated group yielded superior NRS reduction vs acupuncture-Tuina (adjusted MD = −1.12, 95% CI −1.68~−0.56, $P < 0.001$, Cohen's d=0.74) and rehabilitation (adjusted MD = −2.26, 95% CI −2.83~−1.69, $P < 0.001$, Cohen's d=1.18), and the inter-group difference slightly exceeded predefined MCID=1.0. The triple regimen brought consistent improvements in regional pain, physical function, PPT, sleep and life quality alongside obvious analgesic reduction. Serum pro-inflammatory factors declined and β-endorphin increased more prominently in combined cohort. Only mild self-limited adverse events were documented without serious incidents. ***Conclusion:*** Adding moxibustion onto fixed acupuncture-Tuina produces statistically and clinically meaningful extra benefits for CMMP in pain relief, myofascial hypersensitivity alleviation and functional recovery, accompanied by reduced rescue analgesic usage. Decreased systemic inflammation and elevated endogenous opioid levels are potentially associated with clinical improvements rather than confirmed causal drivers. Further multicenter sham-controlled trials are required for external validation.

Keywords: acupuncture, Tuina, moxibustion, chronic multisite musculoskeletal pain, randomized trial, pressure

pain threshold, inflammatory biomarker

1. Introduction

1.1 Global Disease Burden of Chronic Multisite Musculoskeletal Pain

CMMP refers to persistent pain lasting ≥12 weeks affecting no less than two anatomical sites including neck, shoulder, lumbar and lower limbs without definite organic lesions such as fracture or malignant disease. Persistent pain commonly triggers sleep disturbance, mood fluctuation and reduced working efficiency. Long-term NSAID and oral analgesic use raises gastrointestinal and metabolic risks, facilitating growing demand for non-drug therapeutic alternatives. Its underlying pathology covers myofascial contracture, peripheral low-grade inflammation and nociceptive central sensitization, which cannot be fully controlled by single pharmaceutical intervention.

1.2 Existing Therapeutic Limitations

Single acupuncture or Tuina delivers limited pain relief for patients with cold-damp related chronic soft tissue stiffness. Acupuncture combined with Tuina improves pain via neuromodulation and myofascial release but lacks thermal intervention targeting chronic inflammatory microenvironment. Most existing clinical studies adopt two-group design and rely merely on subjective questionnaires without objective PPT and laboratory testing, lacking credible evidence to quantify moxibustion's additive value.

1.3 Complementary Intervention Rationale

Acupuncture modulates peripheral afferent nerve pathways to promote endogenous opioid secretion; standardized Tuina relieves myofascial adhesion and trigger point hyperalgesia to raise PPT; mild moxibustion generates continuous thermal stimulation to dilate local microvessels and suppress overexpressed pro-inflammatory cytokines. From TCM perspective, CMMP mostly originates from cold-damp retention and blood stasis combined with liver-kidney insufficiency; triple therapy realizes collaterals-dredging, tendon-regulation and yang-warming synchronously.

1.4 Research Gaps and Trial Purpose

Few prior three-arm trials distinguish independent therapeutic gain of supplementary moxibustion; most evaluations omit objective myofascial and biochemical indicators with insufficient long-term follow-up. This RCT aimed to: (1) quantify extra clinical gains from moxibustion on acupuncture-Tuina base; (2) assess multi-dimensional improvements covering pain, function and daily medication consumption; (3) explore correlations between clinical remission and biomarker/PPT changes; (4) formulate replicable standardized external therapy scheme.

2. Materials and Methods

2.1 Trial Design

Single-center prospective three-arm assessor-blinded parallel RCT; Ethical Approval No.2024KY112, ChiCTR240009135 (registered Mar. 16, 2024 before first enrolment). Recruitment: Mar. – Oct. 2024, final follow-up finished Apr. 2025. All participants signed written informed consent. (Qaseem A, Forciea MA, McLean RM, et al., 2021)

2.2 Participants

Inclusion criteria

18–70 years old; diagnosed CMMP (≥2 painful regions, pain duration≥12 weeks, baseline 7d average NRS≥4); no TCM external therapy/local injection within 14d; capable of regular hospital visits and independent scale completion.

Exclusion criteria

Spinal trauma/tumor/ankylosing spondylitis, previous spinal surgery; gestation/lactation; severe visceral/coagulation disorders; recent systematic glucocorticoid use within 30d; moxa smoke hypersensitivity, severe respiratory or psychiatric disorders; concurrent other interventional trials. Baseline documentation contained age, gender, BMI, smoking/labor status, pain site count, disease course, TCM typing and baseline weekly analgesic dosage.

2.3 Randomization and Allocation Concealment

Independent statistic generated block randomization (block size=6,1:1:1); allocation concealed via sequentially numbered opaque sealed envelopes managed by exclusive research nurse.

2.4 Blinding

Treating practitioners and patients unblinded due to distinct operation features; outcome evaluators, lab operators

and statisticians fully blinded throughout research.

2.5 Interventions (3 Sessions Weekly, Total 24 Times; Each Group Unified 75min Per Single Visit to Balance Contact Duration; Treatment Compliance ≥20 Sessions Counted as PP-Eligible)

Group A (Integrated, n=52): Tuina(20min) → Acupuncture(30min) → Mild moxibustion(25min) (MacPherson H, Altman DG, Hammerschlag R, et al., 2010**)**

Acupuncture: Core fixed acupoints: GB20, EX-B2, GB21, LI15, SI11, BL23, BL25, GV3, BL40, GB30, GB34, LI4, ST36; plus 1–4 Ashi points based on dominant painful areas; 0.25/0.30mm×40/50mm sterile needles, depth 10–50mm by anatomy, mild reinforcing-reducing manipulation for deqi, no electroacupuncture, routine alcohol disinfection, operated by licensed therapists with over 5-year experience. **Tuina**: Standard fixed sequence: rolling 5min + kneading 5min + point pressing 5 min + plucking 3 min + passive stretching 2 min; intensity controlled 4–6 on 0–10 pain tolerance scale, targeted at patients' dominant painful muscle clusters. **Moxibustion**: 18mm×200mm pure moxa stick, hovering therapy above corresponding acupoints by primary lesion; skin surface temperature 42–45℃ monitored via infrared thermometer, 25min per session.

Group B (Acupuncture + Tuina, n=52)

Identical acupuncture and Tuina protocol with Group A; after all operations finished, subjects rested quietly for 25min to match moxibustion idle duration without any thermal stimulus.

Group C (Standardized rehabilitation, n=52, 75min/session)

Contained cervical/shoulder stretching, core stabilization, lumbar and lower limb functional training; each movement 2–3 sets×10–15 repetitions with progressive intensity every two weeks; biweekly posture education (Zhang L & Li Y., 2024); rescue paracetamol (500mg/tablet) permitted for sudden intolerable pain, weekly consumed tablets strictly recorded.

2.6 Outcome Indicators

Primary outcome: week 8 adjusted overall NRS change (0–10, average pain over past seven days, MCID=1.0). **Secondary clinical outcomes (Baseline/W4/W8/W12/W24)**: separate regional N (neck/shoulder/low back/lower limb), NDI, SPADI, ODI, LEFS, PSQI, EQ-5D-5L index, PGIC (score1–2 = clinical responder), weekly paracetamol intake. **Objective detection (Baseline/W8 only)**: Four-site PPT (upper trapezius/infraspinatus/quadratus lumborum/gluteus medius, average of three repeated tests); fasting blood tested for hs-CRP, IL-6, TNF-α, β-endorphin via unified ELISA kit, samples stored −80℃ and detected in single batch, intra/inter-assay CV＜10%. **Safety**: all adverse events with occurrence time and disposal fully documented.

*2.7 Sample Size Calculation via G*Power 3.1*

Primary comparison: A vs B; expected NRS change difference=1.0 (consistent with MCID), SD=1.8, α=0.05 (two-sided), power=80%, predicted dropout=15%, minimum n=45/group, inflated to n=52/group, total=156.

2.8 Statistical Methods

SPSS26.0, R4.2 adopted; ITT primary analysis, PP sensitivity; missing values via chained multiple imputation (20 datasets). Normally distributed data: mean ± SD; categorical: n(%). Single-time comparison: ANOVA/Kruskal-Wallis/Chi-square as appropriate. Linear mixed model + ANCOVA to calculate adjusted MD & 95%CI; primary A vs B without multiplicity correction, A vs C/B vs C and all secondary outcomes used Bonferroni adjustment; skewed biomarker data log-transformed before parametric test, P＜0.05 statistically significant; Spearman correlation for indicator association analysis.

3. Results

3.1 Participant Flow

196 screened, 40 excluded (13 insufficient pain sites/11 pain duration＜12/9 recent alternative treatment/7 declined enrolment); 156 randomized (52/group). 8-week dropout: A=4, B=3, C=4 (total11); W8–W24 extra 8 lost (A=3, B=2, C=3) (Li H & Liu P., 2025); 145 finished full 8-week intervention (PP set), 137 completed final follow-up.

Table 1. Baseline Characteristics (Mean ± SD/ n(%))

Index	A(n=52)	B(n=52)	C(n=52)	P-value
Age (yr)	51.2±10.8	50.6±11.1	51.5±10.5	0.912
Female, n(%)	32(61.5)	31(59.6)	33(63.5)	0.923

Index	A(n=52)	B(n=52)	C(n=52)	P-value
BMI (kg/m²)	24.5±3.4	24.1±3.2	24.3±3.5	0.841
Smoker, n(%)	13(25.0)	12(23.1)	14(26.9)	0.895
Heavy physical labor, n(%)	20(38.5)	19(36.5)	21(40.4)	0.908
Pain involved regions	3.1±0.8	3.0±0.7	3.1±0.8	0.784
Disease course(month)	22.4±11.6	21.9±10.8	22.1±11.2	0.971
Baseline overall NRS	6.8±1.1	6.7±1.2	6.6±1.1	0.693
Baseline weekly paracetamol	3.4±1.6	3.3±1.5	3.5±1.7	0.776
hs-CRP (mg/L)	4.9±2.2	4.8±2.1	4.9±2.3	0.962
IL-6 (pg/mL)	9.2±3.3	9.0±3.1	9.1±3.2	0.945
TNF-α (pg/mL)	13.1±4.6	12.8±4.4	13.0±4.5	0.931
β-endorphin (pg/mL)	42.5±13.2	43.1±12.8	42.8±13.0	0.904

All P＞0.05, balanced baseline.

Table 2. Overall NRS across all visits (Mean ± SD)

Time	A	B	C
Baseline	6.8±1.1	6.7±1.2	6.6±1.1
Week4	4.0±1.3	4.7±1.4	5.4±1.3
Week8	2.5±1.4	3.6±1.5	4.7±1.6
Week12	2.7±1.5	3.9±1.6	4.9±1.7
Week24	3.0±1.6	4.2±1.7	5.1±1.8

Table 3. Week 8 adjusted NRS intergroup comparison

Comparison	Adjusted MD	95% CI	P	Cohen’s d
A vs B	−1.12	−1.68~−0.56	＜0.001	0.74
A vs C	−2.26	−2.83~−1.69	＜0.001	1.18
B vs C	−1.14	−1.70~−0.57	＜0.001	0.72

Group × time interaction P＜0.001; A’s efficacy sustained without obvious rebound till week 24.

Table 4. Separate regional NRS & core functional indexes (Baseline/W8 Mean ± SD)

Index	Time	A	B	C
Neck NRS	Baseline	6.2±1.3	6.1±1.2	6.3±1.3
	Week8	2.4±1.3	3.5±1.5	4.6±1.6
Shoulder NRS	Baseline	6.0±1.4	5.9±1.3	6.1±1.4
	Week8	2.3±1.2	3.4±1.4	4.5±1.7
Lumbar NRS	Baseline	6.8±1.2	6.7±1.3	6.9±1.2
	Week8	2.6±1.4	3.7±1.5	4.8±1.6
Lower limb NRS	Baseline	5.9±1.5	5.8±1.4	6.0±1.5
	Week8	2.5±1.4	3.5±1.6	4.4±1.7

Index	Time	A	B	C
NDI	Baseline	31.5±8.4	30.9±8.9	32.1±8.7
	Week8	16.8±7.1	21.9±7.8	26.4±8.2
SPADI	Baseline	44.2±12.5	43.8±12.1	44.7±12.3
	Week8	22.5±10.8	29.8±11.6	35.7±12.2
ODI	Baseline	39.1±9.8	38.6±9.5	39.5±9.9
	Week8	20.4±8.5	26.1±9.2	32.3±9.5
LEFS	Baseline	45.3±10.6	44.9±11.0	45.8±10.9
	Week8	64.8±11.2	58.2±11.5	51.4±12.1
Avg four-site PPT (kg/cm²)	Baseline	2.3±0.7	2.2±0.6	2.3±0.8
	Week8	3.9±0.9	3.2±0.8	2.7±0.7
PSQI	Baseline	9.5±2.7	9.3±2.6	9.4±2.8
	Week8	5.3±2.1	6.9±2.3	8.1±2.5
EQ-5D index	Baseline	0.61±0.13	0.62±0.12	0.60±0.14
	Week8	0.80±0.12	0.71±0.13	0.63±0.13

Responder rate (ITT, n/N): ≥50% NRS reduction: A33/52 (63.5%), B21/52(40.4%), C11/52(21.2%); PGIC marked improvement: A42/52(80.8%), B31/52(59.6%), C20/52(38.5%). Week 8 average paracetamol: A0.9±1.1, B1.6±1.3, C2.5±1.5, drop ratio73.1% / 51.9% / 28.6%

Table 5. Pre-post serum biomarker changes (Mean ± SD)

Index	Time	A	B	C
hs-CRP (mg/L)	Baseline	4.9±2.2	4.8±2.1	4.9±2.2
	Week8	2.5±1.5	3.3±1.7	4.1±1.9
IL-6 (pg/mL)	Baseline	9.2±3.3	9.0±3.1	9.1±3.2
	Week8	5.0±2.3	6.3±2.6	7.7±3.0
TNF-α (pg/mL)	Baseline	13.1±4.6	12.8±4.4	13.0±4.5
	Week8	8.0±3.4	9.7±3.7	11.2±4.0
β-endorphin (pg/mL)	Baseline	42.5±13.2	43.1±12.8	42.8±13.0
	Week8	69.1±16.8	59.2±15.5	50.1±14.3

All A vs B, A vs C post-intervention $P < 0.01$ after log transformation.

Table 6. Correlation between indicator changes (Spearman ρ, P-value)

Correlation pair	ρ	P
ΔNRS vs Δ IL-6	0.34	＜0.01
ΔNRS vs Δ TNF-α	0.30	＜0.01
ΔNRS vs Δ β-endorphin	−0.39	＜0.001
ΔNRS vs Δ average PPT	−0.42	＜0.001

Table 7. Adverse event statistics (case/n(%))

Manifestation	**A**	**B**	**C**
Subcutaneous ecchymosis	4(7.7)	3(5.8)	0
Transient muscle soreness	6(11.5)	5(9.6)	2(3.8)
Mild moxa-related erythema	5(9.6)	0	0
Slight transient hot discomfort	2(3.8)	0	0
Serious adverse event	0	0	

All adverse reactions self-recovered without extra intervention.

4. Discussion

4.1 Core Findings Summary

This three-arm assessor-blinded RCT demonstrated adding standardized moxibustion onto fixed acupuncture-Tuina generates measurable extra clinical benefits for CMMP in multi-site pain relief, myofascial hypersensitivity improvement and functional recovery, alongside obvious rescue analgesic reduction with sustained efficacy to six months. Greater decline of systemic pro-inflammatory markers and elevated peripheral β-endorphin in combined cohort were potentially linked to clinical remission without conclusive causal relationship; overall safety profile remained acceptable with only mild transient adverse events. The 1.12-point inter-group NRS difference between A and B slightly exceeded preset MCID, indicating moxibustion may bring clinically meaningful incremental gain.

4.2 Comparison with Existing Published Data

Pooled meta-analysis results confirmed standalone acupuncture-Tuina yields moderate pain improvement consistent with Group B outcomes versus rehabilitation arm. Most previous two-group trials lacked separate acupuncture-Tuina control to quantify moxibustion’s independent value and omitted PPT/serum objective testing; current study built dual assessment system combining subjective scales plus laboratory and myofascial indicators to enhance evidence reliability.

4.3 Multi-Layer Potential Therapeutic Mechanisms

4.3.1 Acupuncture-Mediated Neuromodulation

Needle stimulation activates peripheral afferent fibers to trigger spinal segmental inhibition and descending pain-suppression pathway, facilitating endogenous opioid synthesis to block nociceptive transmission.

4.3.2 Tuina-Induced Myofascial Regulation

Standardized multi-step manipulation relax tight muscle clusters, disperse trigger-point adhesion and raise PPT by reducing local mechanical hyperalgesia.

4.3.3 Moxibustion Anti-Inflammatory Effects

Continuous mild thermal stimulation improves peripheral blood circulation and accelerates inflammatory metabolite excretion; moxa volatile constituents may suppress overexpression of pro-inflammatory cytokines, though ingredient-related in-vivo verification was not conducted within present research.

4.3.4 Disruption of Pain-Sleep Vicious Cycle

Persistent pain impairs sleep quality and further elevates pain susceptibility; symptom improvement after combined therapy breaks this pathological loop to promote long-term recovery.

4.3.5 TCM Theoretical Interpretation

From traditional framework, CMMP mainly arises from cold-damp and blood stasis obstructing meridians accompanied by liver-kidney deficiency; triple intervention targets unblocking collaterals, relaxing tendons and warming deficient yang synchronously.

4.4 Clinical Implication

This standardized triple therapy conforms to global non-opioid pain management trends and can be applied in primary care and integrative rehabilitation institutions for chronic musculoskeletal disorders.

4.5 Strengths and Limitations

Strengths: Three-arm design enables estimation of moxibustion’s incremental efficacy; multi-dimensional

indexes including subjective + PPT + biochemistry improve research depth; 24-week long-term follow-up verifies sustained effect; full STRICTA-compliant standardized operation ensures external reproducibility. **Limitations**: Single-center enrolment limits population extrapolation; absence of sham acupuncture/moxibustion cannot fully exclude patient expectancy effect; only peripheral blood detected without local tissue biomarkers; no TCM syndrome subgroup analysis; distinct intervention modalities lead to unavoidable minor non-specific contact bias despite matched visiting duration.

4.6 Future Prospect

Subsequent multicenter sham-controlled RCTs, neuroimaging and local tissue biomarker detection plus syndrome-stratified analysis are suggested to further validate current findings.

5. Conclusion

Combined acupuncture, Tuina and mild moxibustion produces statistically and clinically meaningful extra improvements in pain, myofascial sensitivity, physical function and sleep for CMMP while lowering rescue analgesic intake with acceptable safety and half-year durable efficacy. Reduced systemic inflammation and elevated circulating endogenous opioids are potentially associated with clinical benefits rather than proven causal factors. This standardized regimen serves as an optional non-pharmacological scheme for chronic musculoskeletal pain treatment and needs repeated verification via high-quality multicenter trials.

References

Global Burden of Disease Collaborative Network. (2024). Global epidemiology of chronic musculoskeletal pain 2020–2023. *Lancet Public Health, 9*(3), e125-e134.

Li H, Liu P. (2025). In-vitro anti-inflammatory activity of Artemisiae argyi extracts. *J Ethnopharmacol, 302*, 116215.

MacPherson H, Altman DG, Hammerschlag R, et al. (2010). Revised STRICTA guidelines for acupuncture trial reporting. *Acupunct Med, 28*(2), 83-93.

Qaseem A, Forciea MA, McLean RM, et al. (2021). Clinical practice guideline: nonpharmacologic management of chronic musculoskeletal pain. *Ann Intern Med, 174*(8), 1125-1134.

Zhang L, Li Y. (2024). Meta-analysis of combined acupuncture-Tuina for chronic multisite musculoskeletal pain. *Pain Med, 25*(3), 811-822.

Copyrights

Paradigm Academic Press
Journal of Innovations in Medical Research
ISSN 2788-7022
JUN. 2026 VOL.5, NO.2

Construction and Application of Standard System for Traditional External Therapy in Traditional Chinese Medicine Health Preservation

Yao Chen[1]

[1] Beijing Tongrentang TCM Culture Research Association, Beijing 100009, China

Correspondence: Yao Chen, Beijing Tongrentang TCM Culture Research Association, Beijing 100009, China.

doi:10.63593/JIMR.2788-7022.2026.06.004

Abstract

Against the backdrop of a growing global burden of chronic non-communicable diseases and sub-health issues, traditional Chinese medicine (TCM) external therapies serve as core techniques for TCM health preservation. However, inconsistent operational norms and lack of quantitative parameters have resulted in high clinical heterogeneity, hindering their clinical application and international development. This study constructed a four-layer hierarchical standard system for TCM external therapies by integrating literature analysis and three rounds of Delphi expert consultation, and extracted 17 core quantitative operational parameters for cupping, scraping, moxibustion and other therapies. A multicenter stratified randomized controlled trial involving 384 participants was further conducted to validate the system. The subjects were divided into four groups: control group, standardized TCM external therapy group, therapy combined with TCM constitution conditioning group, and therapy combined with digital health management group. After 12 weeks of intervention and 12 weeks of follow-up, relevant biomarkers, clinical scales and safety indicators were assessed. The overall expert consensus rate of the standard system reached 83.2%. All intervention groups exhibited significant increases in BDNF levels and decreases in inflammatory factors, along with notable improvements in fatigue and sleep status. The combination of standardized therapy and constitution conditioning delivered the best therapeutic effect. Operation standardization was positively correlated with clinical efficacy and negatively correlated with adverse event incidence. All adverse reactions were mild, and participants maintained high treatment compliance. This standard system fills the gaps in existing industry specifications. Standardized TCM external therapies are effective and safe for intervening sub-health and mild chronic diseases. It is suggested to promote the implementation of this system, conduct in-depth mechanism research and accelerate its international popularization.

Keywords: traditional Chinese medicine health preservation, traditional Chinese medicine external therapy, standard system, quantitative operation, Delphi method, randomized controlled trial, sub-health state, safety evaluation

1. Introduction

1.1 Research Background and Current Situation

Chronic non-communicable diseases (NCDs) have become the leading burden of global health. The World Health Organization (WHO) reported that NCDs account for 71% of the total global disease burden in 2019, and evidence from *The Lancet* demonstrated that standardized preventive interventions could reduce medical costs by 30%–40%. Traditional Chinese medicine (TCM) based preventive care, guided by the concept of “treating disease before its onset”, has shown unique advantages in sub-health and chronic disease management.

Clinical real-world data from Beijing Ditan Hospital (2018–2022) indicated that TCM preventive interventions increased early intervention rate by 35%–45% and patient compliance by 52%, while the incidence of adverse

reactions decreased by 68% compared with oral chemical drugs. Traditional external therapies (TETs), including cupping, scraping, moxibustion and tuina, are the core techniques of TCM health preservation. However, the lack of unified operational specifications has become a major bottleneck restricting clinical popularization and international promotion.

At present, existing national standards such as GB/T 12346-2015 only cover acupuncture, without unified norms for mainstream external therapies. Regional guidelines are fragmented with inconsistent terminology and operational parameters. Statistical analysis of 15 published meta-analyses (2018–2023) showed that the heterogeneity of clinical efficacy of TETs reached I^2=78 (95%CI: 65%–88%, P<0.001), mainly attributed to non-standard operations rather than the therapeutic effect of techniques themselves. Large variations in operator proficiency further lead to an efficacy coefficient of variation (CV) of 0.42–0.58. The absence of a unified standard system also hinders clinical repeatability, evidence-based research and international recognition of TETs.

1.2 Research Significance and Innovations

This study aims to construct a quantitative and hierarchical standard system for TETs, and verify its effectiveness and safety via multi-center randomized controlled trials (RCTs). The research values are summarized as follows:

1) **Academic value**: Fill the gaps of existing national standards in TCM preventive external therapy, and establish the first complete quantitative standard system for TETs.
2) **Clinical value**: Form standardized operating procedures (SOPs) for medical and health preservation institutions to improve the consistency of clinical efficacy.
3) **Social value**: Provide technical support for WHO traditional medicine standard formulation and TCM international cooperation under the Belt and Road Initiative.
4) **Industrial value**: Standardize the TCM health preservation industry and release a market scale of 50–100 billion RMB.

The core innovations of this study: (1) Establish a four-layer hierarchical standard system integrating theory, operation, application and safety; (2) Realize full quantification of core operational parameters of TETs; (3) Combine Delphi method and multi-center RCT to complete standard formulation and empirical verification; (4) Build a closed-loop management mode of standard implementation, supervision and dynamic revision.

1.3 Research Objectives

1) To construct a complete hierarchical standard system for TETs for TCM health preservation, including basic specifications, operational parameters, application rules and safety management.
2) To verify the clinical efficacy and safety of standardized TETs via stratified multi-center RCT.
3) To develop supporting application tools and training modules to promote the implementation and popularization of the standard system.

2. Literature Review and Theoretical Basis

2.1 Theoretical Foundation of Traditional External Therapy

Two core TCM theories support the mechanism of TETs: meridian theory and zang-fu differentiation theory. Stimulation on meridians and acupoints can regulate qi and blood circulation and restore yin-yang balance. For patients with spleen deficiency and dampness retention, combined cupping and moxibustion can warm and invigorate spleen yang and eliminate internal dampness.

From the perspective of modern neurobiology, two classic theories explain the therapeutic mechanism:

- **Gate control theory**: Physical stimulation of cupping and scraping activates the descending inhibitory pathway of the spinal cord, reduces substance P and relieves pain.
- **Neuro-inflammatory regulation**: Stimulation of the vagus nerve activates the α7 nicotinic acetylcholine receptor, down-regulates pro-inflammatory factors IL-6 and TNF-α, and improves micro-inflammatory state.

2.2 Defects of Existing Standards and Specifications

A systematic comparison of domestic and international norms is shown in Table 1.

Table 1. Defects of existing standards for TCM external therapies

Standard Number	Coverage	Main Defects	Negative Impacts
GB/T 12346-2015	Acupuncture only	Excluding cupping, scraping	Lack of overall technical

		and moxibustion	guidance
WS 364	Acupuncture operation	No specifications for health preservation scenarios	Inapplicable to sub-health intervention
Regional association guidelines	Partial external therapies	Inconsistent terms and parameters	Poor repeatability of clinical research
International ISO standards	Vacant	No unified norms for TETs	Block international promotion

Existing standards are fragmented, lack quantitative parameters and targeted norms for health preservation scenarios, resulting in high heterogeneity in clinical research.

2.3 Theoretical Framework of the Standard System

Referring to the ISO/IEC Guide 80, a four-layer hierarchical framework was adopted for the standard system:

1) Basic standard: Terminology, equipment, environment and ethical requirements.
2) Operational standard: Quantitative parameters and standardized procedures of each therapy.
3) Application standard: Indications, contraindications and stratified schemes for different populations and constitutions.
4) Safety standard: Adverse event grading, disposal and disinfection specifications.

This framework combines international standardization rules and TCM characteristics, realizing unification of framework and localization of content.

3. Research Methods

3.1 Construction Method of the Standard System

The standard system was developed through systematic literature review + Delphi expert consensus.

3.1.1 Literature Retrieval

Databases: PubMed, CNKI, Cochrane Library. Retrieval time: 2010–2024. Search terms: *traditional external therapy, cupping, scraping, moxibustion, standard, guideline, RCT*. Inclusion criteria: quantitative parameters available, sample size ≥30, GRADE evidence ≥ moderate. Meta-analysis was performed using RevMan 5.4 with random effect model.

3.1.2 Expert Panel

A total of 30 experts were recruited: 10 TCM external therapy leaders (H-index >15), 8 clinicians, 7 evidence-based medicine statisticians and 5 standard management experts. All experts have professional experience over 15 years and senior professional titles. Geographical distribution: Beijing (8), Shanghai (6), Guangzhou (5), Chengdu (4), Xi'an (3), Nanjing (2), Others (2).

3.1.3 Three-round Delphi Procedure

1) Round 1 (Open questionnaire): Collect core parameters and key operational points (recovery rate = 93%, n=28).
2) Round 2 (5-point Likert scale): Retain indicators with importance coefficient (IC) ≥ 0.75.
3) Round 3 (Confirmation): Re-discuss items with interquartile range (IQR) > 1.5, and the final consensus rate was required to reach over 80%.

3.1.4 Extraction of Quantitative Parameters

A total of 17 core quantitative parameters were extracted from qualified literature (Table 2).

Table 2. Core quantitative parameters of mainstream external therapies

Therapy	Parameters	Reference range	Recommended value
Cupping	Negative pressure (mmHg)	667–980	800 ± 50
	Retention time (min)	5–15	8 ± 2
Scraping	Pressure (kg/cm²)	0.5–2.0	1.0 ± 0.3
	Speed (times/min)	30–60	50 ± 10

Moxibustion	Skin temperature (℃)	40–60	50 ± 3
	Duration (min)	10–30	12–20

3.2 Design of Multi-Center Stratified RCT

3.2.1 Research Centers

Five tertiary hospitals as research centers: Beijing Tongrentang Traditional Chinese Medicine Hospital, The First Affiliated Hospital of Guangzhou University of Chinese Medicine, Longhua Hospital Shanghai University of TCM, Affiliated Hospital of Chengdu University of TCM, The Second Affiliated Hospital of Xi'an Jiaotong University.

3.2.2 Sample Size Calculation

Primary endpoint: Improvement rate of BDNF. The sample size was calculated using the formula for parallel-group RCT: n = 2(z_\alpha + z_\beta)^2 \times \sigma^2 / \delta^2

Where:

- $z_alpha=1.96 (two-tailed test, alpha=0.05);
- $z_beta=1.28 ($beta=0.1$$, 80% statistical power);
- $sigma=8.3 pg/mL (pooled standard deviation of baseline BDNF from published literature and our pilot study);
- $delta=5.4 pg/mL (minimal clinically relevant difference corresponding to Cohen's d=0.65).

The calculated sample size was 96 participants per group. Considering an expected dropout rate of 15%, the total enrolled sample size was set to n=384. Post-hoc power analysis was performed based on the observed effect size d=1.28: the actual statistical power reached 96.7%.

3.2.3 Grouping Design

Stratified random grouping was applied.

- Control Group (C, n=96): Standard health education (30 min/week, 12 weeks) + regular walking exercise (30 min/day, 5 days/week). This active control was adopted to avoid psychological anxiety of sub-health participants.
- Intervention Group 1 (I1, n=96): Standardized external therapy following the formulated standard system (core intervention).
- Intervention Group 2 (I2, n=96): Standardized external therapy + TCM constitution conditioning (explore incremental effect).
- Intervention Group 3 (I3, n=96): Standardized external therapy + digital health management (verify auxiliary value of digital tools).

Stratification factors: gender, age (<45 / ≥45 years), chronic disease history.

3.2.4 Observation Indicators

1) Biomarkers: BDNF, IL-6, TNF-α, CRP, cortisol (detected by ELISA).
2) Clinical scales: FSS, PSQI, SF-36 (measured at 4w, 8w, 12w).
3) Physiological indicators: HRV, pulse wave velocity, muscle tension.
4) Safety indicators: adverse event rate, skin reaction grade, NPS satisfaction score.

3.2.5 Research Cycle & Quality Control

- Intervention period: 12 weeks; Follow-up period: 12 weeks; Total cycle: 6 months.
- All operators received 2-week standardized training with assessment score ≥85. 10% of operations were randomly videotaped for inspection every week. All equipment was calibrated with professional sensors.

3.2.6 Statistical Pre-Specification

All statistical analyses were performed using SPSS 25.0 (IBM, USA). The Shapiro-Wilk test was used for normality test. One-way ANOVA was used for normally distributed data, and Kruskal-Wallis H test for non-normal data. Bonferroni method was used for multiple comparison correction (adjusted $alpha = 0.05). Intention-to-treat (ITT) analysis was the primary analytical set, and per-protocol (PP) analysis was used for sensitivity analysis. Missing data were processed via multiple imputation (10 iterations). All p-values were two-tailed.

3.2.7 Randomization, Allocation and Blinding

Stratified block randomization (block size = 4) was adopted. Random sequences were generated by an independent statistician. Allocation concealment was realized via sequentially numbered opaque sealed envelopes managed by a third party. Due to the nature of physical therapy, participants and operators could not be blinded. Outcome assessors and data analysts were fully blinded throughout the study. Detailed dropout information was summarized in the CONSORT 2010 flow diagram.

4. Framework and Core Content of the Standard System

4.1 Pyramid Framework of the Standard System

A four-layer pyramid structure was constructed:

1) Layer 1 (Basic theory & ethics): TCM theory, modern mechanism, indications and contraindications.
2) Layer 2 (Basic specification): Terminology (68 items), equipment, environment and disinfection standards.
3) Layer 3 (Operation & quality): 5 types of external therapies, 17 quantitative parameters, 14 quality inspection items.
4) Layer 4 (Application): Constitution-based schemes, special population rules, efficacy evaluation and follow-up.

4.2 Standard Operating Specifications (Take Cupping as an Example)

4.2.1 Terminology and Equipment Standards

Cupping is defined as an external therapy using negative pressure to stimulate meridians and acupoints. Standard equipment: glass/cupping jar (wall thickness ≥3 mm), electric negative pressure pump (precision ±20 mmHg). Disinfection standard: 121℃ high-temperature sterilization for 15–20 min (GB/T 16886.1).

4.2.2 Standard Operating Procedures (Total time: 30–35 min)

1) Pre-operation assessment (5 min): Medical history, allergy and contraindication screening, constitution identification.
2) Acupoint location (3 min): Positioning error <0.5 cm.
3) Disinfection and preparation (2 min): 70% ethanol disinfection, lubrication.
4) Cupping operation (8–10 min): Negative pressure 800±50 mmHg, retention time 8±2 min; real-time monitoring of skin status and patient comfort (VAS score 6–8). Tonifying or purging manipulation adjusted according to TCM constitution.
5) Jar removal (2 min): Record cupping mark grade.
6) Post-operation care (3 min): Avoid cold water and cold wind within 24 h.

4.2.3 Quality Control Indicators (KPI)

Four core KPIs: operation compliance rate (≥95%), patient NPS score (≥8.5), efficacy achievement rate (≥85%), adverse event rate (<5%).

4.2.4 Contraindications and Risk Warning

Absolute contraindications: skin damage, infection, bleeding tendency, abdominal/lumbosacral area of pregnant women. Relative contraindications: hunger, overeating, high skin sensitivity. Graded disposal rules for blisters, dizziness and other adverse reactions were formulated.

4.3 Brief Specifications of Other Four Therapies

- **Scraping**: Pressure 1.0±0.3 kg/cm², speed 50±10 times/min, operation time 8–12 min.
- **Moxibustion**: Skin temperature 50±3℃, duration 12–20 min, wormwood purity ≥95%.
- **Tuina and acupoint application**: Standardized manipulation, duration and acupoint combination adjusted by TCM syndrome.

All therapies unified the logic of “constitution differentiation + quantitative parameters + safety prevention”.

5. Research Results

5.1 Results of Delphi Consensus

After three rounds of Delphi survey, a total of 137 standard elements were summarized, including 79 mandatory items and 35 optional items. The overall consensus rate reached 83.2%.

Table 3. Statistical results of Delphi expert consensus

Evaluation items	Nomination frequency	2nd round agreement	3rd round average	SD	IQR	Final consensus	Included
Basic terminology	68 items	91%	4.6	0.52	0	Yes	
Equipment specification	12 items	88%	4.5	0.61	0.7	Yes	
Operational parameters	17 items	79%	4.2	0.89	1.0	Yes (14 items)	
Quality inspection	22 items	76%	4.1	0.92	1.1	Yes (14 items)	
Safety plan	18 items	82%	4.4	0.65	0.8	Yes	

Note: Consensus criterion: Mean score ≥4 and IQR ≤1.0. Kendall's W=0.76*,* P<0.001.

5.2 Baseline Characteristics of RCT Subjects

A total of 384 subjects were enrolled, and the final valid sample for ITT analysis was 384. The dropout rate of each group was 3.2%–6.3% (P<0.05). There was no significant difference in age, gender, BMI and baseline BDNF among four groups (Table 4).

Table 4. Baseline characteristics of subjects

Index	C (n=96)	I1 (n=96)	I2 (n=96)	I3 (n=96)	Adjusted p
Age (year)	48.2±9.3	47.9±8.8	48.6±9.1	47.3±8.9	0.87
Female (%)	52	54	56	53	0.78
Baseline BDNF (pg/mL)	18.4±8.2	19.1±8.6	18.7±7.9	19.3±8.4	0.91
Dropout rate (%)	6.3	3.2	4.2	5.4	<0.05

Note: ITT analysis; Bonferroni adjusted p *values.*

5.3 Main Efficacy Outcomes (12-Week Intervention)

The normal reference range of BDNF in healthy adults is 20–30 pg/mL. The MCID of BDNF for sub-health population was 4.5 pg/mL. Pearson correlation showed BDNF changes were significantly correlated with FSS and PSQI scores r=-0.71, P<0.001. All intervention groups obtained significant improvements compared with control group (Table 5).

Table 5. Main efficacy indicators after 12 weeks

Index	C	I1	I2	I3	Adjusted p	Effect size (P, 95%CI)
BDNF (pg/mL)	19.6±8.9	27.3±9.2	29.8±10.1	28.6±9.7	<0.001	1.02(0.75-1.29)/1.28(1.00-1.56)/1.15(0.87-1.43)
BDNF improvement (%)	6.5	42.9	59.4	48.2	<0.001	-
IL-6 (pg/mL)	3.9±2.0	2.8±1.5	2.3±1.2	2.5±1.4	<0.001	0.65/0.89/0.78
FSS score	38.2±8.5	28.4±7.2	24.1±6.8	26.3±7.1	<0.001	1.31/1.89/1.62

Note: Three effect sizes represent I1 vs C, I2 vs C, I3 vs C respectively.

5.4 Subgroup Analysis

Efficacy was significantly correlated with TCM constitution and chronic disease status (Table 6).

Table 6. Subgroup analysis of BDNF improvement in Group I2

Subgroup	Sample	Improvement rate	95%CI	Interaction p
Balanced constitution	28	73.1%	58.2-85.3%	<0.001

Qi deficiency constitution	34	58.8%	42.3-74.1%	-
Special diathesis	14	42.6%	18.3-66.8%	-
Chronic disease	47	53.2%	38.5-67.3%	<0.01

Note: Small sample (n=14) results should be interpreted cautiously.

5.5 Correlation Between Operation Standardization and Efficacy

Operation standardization was strongly positively correlated with clinical efficacy (Table 7).

Table 7. Efficacy of different standard implementation levels

Grade	Operation score	BDNF improvement (%)	Adverse event rate (%)	Adjusted p
A (≥90)	95.2±3.1	62.8	2.3	<0.001
B (80-89)	84.6±5.2	51.4	4.1	<0.001
C (<80)	72.1±7.8	38.2	6.7	<0.01

Note: Grading criteria defined via ROC analysis, AUC=0.87.

5.6 Safety Outcomes

All adverse events were mild, and no severe adverse events or infection cases occurred (Table 8).

Table 8. Statistics of adverse events

Adverse event	C	I1	I2	I3	Total rate
Skin ecchymosis	2.2%	4.3%	5.3%	4.3%	4.5%
Dizziness	0	2.1%	3.2%	2.2%	1.8%
Total severe events	0	0	0	0	0

5.7 Treatment Compliance

A total of 334 participants completed all 24 treatments, overall compliance rate 91.5%. Group I2 had higher compliance (96.8%, P=0.034). Main reasons for incompletion: schedule changes, mild skin irritation.

6. Discussion

6.1 Scientificity and Innovation of the Standard System

This study constructed the first four-layer hierarchical standard system for TETs, breaking fragmented norms. The overall expert consensus rate reached 83.2% with W=0.76, indicating good recognition. The system realized full quantification of traditional descriptive operations, and operator consistency Kappa=0.92.

6.2 Interpretation of Clinical Efficacy

The improvement of BDNF was clinically meaningful. The effect size d=1.28 represented large clinical effect. After 12-week follow-up, efficacy did not regress obviously (P=0.85), indicating the intervention activated self-repairing ability rather than simple symptomatic relief. Subgroup results reflected the characteristics of TCM treatment based on syndrome differentiation.

6.3 Mechanism Analysis

A multi-axis potential mechanism was summarized based on published literature and our data:

1) Nerve pathway: Standard stimulation regulated pain-related neurotransmitters (referring to gate control theory); this study did not directly detect substance P.
2) Immune pathway: Improved microcirculation and inhibited inflammatory factors IL-6, TNF-α.
3) Endocrine pathway: Regulated HPA axis and stress status.
4) Neuroplasticity: Persistent BDNF elevation suggested improved neuroplasticity.

All above pathways were supported by existing studies, while direct mechanistic detection will be carried out in follow-up research.

6.4 Comparison with Previous Studies

Compared with published RCTs, this study had larger sample size and stricter operation control. The higher effect size was mainly attributed to unified quantitative parameters and standardized procedures. Detailed cross-study data are listed in supplementary materials.

6.5 Difficulties and Countermeasures for Implementation

Main difficulties included incomplete training system and equipment investment. Corresponding solutions: hierarchical skill training, graded equipment promotion, and regular standard revision.

6.6 Limitations and Future Directions

1) The subjects were mainly mild sub-health and chronic disease patients, limiting generalizability to severe cases.
2) Participants and operators could not be blinded, which may cause expectancy bias; we adopted blinded assessors to reduce bias.
3) The 12-week follow-up period was relatively short.

No high-throughput omics or neuroimaging detection was conducted.

Future studies will expand sample types, extend follow-up time and explore deeper molecular mechanisms.

7. Conclusion and Prospect

7.1 Main Conclusions

1) The four-layer hierarchical standard system for TCM health preservation external therapy has high scientificity and expert recognition, filling gaps in existing industry standards.
2) Standardized TETs can significantly improve neurotrophic factors and relieve sub-health symptoms, with stable long-term efficacy and good safety.
3) Operation standardization is positively correlated with clinical efficacy, which verifies the value of standard implementation.
4) Constitution-based differentiated schemes have good practical application value.

7.2 Prospect

It is suggested to incorporate this standard system into national TCM standard planning. Relying on digital tools to promote standard popularization, and carry out in-depth mechanism research. Accelerate international translation and promotion of the standards to boost the development of global traditional medicine.

References

Cohen J. (1988). *Statistical Power Analysis for the Behavioral Sciences*. New York: Routledge, 1988.

Liu H, et al. (2021). Clinical observation of cupping therapy on chronic fatigue based on different operational parameters. *Evidence-Based Complement Altern Med, 2021*, 1-8.

Schulz K F, Altman D, Moher D. (2010). CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ, 340*, c332.

Standardization Administration of China. (2015). GB/T 12346-2015, Standardized manipulations of acupuncture and moxibustion. Beijing: Standards Press of China.

The Lancet. (2020). Global burden of disease collaborators. Global, regional, and national burden of diseases and injuries for 195 countries, 1990–2019. *Lancet, 395*(10223), 1700-1720.

Tracey K J. (2002). The inflammatory reflex. *Nature, 420*(6917), 853-859.

Wang L, Zhang Y. (2022). Meta-analysis on clinical efficacy of traditional Chinese external therapies for sub-health state. *China Journal of Traditional Chinese Medicine and Pharmacy, 37*(5), 2689-2693.

World Health Organization. (2019). *Global status report on noncommunicable diseases 2019*. Geneva: WHO Press.

Yu M, et al. (2022). Brain-derived neurotrophic factor changes in sub-health populations receiving TCM external interventions. *J Clin Nurs Res, 6*(5), 44-51.

Copyrights

Paradigm Academic Press
Journal of Innovations in Medical Research
ISSN 2788-7022
JUN. 2026 VOL.5, NO.2

The Model of End-Stage Liver Disease (MELD) Score Predicts the Survival Period of Patients with Liver Failure

Haradhan Kumar Mohajan[1]

[1] Associate Professor, Department of Mathematics, Premier University, Chittagong, Bangladesh

Correspondence: Haradhan Kumar Mohajan, Associate Professor, Department of Mathematics, Premier University, Chittagong, Bangladesh.

doi:10.63593/JIMR.2788-7022.2026.06.005

Abstract

The liver is the largest essential internal organ in the body. A healthy liver is necessary for survival that can regenerate most of its own cells when these are damaged. The Model of End-Stage Liver Disease (MELD) is a numerical scale that is reported as a whole number, and is used to predict survival in patients with cirrhosis and liver failure. It is an objective measure incorporating three quantitative values, such as serum creatinine, international normalized ratio (INR), and serum bilirubin that are readily available, reproducible, and objective. It is used to prioritize and allocate adult patients with liver cirrhosis waiting for a liver transplantation (LT). The transplant teams should take decision of LT for patients with higher MELD scores. Liver failure patients with MELD score≥20 should be regarded as high risk for mortality. Although, MELD is an ideal score, it cannot provide accurate information of survival in 15–20% cases. In this study an attempt has been taken to highlight the importance of MELD score for LT patients.

Keywords: MELD, liver cirrhosis, liver transplantation, prediction of survival, mortality

1. Introduction

The Model of End-stage Liver Disease (MELD) is a scoring system that provides the severity of the end-stage liver disease when the liver is almost completely damage due to liver cirrhosis, liver failure, and hepatocellular carcinoma (HCC). It is developed to predict survival following transjugular intrahepatic portosystemic shunt (TIPS) was subsequently found to be accurate predictor of mortality amongst patents with end-stage liver disease (Malinchoc et al., 2000). It accurately predicts most patients' short-term risk of death without a liver transplant. It is calculated from laboratory values of serum bilirubin, serum creatinine, and the International Normalized Ratio (INR) for prothrombin time (Khan et al., 2009). It is most accurate predictor of short-term mortality amongst patents with end-stage liver disease. The waitlist mortality among women is by 13% more compared to men due to the given renal function, women tend to have lower serum creatinine compared to men for lower muscle mass in women (Zhang et al., 2012).

The MELD was originally developed at the Mayo Clinic of the USA around 2000 through the effort of a group of researchers lead by Dr. Patrick Kamath, professor of gastroenterology and hepatology; and at that time, it is called the "Mayo End-Stage Liver Disease" score (Malinchoc et al., 2000). It was developed to predict mortality within three months of surgery in patients who had undergone a transjugular intrahepatic portosystemic shunts (TIPS), acute liver failure, alcoholic hepatitis, acetaminophen-induced liver injury, and hepatorenal syndrome to assess the surgical mortality risk in patients with liver cirrhosis (Schmidt & Larsen, 2007). In February 27, 2002, the MELD score is adopted and approved as the core system for organ allocation and implementation by the United Network for Organ Sharing (UNOS) that is a score to allocate organs for patients awaiting liver transplantation (LT) in the USA (Kamath & Kim, 2007). In January 2016, the MELD scoring system for donor allocation in the USA was further modified to incorporate serum sodium, using the MELD-Na equation. It is

incorporated in only for persons with a MELD score greater than 11 (Kalra et al., 2016).

2. Literature Review

Literature review is an introductory section where research works of previous researchers are highlighted to make familiar with the new researchers in the research world (Polit & Hungler, 2013). It helps the researchers to understand the core concept of the subject that serves as an indicator of the subject that has been carried out previously (Creswell, 2007). Patrick S. Kamath and his coauthors have investigated that the MELD scale is a reliable measure of mortality risk in patients with end-stage liver disease and is suitable for use as a disease severity index to determine organ allocation priorities (Kamath et al., 2001). Ashwani K. Singal and Patrick S. Kamath have stated that the MELD score is initially developed to predict survival following transjugular intrahepatic portosystemic shunt (TIPS) that is an accurate predictor of mortality amongst patents with end-stage liver disease (Singal & Kamath, 2013).

Rustam Khan and his coauthors have tried to determine the relationship of MELD scores to the outcome of post-viral hepatitis cirrhosis with infection and to compare it with Child-Turcott-Pugh (CTP) score. However, better improved models need to be developed for prioritization of patients in the waiting list (Khan et al., 2009). Nasim Rahimi-Dehkordi and his coworkers have compared the ability of the CTP score and the MELD score to predict mortality or removal from the waiting list due to poor medical conditions (Rahimi-Dehkordi et al., 2014). Patrick G. Northup and his coworkers have tried to determine the ability of the MELD score to predict 30-day postoperative mortality for patients with cirrhosis undergoing non-transplant surgical procedures (Northup et al., 2005). Isioma Emenena and her coauthors have taken attempt to find the value of the MELD score in assessing the mortality of patients with decompensated liver cirrhosis over one month period (Emenena et al., 2023).

Prathvi Nandalike and her coauthors have observed that chronic liver disease (CLD) is one of the common non-communicable diseases that is related to significant morbidity and mortality in developing countries. The MELD-Na score is higher among the patients with outcome of death compared to the MELD score among the patient (Nandalike et al., 2022). Uri Kartoun and his coworkers have stressed on accurate assessment of the risk of mortality following a cirrhosis-related admission can enable healthcare providers to identify high-risk patients and modify treatment plans to decrease the risk of mortality. They are hopeful that the improvement of current standard models, such as MELD and MELD-Na that can guide clinicians in better targeting treatment to improve cirrhosis care and outcomes for high-risk patients (Kartoun et al., 2017). W. Ray Kim and his coworkers have found that the MELD has been established as a reliable indicator of short-term survival in patients with end-stage liver disease. Their objective was to optimize MELD further by taking into account additional variables and updating coefficients with contemporary data. The final model MELD 3.0 affords more accurate mortality prediction than MELD-Na and addresses determinants of wait list outcomes, including the sex disparity (Kim et al., 2021).

3. Research Methodology of the Study

Research is an essential part for academicians to develop their academic world (Pandey & Pandey, 2015). Methodology is a guideline to prepare a good research (Kothari, 2008). Therefore, research methodology is the collection of a set of principles for planning, designing, organizing, and conducting a successful research (Legesse, 2014). To prepare this article, I have dependent on the secondary data sources related to MELD score for the prediction of the mortality of the liver failure patients (Mohajan, 2017, 2018, 2020). I have consulted books of famous authors, national and international journals, e-journals, handbooks, theses, etc. to enrich the study (Mohajan, 2024a-r).

4. Objective of the Study

Main objective of this article is to discuss the basic concept of MELD score that is a good predictor of mortality among patients with decompensated liver cirrhosis. It is developed by a group of researchers at the Mayo Clinic initially as a model to predict survival following transjugular intrahepatic portosystemic shunt (TIPS) for refractory variceal bleeding or refractory ascites. It gives each patient a ‘score’ or number based on how urgent s/he needs a liver transplant in the next three months (Malinchoc et al., 2000). Other minor objectives of the study are as follows:

- to focus on overview of liver and liver transplantation,
- to highlight on MELD scores, and
- to discuss the importance of MELD scores.

5. An Overview of Liver

The liver is the largest and the most complex internal organ of the body that weighs approximately 1500 gm. It has a remarkable capacity to regenerate its injured tissues (Mohajan, 2024b). It is a wedge or cone shaped with the base on the right and the apex to the left (Ramachandran & Kumar, 2019). It is an essential organ in the

human body that performs up to 5,000 different vital functions in combination with other organs and systems, such as supporting digestion, immunity, proteins synthesis, amino acid metabolism, blood coagulation, detoxification, vitamin storage, etc. (Hettiaratchi, 2022). In an adult human it weighs between 1.5 and 2 kg. It is divided into right and left lobes; the right lobe being larger than the left. It is located in the right upper quadrant of the abdomen and spans across the midline to the left upper quadrant (Mohajan, 2024j).

6. An Overview of LT

Complications of end-stage liver disease (ESLD) are ascites, variceal hemorrhage, hepatic encephalopathy, and renal impairment primarily that account for numerous deaths. LT is a valid treatment option for these patients (Cox-North et al., 2013). LT is a life-saving treatment option of a diseased liver through the replacement with a healthy liver from a deceased donor or a portion of a healthy liver from a living donor. It is the second most common solid organ transplantation after kidney transplantation worldwide (Lucas, 2021). It is a well-recognized life-saving treatment option for people when liver cannot regenerate and the damage becomes about life-threatening due to liver cirrhosis, decompensated disease, liver cancer, acute liver failure, and hepatocellular carcinoma (HCC) (Mohajan, 2024q). The first attempted of human LT was performed in the world in 1st March 1963 by American physician, researcher, and expert on organ transplants Thomas Earl Starzl (1926-2017) who has often been referred to as "the father of modern transplantation" (Starzl et al., 1963). The LT can be orthotopic (same place) or heterotopic (other place), and can be performed in patients of all ages (Freeman et al., 2002).

A LT is a complex process that requires hundreds of steps before, during and after LT. The LT centers match donors with recipients based on compatible liver size and blood type. In 2021, there were about 34,694 LTs performed globally that is an increase of 6.5% from 2020 and a 20% increase from 2015 (Terrault et al., 2023). However, donor organ shortage and lifelong need for immunosuppression are the main restrictions to LT (Adam et al., 2018). Most of the LT persons are able to return to a normal and healthy lifestyle, and can enjoy an improved quality of life. They are able to start normal exercise after their recuperation, and women are able to conceive and have normal post-transplant pregnancies and deliveries. Proper nutrition maintenance is necessary after LT to control the changes in the body (Lewis & Howdle, 2003). However, with increased waiting times for organ transplantation, some listed patients die annually while waiting for LT, and many other patients with ESLD are not candidates for LT (Montgomery et al., 2005).

7. MELD Scores

The MELD scoring has been applied as a new liver organ allocation system for LT since 2002 in the USA and since 2006 in Europe, and at present it is using worldwide (Aiello et al., 2017). Decompensated liver disease is developed at the end-stage of the disease, such as liver cirrhosis, liver cancer, liver failure, and hepatocellular carcinoma (HCC). LT is the only life-saving treatment option of these patients that can be performed by a diseased liver through the replacement with a healthy liver from a deceased donor or a portion of a healthy liver from a living donor (Lucas, 2021).

The MELD scoring has three objective variables: serum bilirubin, serum creatinine, and institutional normalized ratio (INR). It has been used worldwide for listing and transplanting patients with end-stage liver disease allowing transplanting sicker patients first irrespective of the wait time on the list (Singal & Kamath, 2013). It is defined by American hepatologist Michael Malinchoc, and is calculated according to the following formula (Malinchoc, et al., 2000):

$$\text{MELD} = 3.78 \times \ln(\text{serum bilirubin (mg/dL)}) + 11.2 \times \ln(\text{INR}) + 9.57 \times \ln(\text{serum creatinine (mg/dL)}) + 6.43 \quad (1)$$

Of the three variables of equation (1), serum total bilirubin is the most important that has a linear relationship with 90-day mortality in patients waiting for LT in clinical practice. The INR reflects coagulopathy associated with synthetic dysfunction in patients with end-stage liver disease. After the adjustment of serum bilirubin and serum creatinine, the INR is associated with a steep increase in mortality risk (Leise et al., 2011).

The MELD uses a continuous scale from 6 to 40, based on serum bilirubin, international normalized ratio (INR) of prothrombin time, and serum creatinine (Kamath et al., 2001). The MELD<16 indicates low-risk patients and the MELD≥16 indicates high-risk patients (Angermayr et al., 2009). It has proven to be a robust predictor of short-term mortality in patients with cirrhosis, including candidates for LT (Wiesner et al., 2003). Mortality and MELD score are linearly correlated, and 3-month mortality estimated to be 4%, 27%, 76%, 83%, and 100% for MELD scores are of <10, 10-19, 20-29, 30-39, and 40 or more respectively. The MELD score of greater than 30 is the significant predictor of the mortality (Singal & Kamath, 2013).

The MELD-Na scale is defined as (Kartoun et al., 2017),

$$\text{MELD} - \text{Na} = \text{MELD} + 1.32 \times (137 - \text{Na}) - [0.033 \times \text{MELD} \times (137 - \text{Na})] \quad (2)$$

where the serum sodium concentration (Na) is bound between 125 and 137 mmol/L, as defined by the Organ Procurement and Transplantation Network (OPTN). In the USA, the MELD-Na is applied only if MELD is greater than 11. During 2005 to 2006, using MELD-Na instead of MELD has save 90 more lives (Kim et al., 2021). The model (2) has four objective variables: serum bilirubin, serum creatinine, and institutional normalized ratio (INR), and sodium. It has been used to determine organ allocation priorities for LT in the USA since 2016 (Nagai et al., 2018).

8. Importance of MELD Scores

Chronic liver failure affects multiple vital organs of the body that shortened life expectancy. As a result, the disease increases perioperative morbidity and mortality in patients with cirrhosis. Mortality and MELD score are linearly correlated amongst patients with end-stage liver disease listed for LT. For the survival of the patients; a surgical procedure, such as LT is necessary when there is no other option (Northup et al., 2005).

After the introduction of MELD score for organ allocation in the USA in the very first year have reduced about 12% in waitlist mortality. For example, the deaths on waitlist in the USA from 2,046 in 2001 to 1,364 in 2005 with the reduction in waiting time from 656 days to 416 days. On the other hand, the numbers of liver donors have increased from 4,671 in 2001 to 5,160 in 2005 (Wiesner et al., 2006).

The liver disease is increasing alarmingly worldwide and some of them are in end-stage liver disease. There are many patients waiting for LT. But only few living and deceased donors are providing the organs (Rahimi-Dehkordi et al., 2014). The criteria of LT have changed due to the development of CTP and MELD scores. At present LT are arranged through the changing allocation, immunosuppression, and liver failure etiologies, as well as better supportive therapies (Gotthardt et al., 2014). The MELD score has been widely validated in different populations of cirrhotic patients. Despite some concerns, it is currently useful for guiding LT allocation (Aiello et al., 2017).

9. Conclusions

From this study, we have observed that the MELD score is highly sensitivity and specificity, and predict the mortality among the patients with decompensated liver cirrhosis. It can accurately predict mortality, morbidity and long-term survival in patients with HCC and cirrhosis. It has been found to be well-suited for prioritizing patients who would be benefitted from LT. About the last three decades of discovery many efforts have been made by the scientific researchers for further improvement and refinement of MELD score. We should confidently depend on MELD score for liver transplantation until a better score is developed.

References

Adam, R., et al. (2018). Annual Report of the European Liver Transplant Registry (ELTR): 50-Year Evolution of Liver Transplantation. *Transplant International*, *31*(12), 1293-1317.

Aiello, F. I., et al. (2017). Model for End-Stage Liver Disease (MELD) Score and Liver Transplant: Benefits and Concerns. *AME Medical Journal*, 2, 168.

Angermayr, B., et al. (2009). Aetiology of Cirrhosis of the Liver has an Impact on Survival Predicted by the Model of End-Stage Liver Disease Score. *European Journal of Clinical Investigation*, *39*(1), 65-71.

Cox-North, P., et al. (2013). The Transition to End-of-Life Care in End-Stage Liver Disease. *Journal of Hospice & Palliative Nursing*, *15*(4), 209-215.

Creswell, J. W. (2007). *Qualitative Inquiry and Research Design: Choosing Among Five Approaches*. Thousand Oaks, CA: Sage Publications.

Emenena, I., et al. (2023). Model for End Stage Liver Disease (MELD) Score: A Tool for Prognosis and Prediction of Mortality in Patients with Decompensated Liver Cirrhosis. *Cureus*, *15*(5), e39267.

Freeman, R. B., et al. (2002). The New Liver Allocation System: Moving toward Evidence based Transplantation Policy. *Liver Transplantation*, *8*(9), 851-858.

Gotthardt, D. N., et al. (2014). Current Strategies for Immunosuppression Following Liver Transplantation. *Langenbeck's Archives of Surgery*, *399*(8), 981-988.

Hettiaratchi, L. (2022). A Case Study of Physiotherapy on a Patient after Liver Transplantation. Bachelor Thesis, Physiotherapy Department, Faculty of Physical Education and Sport, Charles University.

Kalra, A., et al. (2016). Changing Prioritization for Transplantation: MELD-Na, Hepatocellular Carcinoma Exceptions, and More. *Current Opinion in Organ Transplantation*, *21*(2), 120-126.

Kamath, P. S., et al. (2001). A Model to Predict Survival in Patients with End-Stage Liver Disease. *Hepatology*, *33*(2), 464-470.

Kamath, P. S., & Kim, W. R. (2007). The Model for End-Stage Liver Disease (MELD). *Hepatology*, *45*(3), 797-805.

Kamath, P. S., et al. (2001). A Model to Predict Survival in Patients with End-Stage Liver Disease. *Hepatology*, *33*(2), 464-470.

Kartoun, U., et al. (2017). The MELD-Plus: A Generalizable Prediction Risk Score in Cirrhosis. *PLoS ONE*, *12*(10), e0186301.

Khan, R., et al. (2009). Model for End-Stage Liver Disease (MELD) Score as a Useful Prognostic Marker in Cirrhotic Patients with Infection. *Journal of the College of Physicians and Surgeons Pakistan*, *19*(11), 694-698.

Kim, W. R., et al. (2021). MELD 3.0: The Model for End-Stage Liver Disease Updated for the Modern Era. *Gastroenterology*, *161*(6), 1887-1895.

Kothari, C. R. (2008). *Research Methodology: Methods and Techniques* (2nd Ed.). New Delhi: New Age International (P) Ltd.

Legesse, B. (2014). *Research Methods in Agribusiness and Value Chains*. School of Agricultural Economics and Agribusiness, Haramaya University.

Leise, M. D., et al. (2011). A Revised Model for End-Stage Liver Disease Optimizes Prediction of Mortality Among Patients Awaiting Liver Transplantation. *Gastroenterology*, *140*(7), 1952-1960.

Lewis, M. B., & Howdle, P. D. (2003). Neurologic Complications of Liver Transplantation in Adults. *Neurology*, *61*(9), 1174-1178.

Lucas, A. R. (2021). Liver Transplantation. *Journal of Transplantation Technologies & Research*, *11*(3), e104.

Malinchoc, M., et al. (2000). A Model to Predict Poor Survival in Patients Undergoing Transjugular Intrahepatic Portosystemic Shunts. *Hepatology*, *31*(4), 864-871.

Mohajan, H. K. (2017). Two Criteria for Good Measurements in Research: Validity and Reliability. *Annals of Spiru Haret University Economic Series*, *17*(3), 58-82.

Mohajan, H. K. (2018). Aspects of Mathematical Economics, Social Choice and Game Theory. PhD Dissertation, Jamal Nazrul Islam Research Centre for Mathematical and Physical Sciences (JNIRCMPS), University of Chittagong, Chittagong, Bangladesh.

Mohajan, H. K. (2020). Quantitative Research: A Successful Investigation in Natural and Social Sciences. *Journal of Economic Development, Environment and People*, *9*(4), 50-79.

Mohajan, H. K. (2024a). Alcoholic Liver Disease: Diagnosis and Treatment Strategies. Unpublished Manuscript.

Mohajan, H. K. (2024b). Anatomy of Human Liver: A Theoretical Study. Unpublished Manuscript.

Mohajan, H. K. (2024c). Liver Diseases: Epidemiology, Prevention, and Management Strategy. Unpublished Manuscript.

Mohajan, H. K. (2024d). Management Strategies of Fatal Liver Infection Due to Hepatitis C Virus (HCV). Unpublished Manuscript.

Mohajan, H. K. (2024e). Transmission, Diagnosis, and Treatment of Acute and Chronic Hepatitis E. Unpublished Manuscript.

Mohajan, H. K. (2024f). Management of Acute and Chronic Hepatitis B and C Viral Infections. Unpublished Manuscript.

Mohajan, H. K. (2024g). Epidemiological Investigation of Hepatitis F Viruses (HFV). Unpublished Manuscript.

Mohajan, H. K. (2024h). Hepatitis A and Hepatitis E Viruses can Develop Acute Viral Hepatitis: Prevention is the Best Policy. Unpublished Manuscript.

Mohajan, H. K. (2024i). Alcoholic Hepatitis: Diagnosis and Management Procedures. Unpublished Manuscript.

Mohajan, H. K. (2024j). A Study on Functions of Liver to Sustain a Healthy Liver. Unpublished Manuscript.

Mohajan, H. K. (2024k). Hepatitis A Virus (HAV) Infection: A Prevention Strategy through Hygienic Maintenance and Vaccination. Unpublished Manuscript.

Mohajan, H. K. (2024l). Prevention of Hepatitis B Virus (HBV) is Essential to Avoid Chronic Liver Disease. Unpublished Manuscript.

Mohajan, H. K. (2024m). Clinical Practice, and Diagnosis and Treatment Strategies of Chronic Hepatitis D Virus (HDV). Unpublished Manuscript.

Mohajan, H. K. (2024n). Hepatitis G Viruses (HGV): A Study on Prevalence, Transmission, and Co-Infection. Unpublished Manuscript.

Mohajan, H. K. (2024o). Prevention and Treatment Strategies of Viral Hepatitis. Unpublished Manuscript.

Mohajan, H. K. (2024p). Hepatitis D and E Viruses Cause Liver Damage: Management and Prevention are the Best Policies of Elimination These. Unpublished Manuscript.

Mohajan, H. K. (2024q). Liver Transplantation: A Treatment Option for Survival in End-Stage Liver Disease. Unpublished Manuscript.

Mohajan, H. K. (2024r). Alcoholic Liver Cirrhosis: A Chronic Liver Failure Due to Alcohol Abuse. Unpublished Manuscript.

Montgomery, A., et al. (2005). MELD Score as a Predictor of Early Death in Patients Undergoing Elective Transjugular Intrahepatic Portosystemic Shunt (TIPS) Procedures. *CardioVascular and Interventional Radiology*, *28*(3), 307-312.

Nagai, S., et al. (2018). Effects of Allocating Livers for Transplantation Based on Model for End-Stage Liver Disease-Sodium Scores on Patient Outcomes. *Gastroenterology*, *155*(5), 1451-1462.

Nandalike, P., et al. (2022). Comparison of the Model for End-Stage Liver Disease and Disease Sodium Values in Prognosticating Short Term 3-Month Mortality in Chronic Liver Disease. *International Journal of Research in Medical Sciences*, *10*(9), 1930-1935.

Northup, P. G., et al. (2005). Model for End-Stage Liver Disease (MELD) Predicts Nontransplant Surgical Mortality in Patients with Cirrhosis. *Annals of Surgery*, *242*(2), 244-251.

Pandey, P., & Pandey, M. M. (2015). *Research Methodology: Tools and Techniques*. Bridge Center, Romania, European Union.

Polit, D. F., & Hungler, B. P. (2013). *Essentials of Nursing Research: Methods, Appraisal, and Utilization* (8th Ed.). Philadelphia: Wolters Kluwer/Lippincott Williams and Wilkins.

Rahimi-Dehkordi, N., et al. (2014). Model for End-stage Liver Disease (MELD) and Child-Turcotte-Pugh (CTP) Scores: Ability to Predict Mortality and Removal from Liver Transplantation Waiting List Due to Poor Medical Conditions. *Archives of Iranian Medicine*, *17*(2), 118-121.

Ramachandran, K., & Kumar, R. D. (2019). A Study on the morphological Variations of the Liver and Its Clinical Significance. *Indian Journal of Anatomy and Surgery of Head, Neck and Brain*, *5*(4), 110-113.

Schmidt, L. E., & Larsen, F. S. (2007). MELD Scores as a Predictor of Liver Failure and Death in Patients with Acetaminophen-Induced Liver Injury. *Hepatology*, *45*(3), 789-796.

Singal, A. K., & Kamath, P. S. (2013). Model for End-stage Liver Disease. *Journal of Clinical and Experimental Hepatology*, *3*(1), 50-60.

Starzl, T. E., et al. (1963). Homotransplantation of the Liver in Humans. *Surgery, Gynecology and Obstetrics*, 117, 659-676.

Terrault, N. A., et al. (2023). Liver Transplantation 2023: Status Report, Current and Future Challenges. *Clinical Gastroenterology and Hepatology*, *21*(8), 2150-2166.

Wiesner, R., et al. (2003). Model for End-Stage Liver Disease (MELD) and Allocation of Donor Livers. *Gastroenterology*, *124*(1), 91-96.

Wiesner, R., et al. (2006). Model for End-Stage Liver Disease (MELD) Exception Guidelines. *Liver Transplantation*, *12*(12 Suppl 3), S85-S87.

Zhang, M., et al. (2012). Pretransplant Prediction of Posttransplant Survival for Liver Recipients with Benign End-Stage Liver Diseases: A Nonlinear Model. *PloS ONE*, *7*(3), e31256.