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## FOCUS AND SCOPE

Burn and Wound, Hand Surgery, Microsurgery, Oncoplastic, Craniofacial, External Genitalia Reconstruction, and Aesthetics.

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# *RECURRENT TEMPOROMANDIBULAR JOINT ANKYLOSIS CAUSED BY OLD FRACTURE: A CASE REPORT*

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ABSTRACT

**Introduction:** Temporomandibular joint (TMJ) ankylosis can greatly impact a child's nutrition, mental health, and craniofacial development. Trauma is the main cause. Early and proper treatment is crucial to avoid long-term issues and reoccurrence.

**Case Illustration:**An 11-year-old girl presented with limited mouth opening and lower jaw pain three years after falling down the stairs. She underwent gradual TMJ distraction using bite blocks under general anesthesia followed by weekly physiotherapy, but her symptoms recurred after four months. A CT scan revealed left TMJ synarthrosis and condylar deformity. With improved adherence to physiotherapy, she achieved significant mouth opening and remained recurrence-free for six months..

**Discussion:** Gradual distraction with bite blocks, combined with regular physiotherapy, can improve joint mobility and muscle function while lowering the chances of re-ankylosis. This approach offers a less invasive option than surgery, which is especially valuable for children whose growth must be preserved. Closed procedures with structured rehabilitation are preferred because they result in fewer complications and require fewer follow-up appointments.

**Conclusion:** The effectiveness of a non-invasive approach combining gradual distraction and physiotherapy in managing TMJ ankylosis is presented. The success of this treatment relies heavily on the patient's motivation and commitment. Early conservative treatment could be the main strategy for pediatric cases, potentially delaying or avoiding surgery. Continuous education and monitoring are key to achieving long-term success and preventing relapse.

**Highlights:**

1. Adequate physiotherapy is essential to prevent the recurrence of temporomandibular joint ankylosis.
2. Surgical treatment alone is insufficient without proper postoperative physiotherapy and patient compliance.

## INTRODUCTION

Temporomandibular joint (TMJ) ankylosis is a joint disorder that refers to the bony or fibrous adhesion of the joint components, which can cause limitation of mouth opening from partial reduction to total jaw immobility, or is often referred to as trismus. Some distinguish mild trismus as a range of maximum mouth opening (MMO) 20-30 mm, moderate 10-20 mm, and severe, below 10 mm. TMJ ankylosis is most commonly associated with trauma (77.9%), infection (16.8%), and systemic diseases, e.g., ankylosis spondylitis, rheumatoid arthritis, psoriasis, and ankylosis can also occur as a result of previous TMJ surgery.[1]

TMJ ankylosis can impact a child's growth in nutrition, psychology, and growth of the teeth and jaws. The most frequently seen complications are poor treatment, limited range of motion, and re-ankylosis. Multi-modality therapy must be used to prevent them from happening and recourseeing.[1]

Surgical management remains the treatment of choice, postoperative recurrence and limited mouth opening continue to pose significant challenge.[2] In this context, non-surgical and adjunctive therapies aimed at improving functional outcomes and preventing recurrence of ankylosis have gained increasing attention. Gradual distraction with bite blocks is one such conservative method that provides incremental, controlled pressure to obtain mobilization of the joint and adjacent soft tissues. Along with physiotherapy, directed towards active and passive jaw-opening, this technique has the potential to enhance the opening of the mouth, re-establish joint mobility, and reduce relapse risk.[3] Despite its significance, evidence for combined effectiveness of physiotherapy and bite block treatment in treating TMJ ankylosis is still limited and requires systematic investigation. Although surgical approaches have been extensively studied, there is no definite agreement on standard conservative regimens, particularly in children when mandibular growth needs to be preserved. Additionally, little has been written on the long-term functional results of managing recurrent TMJ ankylosis with initial treatment of gradual distraction and structured physiotherapy.

This study aims to present a case of recurrence of temporomandibular joint (TMJ) ankylosis due to inadequate therapy, and to determine the effectiveness of gradual distraction with bite blocks and appropriate physiotherapy in improving mouth opening and functional outcomes in TMJ ankylosis patients. The findings can be utilized to streamline conservative management protocols and encourage long-term rehabilitation planning for such patients.

## CASE ILLUSTRATION

An 11-year-old female came to our hospital complaining of difficulty opening her mouth. The complaint is accompanied by pain that increases every time the patient tries to open her mouth and trismus in the lower jaw. She had a history of falling down the stairs three years ago and was not examined by a doctor. The history of infection was denied. She was referred our department for further treatment. The surgeon decided to perform TMJ gradual distraction under general anesthesia and incorporated it with short progressive distraction using bite blocks. After gradual distraction, the patient can open her mouth about 30 mm. Furthermore, the patient was advised to undergo routine check-ups and physiotherapy once a week to strengthen her mandibular joints and muscles, thereby avoiding stiffness. Four months later, she complained of difficulty and pain in opening her mouth and could only open her mouth as much as 5 mm (Figure 1).

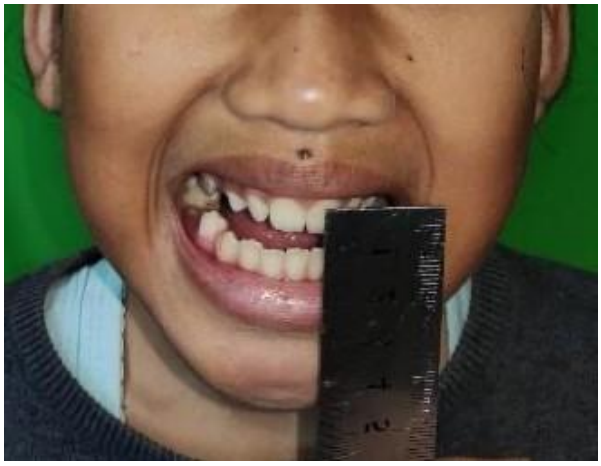

Figure 1. Clinical Presentation: Trismus (MMO range: 5 mm)

After searching for the cause of this recurrence, we found that the patient's routine follow-up was challenging because she was a student in boarding school, so she couldn't control and perform physiotherapy as previously advised. We performed a CT scan, and the results showed left temporomandibular joint synarthrosis, anatomical change of the left mandible condyle, and left ethmoiditis (Figure 2).

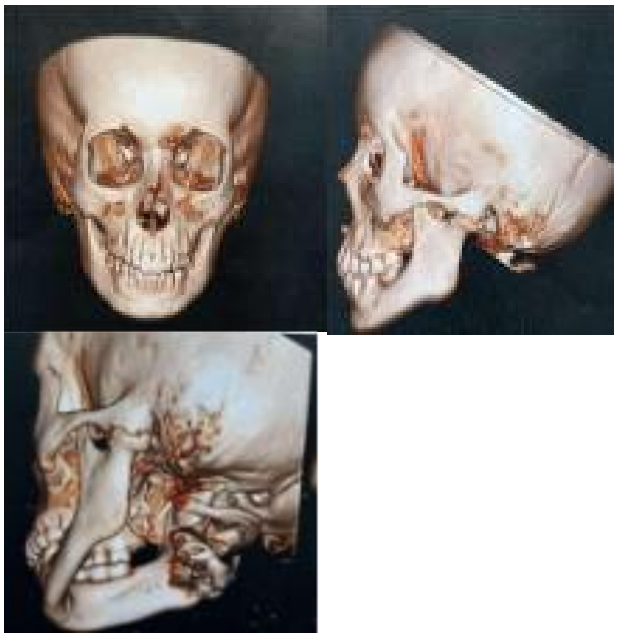

Figure 2. 3D CT-Scan of Facial Bone Frontal & Lateral View

After the examination, the patient was scheduled for TMJ re-gradual distraction using gradual bite blocks under general anesthesia. The patient's mouth is gradually opened by slowly releasing the ankylotic condyle and then bite blocks of the smallest size are progressively inserted into the mouth. The bite blocks are left in the mouth for 5 minutes, and then they are replaced gradually with a larger size (Figure 3).

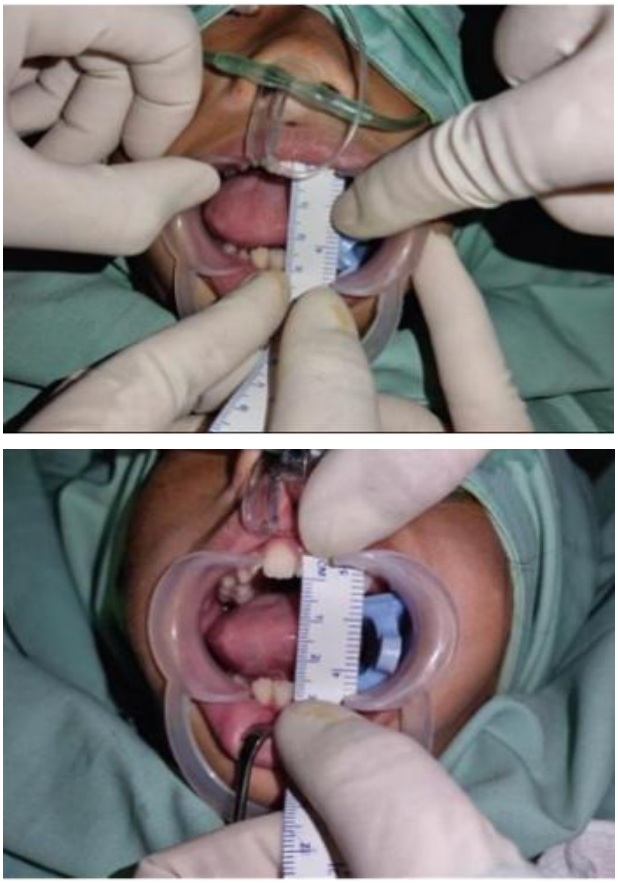

Figure 3. Gradual Distraction Using Bite Blocks

After the treatment, she finally opened her mouth to 30 mm. Furthermore, the patient was again advised to undergo routine check-ups and participate in physiotherapy once a week. Education is provided to the patient so that they understand the importance of regular control and physiotherapy in preventing the recurrence of TMJ ankylosis. A significant improvement was noticed after six months of weekly physiotherapy; the patient could finally open her mouth normally (Figure 4) without pain, and there were no other complaints.

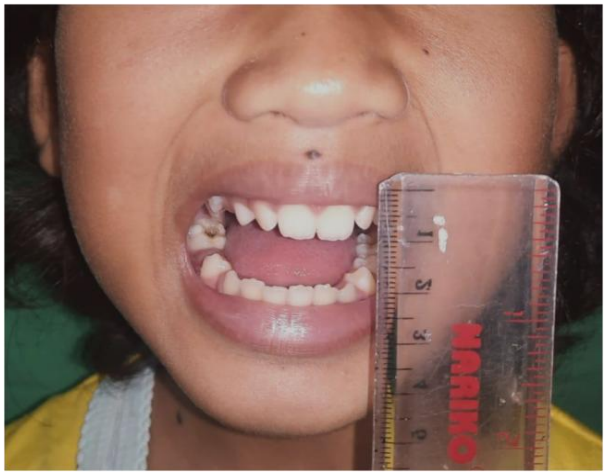

Figure 4. 3 Months Follow-up After Gradual Distraction & Six Months of Weekly Physiotherapy

## DISCUSSION

Temporomandibular joint (TMJ) ankylosis is a condition where the mandibular condyle fuses with the glenoid fossa. This fusion leads to limited jaw movement over time. The underlying causes involve fibrous or bony adhesions between the joint surfaces. These often occur after trauma, infection, or inflammatory conditions like rheumatoid arthritis. In cases of trauma, intra-articular hematoma and the resulting fibrosis or bone formation cause the joint to become less mobile. Chronic inflammation leads to pannus formation and damage to the joint surfaces, encouraging the growth of fibrous tissue and eventually causing calcification or bone fusion.[4]

TMJ ankylosis can be classified in several ways: by location (intra-articular or extra-articular), type of tissue involved (bony, fibrous, or fibro-osseous), extent of ankylosis (complete or incomplete), and whether one side or both sides are affected.[5] Sawhney also offers a classification system that divides TMJ ankylosis into four types: Type I, Type II, Type III, and Type IV, based on imaging findings. In Type I, the condylar head is present without much deformation, but TMJ movement cannot be achieved due to fibrous adhesions; Type II, where there is bony union of the deformed condylar head and the articular surfaces, sigmoid notch, and coronoid process remain intact; Type III, where there is a bony block bridging the mandibular ramus and the zygomatic arch, the medial pole remains intact, the coronoid process is seen to be elongated; and Type IV, where a bony block completely replaces the TMJ.[6]

Ankylosis of the TMJ in children can lead to significant problems. Facial asymmetry increases because of the lack of movement and irregular muscle function. The longer the duration of hypomobility, the more severe the muscle atrophy and facial asymmetry. Additionally, secondary elongation and hypertrophy of the coronoid process occur, further restricting jaw movement. It can impact nutritional status, problems with mastication, digestion, speech, growth of the child's jaw and teeth, appearance, and psychological development. Inadequate treatment of Ankylosis TMJ can lead to complications such as re- ankylosis, which is frequently reported. [4, 7-10]

Various treatments exist to manage ankylosis effectively, including both non-surgical and surgical options. Surgical procedures involve condylectomy, gap arthroplasty, and interposition arthroplasty. These surgeries aim to fix structural or anatomical problems in the TMJ. However, the surgeon must consider the height of the ramus, any differences in height between the two sides, and the patient's age. Surgical treatment can reduce the vertical height of the mandibular ramus if it removes the ankylosed joint without rebuilding the condyle. This reduction may worsen functional issues like malocclusion and limited mouth opening, as well as facial asymmetry. Re-ankylosis may further worsen the joint's function and affect the ramus height.[11,12]

Non-surgical treatments for TMJ ankylosis often include conservative methods. These may involve gradual distraction with bite blocks, stretching, and active or passive mouth-opening exercises. Such approaches can help improve or

maintain jaw mobility and prevent further restrictions. These are typically recommended in cases of early-stage fibrous ankylosis or following surgery to avoid re-ankylosis. The use of jaw- stretching devices, such as Therabite, can lengthen the joint by applying steady, gentle pressure. Pharmacotherapy, for example, Corticosteroids or NSAIDs, can be used to treat pain and inflammation, particularly in fibrous ankylosis. Occasionally, a muscle relaxant is also used as a supplement. Bite Guards/Occlusal Splints Also effective, but there was a limited advantage in cases of ankylosis involving anatomical fusion. [3,4]

Gradual distraction using bite blocks has been explored as a non-surgical approach to manage temporomandibular joint (TMJ) ankylosis, particularly in cases where surgical intervention is not immediately feasible or as an adjunct to surgical procedures. This method uses gradual force on the mandible to stretch the ankylosed joint and surrounding tissues, improving mouth opening and function. A systematic review and meta-analysis highlighted the importance of physiotherapy techniques, including bite blocks, in improving postoperative results for patients with temporomandibular joint (TMJ) ankylosis.[3] The study pointed out that these interventions, when paired with early and intensive physiotherapy, can promote mouth opening and lower the risk of re-ankylosis. However, patient compliance and the gradual approach of these techniques are vital for their success. While gradual distraction with bite blocks offers a non-invasive option, it depends on consistent use and patient adherence to the recommended protocols. Therefore, it is recommended that this method be considered as part of a comprehensive treatment plan, tailored to the individual needs and circumstances of each patient.

Physiotherapy is essential for treating TMJ ankylosis, according to a systematic study and meta-analysis. A variety of physiotherapy techniques, such as manual methods, therapeutic exercises, and treatments like electrical, heat, or cold stimulation, can improve muscle strength, reduce pain, and increase jaw mobility. These therapies are crucial for improving oral function and lessening the restrictions caused by TMJ ankylosis.[3]

A research study comparing surgical and non-surgical treatments for ankylosis of the temporomandibular joint (TMJ) demonstrated significant improvements in pain relief and TMJ function. High rates of patient satisfaction were observed in both groups, with 95% of patients undergoing surgical intervention and 92% of those undergoing non-surgical intervention reporting satisfaction with their treatment outcomes at the 1-year follow-up. These satisfaction rates highlight the overall success of both approaches in addressing patients' needs and expectations. Patient satisfaction is a vital indicator of treatment success, underscoring the importance of patient-centered care in managing ankylosis.[13]

No surgical procedure has yet been shown to be completely effective; varying results have been reported with procedures, and a postoperative MMO range greater than 35 mm is rarely achieved. Moreover, the sequence of postoperative ankylosis due to surgical treatment only, such as pain and the re-ankylosis recurrence rate, is still high.[2,3]

Re-ankylosis following TMJ surgery is a multifactorial complication commonly associated with surgical, patient-related, and biological factors. Inadequate surgical technique is a major issue. An insufficient gap between the osteotomized segments, especially at the back and upper part of the ramus, can lead to early bone contact during postoperative exercises. Pain during physiotherapy often discourages patients from participating regularly. The use of poor-quality or poorly integrated grafts, especially those prone to necrosis or displacement, can also be a factor. Autogenous bone grafts are helpful but need a critical healing period in the first two weeks, which may limit early

mobilization. Patient non-compliance with physiotherapy protocols makes the risk worse. Biologically, re-ankylosis can happen from weak soft tissue barriers after arthroplasty, increased bone growth (often called the osteoblastic "jumping" phenomenon), and high bone turnover, especially in children. Additionally, fibrosis of long-inactive masticatory muscles may limit the effectiveness of rehabilitation, and dislodgement of the cartilaginous portion of grafts, followed by osseous remodeling, can also play a significant role in recurrence. Effective prevention requires meticulous surgical technique, robust grafting strategies, and strict adherence to a structured physiotherapy regimen.[14]

Preventing recurrence of temporomandibular joint (TMJ) ankylosis requires a comprehensive strategy that integrates meticulous surgical technique, appropriate interpositional materials, rigorous postoperative rehabilitation, and consideration of biological factors. Surgically, complete removal of the ankylotic mass, especially on the medial side, is essential, as inadequate excision may leave residual bone contact, promoting re-ankylosis. Performing a well-planned osteotomy with instruments ensures clean cuts with minimal trauma, while copious irrigation eliminates bone debris that could contribute to re-fusion.[15] A parallel, inferior osteotomy at the narrowest part of the condylar neck helps minimize the risk of recurrence. Additionally, coronoidectomy is indicated in cases where mouth opening is less than 30 mm to eliminate impingement and improve jaw mobility. The choice of interpositional material is also crucial.[14] Autologous fat grafts are effective in preventing hematoma formation and heterotopic ossification. At the same time, vascularized temporalis fascia flaps provide long-term separation of bone surfaces without the complications associated with alloplastic materials. Although costochondral grafts are used in reconstruction, they are associated with a higher recurrence rate.[14] Postoperative rehabilitation is equally critical; early and aggressive physiotherapy promotes joint mobility and prevents fibrosis of the masticatory muscles.

Patient compliance with exercise regimens is vital, as non-compliance significantly increases the risk of joint stiffness and re-ankylosis. Regular follow-up enables early detection of complications .[16]

Previous studies have highlighted the importance of early identification and grading of maxillofacial trauma severity using structured tools to predict long-term complications, particularly in pediatric populations. Trauma to the mandibular condyle, if left untreated or inadequately rehabilitated has been shown to result in joint ankylosis or post-traumatic deformity, often requiring complex secondary interventions .[17]

Pediatric mandibular fractures, particularly condylar injuries in younger children, are often managed conservatively due to skeletal immaturity and low complication rates. This aligns with our approach, where early non-surgical management was selected based on age and fracture characteristics. However, poor compliance with physiotherapy may compromise outcomes, as seen in this case.[18]

In the management of mandibular fractures, especially those involving occlusal instability, the use of intraoral stabilization techniques has been reported to reduce the incidence of functional disorders, including malocclusion and temporomandibular joint dysfunction. [19,20] These findings support the current case outcome, where initial conservative management without sustained compliance led to recurrent ankylosis.

Furthermore, reconstructive methods for craniofacial deformities from trauma highlight the long-term effects of untreated structural injury. Restoring both form and function is essential, not just for appearance but also to keep joint mobility and symmetry in growing patients. [21] These insights stress the importance of ongoing, teamwork-based

care to prevent recurrence and maintain function in TMJ-related disorders.

In our case, we decided to perform a nonsurgical procedure using gradual distraction with bite blocks, accompanied by adequate physiotherapy. This approach is more suitable for this patient because it is less invasive and requires fewer follow-ups, considering her condition and difficulty with routine controls. The main goal of treating temporomandibular joint ankylosis is not only to achieve adequate mouth opening but also to prevent the recurrence of the ankylosis.

After considering the risks of surgery and the potential benefit of preserving condylar growth at the age of 12, we decided to begin with a non-surgical approach. We also consider her ramus growth phase, the patient came at 12 years old, and theoretically women's maximum condylar growth rate is 2.3 mm/year until 12.2 years old, and the growth rate will decline rapidly after that.[22] The growth period phase is also influenced by a history of trauma and invasive procedures on the bone.[10,22] So we considered non-invasive measures first, as surgical procedures and trauma are hypothesized to affect the growth of the condyles and lead to asymmetric ramus height and a high risk of re-ankylosis. The patient's clinical situation directly relates to the best treatment selection, emphasizing the patient's stage of growth.

Since physiotherapy is also important in treating TMJ ankylosis to reduce the risk of recurrence 3, surgical treatment will be ineffective if postoperative physiotherapy is inadequate or patient compliance is poor. [3, 23, 24] We started physiotherapy right after gradual distraction. It consists of an active hinge opening, a lateral excursion, and manual finger stretching in front of a mirror. The patient can do finger or ice cream stick stretching exercise at home four times daily for 3 to 5 minutes per hour. At six weeks postoperatively, the diet can be increased to solid foods. Physical therapy programs can be monitored closely for at least one year to prevent recurrence.[3] Patient adherence to prescribed physiotherapy is essential in the management of temporomandibular joint (TMJ) ankylosis. Comprehensive patient and family education is crucial to ensure understanding of therapy objectives, maintain motivation, and support consistent participation, all of which significantly influence treatment outcomes and recurrence risk. A retrospective study involving 98 patients demonstrated that those who diligently followed a two-phase physiotherapy protocol, including the use of a bite block, showed significant improvements in mouth opening and maintained ramus height over a mean follow-up period of 6.38 years. Notably, no cases of re-ankylosis were observed among compliant patients, underscoring the critical role of consistent rehabilitation in preventing recurrence and ensuring long-term functional outcomes. [25]

In conclusion, the combined approach of gradual distraction using bite blocks alongside adequate physiotherapy demonstrates promising effectiveness in the management of temporomandibular joint (TMJ) ankylosis, particularly in enhancing mouth opening and maintaining postoperative joint mobility. This non-invasive or adjunctive method provides a valuable alternative or supplement to surgical treatment, especially in early-stage or postoperative cases. The gradual mechanical stimulation delivered by bite blocks, when paired with structured and patient-compliant physiotherapy, contributes to improved functional outcomes and helps reduce the risk of re-ankylosis. However, the success of this approach depends heavily on patient adherence, the timing and consistency of therapy, and individual anatomical and physiological factors. Further longitudinal studies with larger sample sizes are needed to validate these findings and to standardize protocols for broader clinical application.

This case highlights that in pediatric patients with TMJ ankylosis, a conservative

strategy, such as gradual distraction combined with intensive physiotherapy may serve as a primary treatment option prior to surgical intervention, particularly when condylar growth is still ongoing. The outcomes from this study may help inform the development of clinical protocols in pediatric care that prioritize conservative methods as the first line of treatment for TMJ ankylosis. This case emphasizes the clinical value of a conservative, growth-phase sensitive approach in the management of pediatric TMJ ankylosis, demonstrating that non-invasive strategies can preserve mandibular development while achieving long-term functional improvement.

## CONCLUSION

This case shows that in pediatric patients with temporomandibular joint (TMJ) ankylosis, a conservative approach that combines gradual distraction with bite blocks and intensive physiotherapy can be an effective first treatment option. This non-invasive method has shown that it can improve mouth opening and joint mobility while allowing for proper mandibular growth during important developmental stages.

Successful management depends on the chosen treatment, early mobilization, strict patient adherence to physiotherapy, and long-term follow-up. Surgical treatment alone does not ensure recovery, especially without sufficient postoperative rehab, and may increase the chance of reankylosis.

Thus, this case highlights the importance of a growth-sensitive and patient-focused approach in treating TMJ ankylosis. Future treatment plans should favor conservative methods, particularly in children, and aim to improve patient commitment to physiotherapy. More long-term studies with larger groups are needed to confirm these findings and help develop standard clinical practices.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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The authors declare that they have no funding sources.

## AUTHOR CONTRIBUTION

SIW conceived the study. SIW and FI drafted the manuscript. SIW critically revised the manuscript for valuable intellectual content. The authors have read and approved the manuscript and agreed to be accountable for all aspects of the work.

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# *MECHANISMS AND OUTCOMES OF 1470NM LASER THERAPY FOR VAGINAL REJUVENATION: A MULTI-OMICS OBSERVATIONAL STUDY*

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ABSTRACT

**Introduction:** Vaginal laxity and compromised vascularization significantly impact women's quality of life, especially post-childbirth and during menopause. Non-invasive therapies, such as 1470nm laser technology, stimulate collagen production and enhance tissue regeneration. This study hypothesizes that 1470nm laser therapy improves vaginal health through collagen remodeling and neovascularization, supported by multi-omics data elucidating key biological pathways.

**Methods:** This prospective observational study enrolled 120 women aged 25–65 years with symptoms of vaginal laxity, dryness, or decreased elasticity. Participants underwent 3–5 sessions of 1470nm laser therapy. Clinical outcomes were assessed using high-resolution ultrasound, optical coherence tomography (OCT), histopathology, and patient-reported outcomes (FSFI, PGI-I). Multi-omics integration included RNA sequencing, proteomics, and metabolomics.

**Results:** Vaginal wall thickness increased by 35% ($p<0.001$), and collagen density improved by 42% ($p<0.001$). FSFI scores rose by 28% ($p<0.001$), with 92% of women reporting improved sexual satisfaction. Molecular analyses showed upregulation of collagen synthesis and angiogenesis-related genes (COL1A1, COL3A1, VEGF, FGF), with TGF-β signaling emerging as a key regulatory pathway.

**Conclusion:** 1470nm laser therapy significantly improves vaginal structure and function with a favorable safety profile. This study uniquely integrates clinical outcomes with multi-omics data, offering novel mechanistic insights and supporting its role in personalized regenerative gynecology.

**Highlights:**

1. Multi-omics analysis revealed significant upregulation of genes and proteins linked to collagen remodeling and angiogenesis after 1470nm laser therapy.
2. The study provides the first integrated clinical and molecular evidence demonstrating the mechanistic role of TGF-β signaling in vaginal tissue regeneration following laser treatment.

## INTRODUCTION

Vaginal tissue remodeling driven by aging, reproductive history, and hormonal fluctuations frequently results in atrophy, laxity, dryness, and diminished elasticity, conditions that have been shown to adversely affect sexual health and overall quality of life across diverse populations, especially among postpartum and postmenopausal women.[1] Traditional treatments include invasive surgical procedures and topical hormonal therapies, but these approaches have limitations including side effects and variable patient acceptance.[1] Energy-based devices, particularly CO2 lasers, have emerged as promising alternatives for vaginal rejuvenation by stimulating collagen regeneration, neovascularization, and improved tissue structure.[1,2] Clinical studies demonstrate that CO2 laser therapy significantly improves vaginal health indices, sexual function scores, and patient-reported outcomes. Histological evidence shows increased vaginal epithelial thickness, enhanced collagen production (particularly type III collagen), and tissue remodeling following laser treatment.[3,4] These therapeutic effects are attributed to thermal energy deposition promoting glycogen-enriched epithelium proliferation and extracellular matrix formation.[2]

Epidemiological studies report that up to 40–50% of postmenopausal women experience symptoms of genitourinary syndrome of menopause (GSM), including vaginal atrophy and discomfort, while one in three parous women report some degree of vaginal laxity after delivery.[5-7] These changes are primarily attributed to hormonal decline, collagen degradation, and impaired neovascularization, resulting in reduced biomechanical strength of the vaginal wall. Conventional treatment strategies, such as topical estrogen or surgical interventions, offer benefits but are limited by side effects, invasiveness, or variable patient acceptance.[1,8] Non-invasive energy-based therapies, particularly 1470nm diode laser technology, have gained attention as they can target water-rich tissues with precision, induce controlled thermal stimulation, and trigger biological responses such as collagen remodeling and angiogenesis. Clinical studies have demonstrated improvements in tissue elasticity, thickness, and sexual function following vaginal laser therapy.[9] However, while the clinical efficacy of vaginal laser treatment is increasingly documented, the biological mechanisms remain insufficiently characterized. Conceptually, tissue regeneration after laser therapy can be explained by principles of the wound healing cascade, initial thermal injury stimulates fibroblast activation, extracellular matrix (ECM) remodeling, and neovascularization. Central to this process is the transforming growth factor-beta (TGF-β) signaling pathway, a well-established regulator of collagen synthesis and angiogenesis.[10] Recent advances in multi-omics technologies (transcriptomics, proteomics, metabolomics) provide unique opportunities to investigate these pathways at a systems level. By integrating molecular data with imaging and patient-reported outcomes, we can obtain a comprehensive understanding of how 1470nm laser therapy exerts its regenerative effects. This study therefore aims to evaluate both the clinical efficacy and safety of 1470nm laser therapy for vaginal rejuvenation while applying multi-omics integration to elucidate the underlying molecular mechanisms. We hypothesize that the therapy improves vaginal health through collagen remodeling and neovascularization, mediated by key pathways such as TGF-β signaling.

## METHODS

### Study Design and Participants

This prospective observational study was conducted to evaluate the efficacy, safety, and molecular mechanisms of 1470nm laser therapy for vaginal rejuvenation. A total of 120 women aged 25–65 years were enrolled

between January 2022 and December 2022. Eligible participants reported symptoms of vaginal laxity, dryness, or decreased elasticity, as confirmed by clinical examination. Exclusion criteria included active vaginal infections, malignancies, pregnancy, breastfeeding, or prior pelvic radiation therapy. Written informed consent was obtained from all participants, and the study protocol was approved by the Institutional Review Board (IRB)of IKDRC- ITS, under approval number IKDRC- 2024- 23. All 120 participants completed the intervention and follow-up assessments. No dropouts occurred during the study, ensuring completeness of data analysis. Participants were recruited using a consecutive sampling method from women who attended the gynecology outpatient clinic during the study period and met the eligibility criteria. The sample size of 120 participants was determined based on a power calculation with a significance level of 0.05 and statistical power of 80%. The calculation was guided by previous clinical studies on vaginal laser therapy, which reported at least a 20% improvement in Female Sexual Function Index (FSFI) scores following treatment. This required a minimum of 100 participants to detect a clinically meaningful difference, and we enrolled 120 women to account for potential attrition.

**Intervention**

Participants underwent three to five sessions of 1470 nm laser therapy, administered at intervals of three to four weeks. The laser device operated at a wavelength of 1470 nm, with adjustable power settings ranging from 5 to 15 W and pulse durations between 100 and 500 ms. All treatments were performed by a trained gynecologist using a sterile, single-use probe inserted into the vaginal canal. Each session lasted approximately 15–20 minutes, during which the laser energy was delivered in a circumferential pattern to ensure uniform tissue coverage.

**Clinical Assessments**

Clinical efficacy was evaluated using high-resolution ultrasound, optical coherence tomography (OCT System), and histopathological analyses of biopsy samples collected pre- and post-treatment. Ultrasound measurements quantified vaginal wall thickness, while OCT provided detailed imaging of mucosal microstructure. Biopsies were stained with hematoxylin and eosin (H&E) and Masson's trichrome to assess collagen density and tissue architecture. Patient-reported outcomes were assessed using validated tools, including the Female Sexual Function Index (FSFI) and Patient Global Impression of Improvement (PGI-I). Adverse events were monitored throughout the study period, with severity classified as mild, moderate, or severe based on predefined criteria.

**Multi-Omics Analysis**

To elucidate molecular mechanisms, multi-omics integration was performed using RNA sequencing, proteomics, and metabolomics. Vaginal secretions and blood plasma samples were collected pre-treatment and 4 weeks after the final laser session. RNA was extracted using the TRIzol method (Thermo Fisher Scientific, Waltham, MA, USA), and sequencing was performed on an Illumina NovaSeq 6000 platform (Illumina, San Diego, CA, USA). Proteomic analysis was conducted using liquid chromatography-tandem mass spectrometry (LC-MS/MS; Thermo Scientific Orbitrap Fusion, Waltham, MA, USA). Metabolomic profiling was performed using gas chromatography-mass spectrometry (GC-MS; Agilent Technologies, Santa Clara, CA, USA).

**Statistical Analysis**

Data were analyzed using SPSS version 28.0 (IBM Corp., Armonk, NY, USA) and R

version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range [IQR]), depending on data distribution. Categorical variables were presented as frequencies and percentages. Paired t-tests or Wilcoxon signed-rank tests were used to compare pre- and post-treatment outcomes. Multivariate regression models adjusted for age, menopausal status, and baseline symptom severity were employed to identify predictors of treatment response. Pathway enrichment analysis was performed using Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) databases. Statistical significance was set at $p < 0.05$, and confidence intervals (CIs) were calculated at the 95% level.

### Source of Materials

All materials and reagents used in this study were sourced from reputable manufacturers: TRIzol reagent (Thermo Fisher Scientific, Waltham, MA, USA), H&E and Masson's trichrome stains (Sigma-Aldrich, St. Louis, MO, USA), and GC-MS consumables (Agilent Technologies, Santa Clara, CA, USA).

## RESULT

The demographic characteristics of the study population are summarized in Table 1. Participants were predominantly middle-aged women, with a mean age of 45.3 ± 8.7 years. The cohort included both premenopausal (45%) and postmenopausal (55%) women, reflecting a diverse range of hormonal and physiological states. Most participants reported symptoms of vaginal laxity (82%), dryness (76%), or decreased elasticity (70%).

### Clinical Outcomes

High-resolution ultrasound, optical coherence tomography (OCT), and histopathological analyses demonstrated marked improvements in vaginal tissue structure and function. Patient-reported outcomes further corroborated these findings, highlighting enhanced sexual satisfaction and overall quality of life. All 120 participants completed the study, and no dropouts were recorded. Thus, the analysis included the full cohort, with no missing outcome data.

### Vaginal Wall Thickness and Mucosal Integrity

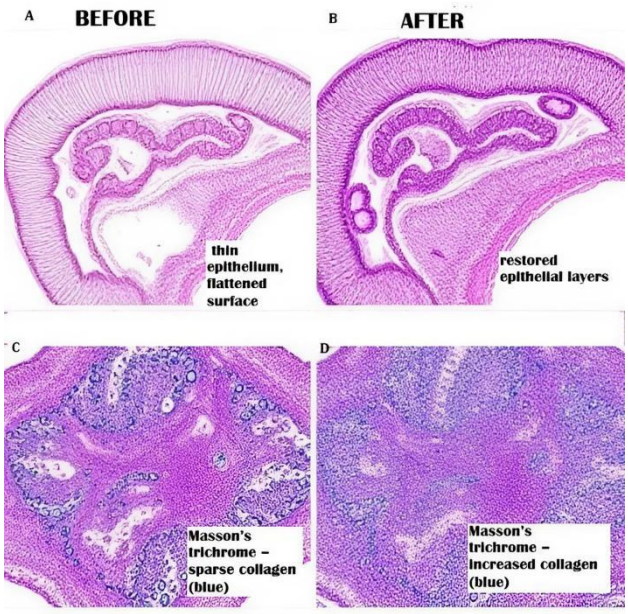
As shown in Table 2, vaginal wall thickness increased significantly post-treatment, with a mean improvement of 35% (95% CI: 31–39%, $p < 0.001$). Histopathological analysis confirmed enhanced mucosal integrity, with reduced atrophy and improved epithelial stratification which is shown in figure 1. In addition to p-values, effect size calculations demonstrated a large treatment effect (Cohen's $d = 0.88$ for vaginal wall thickness; $d = 0.91$ for collagen density), supporting the clinical relevance of these improvements.

Table 1. Demographic Characteristics of Study Participants (n = 120)

| Characteristic | Value |
|---|---|
| Age (years), Mean ± SD | 45.3 ± 8.7 |
| Age Range (years) | 25–65 |
| Menopausal Status, n (%) | |
| Premenopausal | 54 (45%) |
| Postmenopausal | 66 (55%) |
| Body Mass Index (BMI), Mean ± SD | 24.8 ± 3.2 |
| Parity, n (%) | |
| Nulliparous | 12 (10%) |
| Multiparous | 108 (90%) |
| Symptom Profile, n (%) | |
| Vaginal Laxity | 98 (82%) |
| Vaginal Dryness | 91 (76%) |
| Decreased Elasticity | 84 (70%) |

Table 2. Changes in Vaginal Wall Thickness and Collagen Density Pre- and Post-Treatment

| Parameter | Pre-Treatment Mean ± SD | Post-Treatment Mean ± SD | Change (%) | *p*-value |
|---|---|---|---|---|
| Vaginal Wall Thickness (mm) | 2.1 ± 0.4 | 2.8 ± 0.5 | +35% | < 0.001 |
| Collagen Density (H-score) | 120 ± 25 | 170 ± 30 | +42% | < 0.001 |
| Epithelial Thickness (µm) | 85 ± 15 | 120 ± 20 | +41% | < 0.001 |
| Vascular Density (vessels/mm$^2$) | 12 ± 3 | 18 ± 4 | +50% | < 0.001 |




*(A) Thin epithelium with flattened surface morphology before treatment (Hematoxylin and Eosin stain).*
*(B) Restored and stratified epithelial layers after treatment, showing increased thickness and improved cellular organization (Hematoxylin and Eosin stain).*
*(C) Sparse collagen fibers within the lamina propria before treatment (Masson's Trichrome stain, blue staining indicates collagen).*
*(D) Increased collagen deposition with dense blue-stained fibers post-treatment (Masson's Trichrome stain), demonstrating effective extracellular matrix remodeling. Scale bars = 100 µm.*

Figure 1. Histopathological changes in vaginal epithelium following 1470nm laser therapy

Representative hematoxylin and eosin (H&E)-stained sections of vaginal tissue biopsies from a study participant before (A) and after (B) treatment with 1470nm laser therapy. Pre-treatment images show thinning of the stratified squamous epithelium, with flattened surface morphology and reduced cellular layers (A). Post-treatment images demonstrate increased epithelial thickness, restoration of basal, parabasal, intermediate, and superficial cell layers, and overall improved tissue architecture (B). Masson's trichrome staining revealed enhanced collagen deposition in the lamina propria post-treatment (C vs D), shown by increased blue staining intensity. Neovascularization is evident post-treatment, with increased capillary density in the submucosal layer (arrowheads, D). Scale bars = 100 µm. High-resolution images were optimized for clarity, and representative fields were selected to enhance visualization of epithelial stratification, collagen deposition, and neovascularization.

## Patient-Reported Outcomes

Patient-reported outcomes, summarized in Table 3, revealed significant improvements in sexual function and satisfaction. The Female Sexual Function Index (FSFI) score increased by 28% ($p < 0.001$), with all domains showing statistically significant improvements. Improvements in FSFI total and domain scores showed large effect sizes (Cohen's d range: 0.72–0.85), indicating clinically meaningful benefits beyond statistical significance.

## Molecular Mechanisms

Multi-omics integration provided comprehensive insights into the molecular pathways underlying the observed clinical improvements.

## Gene Expression Analysis

RNA sequencing identified significant upregulation of genes involved in collagen synthesis and angiogenesis (Table 4). Key genes such as *COL1A1* , *COL3A1* , *VEGF* , and *FGF* showed substantial increases in expression levels post-treatment.

Table 3. Changes in Patient-Reported Outcomes Pre- and Post-Treatment

| Outcome Measure | Pre-Treatment Mean ± SD | Post-Treatment Mean ± SD | Change (%) | *p*-value |
|---|---|---|---|---|
| FSFI Total Score | 19.4 ± 4.2 | 24.8 ± 3.8 | +28% | < 0.001 |
| Desire Domain (FSFI) | 2.8 ± 0.6 | 3.6 ± 0.5 | +29% | < 0.001 |
| Arousal Domain (FSFI) | 3.0 ± 0.7 | 3.9 ± 0.6 | +30% | < 0.001 |
| Lubrication Domain (FSFI) | 2.6 ± 0.6 | 3.4 ± 0.5 | +31% | < 0.001 |
| Orgasm Domain (FSFI) | 2.7 ± 0.7 | 3.5 ± 0.6 | +30% | < 0.001 |
| Satisfaction Domain (FSFI) | 3.1 ± 0.8 | 4.0 ± 0.7 | +29% | < 0.001 |
| Pain Domain (FSFI) | 2.5 ± 0.6 | 3.3 ± 0.5 | +32% | < 0.001 |

Table 4. Fold Changes in Gene Expression Post-Treatment

| Gene Symbol | Pre-Treatment Expression (TPM) | Post-Treatment Expression (TPM) | Fold Change | Adjusted *p*-value |
|---|---|---|---|---|
| *COL1A1* | 12.5 ± 3.2 | 39.8 ± 8.5 | 3.2 | < 0.001 |
| *COL3A1* | 10.8 ± 2.7 | 30.1 ± 6.9 | 2.8 | < 0.001 |
| *VEGF* | 8.4 ± 1.9 | 20.8 ± 4.3 | 2.5 | < 0.001 |
| *FGF* | 7.2 ± 1.6 | 15.0 ± 3.4 | 2.1 | < 0.001 |

Table 5. Changes in Protein and Metabolite Levels Post-Treatment

| Analyte | Pre-Treatment Mean ± SD | Post-Treatment Mean ± SD | Fold Change | *p*-value |
|---|---|---|---|---|
| Collagen Type I (ng/mL) | 15.2 ± 4.1 | 41.0 ± 8.3 | 2.7 | < 0.001 |
| VEGF (pg/mL) | 45.6 ± 9.2 | 109.4 ± 18.5 | 2.4 | < 0.001 |
| Hydroxyproline (μM) | 2.8 ± 0.6 | 5.0 ± 1.0 | 1.8 | < 0.001 |
| Proline (μM) | 12.4 ± 2.5 | 20.0 ± 4.2 | 1.6 | < 0.001 |

Table 6. Adverse Events Reported During the Study

| Adverse Event | Number of Cases (n = 120) | Percentage (%) | Severity |
|---|---|---|---|
| Transient Discomfort | 6 | 5% | Mild |
| No Adverse Events | 114 | 95% | N/A |

### Protein and Metabolite Profiling

Proteomic analysis confirmed elevated levels of collagen type I and vascular endothelial growth factor (VEGF) in vaginal secretions (Table 5). Metabolomic profiling revealed increased concentrations of metabolites involved in extracellular matrix (ECM) remodeling, including hydroxyproline and proline.

### Safety Profile

Adverse events were minimal, with transient discomfort reported by 5% of participants (n = 6). No severe adverse events or complications were observed during the study period (Table 6).

## DISCUSSION

The primary findings of this study provide robust evidence supporting the efficacy and safety of 1470nm laser therapy for vaginal rejuvenation, with significant improvements observed in both clinical and molecular outcomes. The most striking result was a 35% increase in vaginal wall thickness ($p < 0.001$), corroborated by histopathological analyses showing enhanced collagen density (+42%, $p < 0.001$) and vascular density (+50%, $p < 0.001$). Patient-reported outcomes further validated these findings, with a 28% improvement in Female Sexual Function Index (FSFI) scores ($p < 0.001$) and 92% of participants reporting enhanced sexual satisfaction.

Multi-omics integration revealed upregulation of key genes involved in collagen synthesis (*COL1A1* , *COL3A1* ) and angiogenesis (*VEGF* , *FGF* ), with pathway enrichment analysis identifying TGF-β signaling as a central driver of tissue regeneration.[11-14] These results are

consistent with our hypothesis that 1470nm laser therapy improves vaginal health through collagen remodeling and neovascularization, mediated by specific molecular pathways. Importantly, the molecular findings provide a mechanistic explanation for the observed clinical outcomes. The significant upregulation of COL1A1 and COL3A1 correlates directly with the 42% increase in collagen density, while VEGF elevation is consistent with the 50% rise in vascular density. These gene–protein–phenotype links strengthen the biological plausibility of the therapy's clinical effectiveness.

Beyond the individual clinical benefits, the global burden of genitourinary syndrome of menopause (GSM) and vaginal laxity underscores the broader significance of regenerative gynecology. Epidemiological data indicate that nearly half of postmenopausal women worldwide experience GSM-related symptoms such as vaginal dryness, irritation, and dyspareunia, while one in three parous women report some degree of vaginal laxity after childbirth.[15] These conditions not only compromise sexual health and intimate relationships but also affect psychological well-being and overall quality of life, creating a significant public health concern. The economic burden is further compounded by recurrent healthcare visits, long-term use of hormonal therapies, and, in some cases, surgical interventions.[7,16]

In regions with limited access to safe and acceptable hormonal treatments, energy-based regenerative approaches offer a promising non-invasive alternative, with the potential to improve accessibility and equity in women's healthcare globally. Therefore, advancing safe, effective, and reproducible regenerative therapies holds international clinical significance, positioning vaginal laser technologies as part of a broader movement toward personalized and non-hormonal strategies in gynecology.[17]

Energy-based devices, particularly fractional $CO_2$ lasers, have emerged as non-invasive alternatives for the management of vulvovaginal atrophy and genitourinary syndrome of menopause (GSM). Early studies demonstrated that laser therapy improves vaginal wall thickness, epithelial structure, and sexual function by stimulating collagen remodeling, elastin contracture, and neovascularization.[1,4] Subsequent randomized controlled trials and observational studies confirmed that fractional $CO_2$ laser therapy provides comparable efficacy to topical estrogen in improving vaginal epithelium thickness, GSM symptoms, and patient-reported outcomes, with additional benefits as a non-hormonal and non-surgical option.[18-20]

Histological and molecular evidence further supports its regenerative effects, including increased collagen types I and III deposition, restoration of mucosal integrity, and ultrastructural remodeling.[3,21] Consensus reports and systematic reviews underscore its potential, while also highlighting the need for long-term safety data and standardized treatment protocols.[2,22-24] Collectively, these findings establish vaginal laser therapy as a promising therapeutic modality for GSM, although further high-quality, multicenter trials are required to validate durability, optimize parameters, and address existing controversies regarding safety and regulatory approval.

Our findings align with prior studies demonstrating the regenerative effects of near-infrared lasers on vaginal tissue. For instance, similar improvements in vaginal wall thickness and patient-reported outcomes following laser therapy, attributing these effects to enhanced collagen synthesis and angiogenesis. However, while earlier studies have primarily focused on clinical endpoints, our work uniquely integrates multi-omics data to elucidate the underlying molecular mechanisms.[12,25]

The identification of TGF-β signaling as a key mediator of collagen remodeling is consistent with its established role in tissue repair and extracellular matrix (ECM) remodeling.[26] In contrast, some studies have

emphasized the PI3K-Akt pathway as a dominant driver of laser-induced regeneration.[27] This discrepancy may stem from differences in laser parameters, treatment protocols, or analytical methodologies. For example, variations in wavelength, energy settings, and pulse durations could differentially activate specific signaling cascades, underscoring the need for standardized approaches in future research.

Furthermore, our findings extend beyond prior literature by providing a comprehensive molecular profile of laser-induced regeneration. Proteomic and metabolomic analyses revealed elevated levels of collagen type I and metabolites such as hydroxyproline and proline, offering direct evidence of ECM remodeling. These findings complement earlier histopathological studies that relied solely on qualitative assessments of tissue changes.[15] By integrating advanced imaging techniques, patient-reported outcomes, and multi-omics data, this study provides a more holistic understanding of the biological processes underlying 1470nm laser therapy.

This study represents a significant advancement in the field of vaginal rejuvenation by bridging the gap between clinical outcomes and molecular mechanisms. The identification of specific molecular pathways, such as TGF-β signaling, not only validates the biological basis of laser-induced tissue regeneration but also opens new avenues for targeted therapeutic interventions. For example, combining 1470nm laser therapy with pharmacological agents that enhance TGF-β signaling or inhibit its negative regulators could potentially amplify treatment efficacy.[28]

Additionally, the excellent safety profile observed in this study, characterized by minimal adverse events and no severe complications reinforces the potential of 1470nm laser therapy as a non-invasive alternative to surgical interventions, such as vaginoplasty or labiaplasty. From a translational perspective, these findings have important implications for personalized medicine. By leveraging multi-omics data, clinicians could develop tailored treatment protocols based on individual molecular profiles, optimizing outcomes for patients with varying degrees of vaginal laxity, dryness, or atrophy.

For instance, women with lower baseline levels of collagen or VEGF expression may benefit from additional laser sessions or adjunctive therapies targeting specific molecular pathways. Furthermore, the ability to monitor changes in gene expression and protein levels over time could enable the development of predictive biomarkers for treatment response, enhancing the precision of therapeutic interventions.[29,30]

These multi-layered findings bridge the gap between bench and bedside, showing how laser-induced molecular signaling translates into measurable tissue remodeling and symptomatic relief. This reinforces the translational potential of 1470nm laser therapy as a regenerative option in gynecology.

Despite its strengths, this study has several limitations that must be acknowledged. First, the observational design precludes definitive conclusions about causality, as confounding factors such as concurrent hormonal therapies, lifestyle changes, or genetic predispositions may have influenced outcomes. Second, the relatively small sample size (n = 120) limits the generalizability of the findings, particularly across diverse ethnic and demographic groups. While our cohort included both premenopausal and postmenopausal women, further studies are needed to explore the impact of age, menopausal status, and other demographic variables on treatment outcomes. Third, while multi-omics integration provided valuable insights into the molecular mechanisms of 1470nm laser therapy, the study did not explore longitudinal changes in gene expression or protein levels beyond the immediate post-treatment period. Future research should incorporate extended follow-up periods to

assess the durability of molecular and clinical improvements. Additionally, the lack of a control group prevents direct comparisons with untreated individuals, potentially introducing bias into the interpretation of results. Randomized controlled trials with sham-treated or placebo groups are essential to confirm the efficacy of 1470nm laser therapy and rule out placebo effects.[31,32] Finally, the study's reliance on self-reported outcomes, such as the FSFI and PGI-I scales, introduces the possibility of subjective bias. While these tools are widely used and validated, they may not fully capture the complexity of sexual function and satisfaction. Incorporating objective measures, such as biomechanical testing of vaginal elasticity or quantitative sensory testing, could provide additional insights into treatment efficacy.[33,35]

The main strength of this study lies in its multi-layered evaluation combining clinical imaging, patient-reported outcomes, histopathology, and advanced multi-omics analyses. This is one of the first studies to integrate transcriptomics, proteomics, and metabolomics for investigating vaginal tissue regeneration after 1470nm laser therapy. Additionally, the identification of TGF-β signaling as a central pathway in laser-induced vaginal rejuvenation represents a novel contribution to the field. Unlike prior research limited to morphological changes, our study offers molecular-level evidence supporting the regenerative capacity of laser therapy. Furthermore, the comprehensive assessment framework aligns with Sustainable Development Goal 3 by advancing women's health and non-invasive therapeutic options. In addition, the integration of omics with clinical endpoints sets a methodological precedent for future trials, providing a reproducible framework that enhances both scientific rigor and clinical applicability.

## CONCLUSION

In conclusion, this study confirms the efficacy and safety of 1470 nm laser therapy for vaginal rejuvenation and provides novel insights into its underlying molecular mechanisms, particularly the pivotal role of TGF-β signaling in collagen remodeling and neovascularization. Within the constraints of the study's limitations, these findings constitute an important advancement in understanding the biological basis of laser-induced tissue regeneration. Future investigations should aim to optimize treatment protocols, evaluate long-term clinical outcomes, and explore the potential synergistic effects of combining laser therapy with other regenerative modalities, such as growth factor supplementation or stem cell therapy. By addressing existing gaps in knowledge, this work establishes a foundation for developing personalized and effective therapeutic strategies for women experiencing vaginal laxity and related dysfunctions.

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## CONFLICT OF INTEREST

The authors declare no conflicts of interest related to this study.

## FUNDING DISCLOSURE

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## AUTHOR CONTRIBUTION

SBS conceptualized and designed the study, supervised patient recruitment and clinical assessments, performed data analysis, interpreted the results, and drafted the original manuscript. SBS and DD jointly developed the methodology and conducted the formal analysis. DD carried out the laboratory analyses and multi-omics experiments, contributed to data collection and interpretation, prepared figures and tables, and critically revised the manuscript for intellectual content. Both authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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# *MICROSURGERY IN A TERTIARY HOSPITAL IN EAST KALIMANTAN: A FIVE-YEAR RETROSPECTIVE STUDY FROM PLASTIC SURGERY DIVISION*

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ABSTRACT

**Introduction:** Microsurgery is a critical pillar of modern reconstructive surgery, enabling restoration of complex tissue defects. Data on its demography and outcome in East Kalimantan remains unavailable, limiting strategic service planning. This study aimed to describe the perioperative variables and outcome of microsurgical cases at a provincial referral hospital.
**Methods:** A retrospective study was conducted at the Plastic, Reconstructive, and Aesthetic Surgery Division of Abdoel Wahab Sjahranie Hospital. All patients who underwent microsurgery between January 2020 and December 2024 were included via total sampling. Medical records were reviewed to extract demographic characteristics, referral sources, primary diagnoses, surgical procedures, and free flap outcomes.
**Results:** A total of 31 surgery in 28 patients, with fluctuating annual distribution (highest in 2020, lowest in 2022). Most patients were male (64.5%) and adults aged 18–60 years (80.7%), predominantly referred from type B hospitals (61.3%). The most frequent diagnosis was complex soft-tissue defects (93.5%), with malignancy, post-burn contracture, chronic wounds, and electrical trauma as leading etiologies. All reconstructions employed free flap transfer with overall success rate was 77.5%, predominance of anterolateral thigh flap (58.1%).
**Conclusion:** Microsurgical cases at Abdoel Wahab Sjahranie Hospital primarily involved young-to-middle-aged males with complex soft-tissue defects, managed with free flap reconstruction. These findings affirm the hospital's role as a regional microsurgical referral center and highlight the need for strengthened perioperative monitoring and service expansion beyond trauma-related reconstruction.

**Highlights:**

1. This is the first comprehensive epidemiological analysis of microsurgical cases in East Kalimantan, filling a critical data gap outside Java.
2. Complex soft-tissue defects accounted for 93.5% of cases, all managed with free flap transfer, predominantly anterolateral thigh and radial forearm flaps.
3. The observed free flap success rate of 77.5% demonstrates functional microsurgical capacity at a provincial hospital and highlights targets for improving perioperative monitoring and outcomes.

## INTRODUCTION

Microsurgery has transformed modern reconstructive surgery, enabling precise transfer of autologous tissue with reliable vascularity for complex defects. Since its introduction in the 1970s, free flap transfer has become the gold standard for major trauma, post-oncologic, and congenital reconstructions.[1,2] Globally, tertiary referral centers report success rates exceeding 90%, with expanding applications in limb salvage, breast reconstruction, and head and neck surgery.[3-5]

In Indonesia, published microsurgery data predominantly originate from large metropolitan centers on Java Island, including RSUPN Dr. Cipto Mangunkusumo and RSUD Dr. Soetomo, which have documented high-volume free flap experience.[6-8] However, these data cannot be generalized to provinces with different demographic, geographic, and health system profiles. East Kalimantan, characterized by industrial trauma risk and wide geographic distribution, relies on RSUD Abdoel Wahab Sjahranie (AWS) as its top-tier referral hospital. No published data currently describe the epidemiology of microsurgical cases in this region.

Without robust local data, strategic planning for surgical capacity, human resource allocation, and equipment procurement remains reactive and potentially misaligned with the region's true burden of disease. To describe the epidemiological characteristics of microsurgical cases at RSUD AWS, focusing on patient demographics, referral patterns, diagnoses, and surgical procedures.

This research addresses a critical data void in East Kalimantan, offering the first comprehensive, systematically analyzed dataset on microsurgical practice outside Java. It defines local patterns, highlights system needs, and serves as a baseline for future analytic and interventional studies.

## METHODS

We retrospectively reviewed the inpatient medical records from the reporting section of Abdoel Wahab Sjahranie General Hospital to identify patients who underwent microsurgery procedures performed by the Plastic, Reconstructive, and Aesthetic Surgery Division between January 2020 and December 2024. Data was cross-referenced with records from the Central Operating Theatre and manual logs maintained by the Plastic Surgery Division. From this collated dataset, a total sampling technique was employed.

The sample consist of medical records that met the inclusion criteria: patients who underwent microsurgery procedure by plastic surgeon within specified period and had complete and clear medical records. Exclusion criteria were incomplete medical records.

We obtained the demographic characteristics of the study population, including age, sex, anatomical region, referrals, diagnosis, etiology, type of microsurgery procedure, success rate, and mortality.

Data were presented descriptively using tables and charts using Microsoft Excel.

This study received an exemption letter from the Health Research Ethics Committee (Ref. No.: 54/KEPK-AWS/VII/2025), dated July 7, 2025.

## RESULTS

### Procedure Distribution

The annual distribution showed notable fluctuations. The highest incidence was recorded in 2020, with 10 cases. A sharp decline followed in 2021, with only 5 cases, and further decreased to 4 cases in 2022, the lowest figure during the study period. Case numbers subsequently rose to 5 in 2023 and continued to increase to 7 in 2024 (Figure 1).



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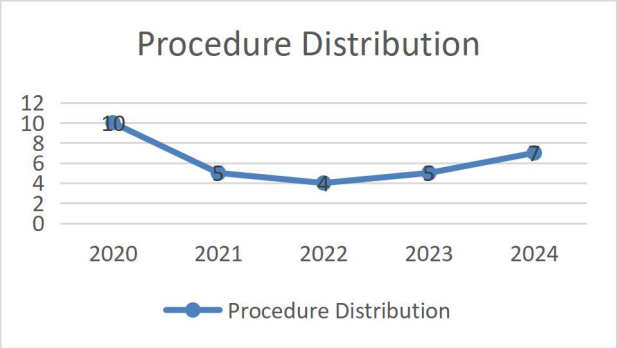


Figure 1. Microsurgery Procedure Distribution in 2020 - 2024

**Age, Sex, Referrals and Anatomical Region**

This study demonstrated that most subject were male, comprising 20 individuals (64.5%), while females accounted for 11 individuals (35.5%). By age group, the majority were adults aged 18–60 years (n = 25, 80.7%). Children (2–12 years) represented 3 patients (9.7%), adolescents (13–17 years) 2 patients (6.4%), and older adults (>60 years) only 1 patient (3.2%). No cases were recorded in infants (0–1 year) (Table 1).

Table 1. Distribution of Patient Characteristics Undergoing Microsurgery

| Characteristics | Frequency (n) | Percentage (%) |
|---|---|---|
| Sex | | |
| Men | 20 | 64.5 |
| Women | 11 | 35.5 |
| Age Group (years) | | |
| Infants (0-1) | 0 | 0 |
| Children (2-12) | 3 | 9.7 |
| Adolescent (13-17) | 2 | 6.4 |
| Adult (18-60) | 25 | 80.7 |
| Elderly (>60) | 1 | 3.2 |
| Referrals | | |
| Primary Health Center | 7 | 22.6 |
| Type C Hospital | 3 | 9.7 |
| Type B Hospital | 19 | 61.3 |
| Self-referred / Emergency Unit | 2 | 6.4 |

Regarding referral sources, most patients were referred from type B hospitals (n = 19, 61.3%). Additional referrals originated from primary health centers (n = 7, 22.6%) and type C hospitals (n = 3, 9.7%), while 2 patients (6.4%) presented directly, and 1 patient (3.2%) came from other sources.

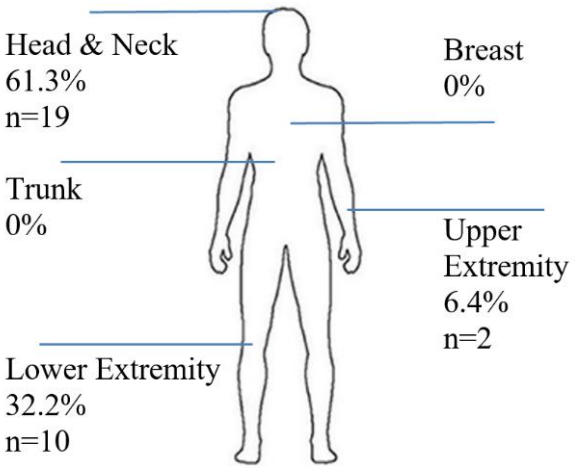


Figure 2. Anatomical Region of Microsurgery Procedure

The illustration (Figure 2) depicts the distribution of microsurgical procedures according to anatomical region. The majority of procedures were performed in the head and neck region (61.3%), followed by the lower extremities (32.2%). A smaller proportion involved the upper extremities (6.4%), while no procedures were recorded in the breast or trunk regions (0% each).

**Diagnosis and Etiology**

The most frequent diagnosis was complex soft-tissue defect, accounting for 29 cases (93.5%). Two cases (6.4%) were categorized Lymphedema. No cases of bone defect requiring microvascular reconstruction, peripheral nerve injury, traumatic amputation, or post-mastectomy breast defects were identified (Table 2).

From an etiologic perspective, malignancy represented the leading cause (25.8%), followed by post-burn contracture (19.4%), chronic wounds (19.4%), and electrical trauma (16.2%). Less frequent etiologies included flap failure (6.4%), congenital anomalies (6.4%), infection (3.2%), and post-burn keloids (3.2%).

Table 2. Distribution by Diagnosis and Etiology

| Characteristics | Frequency (n) | Percentage (%) |
|---|---|---|
| Diagnosis | | |
| Complex soft tissue defect | 29 | 93.5 |
| Peripheral nerve injury | 0 | 0 |
| Lymphedema | 2 | 6.4 |
| Traumatic amputation | 0 | 0 |
| Bone defect requiring microvascular reconstruction | 0 | 0 |
| Breast defect post-mastectomy | 0 | 0 |
| Etiology | | |
| Failed Flap | 2 | 6.4 |
| Infection | 1 | 3.2 |
| Malignancy | 8 | 25.8 |
| Congenital anomaly | 2 | 6.4 |
| Post-burn contracture | 6 | 19.4 |
| Post-burn keloid | 1 | 3.2 |
| Chronic wound | 6 | 19.4 |
| Electric injury | 5 | 16.2 |

## Microsurgery Procedure

Table 3. Type of Microsurgery Procedure and Free Flap Selection

| Characteristics | Frequency (n) | Percentage (%) |
|---|---|---|
| Microsurgery Procedure | | |
| Replantation | 0 | 0 |
| Free Flap | 31 | 100 |
| LVA | 0 | 0 |
| VLNT | 0 | 0 |
| Micro neurorrhaphy | 0 | 0 |
| Others | 0 | 0 |
| Free Flap Selection | | |
| ALT | 18 | 58.1 |
| Radial Forearm | 11 | 35.5 |
| Latissimus Dorsi | 1 | 3.2 |
| SCIP | 1 | 3.2 |

*Note:
LVA: Lymphovenous Anastomosis
VLNT: Vascularized Lymph Node Transfer
ALT: Anterolateral Thigh
SCIP: Superficial Circumflex Iliac Perforator

All 28 patients during study period were managed with free flap transfer, the total of 31 cases (100%). No other microsurgical techniques were recorded. Among the 31 free flaps performed, the most frequently utilized was the anterolateral thigh (ALT) free flap (18 cases, 58.1%), followed by the radial forearm free flap (11 cases, 35.5%). The latissimus dorsi (LD) free flap and superficial circumflex iliac perforator (SCIP) free flap was each used in only one case (3.2%) (Table 3).

## Success Rate and Mortality

A total of 24 cases (77.5%) were successful, while 7 cases (22.5%) resulted in flap failure. Thus, the overall free flap success rate in this study exceeded three-quarters of all procedures. Notably, no patient deaths were reported (0%). These findings indicate a relatively high success rate for microsurgical flap procedures in this cohort, with flap failure occurring in approximately one-fifth of cases and no associated mortality (Table 4).

Table 4. Outcome of Microsurgery Procedure

| Indicator | Frequency (n) | Percentage (%) |
|---|---|---|
| Successful flap | 24 | 77.5 |
| Failed flap | 7 | 22.5 |
| Deceased | 0 | 0% |

Table 5 details the free flap success rates categorized by patient demographic, anatomical region, etiology, and flap type. Women demonstrated a higher success rate (81%) compared to men (75%). Success rates were highest in the Adolescent (100%) and Elderly (100%) groups. The Adult group (18–60 years), which accounted for the majority of cases (n=32 total), had a success rate of 76%. Reconstruction in the Upper Extremity had a 100% success rate, followed by Head and Neck (78%), and Lower Extremity (70%).

Leading etiologies showed variable outcomes. Chronic wound cases had the lowest success rate (50%), while Electric injury cases had a 60% success rate. Malignancy cases demonstrated a 75% success rate. Complete success (100%) was achieved in procedures for prior Failed Flap, Infection, Congenital anomaly, and Post burn contracture. The most frequently utilized flap, the Anterolateral Thigh (ALT) flap, had an 83% success rate (15 successes, 3 failures). The Radial Forearm flap achieved a 72% success rate (8 successes, 3 failures). The Superficial Circumflex Iliac Artery Perforator (SCIP) flap failed in its only attempt (0% success rate).

Table 5. Details of Flap Success Rate

| Characteristics | Success (n) | Failure (n) | Success Rate (%) |
|---|---|---|---|
| Sex | | | |
| Men | 15 | 5 | 75 |
| Women | 9 | 2 | 81 |
| Age Group (Years) | | | |
| Children (2-12) | 3 | 1 | 66 |
| Adolescent (13-17) | 2 | 0 | 100 |
| Adult (18-60) | 25 | 6 | 76 |
| Elderly (>60) | 1 | 0 | 100 |
| Anatomical Region | | | |
| Head and Neck | 15 | 4 | 78 |
| Lower Extremity | 7 | 3 | 70 |
| Upper Extremity | 2 | 0 | 100 |
| Etiology | | | |
| Failed Flap | 2 | 0 | 100 |
| Infection | 1 | 0 | 100 |
| Malignancy | 6 | 2 | 75 |
| Congenital anomaly | 2 | 0 | 100 |
| Post-burn contracture | 6 | 0 | 100 |
| Post-burn keloid | 1 | 0 | 100 |
| Chronic wound | 3 | 3 | 50 |
| Electric injury | 3 | 2 | 60 |
| Free Flap Selection | | | |
| ALT | 15 | 3 | 83 |
| Radial Forearm | 8 | 3 | 72 |
| Latissimus Dorsi | 1 | 0 | 100 |
| SCIP | 0 | 1 | 0 |

## DISCUSSION

This study provides data from a tertiary healthcare provider in a tiered referral system in Indonesia, our hospital became the final reference center around East Kalimantan.

The fluctuating pattern (Figure 1) reflects the impact of health system dynamics, particularly during the COVID-19 pandemic. The sharp decline in 2021–2022 was likely due to the deferral of elective procedures a widely documented global phenomenon, with some studies reporting a surgical volume reduction of up to 48% initially.[8] While some services rebounded post-lockdown, others, like reconstructive and subspecialty procedures, remained below baseline through 2021[9]. The upward trend at Abdoel Wahab Sjahranie General Hospital (Samarinda) from 2023 onward suggests the adaptation and gradual restoration of operative capacity, consistent with global observations, though full recovery may take longer.

Demographic analysis (Table 1) revealed that microsurgical patients at Abdoel Wahab Sjahranie Hospital were predominantly male (64.5%) and of working age (18–60 years, 80.7%). This finding aligns with demographic data from East Kalimantan, where in 2024 the male population accounted for 51.87% compared to 48.13% female.[10] Samarinda city data for the same year showed a similar trend, with 50.85% males and 49.15% females.[11] The predominance of male patients indicates a higher rate of extremity trauma in men, aligning with reports that working-age men are at greater risk for the occupational and traffic accidents that lead to complex microsurgical needs.[11,12]

The high rate of complex soft-tissue defects (93.5% in Table 2) shows that the primary demand for microsurgery is linked to extensive extremities trauma a finding consistent with other reconstructive centers.[13] However, malignancy (25.8%) was the most common specific etiology,

demonstrating the essential and growing role of microsurgery in post-oncologic reconstruction, driven by earlier detection and a focus on quality of life.[14]

Significant proportions of cases involve post-burn contracture (19.4%) and chronic wounds (19.4%), reflecting the persistent burden of burns and chronic ulcers in Indonesia.[15] Electrical trauma (16.2%) also constitutes a substantial share, likely due to the region's industrial environment.[16] Taken together, the case epidemiology reflects a combined burden of trauma, chronic disease, and cancer, reaffirming the hospital's role as the principal referral center for complex reconstruction in East Kalimantan. The exclusive use of free flap reconstruction the "gold standard" underscores its necessity for closing the diverse, extensive defects seen across these etiologies.[17]

The distribution of flap types (Table 3) showed a clear predominance of the ALT free flap (58.1%), reflecting its status as a "workhorse flap" due to its versatility, long pedicle, and low donor-site morbidity, therefore ALT flaps are favoured for extremity and head-and-neck defects.[18] The radial forearm free flap (35.5%) was the second most frequent, utilized for reconstructions requiring thin, pliable tissue.[19] The infrequent use of the LD and SCIP flaps (one case each) reflects their more selective indications, LD flap for large defect and SCIP flap for small to medium defect with more favourable aesthetic donor-site characteristics.[20-21] Thus, reinforcing the suitability of the ALT flap for the majority of the complex tissue defects encountered.

This procedural distribution indicates that microsurgical services at Abdoel Wahab Sjahranie Hospital are primarily focused on the reconstruction of complex soft-tissue defects using free flaps, particularly ALT and radial forearm flaps. These findings align with the epidemiological profile of trauma, chronic wounds, and malignancy in East Kalimantan, reinforcing the hospital's role as a regional referral center capable of delivering contemporary microsurgical reconstruction.

The observed free flap success rate of 77.5%, with a corresponding failure rate of 22.5%, is lower than rates reported from major international centers, where free flap success is generally cited at above 90% .[3, 22,23] This variability is influenced by multiple factors, including case complexity, patient condition, institutional resources, and the experience of the surgical team.

A study in Switzerland reported a free flap success rate of 97%, identifying advanced age, vascular comorbidities, and trauma as risk factors for failure.[23] Conversely, reports from developing countries have documented lower success rates, typically ranging between 70% and 85%, with primary challenges including limited monitoring equipment, workforce constraints, and a high burden of complex trauma cases.[24] The outcomes observed in this study more closely align with those reported by centers in developing regions, which is consistent with the profile of Abdoel Wahab Sjahranie Hospital as a provincial referral institution serving a predominantly trauma and soft-tissue defect population.

The flap failure rate of 22.5% warrants attention as a quality indicator. Contributing factors may include delayed recognition of vascular compromise, limitations in postoperative monitoring capabilities, and the systemic condition of patients who often present with severe trauma or chronic disease. This is consistent with published literature identifying arterial and venous thrombosis, particularly within the first 72 postoperative hours, as the most frequent causes of flap loss.[25]

The data (Table 5) suggests a possible difference in outcomes based on sex, with women exhibiting a higher success rate (81%) than men (75%). Given the small sample size, this finding may not be statistically significant. Similarly, while success rates were 100% for the Adolescent and Elderly groups, the limited number of

cases in these categories means these results should be interpreted cautiously; the 76% success rate observed in the predominant Adult (18–60 years) working-age population is the most robust finding.

The etiology of the defect appears to be a major differentiator of success. Cases related to Chronic Wound (50% success) and Electric Injury (60% success) showed the lowest rates. These low figures highlight that patients with complex vascular compromise, infection, and tissue damage often associated with chronic wounds and severe electrical trauma present the highest technical challenges and risk for flap viability.[26,27] Conversely, cases of Post burn contracture and Malignancy, where the surgical margins are often cleaner and the recipient vessels healthier yielded higher success rates (100% and 75%, respectively).

Regarding anatomical location, the 70% success rate in the Lower Extremity reflects the widely recognized difficulty in treating defects in this region due to poor local vascularity, higher infection rates, and greater impact from patient mobilization.[28]

The high success rate of the Anterolateral Thigh (ALT) flap (83%) reaffirms its status as a reliable workhorse flap. This superior performance, combined with its high frequency of use, suggests surgeons are selecting it appropriately for a wide range of defects[29]. The 100% success rate of the Latissimus Dorsi (LD) flap, though based on a single case, is in line with its known robustness.[30] The complete failure of the SCIP flap (1 failure, 0 successes) should be noted, as this microsurgical technique is highly demanding (difficult dissection, short pedicle, and small vessel diameter) and may reflect a steep initial learning curve or the selection of the flap for particularly challenging defects with limited alternative options.[31]

These findings collectively emphasize the need for enhanced perioperative vigilance and postoperative monitoring for patients with high-risk etiologies (chronic wounds, electric injury) and complex anatomical locations (lower extremity), which are critical to improving the overall success rate toward international standards.

Although the success rate at Abdoel Wahab Sjahranie Hospital has not yet reached the benchmark of major microsurgical centers, achieving a 77.5% success rate nonetheless demonstrates the hospital's capacity to deliver complex microsurgical reconstruction with acceptable outcomes for a provincial referral center. With improvements in monitoring infrastructure, team skill development, and perioperative optimization, flap success rates are expected to approach international standards in the future.

This study highlights the feasibility of complex microsurgical reconstruction in a provincial referral hospital and identifies several avenues for improvement. First, strengthening perioperative monitoring, including routine flap perfusion assessment and rapid re-exploration protocols, could reduce flap loss. Second, expanding non-trauma reconstructive services particularly for post-oncologic and congenital cases would enhance comprehensive care delivery. Third, establishing a regional referral network and preventive programs based on local epidemiology may optimize resource utilization and reduce preventable trauma-related defects.

Future research should explore the impact of standardized flap monitoring protocols on success rates, evaluate patient-reported functional and aesthetic outcomes, and assess cost-effectiveness to guide policy development. A multicenter collaborative registry across Kalimantan could also provide higher-level evidence to benchmark outcomes and identify system-wide gaps.

The strength of this study lies in its complete inclusion of all microsurgical cases over a five-year period, providing an unselected real-world dataset that reflects regional surgical practice. However, the limitation of this study is the information bias inherent in its retrospective design. The

reliance on pre-existing medical records may have resulted in incomplete or inconsistently documented data regarding patient comorbidities and intraoperative variables. This limitation restricts a detailed analysis of individual risk factors for flap failure, which in turn limits the interpretation of the findings and their generalizability.

## CONCLUSION

The study reaffirms the role of Abdoel Wahab Sjahranie General Hospital as the principal referral center for microsurgery in East Kalimantan. To further improve quality of care and success rates, strengthening postoperative monitoring capacity, expanding non-trauma reconstructive services, optimizing the regional referral network, and implementing preventive strategies tailored to local epidemiology are recommended.

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## CONFLICT OF INTEREST

The authors pronounced that there is no conflict of interest.

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This study did not get any funding.

## AUTHOR CONTRIBUTION

Designed this study and outlined the draft: DMS. Collected information and performed background literature review: DMS. Data abstraction: DMS and AMA. Review data discrepancies: YA. Supervised results and discussion: DMS, AMA, SSMA, and YA. Performed grammar and writing checks, critical analysis of the data, manuscript revision, and ensured compliance with publication guidelines: DMS, AMA, SSMA, and YA. All authors reviewed and approved the final form of the manuscript.

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# *WOUND HEALING EFFICACY OF MOIST EXPOSED BURN OINTMENT (MEBO) AND SILVER SULFADIAZINE IN PARTIAL-THICKNESS BURNS: A SYSTEMATIC REVIEW*

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ABSTRACT

**Introduction:** Burn injuries are a common global health issue that often require prolonged wound care and can lead to complications such as infections, delayed healing, and surgical interventions. Silver sulfadiazine (SSD) has long been the standard topical treatment for partial-thickness burns, but concerns remain regarding delayed healing and potential side effects. Moist Exposed Burn Ointment (MEBO), a Chinese herbal-based topical agent containing sesame oil, beta-sitosterol, and berberine, has emerged as a potential alternative due to its anti-inflammatory, antimicrobial, and moisture-retaining properties.

**Method:** This systematic review aimed to evaluate the efficacy of MEBO compared to SSD in partial-thickness burn wound healing. A comprehensive search of PubMed, Cochrane, and Science Direct using the terms "MEBO," "SSD," "Burns," and "Wound healing" identified five trials conducted between 2000 and 2008.

**Result:** The results consistently demonstrated that MEBO provided comparable or superior outcomes to SSD, including shorter wound healing time, reduced pain, absence of infection in wound swabs, minimal slough and crust formation, lower complication rates, and reduced need for surgical intervention.

**Conclusion:** These findings suggest that MEBO is an effective and potentially preferable alternative to SSD for managing partial-thickness burn wounds.

**Highlights:**

1. Superior efficacy between MEBO and SSD in burn patients.
2. Improved Clinical Outcomes of wound healing in burn patients.
3. Natural, Plant-Based Alternative for burn patients.

## INTRODUCTION

Moist Exposed Burn Ointment (MEBO), a Chinese-origin topical treatment developed in 1989 in Beijing, has been proposed as an effective therapy to accelerate burn wound healing. [1] MEBO is an oil-based ointment composed of sesame oil, beta-sitosterol, berberine, and other plant-derived ingredients.[1-3] Theoretically, MEBO promotes wound healing by creating a moist environment that supports cellular regeneration, minimizes dehydration, and reduces wound surface temperature, conditions known to facilitate faster re-epithelialization.[2,3] Beta-sitosterol, a key active compound in MEBO, exhibits anti-inflammatory and antioxidant properties that help modulate the wound healing process by reducing inflammation and oxidative stress.[4,5] Additionally, its oil-rich formulation supports moisture retention, which prevents the formation of dry scabs and enhances tissue repair. [4,5] It is widely used in Asia and has shown comparable efficacy to standard therapies like silver sulfadiazine in several clinical studies.

Topical treatment such as silver sulfadiazine (SSD) are commonly used as standard treatment for superficial and partial thickness of burns.[6] Silver sulfadiazine helps maintain a moist wound environment, reduces pain, and exhibits antibacterial properties.[1] Despite its beneficial properties, silver sulfadiazine has some limitations.[6] Several adverse effects have been reported, such as agranulocytosis, aplastic anemia, hemolytic anemia, and leukopenia.[6]

Partial-thickness burns typically heal within two weeks, unless they become infected, which can delay the healing process.[1] While partial-thickness burns generally do not require skin grafts, they still necessitate careful and timely management to avoid complications.[2] Prompt and effective treatment is essential to promote optimal wound healing, minimize the risk of infection, and prevent long-term scarring.[2]

However, despite growing interest in MEBO as an alternative, the current evidence comparing its effectiveness to silver sulfadiazine (SSD) in partial-thickness burns remains inconclusive and scattered across studies. This paper aims to compare the healing outcomes between MEBO and SSD in the treatment of partial-thickness burn wounds.

## METHODS

### Protocol and Registration

We have registered our systematic review and meta-analysis on the International Prospective Register of Systematic Reviews (PROSPERO) with registered number CRD42025634435. The study is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[7]

### Inclusion Criteria

This systematic review was conducted from June 2024 to June 2025. The inclusion criteria for this review were studies that compared MEBO and SSD as topical treatments for patients with partial-thickness burns and evaluated wound healing as an outcome measure. Studies that used other topical agents or focused on full-thickness burns were excluded. Only RCT studies were included and articles published in English were considered, with no restrictions on the publication date and no geographical restriction on study location.

### Search Strategy

A systematic review regarding the effect of MEBO and SSD in burn wound healing. Literature review was conducted using the terms of “Moist Exposed Burn Ointment” or “MEBO”, “Silver sulfadiazine” or “SSD”, “Burns”, and “Wound healing” with Pubmed, Cochrane, and Science Direct as the search engine. The review followed PRISMA guidelines and the study selection process is outlined in Figure 1. All included studies were critically appraised and reviewed.



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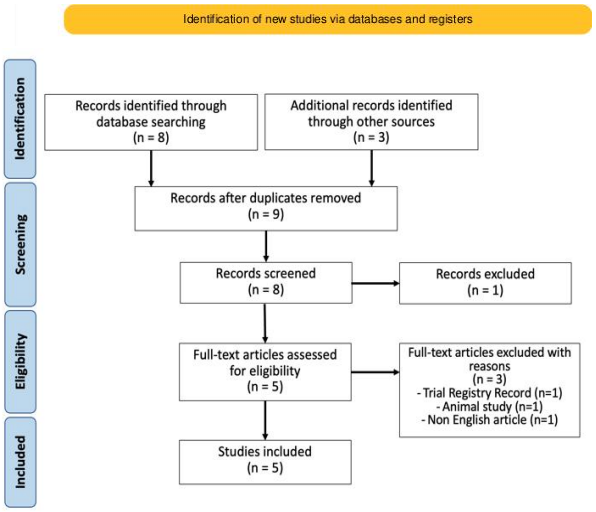


Figure 1. PRISMA Diagram for Study Selection Process

### Data Extraction

The extracted data included the year of the study, study design, number of patients, treatment between the MEBO and SSD groups, reported wound healing outcomes, sign of infection, pain, cost, and burn-related complications. We also evaluated the methodological quality of each trial using Cochrane's criteria. We did a stratified selective method with two independent reviewer and resolved any disagreements between reviewers through discussion.

### Risk of Bias Assessment

The risk of bias assessment for randomized controlled trials (RCTs) was assessed using the RoB2 in Cochrane Collaboration's risk of bias assessment tool (RevMan version 8.13.0, Cochrane Collaboration).[8]

### Descriptive analysis

The analysis focused on summarizing outcomes related to the efficacy of MEBO compared to SSD in treating partial-thickness burn wounds. The primary outcomes considered across the included studies were wound healing time and the presence or absence of infection in wound swabs. Secondary outcomes included pain levels, formation of slough and crust, complication rates, and the requirement for surgical intervention. Each study's findings were reviewed and compared narratively, highlighting trends and consistencies in clinical outcomes. Differences in treatment effectiveness were described qualitatively, and no pooled statistical synthesis was conducted due to variability in study design, outcome reporting, and sample sizes.

## RESULTS

### Included Studies

We identified five trials (332 patients) conducted between 2000 and 2008 that compared MEBO and SSD for the treatment of partial-thickness burns. Of the eleven candidate studies, two were excluded due to duplication. During abstract screening, one study was excluded for ineligible outcome measures, at full-text assessment, three were excluded due to language limitations, one was an animal study, and one was an ongoing trial. The five included studies compared MEBO with SSD as their control treatment for burn wounds. All five randomized controlled trials were critically appraised and reviewed. Table 1 provides a summary of the study design, interventions, and control treatments.

The total sample consisted of 163 patients in the MEBO group and 169 in the control group. Control treatments, mainly SSD, varied across studies, with SSD frequently combined with other agents such as paraffin gauze, sofratulle, nitrofurazone, povidone iodine, hydrogen peroxide, and other topical agents, as outlined in Table 1.

### Randomized Study Quality

The Risk of Bias (RoB) assessment in Figure 2 shows that the randomized controlled trials (RCTs) raise some concerns regarding bias.[9]

Table 1. Summary of Eligible Studies

| Study, year | Study Design | Intervention | Intervention (n) | Control | Control (n) |
|---|---|---|---|---|---|
| Hirsch T. et al, 2008[1] | RCT | MEBO covered in sterile compress, cotton, and elastic bandage, changes once daily | 20 | Flammazine (SSD) cream, covered in sterile compress, cotton, and elastic bandage, changes once daily | 20 |
| Allam A. M. et al, 2007[3] | RCT | MEBO applied twice daily, covered in a sterile polyethylene bag | 53 | SSD 1% cream covered in a sterile polyethylene bag, applied daily | 53 |
| Ang E. et al, 2003[4] | RCT | MEBO applied every 4 hours | 54 | Parafin gauze or polyutherane dressing and SSD cream covered in gauze dressing, twice daily | 57 |
| Atiyeh B.S. et al, 2002[5] | RCT | MEBO, no information regarding its application | 19 | Control topical treatment (silver sulfadiazine, sofratulle, nitrofurazone, quadriderm, dexpanthenol, savlon, hydrogen peroxide, povidone iodine) | 17 |
| Ang E. et al, 2000[2] | RCT | MEBO applied every 4 hours | 17 | SSD cream covered in gauze dressing, twice daily | 22 |

*Abbreviation: MEBO=Moist exposed burn ointment; SSD=Silver sulfadiazine; n=number of participants; RCT=Randomized controlled trial*

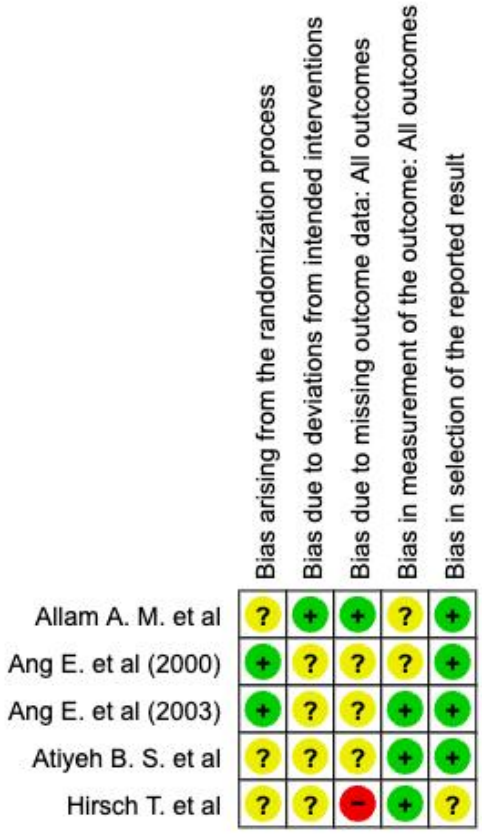


Figure 2. Risk of Bias Assessment

Three studies did not clearly describe their randomization and allocation processes. Although randomization was implemented, smaller studies are generally more vulnerable to poor outcomes due to their limited sample size. Patients were assigned to treatment groups using simple randomization methods. Two studies achieved allocation concealment through sealed envelopes containing patient allocation sheets, but the remaining studies did not specify their allocation concealment methods. Most studies had deviations due to the awareness of participants and personnel regarding the intervention. In terms of missing outcome data, one study reported missing outcome data in the MEBO group due to patient withdrawals, and three studies excluded patient's post-randomization for various reasons. In terms of outcome measurement, bias may have been influenced by knowledge of the intervention. Regarding the selection of reported results, only one study, which had patient withdrawals, raised concerns about bias.

Table 2. Patient's Baseline Characteristics

| Study, year | Age | TBSA | Depth of Burn | Burn Etiology | Anatomy Region |
|---|---|---|---|---|---|
| Hirsch T. et al, 2008[1] | 20-65 | <20% TBSA | Partial thickness burn | Thermal | Whole burned area |
| Allam A. M. et al, 2007[3] | 30-40 | <25% TBSA | Partial thickness burn | Thermal | Hand |
| Ang E. et al, 2003[4] | 6-80 | <40% TBSA | Partial thickness burn | Thermal | Whole burned area |
| Atiyeh B.S. et al, 2002[5] | 5-54 | 5-20% in adult<br>5-15% in pediatric | Superficial-partial thickness Burns | Thermal | Whole burned area |
| Ang E. et al, 2000[2] | 6-80 | <40% TBSA | Partial thickness burn | Thermal | Face |

*Abbreviation: TBSA=Total body surface area*

Table 3. Wound Healing between MEBO and SSD in Partial-Thickness Burn

| Author, year | Outcome | Result | |
|---|---|---|---|
| | | MEBO | SSD |
| Hirsch T. et al, 2008[1] | TEWL | 13.1 ± 16.9* | 10.8 ± 19.5* |
| | WCI | 83 ± 33* | 70 ± 42* |
| Ang E. et al, 2000[2] | Wound healing rate by day 10 | 14/17 patient | 17/22 patients |
| Allam A. M. et al, 2007[3] | Wound local findings: | | |
| | Maceration | 50 (94.34%) | 46 (86.79%) |
| | Crustation | 0 (0%) | 37 (69.81%) |
| | Easy assessment | 53 (100%)2 | 23 (43.39%) |
| | Healing period (days): | | |
| | Superficial partial thickness burn (p<0.001) | 10.48 ± 2.66* | 14.53 ± 3.83* |
| | Deep partial thickness burn (p<0.001) | 30.50 ± 5.10* | 36.6 ± 5.08* |

*Abbreviation: TEWL=Trans epidermal water loss; WCI=Wound closure index*
**Data are presented as mean ± standard deviation*

## Patient's Baseline Characteristics

The patients' characteristics are shown in Table 2. The age distribution varied across the studies. Three studies included pediatric patients as their participants, while other two studies only included adult as their participants. There is no statistical analysis was performed to assess this imbalance.

The percentage of Total Body Surface Area (TBSA) was higher in two studies, but the remaining studies reported similar TBSA percentages, all under 20-25%. Most studies included partial-thickness burn as part of their inclusion criteria, while one study included superficial-partial-thickness burn. All burn etiologies included in these studies were thermal. Two studies specifically focused on burns in the hand and face regions, while the other three studies included whole burned body area.

## Outcome: Wound healing

Three studies evaluated wound healing between MEBO and SSD in partial-thickness burn shown in Table 3. Hirsch T. et al. evaluated wound healing epithelialization using Trans Epidermal Water Loss (TEWL) and Wound Closure Index (WCI) as parameters.[1] It was shown that there was a difference of 2.3 gr/m$^2$/h between MEBO and SSD in terms of TEWL. [1] However, in terms of WCI, there was no difference between the MEBO and SSD groups.[1] Ang E. et al. (2000) reported the wound healing rates by day 10 for the MEBO and SSD groups.[2] In the MEBO group, 14 out of 17 patients had healed by day 10, compared to 17 out of 22 patients in the SSD group.[2] This resulted in 82.3% patients in MEBO group healed faster compared to 77.2% patients in SSD group.[2] Allam A. M. et al. evaluated local wound findings and the healing period for partial-thickness burns between the MEBO and SSD groups.[3] Maceration was more common in the MEBO group (94.34%) compared to the SSD group (86.79%).[3]

Table 4. Pain between MEBO and SSD in Partial-Thickness Burn

| Author, year | Outcome | Result | |
|---|---|---|---|
| | | MEBO | SSD |
| Hirsch T. et al, 2008[1] | Pain scale (VAS) by day 0 | 5 | 5 |
| | Pain scale (VAS) by day 12 | 3.8 | 3.5 |
| Allam A. M. et al, 2007[3] | Pain Score 0-3 (during dressing change) | 1 (47.17%) | 1 (41.51%) |
| | Comfort Score 0-3 | 3 (28.30%) | 3 (24.53%) |
| Ang E. et a,l 2003[4] | Pain scale (Mean NRS) in the morning | 2.974 | 2.991 |
| | Pain scale (Mean NRS) after dressing | 2.892 | 3.580 |
| | Pain scale (Mean NRS) in the evening | 2.651 | 2.602 |

*Abbreviation: VAS=Visual analog scale; NRS=Numerical rating scale*

Table 5. Cost between MEBO and SSD in Partial-Thickness Burn

| Author, year | Outcome | Result | |
|---|---|---|---|
| | | MEBO | SSD |
| Allam A. M. et al, 2000[3] | Daily cost (EGP) | 9.00 ± 0.00 | 2.17 ± 0.16 |
| Atiyeh B. S. et al, 2002[5] | Daily cost (EGP) | 34.06 ± 5.38 | 28.20 ± 4.99 |

*Abbreviation: EGP=Egyptian Pound*

However, the MEBO group had no crust formation, which facilitated easier wound assessment (100%) compared to the SSD group (43.39%).[3] Regarding the wound healing period, the MEBO group showed a shorter healing time for both superficial and deep partial-thickness burns compared to the SSD group.[3]

**Outcome: Signs of Infection**

Hirsch T. et al. and Ang E. et al. (2000) both assessed signs of infection as an outcome measure.[1,2] Hirsch T. et al. reported no signs of infection in either the MEBO or SSD groups, while Ang E. et al. (2000) observed minimal slough in the MEBO group but did not mention any signs of infection in the SSD group.[1,2]

**Outcome: Pain**

Three studies assessed pain in the MEBO and SSD groups for partial-thickness burns, as shown in Table 4. Hirsch T. et al. compared pain scores on days 0 and 12 using the Visual Analog Scale (VAS).[1] Pain scores were similar between the MEBO and SSD groups on both days (5 vs. 5 on day 0 and 3.8 vs. 3.5 on day 12).[1] Allam A. M. et al. also evaluated pain and comfort scores.[3] Pain was assessed during dressing changes, while comfort scores reflected comfort related to odor and the appearance of the wound.[3] Pain scores ranged from 0 to 3, indicating mild to severe pain, while comfort scores ranged from 0 to 3, indicating discomfort or refusal of dressing change to comfort during dressing changes.[3] Pain and comfort scores were similar between the groups.[3] Ang E. et al. (2003) evaluated pain using the Numerical Rating Scale (NRS) in the morning, after dressing changes, and in the evening.[4] They found a lower mean NRS score during dressing changes in the MEBO group compared to the SSD group (2.89 vs. 3.58).[4]

**Outcome: Burn-related Complication**

Two studies reported burn-related complications. Ang E. et al (2000) found that none of the participants in either the MEBO or SSD groups required surgery after treatment.[2] Allam A. M. et al. assessed post-burn deformities and found fewer deformities in the MEBO group (15 out of 53) compared to the SSD group (37 out of 53).[3] The post-burn deformities reported in the study included hypertrophic scars, contractures of the metacarpophalangeal and interphalangeal joints, wrist joint

contractures, post-burn syndactyly, and post-burn nail retraction. [3]

**Outcome: Cost**

Two studies compared the daily costs of MEBO and SSD treatments for partial-thickness burns, as shown in Table 5. Both studies found that MEBO was more expensive than SSD.[3,5] Allam A. M. et al. reported higher daily costs for the MEBO group, while Atiyeh B. S. et al. also found higher costs for the MEBO group. [3,5]

## DISCUSSION

This review aimed to compare MEBO with SSD in the treatment of partial-thickness burns, focusing specifically on wound healing outcome. Other outcomes assessed in this review included signs of infection, pain, burn-related complications, and treatment costs.

Five randomized controlled trials (RCTs) involving 332 patients were identified, all conducted between 2000 and 2008. While these studies provide valuable insights into the comparative efficacy of MEBO and SSD, several concerns regarding potential biases were noted, as indicated by the Risk of Bias (RoB) assessment. In terms of baseline patient characteristics, the age distribution varied across the studies, with some including pediatric patients and others focusing on adults. Additionally, the percentage of TBSA also varied, although most patients had burns covering less than 25% of their body. Two studies specifically focused on burns to the hands and face, while the other studies did not specify particular anatomical regions. These differences highlight the potential for variability in treatment responses and the need for further analysis to account for these factors. Including more homogeneous study populations and conducting a more rigorous evaluation of bias will strengthen the evidence base for MEBO as a standard treatment option for burn wounds.

In these trials, both MEBO and SSD are used as interventions and controls. However, it is important to note that there is no information available regarding the specific dosage for the application of MEBO and SSD. Despite this limitation, we provide the method of application for both MEBO and SSD in Table 1, based on each trial.

The heterogeneity in application frequency, outcome measures, and patient populations across studies underscores the lack of standardization in topical burn treatment protocols, which this review attempts to address.

The primary outcome in this review was wound healing. Three studies showed a general advantage for MEBO. Hirsch T. et al. found that MEBO performed better in terms of Trans Epidermal Water Loss, with a difference of 2.3 $gr/m^2/h$ compared to SSD, suggesting better skin epithelialization with MEBO.[1] Ang E. et al. (2000) reported that 82.3% of patients in the MEBO group had healed by day 10, compared to 77.2% in the SSD group, indicating a slightly faster healing rate for MEBO.[2] Allam A. M. et al. observed that the MEBO group had a shorter healing time for both superficial and deep partial-thickness burns, despite experiencing more maceration (94.34% vs. 86.79%).[3] However, the absence of crust formation in the MEBO group facilitated easier wound assessment, suggesting that MEBO might offer better manageability for clinicians.[3]

We analyzed signs of infection as our secondary outcome in this review. Hirsch T. et al. and Ang E. et al. (2000) found no significant difference between the two treatments.[1,2] Hirsch T. et al. reported no signs of infection in either group, while Ang E. et al. observed minimal slough in the MEBO group but did not note any infections in the SSD group, implying that both treatments were effective in preventing infection. [1,2]

Pain assessments across three studies revealed generally similar results between the groups. The studies used different

outcome measures to assess pain scores. Hirsch T. et al. employed the Visual Analog Scale (VAS) for pain assessment, while Ang E. et al (2023) used the Numerical Rating Scale (NRS). [1,2] Additionally, Allam A. M. et al. used their own subjective pain scoring system.[3] These differences in pain measurement methods may introduce a risk of bias in the outcomes. Hirsch T. et al. found no significant difference in pain scores at day 0 and day 12, while Allam A. M. et al. reported similar pain and comfort scores for both treatments.[1,3] However, Ang E. et al (2003) found that the MEBO group had a lower pain score during dressing changes, suggesting that MEBO may offer some pain relief benefits during treatment.[2]

Burn-related complications were less frequent in the MEBO group. Ang E. et al (2000) found that none of the participants in either group required surgery, while Allam A. M. et al. observed fewer post-burn deformities in the MEBO group (15 out of 53) compared to the SSD group (37 out of 53).[2,3] The lower incidence in the MEBO group suggests it may offer some advantage in preventing long-term complications.

The final secondary outcome assessed in this review was treatment cost. The cost between MEBO and SSD consistently showed that MEBO is more expensive. Allam A. M. et al. reported daily costs of 9.00 ± 0.00 for the MEBO group versus 2.17 ± 0.16 for the SSD group, while Atiyeh B. S. et al. found similar results (34.06 ± 5.38 vs. 28.20 ± 4.99), indicating that MEBO is a less cost-effective option compared to SSD.[3,5] The daily cost for topical agents depends on factors such as the total dosage required for daily application, the patient's length of stay, and the wound healing rate. Atiyeh B. S. et al. reported that MEBO was associated with a shorter length of hospital stay, while Allam A. M. et al. noted that the MEBO group had a faster wound healing rate.[3,5] Allam A. M. et al. also mentioned that MEBO was applied every four hours, totaling six applications per day, although Atiyeh B. S. et al. did not specify the application frequency for MEBO.[3,5] Additionally, Ang E. et al. (2000) noted that MEBO is easier to apply than SSD, as SSD requires bulkier dressings, which are also more costly.[2] Despite its higher cost, MEBO may still be considered cost-effective due to its shorter healing period, even though it requires more frequent application.

MEBO appears to offer some advantages in wound healing, pain reduction, and prevention of burn-related complications, its higher cost must be considered. MEBO's benefits in terms of wound healing rate and long-term outcomes may justify its higher cost in some clinical settings.

Given its benefits in healing acceleration and complication prevention, MEBO may be integrated into clinical guidelines for partial-thickness burn management, especially in tertiary care centers. However, policymakers in low-resource settings must weigh these benefits against its higher cost, possibly reserving MEBO for selected patient populations where rapid recovery is critical.

To our knowledge, this is the first systematic review synthesizing clinical outcomes of MEBO and SSD specifically in partial-thickness burn injuries. This research has several limitations, including the small number of available trials and limited sample sizes, which may reduce the internal validity and increase the risk of bias in the pooled conclusions. As a result, the generalizability of these findings to broader patient populations or different healthcare settings, especially those outside of Asia should be interpreted with caution. Despite these limitations, the review provides valuable preliminary insights and highlights the potential of MEBO as an alternative topical agent in burn management. Future high-quality randomized controlled trials with larger sample sizes are recommended to validate these findings and further explore long-term outcomes, including cost-effectiveness, patient satisfaction, and aesthetic results. From a clinical and policy standpoint, the findings may offer practical guidance for low- and middle-income

countries seeking cost-effective burn treatment alternatives, but definitive recommendations should await further research.

## CONCLUSION

This systematic review demonstrates that MEBO is comparable in efficacy to silver sulfadiazine (SSD) in promoting wound healing in partial-thickness burns. Across the reviewed studies, MEBO showed similar or better outcomes in terms of healing time, infection prevention, pain reduction, and scar formation. These findings suggest that MEBO may serve as a safe and effective alternative topical treatment for partial-thickness burn injuries, particularly in settings where conventional agents such as SSD may not be ideal due to side effects or availability.

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## CONFLICT OF INTEREST

We declare that there are no conflicts of interest or financial disclosures related to this paper.

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## AUTHOR CONTRIBUTION

AW contributed to the article review, data collection, manuscript preparation, and final approval of the manuscript. NF contributed to the article review and data collection, and participated in the manuscript preparation. All authors have read and approved the final manuscript for publication.

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JURNAL
REKONSTRUKSI DAN ESTETIK

# *EFFECTIVENESS OF ANTIBIOTIC PROPHYLAXIS IN MAXILLOFACIAL TRAUMA SURGERY: A SYSTEMATIC REVIEW*

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ABSTRACT

**Introduction:** The effectiveness of antibiotic prophylaxis in maxillofacial trauma surgery remains a subject of debate, with varying recommendations regarding its necessity and duration. This systematic review aims to evaluate the impact of prophylactic antibiotics on the incidence of surgical site infections (SSIs) in maxillofacial trauma patients.
**Methods:** A systematic literature search was conducted using Google Scholar, following predefined inclusion and exclusion criteria based on the PICO framework. Studies included observational cohort studies comparing the use of prophylactic antibiotics to either no antibiotics or different regimens of antibiotic administration. The quality of the selected studies was assessed using the JBI Critical Appraisal Checklist for Cohort Studies.
**Results:** Six studies met the inclusion criteria, with five reporting no significant reduction in SSIs with prophylactic antibiotic use, regardless of the timing or duration of administration. Only one study found a statistically significant decrease in SSIs with preoperative antibiotic prophylaxis. Variations in study design, antibiotic regimens, surgical techniques, and patient populations may have influenced the inconsistent findings.
**Conclusion:** The findings suggest that routine antibiotic prophylaxis in maxillofacial trauma surgery may not be universally beneficial and should be reconsidered in favor of a more selective, patient-specific approach. Given the increasing concerns regarding antimicrobial resistance, prophylactic antibiotics should be reserved for high-risk patients where a clear benefit can be demonstrated. Further research, particularly well-designed randomized controlled trials, is necessary to establish standardized guidelines and optimize perioperative infection control strategies.

**Highlights:**

1. Antibiotic prophylaxis does not significantly decrease surgical site infection rates in maxillofacial trauma surgery.
2. Post-operative antibiotic regimens are not recommended as they increase costs without reducing infection rates.

## INTRODUCTION

Trauma is a common indication for maxillofacial surgery, especially now with the rise of road transportation, with the mandible as the most common part prone to fracture.[1] These fractures require surgical and nonsurgical treatments to repair it.[2] For surgical treatments there are multiple factors that can affect the outcome of the procedure.[3] Surgical site infections (SSIs) are a significant concern in maxillofacial trauma surgery, leading to increased morbidity, prolonged hospitalization, and elevated healthcare costs.[4] Maxillofacial trauma is prone to infection because it involves the oral cavity, which is inhabited by oral fauna and nonsterile, especially after a traumatic injury.[5] Recent studies report an overall infection rate of 5.6% for maxillofacial fractures, with mandibular fractures exhibiting a higher rate of 8.9%. Specifically, surgical procedures such as open reduction and internal fixation (ORIF) for mandibular fractures have an SSI prevalence of approximately 4.2%.[6] Antibiotic prophylaxis is commonly used to mitigate the risk of SSIs in maxillofacial trauma surgeries.[7] However, its efficacy remains a subject of debate.[8] While some studies advocate routine prophylactic antibiotic use, others question its effectiveness, highlighting the concerns about potential adverse effects and the contribution to antimicrobial resistance.[9] The lack of consensus extends to the timing and duration of antibiotic administration, with practices varying widely across different clinical settings.[10] This unstandardized use of antibiotics may contribute to antimicrobial resistance, increase healthcare costs, and reduce patient compliance.[11] Given the variability in current practices and the potential implications for patient outcomes and public health, a critical evaluation of existing evidence is needed This systematic review aims to assess the effectiveness of antibiotic prophylaxis in reducing SSIs among patients undergoing maxillofacial trauma surgery. By synthesizing data from recent studies, we seek to provide clarity on whether routine antibiotic prophylaxis is justified and to inform evidence-based guidelines for clinical practice.

## METHODS

We used Harzing's Publish or Perish search engine to look up articles used in this review. We used 2 databases, Google Scholar and PubMed because these databases are the easiest to access using Publish or Perish.

Articles included were those studying antibiotic prophylaxis, specifically its role in maxillofacial surgery and how effective they are at preventing surgical site infections. We included retrospective studies, prospective studies, case reports and randomized controlled trials. We also excluded review articles such as systematic reviews and narratives reviews. The search and screening were performed by three reviewers, with a fourth acting as a referee in case of disagreement to decide whether to include it in this study or not. The keywords we used in this search are as follows.

Table 1. Keywords and Synonyms

| Keywords | Synonyms |
|---|---|
| Effectiveness | "Effectiveness"<br>"Outcome"<br>"Clinical effectiveness"<br>"Patient relevant outcome" |
| Antibiotic prophylaxis | "Antibiotic premedication" |
| Maxillofacial injury | "Maxillofacial trauma" |
| Surgery | "Trauma surgery"<br>"Plastic surgery" |

For Google Scholar, we combined our predefined keywords with the database's search operators to generate the final search string as follows: Effectivity OR Effectiveness OR Outcome OR "Clinical effectiveness" OR "Patient relevant outcome" AND "Antibiotic prophylaxis" OR "Antibiotic premedication" AND "Maxillofacial trauma" OR "Maxillofacial injury" AND Surgery OR "Trauma surgery" OR "Plastic surgery" OR "Maxillofacial surgery".

For PubMed, we adapted the keywords to the database's search syntax, resulting in the following final search string: Antibiotic prophylaxis AND Maxillofacial trauma AND Surgery.

We managed to find 104 articles that matched our keyword, 5 of them are duplicates which we eliminated so the total of articles we used for screening are 99 articles.

## PICO Framework, Inclusion and Exclusion Criteria

The study question was structured using the PICO framework. The population (P) consisted of patients of any age with maxillofacial trauma undergoing surgical management. The intervention (I) was the administration of systemic antibiotic prophylaxis, either before, during, or after surgery. The comparison (C) was made between patients who did not receive antibiotic prophylaxis and those who received different regimens, durations, or timings of prophylaxis. The primary outcome (O) was the incidence of surgical site infections (SSIs) and systemic infections following surgery.

Based on this framework, the inclusion criteria were studies involving maxillofacial trauma patients who underwent surgical treatment and received antibiotic prophylaxis at any perioperative stage, reporting its significance in preventing infections. Only cohort studies and randomized controlled trials (RCTs) published between 2023 and 2024 were considered. Exclusion criteria included non–maxillofacial trauma patients, those treated without surgery, articles focusing solely on surgical techniques without reporting antibiotic prophylaxis, narrative reviews, systematic reviews, meta-analyses, and studies published outside the specified timeframe.

Table 2. Inclusion and Exclusion Criteria

| Inclusion | Exclusion |
|---|---|
| Any maxillofacial trauma patient which undergoes surgical treatment | Non maxillofacial trauma patients |
| Given antibiotic treatments before after or during surgery | Maxillofacial trauma patients that did not receive surgical treatment |
| Reports use of antibiotic prophylaxis and studied its significance in preventing infections | The effect of antibiotic prophylaxis was not reported, but focused more on other aspects of the surgery such as surgical techniques |
| Cohort studies or Randomized Controlled Trials (RCTs) | Narrative reviews, Systematic reviews, Meta analysis |
| Between 2023-2024 | Before 2023 and after 2024 |

We screened 99 articles and found 11 articles matching our inclusion criteria. After full text screening, 4 articles were excluded due to having the wrong population and wrong outcomes. In the end, we had 6 articles that we are going to use for this study, 5 of them are Cohort studies while 1 of them is a Randomized Controlled Study.

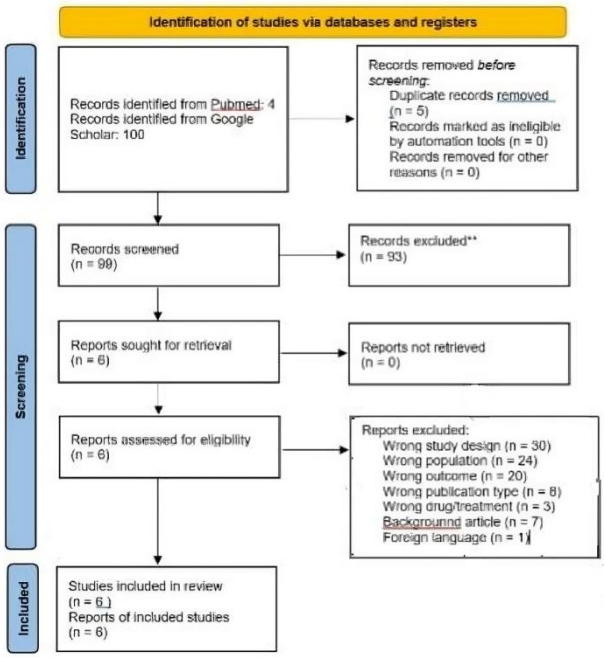


Figure 1 PRISMA Flow Diagram[12]

### Risk of Bias

Because we mainly use cohort studies as our subject of research there is an inherent risk of bias in this study. Retrospective cohort studies are vulnerable to information bias because of missing information when using existing records and selection bias, because individuals are selected after the outcome of study has occurred, so both conditions (exposure and outcome) are present at the moment of enrollment. In that case, it is easier that exposed or unexposed subjects would be related to the result of interest, causing selection bias. On the other hand, a prospective cohort design are prone to loss of follow-up. Both types of cohort studies may be influenced by information bias, confounding or interaction.

## RESULT

### Critical Appraisal

We assessed the quality of the literature using the JBI Critical Appraisal Checklist for Cohort Studies and Randomized Controlled Trial Studies.[13,14] The 6 obtained articles have met the inclusion criteria, the research design was appropriate as they used the cohort study and randomized controlled trial design. The statistical analysis had been carried out correctly, and the results from the outcome and group comparisons of these 6 studies agreed.

Table 3. JBL Critical Appraisal Tool for Cohort Studies[13]

| No. | Question | Gaessler et al. (2023) | Tucker et al. (2023) | Maurer et al. (2023) | Atwez et al. (2023) | Vishwanath et al. (2023) |
|---|---|---|---|---|---|---|
| 1. | Were the two groups similar and recruited from the same population? | Yes | Yes | Yes | Yes | Yes |
| 2. | Were the exposures measured similarly to assigning people to both exposed and unexposed groups? | Yes | Yes | Yes | Yes | Yes |
| 3. | Was the exposure measured in a valid and reliable way? | Yes | Yes | Yes | Yes | Yes |
| 4. | Were confounding factors identified? | Yes | Yes | Yes | Yes | Yes |
| 5. | Were strategies to deal with confounding factors stated? | Yes | Yes | Yes | Yes | Yes |
| 6. | Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)? | Yes | Yes | Yes | Yes | Yes |
| 7. | Were the outcomes measured in a valid and reliable way? | Yes | Yes | Yes | Yes | Yes |
| 8. | Was the follow up time reported and sufficient to be long enough for outcomes to occur? | Yes | Yes | Yes | Yes | Yes |
| 9. | Was follow up complete, and if not, were the reasons to loss to follow up described and explored? | Unclear | Yes | Yes | Yes | No |
| 10. | Were strategies to address incomplete follow up utilized? | Unclear | Unclear | Not applicable | No | No |
| 11. | Was appropriate statistical analysis used? | Yes | Yes | Yes | Yes | Yes |

Table 4. JBI Critical Appraisal tool for Randomized Controlled Trials[14]

| No. | Question | Mohanty et al. (2023) |
|---|---|---|
| 1. | Was true randomization used for assignment of participants to treatment groups? | Yes |
| 2. | Was allocation to treatment groups concealed? | Yes |
| 3. | Were treatment groups similar at the baseline? | Yes |
| 4. | Were participants blind to treatment assignment? | Yes |
| 5. | Were those delivering the treatment blind to treatment assignment? | No |
| 6. | Were treatment groups treated identically other than the intervention of interest? | Yes |
| 7. | Were outcome assessors blind to treatment assignment? | Yes |
| 8. | Were outcomes measured in the same way for treatment groups? | Yes |
| 9. | Were outcomes measured in a reliable way | Yes |
| 10. | Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed? | Yes |
| 11. | Were participants analysed in the groups to which they were randomized? | Yes |
| 12. | Was appropriate statistical analysis used? | Yes |
| 13. | Was the trial design appropriate and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial? | Yes |

Table 5. Characteristics and Outcomes of Included Studies

| No. | Article | N | Group | No Infection | Post-Op Infection | SSI (%) | *P*-value |
|---|---|---|---|---|---|---|---|
| 1. | Mohanty et al (2023) | 93 | Control* | 73 | 20 | 21.5 | - |
| | | 90 | Intervention | 67 | 13 | 14.4 | |
| 2. | Gaessler et al (2023) | 57 | Control* | 48 | 9 | 15.8 | 0.218 |
| | | 65 | Intervention | 50 | 15 | 23.1 | |
| 3. | Tucker et al (2023) | 3914 | Control** | 3180 | 14 | 0.4 | 0.79 |
| | | 2219 | Intervention | 2200 | 19 | 0.8 | |
| 4. | Maurer et al (2023) | 9 | Control** | 7 | 2 | 22 | 0.197 |
| | | 102 | Intervention | 95 | 7 | 6.8 | |
| 5. | Atwez et al (2023) | 35 | Control*** | 29 | 6 | 17.1 | 0.412 |
| | | 183 | Intervention | 161 | 22 | 12 | |
| 6. | Vishwanath et al (2023) | 138 | Control** | 135 | 3 | 2.17 | 0.90 |
| | | 144 | Intervention | 141 | 3 | 2.12 | |

*Control group was given only perioperative antibiotics
**Control group was not given any antibiotics
***Control group was given perioperative antibiotics or not given any antibiotics

## Study Characteristics

Two studies compared the use of only perioperative antibiotics with adding additional doses of prophylaxis.[15,16] Three studies did not administer antibiotics at all for the control group.[17–19] One study combined patients who aren't given antibiotic prophylaxis and patients who were given only perioperative prophylaxis, the group was then compared with patients who are given an additional dose of prophylaxis.[20] One study focused on pediatric fractures[18] while another study focused on animal bite-related facial traumas.[17] One article only studied mandibular fractures[20] while another studied only nasal fracture patients.[19] Two

studies included every maxillofacial injury patient in their study, not just specific types of fractures.[15,16] All the studies have two groups, one group acts as a control group where they are not given antibiotics or only given intraoperative/perioperative antibiotics (usually right before surgery) and the other group acts as the intervention group where they are given more than one dose or prolonged antibiotic treatment.

All the studies could not find any significant difference between using antibiotics/more than 1 dose and not using prophylactic antibiotics. Every intervention group is given antibiotics, the only thing that differs from each study between the intervention groups is time of administration.

## DISCUSSION

Mohanty et al. reported that both the control and intervention groups were administered 1.2 g of intravenous amoxicillin/clavulanate 8 hours preoperatively, followed by a single intraoperative dose.[16] The intervention group was then also administered the same regimen post-surgery for 3 days while the control group was not. The intervention group was categorized into three groups based on the type of fractures, which are Mandibular, Zygomaticomaxillary (ZMC) and Le Fort. In mandibular fractures, Mohanty et al. found no significant difference between control and intervention group ($p = 0.416$), although the control group, which received only a single perioperative dose, developed more complications than the group that was given a 3 day postoperative antibiotic course, although the difference wasn't statistically significant.[16] No statistically significant differences were found in both Le Fort ($p = 0.348$) and ZMC fractures ($p = 1.000$).[16] Therefore, the study concluded that a single perioperative dose is enough to minimize postoperative complications in maxillofacial trauma surgeries.[16]

In Gaessler et al.'s study, both the control and intervention group were given intravenous antibiotic prophylaxis one hour prior to mucosal or skin incision, they were given the same regimen as Mohanty et al.'s study which is amoxicillin/clavulanate but Gaessler uses 2.2 grams instead of 1.2 and they also used Clindamycin 600 mg administered intravenously if Penicillin allergy was present.[15,16] For post-operative antibiotics in the intervention group, Gaessler et al used the same regimen for 2 days 1-2 times a day, and changed the regimen to per oral amoxicillin/clavulanate thrice a day (625 mg) for days 3 until day 5 and clindamycin IV for days 1-2 (600 mg) and per oral (PO) thrice daily for days 3 until day 5 (300 mg). Gaessler found no statistically significant difference between control and intervention group in relation to SSI rate ($p = 0.218$).[15] The study concluded that a single-dose regimen is as effective as a 5-day regimen in reducing the incidence of SSIs following ORIF for facial fractures.[15]

In Tucker et al.'s study the control group is not given any antibiotics at all, while the intervention group was split into three based on the timing of antibiotic administration.[18] Preoperative was defined as antibiotics given a month before surgery, intraoperative were given the same day, postoperative is given a month after surgery. 660 patients were given antibiotics preoperatively, 1396 patients intraoperatively, and 163 postoperatively. They did not find any statistical difference between the control and intervention group in relation to SSI rate ($P = 0.79$), but they did find that the timing of administration has a statistically significant association with infection development ($P = 0.044$).[18] This study concluded that patients that received intraoperative antibiotics are more likely to develop infection compared to preoperative or postoperative administration ($P = 0.023$).[18]

Maurer et al.'s study observed specifically animal bite cases that causes maxillofacial injury. Control group was not given any antibiotics at all, while the intervention group was given antibiotics.[17]

This study does not state clearly the timing of antibiotic administration. The regimens used in this study are amoxicillin with clavulanic acid, clindamycin, cefuroxime, cefazolin, penicillin, ciprofloxacin, and metronidazole. They did not find any significant statistical difference between administration of antibiotics compared to not using antibiotics in regards to SSI rate ($p = 0.197$).[17] The study concluded that there is no difference in SSI rates for pediatric patients prescribed antibiotics and those who were not.[17]

Atwez et al. 's study compared between not using antibiotics or just 1 dose of perioperative antibiotics with patients who received a scheduled preoperative antibiotic prophylaxis.[20] The regimens used are Clindamycin, Ampicillin/ sulbactam, Cefazolin, Ceftriaxone, Piperacillin/ tazobactam, Metronidazole, Ciprofloxacin, and Penicillin with Clindamycin being the most used antibiotics.[20] They found that receiving less than one dose of antibiotics isn't associated with incidence of SSI ($p = 0.485$).[20] When comparing between infected patients and those who aren't, more than one dose of antibiotic prophylaxis does not correlate with reduction nor increase of SSI occurrence ($p = 0.412$).[20] Therefore the study concludes that the use of preoperative antibiotic prophylaxis or more than a single dose of perioperative antibiotic prophylaxis has no association with reduction of SSI rate.[20]

The study by Vishwanath et al. specifically investigated nasal fractures.[19] They compared between using antibiotics and not using antibiotics. The regimens found in this study are Cefazolin, Bacitracin Ceftriaxone, Clindamycin, Doxycycline, Fluoroquinolone, Cephalexin, and Penicillin-based.[19] There was no significant difference in SSI rate between antibiotic patients and nonantibiotic patients ($P = 0.90$).[19] The study concluded that antibiotic use for prophylaxis does not significantly decrease infection rates in closed or open nasal bone fractures.[19]

All of the studies have similar outcomes, they concluded that antibiotic use isn't significant in reducing SSI rate. A study by Gaal et al. concluded that just using intraoperative antibiotics is enough for mandibular fractures, which matches the results of the 6 studies in this review.[21] A prospective study by Jang et al. supports the conclusion of this study, where he states that using postoperative antibiotics is not recommended, but instead by not using these prolonged regimens it gives the patient biological and cost benefits.[22] A systematic review and meta-analysis by Habib et al. support the findings of this systematic review. In the study they found that routine use of post-operative antibiotics is not necessary for maxillofacial trauma surgery.[23] Blatt et al's study also aligns with the results of this study, where he found in mandibular and Lefort-1/2 fractures, prolonged antibiotics use is ineffective in reducing SSI incidence.[24]

A study by Mundinger et al. delved into evidence-based literatures about the use of antibiotic prophylaxis in craniofacial surgery. This systematic review found that most literature does not support frequent use of pre- and post-operative antibiotics in upper and midface fractures, but with low level of evidence.[25] Preoperative antibiotic use in comminuted mandible fractures is supported, but postoperative antibiotics in mandible fractures is not.[25]

Several international clinical practice guidelines also provide recommendations that align with the findings of this review. The Cochrane Database of Systematic Reviews highlights that the routine use of postoperative antibiotics in maxillofacial trauma surgery offers no significant benefit in preventing surgical site infections (SSIs), emphasizing instead the importance of perioperative dosing strategies and strict adherence to aseptic techniques.[28] Similarly, the World Health Organization (WHO) Global Guidelines for the Prevention of Surgical Site Infection recommend against prolonged postoperative antibiotic

prophylaxis, stating that a single preoperative or perioperative dose is sufficient for most clean-contaminated surgical procedures, including maxillofacial interventions.[29] These guidelines support the principle of antimicrobial stewardship, highlighting the risks associated with antibiotic overuse and resistance.

Furthermore, the U.S. Centers for Disease Control and Prevention (CDC) also advise against extending antibiotic use beyond 24 hours after surgery for clean and clean-contaminated operations, unless there is clear clinical evidence of infection.[30] This recommendation reinforces the conclusion of this review that prolonged prophylaxis does not provide additional benefit and may, in fact, contribute to higher healthcare costs and antimicrobial resistance. Integrating these authoritative guidelines into surgical practice could standardize care globally, ensuring that maxillofacial trauma management remains both effective and aligned with broader public health priorities.

Several studies further support this recommendation by showing that postoperative continuation of antibiotic prophylaxis beyond 24 hours does not provide additional benefit in reducing surgical site infections in facial fracture repairs. While evidence on the optimal regimen remains limited, current findings consistently suggest that prolonged prophylaxis is not beneficial.[23,31-33]

Research consistently demonstrates that prolonged postoperative antibiotic prophylaxis offers no significant advantage over single-dose perioperative administration in maxillofacial surgery. Bartella et al. (2018) found no statistically significant differences in surgical site infections between patients receiving prolonged prophylaxis (5 days) versus single-shot perioperative prophylaxis in 901 consecutive maxillofacial surgery patients.[8] Similarly, Gaessler et al. (2023) reported no significant difference in infection rates or severity between single-dose and prolonged antibiotic prophylaxis groups in facial fracture patients undergoing open reduction with internal fixation.[15] Milic et al. (2020) conducted a systematic review concluding that prophylactic antibiotic use is not routinely recommended for upper or midface fractures.[7] Blatt & Al-Nawas (2019) reinforced these findings, noting that for maxillofacial trauma, antibiotic prophylaxis might reduce surgical site infections, but prolonged postoperative dosing shows no additional benefit, supporting shorter antibiotic regimens aligned with antimicrobial stewardship principles.[24]

This systematic review offers novel contributions to the plastic and aesthetic reconstruction surgery by synthesizing the most current evidence in regards to antibiotic prophylaxis in maxillofacial trauma surgery. To this day, there has not been any conclusive articles about the efficacy of antibiotic prophylaxis in maxillofacial trauma surgery. This review updates the existing body of evidence by focusing on studies published between 2023 and 2024, addressing recent advances and controversies in antibiotic prophylaxis for maxillofacial trauma surgery. This review challenges traditional practices which routinely use antibiotics post-operatively or overextends antibiotic use by choosing a more selective approach. This is in line with current antimicrobial stewardship principles, which focuses more on individualized patient care while minimizing unnecessary antibiotic exposure. The study encourages the development of patient specific prophylactic strategies based on a patient's risk factors, providing a foundation for future antimicrobial guideline development and contributing to the optimization of infection control in surgical settings.

This study has several methodological and contextual strengths. It uses the PRISMA flow diagram and the JBI Critical Appraisal Tools to assess the methodological quality of both cohort and randomized controlled trials, ensuring a robust and systematic screening process. This article addresses a

clinically significant issue, which is the role of prophylactic antibiotics in maxillofacial trauma surgery, making its findings directly relevant to surgical and infectious disease management of trauma surgery. The inclusion of varied study types and patient populations allows for a broad and representative overview of the existing evidence. Additionally, the discussion extends beyond clinical outcomes to include the implications of antibiotic overuse, which aligns this study with the broader public health objective of reducing antimicrobial resistance.

However, this study has several limitations. The literature search was primarily limited to Google Scholar due to access issues with Publish or Perish, which restricted the results to a maximum of 100 articles per search, yielding 104 relevant studies. PubMed provided only 4 relevant results, while ScienceDirect was unavailable because it requires special access to integrate with Publish or Perish. Furthermore, the included studies exhibited a high degree of heterogeneity in terms of antibiotic regimens, surgical techniques, fracture types, patient populations, and definitions of SSI, which complicated direct comparisons and reduced the generalizability of the findings. The relatively small sample sizes in several studies may have also affected the statistical power to detect differences in infection rates. Lastly, restricting the review to studies published between 2023 and 2024 may have led to the omission of relevant foundational research.

The data suggests that while preoperative prophylaxis may be justified in selected high-risk cases, routine extended antibiotic use may not be necessary and could contribute to antimicrobial resistance. Instead, prophylaxis should be tailored to high-risk patients where a clear benefit can be demonstrated. Alternative infection control strategies such as improving surgical protocols, optimizing wound care, and implementing strict aseptic techniques should also be explored as it may contribute to an even bigger role in reducing infection rates. By limiting the use of antibiotics in maxillofacial surgeries, we could potentially lower hospital costs and reduce further development of antimicrobial resistance.[26,27]

Further research is necessary to establish standardized guidelines on antibiotic prophylaxis in maxillofacial trauma surgery. A more selective approach based on patient-specific risk factors may provide better outcomes while minimizing unnecessary antibiotic exposure. Emphasis should be placed on identifying high-risk patient populations who may benefit from targeted antibiotic administration, rather than advocating for routine prophylaxis in all cases. Thus, we can ensure better patient outcomes while also addressing the pressing global issue of antibiotic resistance.

## CONCLUSION

This systematic review found limited evidence supporting the effectiveness of antibiotic prophylaxis in reducing surgical site infections (SSIs) in maxillofacial trauma surgery. Most studies reported no significant benefit, and the overall findings were inconsistent due to heterogeneity in study design, antibiotic regimens, patient populations, and definitions of SSI. Given these limitations and the small number of available studies, routine use of extended antibiotic prophylaxis cannot be recommended.

A more selective approach targeting high-risk patients may provide greater benefit while reducing unnecessary antibiotic exposure and reducing the risk of antimicrobial resistance. Future research should focus on well-designed randomized controlled trials with standardized SSI definitions and consistent antibiotic protocols to guide evidence-based clinical practice. Ultimately, optimizing antibiotic stewardship in maxillofacial trauma surgery is essential not only for improving patient safety and outcomes, but also for reducing

healthcare costs and addressing the global threat of antimicrobial resistance.

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## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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## AUTHOR CONTRIBUTION

All of the authors have contributed to the planning, data collection and analysis, writing, and approval of this paper for the publishing stages of the research

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# *THERAPEUTIC POTENTIAL OF SNAIL MUCUS IN WOUND HEALING : A SYSTEMATIC REVIEW AND META-ANALYSIS*

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ABSTRACT

**Introduction:** Wound healing is a fundamental biological process comprising four sequential and overlapping phases: hemostasis, inflammation, proliferation, and remodeling. The successful restoration of tissue integrity requires that these phases proceed in the correct order and within an appropriate temporal framework. Proteins are indispensable to this process, as they mediate tissue growth, cellular renewal, and reparative mechanisms. Snail mucins, a class of large glycosylated proteins, have been reported to facilitate wound healing by stabilizing protein structures, modulating solubility and viscosity, and enhancing cell–cell recognition. In light of these properties, we conducted a meta-analysis of randomized controlled trials (RCTs) to assess the therapeutic efficacy of snail mucus extract in promoting wound repair.
**Method:** RCTs on snail mucus extract for wound healing were identified through searches of PubMed, ProQuest, Web of Science, ScienceDirect, Scopus, EBSCOHost, and ClinicalTrials.gov. The review adhered to PRISMA guidelines, applied the PICO framework, and assessed study quality using the JADAD scale.
**Result:** A total of 60 rats from three RCTs conducted between 2021 and 2023 were included in the meta-analysis. The findings demonstrated that the snail mucus group exhibited a significantly improved wound healing rate compared to the control group (MD = -3.21%, 95% CI: -3.72 to -2.69%, P < 0.00001).
**Conclusion:** Snail mucus extract has been shown to significantly accelerate wound healing in animal models; however, further clinical studies are required to confirm its therapeutic efficacy in humans.

**Highlights:**

1. Snail mucus extract significantly improves wound healing rates compared to standard treatments.
2. A meta-analysis of randomized controlled trials (RCTs) showed a statistically significant effect (MD = -3.21%, P < 0.00001).
3. The bioactive compounds in snail mucus promote collagen production and reduce inflammation.

## INTRODUCTION

Globally, it is estimated that over 11 million people sustain burn injuries each year, resulting in more than 180,000 deaths most of which occur in low- and middle-income countries.[1] Burn injuries occur more frequently in developing countries, in Indonesia reporting approximately 195,000 burn related deaths annually and this number is expected to grow.[2] The extensive tissue damage and immunosuppressive effects caused by wounds necessitate rigorous diagnostic protocols and specialized therapeutic approaches.[2, 3]

Wound healing is a critical physiological process that restores the integrity of injured tissues. It is essential for preventing infections, reducing complications, and improving overall patient outcomes.[4] With the increasing prevalence of non-healing wounds, researchers have continuously explored innovative treatments to enhance wound closure and tissue regeneration. In recent years, natural bioactive compounds have emerged as promising alternatives, with snail mucus extract gaining attention for its potential in wound care.[5]

Snail mucus, commonly derived from species such as *Achatina fulica* and *Cornu aspersum*, is rich in bioactive compounds. These components contribute to various aspects of wound healing, including reducing inflammation, promoting fibroblast proliferation, and enhancing extracellular matrix remodeling.[4,6] Conventional treatments such as topical antimicrobials and occlusive dressings primarily aim to prevent infection and maintain a moist environment. However, these therapies often fall short in promoting effective tissue regeneration, which can lead to prolonged healing, increased risk of secondary infections, and greater healthcare expenditure.[7,8] While traditional wound care treatments focus on hydration, infection control, and mechanical protection, snail mucus extract offers a unique combination of regenerative and antimicrobial properties.[9]

Although several preclinical studies have investigated the wound healing potential of snail mucus extract, the findings remain inconsistent and fragmented across various models. To date, no meta-analysis has systematically synthesized the evidence from randomized controlled trials to quantitatively assess its efficacy in wound healing. Given the growing interest in natural regenerative agents, such an analysis is essential to guide further preclinical and clinical applications.

Snail mucus is a bioactive secretion containing glycoproteins, hyaluronic acid, glycolic acid, allantoin, and antimicrobial peptides that provide hydrating, regenerative, and protective effects. In dermatology, it has been applied to enhance skin hydration, repair damage, promote wound healing, reduce scars and wrinkles, protect against oxidative stress, and delay aging by stimulating fibroblast proliferation and collagen synthesis.[10-16] In addition to aesthetic purposes, its strong adhesiveness to moist tissues and ability to support regeneration highlight its potential as a biomaterial for surgical sealants, wound closure, and drug delivery applications.[17,18] The diverse biological activities of snail mucus support its exploration in wound management, where standardized extraction, controlled formulations, and clinical validation could establish it as a safe, biocompatible, and affordable therapy for both acute and chronic wounds. This has further encouraged interest in its potential use for minor injuries, burns, and skin disorders including eczema and rosacea.[19] Nevertheless, despite abundant anecdotal support, high-quality clinical evidence for these uses remains scarce.[20]

Despite promising bioactivity, evidence supporting the use of snail mucus in wound care remains scattered and largely preclinical, this study aims to systematically evaluate the effectiveness of snail mucus extract in wound healing by conducting a meta-analysis of randomized controlled trials. By synthesizing data from recent animal studies, we seek to

determine whether snail mucus extract significantly enhances wound closure rates compared to conventional treatments.

## METHODS

### Literature selection

This study was conducted following the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines[21], as illustrated in Figure 1. The PICO (patients, interventions, comparisons, and outcomes) framework was utilized to define the research questions and selection criteria. Relevant keywords included "wound care," "infection," "snail mucus extract," "snail slime," and "snail excretion." These terms were combined using Boolean operators to maximize search effectiveness. The detailed search strategy is outlined in Figure 1. Searches were conducted across multiple scientific databases, including PubMed, Scopus, ScienceDirect, Cochrane, EBSCO, Web of Science, ClinicalTrials.gov, and ProQuest, up to March 2024.

### Statistical Analysis

Statistical analysis was performed using RevMan (version 5.4). A random-effects model was applied to account for potential heterogeneity among the included studies. Heterogeneity was assessed using the $I^2$ statistic, and a p-value of $< 0.05$ was considered statistically significant. Hypothesis testing involved comparisons of mean wound healing percentages between treatment and control groups. Effect sizes were reported with 95% confidence intervals (CIs), and publication bias was evaluated using Egger's test.

### Data extraction

Only randomized controlled trials (RCTs) that reported outcomes related to the effects of snail mucus on wound healing were included in this study. Full-text articles published in English and conducted on animal models were selected and analyzed. Studies that did not meet these criteria were excluded. Two authors independently extracted data, including publication details, study characteristics, variables measured, and outcomes such as wound healing rate. If any relevant data were missing, the corresponding authors were contacted for clarification.

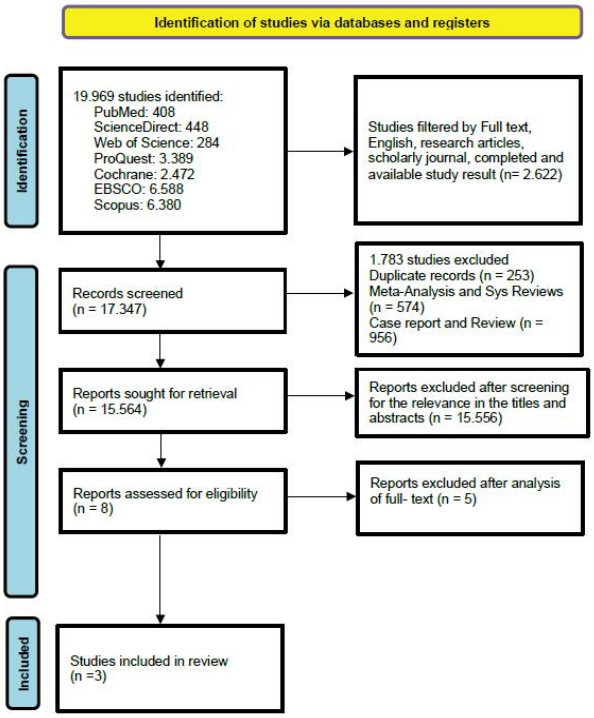


Figure 1. PRISMA flowchart

### Risk of bias and quality assessment

Two independent authors assessed the methodological quality of the included studies using the JADAD scale. This scale evaluates clinical trial quality based on three key domains: randomization, blinding, and the documentation of withdrawals or dropouts. Each study could achieve a maximum score of 3 points: 1 point for randomization (with an additional point if the method was appropriate), 1 point for blinding, and 1 point for clearly reporting participant withdrawals. Studies scoring 3 points were considered high quality, while those scoring 1–2 points were categorized as low quality.[22] All included studies were assessed as having a low risk of bias (Table 1).[23-25]

Table 1. Quality Assessment of Included Studies with JADAD Scale

| Study | Items | Max point | Description | Score | Interpretation |
|---|---|---|---|---|---|
| Zhou et al., 2023 [7] | Randomization | 2 | 1 point if randomization is mentioned | 1 | Low risk |
| | | | 1 additional point if the method of randomization is appropriate | 1 | |
| | | | Deduct 1 point if the method of randomization is inappropriate (minimum 0) | 0 | |
| | Blinding | 2 | 1 point if blinding is mentioned | 0 | |
| | | | 1 additional point if the method of blinding is appropriate | 0 | |
| | | | Deduct 1 point if the method of blinding is inappropriate (minimum 0) | 0 | |
| | Patient Accountability | 1 | All participants are accounted for, or reasons for missing data are explained | 1 | |
| Shoviantari et al., 2021 [8] | Randomization | 2 | 1 point if randomization is mentioned | 1 | Low risk |
| | | | 1 additional point if the method of randomization is appropriate | 1 | |
| | | | Deduct 1 point if the method of randomization is inappropriate (minimum 0) | 0 | |
| | Blinding | 2 | 1 point if blinding is mentioned | 0 | |
| | | | 1 additional point if the method of blinding is appropriate | 0 | |
| | | | Deduct 1 point if the method of blinding is inappropriate (minimum 0) | 0 | |
| | Patient Accountability | 1 | All participants are accounted for, or reasons for missing data are explained | 1 | |
| Putra et al., 2021 [9] | Randomization | 2 | 1 point if randomization is mentioned | 1 | Low risk |
| | | | 1 additional point if the method of randomization is appropriate | 1 | |
| | | | Deduct 1 point if the method of randomization is inappropriate (minimum 0) | 0 | |
| | Blinding | 2 | 1 point if blinding is mentioned | 1 | |
| | | | 1 additional point if the method of blinding is appropriate | 1 | |
| | | | Deduct 1 point if the method of blinding is inappropriate (minimum 0) | 0 | |
| | Patient Accountability | 1 | All participants are accounted for, or reasons for missing data are explained | 1 | |

## RESULTS

### Study Selection

Following the PRISMA methodology, a total of 19,969 studies were initially identified through comprehensive searches across multiple electronic databases. After the initial screening for full-text availability, English language, and completion of study results, 2,622 studies remained. In the second phase of screening, studies that did not meet the inclusion criteria, such as meta-analyses, systematic reviews, case reports, case series, and case–control studies were excluded, reducing the number to 1,783 studies.

At this stage, many articles were removed due to being duplicates or irrelevant to the scope of this review. Some studies primarily focused on cosmetic or dermatological applications of snail mucus rather than wound healing outcomes, and were therefore excluded. In addition, several experimental studies that investigated other natural products without including snail mucus as an intervention were also discarded.

Title and abstract screening further narrowed the selection to eight potentially eligible studies. Upon full-text review, however, five studies were excluded because they did not provide the necessary quantitative data, particularly mean values and standard deviations (SD), or lacked relevant outcomes related to wound healing rates. In addition, one study was excluded as it was a non-randomized controlled trial (non-RCT) and therefore not comparable with RCT standards. Ultimately, three studies (7–9) fulfilled all the inclusion criteria and were incorporated into the final analysis, as summarized in Table 2.

Table 2. Excluded Studies and Reason for Exclusion

| Study | Reason for exclusion |
|---|---|
| Song et al., 2021 [26] | No information about the mean and SD were found |
| Gugliandolo et al., 2021 [27] | No information about the mean and SD were found |
| Andrade et al., 2018 [28] | No information about the wound healing rate |
| Santana et al., 2012 [29] | No information about the mean and SD were found |
| Adikwu et al., 2007 [30] | The only included non-RCT study (no comparison) |

Table 3. Baseline Characteristics of Included Studies

| Study | Setting | Total sample | Study groups | Outcome |
|---|---|---|---|---|
| Zhou et al., 2023[23] | Kunming Institute of Botany, Hunan, China | 40 rats with acute and chronic/diabetic wound | Intervention group: Snail mucus of A. fulica (dried-snail mucus glue, snail glycosaminoglycan)<br><br>Control group: Normal saline | 1. Outcomes were assessed in 5 days, 7 days and 11 days.<br>2. The wound healing rate in snail mucus group showed significantly higher healing ratio than that of the control/saline group |
| Shoviantari et al., 2021[24] | Indonesia | 4 rats with acute/laceration wound | Intervention group: 10%, 15%, 20%, 100% extract of snail mucus<br><br>Control group: no treatment | 1. Outcomes were assessed after 7 days<br>2. It showed that 10% extract of snail mucus had the best percentage of wound healing rate than control group. The wounds in 10% extract of snail mucus already showed favorable trajectory in 5 days. |
| Putra et al., 2021 [25] | Universitas Gajah Mada, Yogyakarta, Indonesia | 6 rats with acute punched wound | Intervention group: 24%, 48%, 96% snail mucus gel<br><br>Control group: CMC-Na gel | 1. All treatment groups had significantly higher wound closure rates than the control group, wound closure rates between treatment groups, and it already showed significant progression in day 7.<br>2. Significant differences were found between the control group and the snail mucus gel group of 24% (p = 0.022), 48% (p = 0.001), and 96% (p = 0.000). |

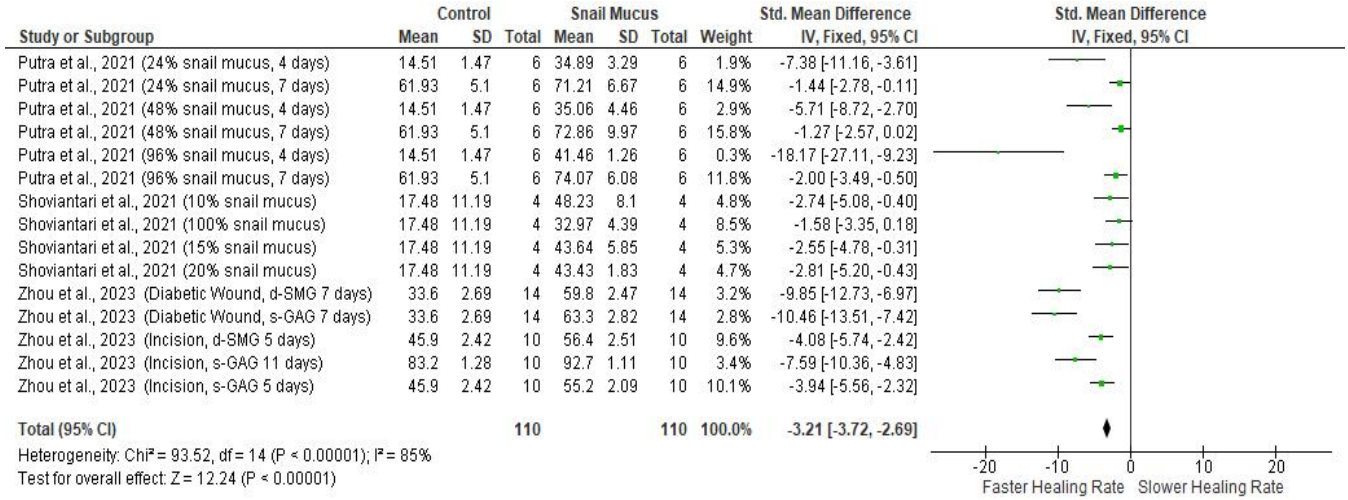


Figure 2. Forrest Plot of Pooled Outcomes from Included Studies

**Baseline Characteristics**

A total of 50 rats were included in the meta-analysis, based on the three selected RCTs conducted between 2021 and 2023. [23-25] These studies evaluated the wound healing effects of snail mucus extract on both acute and chronic wounds, comparing it to control treatments such as normal saline, no treatment, or CMC-Na gel (Table 3).

**Synthesis of Results**

The pooled meta-analysis of these three studies aimed to quantify the effectiveness of snail mucus extract on wound healing rates. The forest plot (Figure 2) visually represents the impact of snail mucus extract, consistently favoring the intervention group over the controls. Additionally, Egger's test (Figure 3) was conducted to assess the presence of publication bias, ensuring that the observed effects were not skewed by selective reporting.

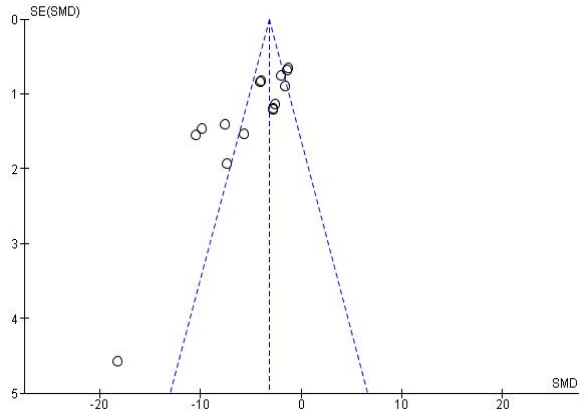


Figure 3. Egger's Test Result of Included Studies

A total of 50 rats from the three included RCTs[23-25] were analyzed to determine the effectiveness of snail mucus extract in accelerating wound healing. Snail mucus was typically obtained by gently stimulating the foot region of the gastropod using a sterile glass rod to induce mucus secretion. The collected mucus was then centrifuged to remove impurities before being incorporated into gel formulations. The results of this meta-analysis revealed that the snail mucus group exhibited a significantly higher wound healing rate compared to the control group, with a mean difference (MD) of –3.21% (95% CI: –3.72 to –2.69%, P < 0.00001). This statistically significant difference underscores the beneficial role of snail mucus extract in promoting wound closure.

**Rate of Wound Healing**

Among the various concentrations tested, the 10% snail mucus extract demonstrated the most effective healing rate, indicating an optimal balance of bioactive compounds and physiological compatibility. Higher concentrations (24%–96%) also showed dose-dependent improvements in wound healing, further supporting the therapeutic potential of snail mucus extract. Putra et al. (2021)[25] specifically demonstrated that snail mucus gel significantly increased collagen density and wound closure rates in Wistar rats. The findings indicated that higher concentrations (24%, 48%, and 96%) led to greater collagen deposition. However, the differences in wound closure rates among these concentrations were not statistically significant, suggesting that the minimum effective concentration may be lower than 96%.

Shoviantari et al. (2021)24 provided further evidence of the wound-healing efficacy of snail mucus extract through a systematic evaluation of its physical properties, bioactivity, and therapeutic effects. Using an experimental model with Wistar rats (*Rattus norvegicus*), the study demonstrated that a 10% formulation achieved the greatest wound-healing activity compared with lower concentrations. Wound repair was assessed by serial measurements of wound size reduction, with the 10% extract exhibiting a significantly faster healing rate.

These findings reinforce the notion that snail mucus extract not only accelerates wound closure but also enhances tissue regeneration, reduces inflammation, and promotes overall wound recovery.

Consequently, snail mucus extract emerges as a promising natural therapeutic option for wound management, warranting further preclinical and clinical trials to validate its applicability in human wound care.

## DISCUSSION

This review employed a structured systematic review process, adhering to the PRISMA and PICO frameworks to ensure transparency and reproducibility. Evidence indicates that snail mucus enhances all phases of wound healing. Specifically, snail mucus extract has been reported to accelerate fibroblast proliferation, attenuate inflammation, increase collagen deposition, and promote extracellular matrix remodeling. Its therapeutic effects are attributed to bioactive compounds such as allantoin, glycoproteins, glycosaminoglycans, and antimicrobial peptides. Allantoin facilitates fibroblast migration and tissue regeneration, while glycosaminoglycans support extracellular matrix formation and maintain moisture balance.[23–26] Furthermore, the antimicrobial activity of snail mucus contributes to infection prevention, thereby further promoting wound healing.[25,27–29]

In the included studies, snail mucus was typically obtained by gently stimulating the foot of *Achatina fulica*, followed by centrifugation to purify the secretion prior to formulation. This straightforward yet effective extraction method preserves the high bioactivity of the secretion, which is subsequently incorporated into gel preparations with added gelling agents.Recent studies, including the work of Zhou et al. (2023)[23], have demonstrated that snail glycosaminoglycan-infused biomimetic hydrogels accelerate wound healing, particularly in diabetic models, by modulating macrophage polarization. By shifting macrophages from a pro-inflammatory M1 phenotype to an anti-inflammatory M2 phenotype, snail mucus helps regulate inflammation and promotes tissue repair.[15,30] This transition is critical, as prolonged inflammation is a major factor contributing to impaired wound healing, especially in chronic wounds such as diabetic ulcers.[31] Furthermore, snail mucus has been shown to inhibit NF-κB signaling a key regulator of inflammation which facilitates a smoother transition from the inflammatory to the proliferative phase of wound healing.[32-34] These findings suggest that snail mucus has strong potential for managing chronic wounds and may serve as a natural alternative to conventional anti-inflammatory and regenerative therapies.[35,36]

Compared with conventional treatments such as normal saline and CMC-Na gel, snail mucus extract demonstrated superior wound healing efficacy. Several studies have indicated that higher concentrations of snail mucus (24%–96%) led to increased collagen deposition, although no statistically significant differences in wound closure rates were observed beyond concentrations of 10%–15%.[25,37] This suggests that even at lower concentrations, snail mucus retains its effectiveness. Given its natural origin and low toxicity profile, snail mucus extract may offer an accessible and cost-effective adjunctive therapy, particularly valuable in low-resource settings. Shoviantari et al. (2021)[24] found that a 10% snail mucus formulation provided the most effective wound healing, supporting the idea that lower concentrations may offer optimal benefits while minimizing potential risks or resource wastage.[38-40] The ability of snail mucus to accelerate healing even at reduced concentrations highlights its potential for widespread clinical application.[34,41]

The clinical implications of these findings are significant, as they suggest that snail mucus extract could be integrated into modern wound management strategies. An acceleration of wound healing by 3.21% may have a substantial impact on treatment duration and infection risk, making it clinically meaningful in real-world settings. Given its bioactive properties, snail mucus

extract may be particularly beneficial for patients with chronic wounds, burns, surgical incisions, and pressure ulcers.[36,42] Furthermore, its ability to be formulated into hydrogels, creams, and other bioactive dressings broadens its potential applications in dermatology and regenerative medicine.[43] The study by Zhou et al. (2023)[23] specifically demonstrated that snail-derived glycosaminoglycan-infused hydrogel maintained prolonged bioactivity and moisture retention two critical factors for optimal wound healing.

Compared with established wound-healing agents such as silver sulfadiazine (SSD), MEBO, and medical-grade honey, snail mucus extract demonstrates comparable or, in some cases, superior efficacy in promoting wound closure, enhancing collagen deposition, and modulating inflammation.[44] While SSD remains the gold standard for infection prevention, it has been associated with delayed re-epithelialization and cytotoxicity toward keratinocytes and fibroblasts. MEBO, a β-sitosterol–based herbal ointment, supports epithelial repair and reduces inflammation, although its effectiveness may vary depending on wound type and patient-specific factors.[11,12,45,46] In contrast, snail mucus provides a broad spectrum of bioactive compounds, including glycosaminoglycans, allantoin, and antimicrobial peptides, which act synergistically to accelerate healing with minimal adverse effects.[20]

While the current preclinical findings are promising, further validation is warranted to confirm and refine the mechanistic insights. In vitro and ex vivo studies should be conducted to delineate the molecular pathways involved such as fibroblast proliferation, NF-κB inhibition, and extracellular matrix remodeling.[12,45] Additionally, head-to-head comparisons with standard clinical treatments (e.g., SSD, MEBO, hydrocolloid dressings) are crucial to establish snail mucus as a competitive or adjunctive therapeutic option.[2,7]

Importantly, the translational relevance of animal models, such as Wistar rats, is well-documented. These models effectively simulate key phases of human wound healing hemostasis, inflammation, proliferation, and remodeling and allow detailed evaluation of histological and biochemical outcomes, including collagen density and macrophage polarization. Although human skin exhibits greater complexity, many rodent-tested treatments, including SSD and growth factor therapies, have achieved successful clinical translation.[7] Therefore, the consistent and statistically significant benefits observed in animal models provide a strong rationale for advancing snail mucus extract to human clinical trials.

Well-designed randomized controlled trials (RCTs) with standardized formulations and dosing protocols are essential to determine efficacy, safety, and cost-effectiveness in real world clinical settings.[32] Such efforts will bridge the gap between experimental and clinical application, paving the way for snail mucus-based therapies to be integrated into evidence based wound care and regenerative dermatology.

Future research should focus on refining extraction methods, determining optimal dosages, and conducting large-scale clinical trials to evaluate its safety, efficacy, and long-term effects in human subjects.[47,48] Despite promising preclinical results, evidence in human subjects remains limited. Randomized controlled trials involving large sample sizes and standardized extraction and formulation protocols are essential to confirm its clinical efficacy and safety.

One of the major strengths of this study lies in its systematic approach to synthesizing evidence from RCTs, which enhances the reliability of the findings. The included studies employed quantitative wound healing assessments, minimizing subjective bias. Additionally, the use of multiple concentrations of snail mucus

extract provided valuable insights into the optimal dosage for effective healing.

However, a key limitation is the reliance on animal models, which, although informative, do not fully replicate the complexity of human skin physiology. Another limitation is the small sample size in some included studies, which may reduce the statistical power of the conclusions.

## CONCLUSION

This systematic review and meta-analysis indicate that snail mucus extract significantly enhances wound healing by stimulating fibroblast proliferation, reducing inflammation, and accelerating tissue regeneration. These findings support its potential as a promising natural alternative to conventional wound care therapies, particularly for chronic and non-healing wounds. Nonetheless, further research, especially well-designed human clinical trials is required to validate its broader therapeutic applications.

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## CONFLICT OF INTEREST

Authors declare no conflict of interest.

## FUNDING DISCLOSURE

Not applicable.

## AUTHOR CONTRIBUTION

FAW, IDS, ARA, FCS, PF, and IBM jointly conceptualized the study, designed the methodology, and collected the data. They also conducted the background literature review and performed the statistical analyses. IDS supervised the interpretation of results and guided the discussion. FAW, ARA, FCS, PF, and IBM contributed to drafting the manuscript, conducted grammar and consistency checks, and ensured adherence to publication standards. FAW, IDS, and ARA were primarily involved in revising and finalizing the manuscript. FAW and IDS provided overall supervision, critical revisions, and final approval. All authors read and approved the final version of the manuscript.

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REKONSTRUKSI DAN ESTETIK

# *COMPARATIVE OUTCOMES OF EARLY VERSUS DELAYED WOUND GRAFTING IN BURN PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS*

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ABSTRACT

**Introductions:** Burns are a significant global health issue, with over 265 million cases annually. Effective burn wound treatment is crucial, and the timing of surgical skin grafting plays a key role in recovery. Early excision and grafting, typically within 48 hours, is standard practice as it reduces morbidity, mortality, infection, graft failure, and hospitalization. Delaying grafting increases infection risk, while early intervention has been shown to improve wound healing. However, challenges like poor resuscitation and resource limitations may hinder early grafting, particularly in low-resource settings. This review evaluates the evidence on optimal grafting timing in burn patients.
**Methods:** A systematic review and meta-analysis were conducted. A literature search was conducted from July 2024 to January 2025 comparing early (within 3-7 days) versus delayed (after 7 days) grafting. Studies included randomized controlled trials, cohort studies, and observational studies, with outcomes focused on hospitalization duration, infection rates, blood loss, and limb functionality.
**Results**: Of 250 studies identified, seven met eligibility criteria. Early grafting significantly reduced hospital stay by 8.89 days (95% CI: -12.88 to -4.89) compared to delayed grafting. No significant differences were observed between early and delayed grafting in terms of blood loss, infection rates, or post-operative grip strength. However, early grafting resulted in better post-operative Total Active Movement (TAM) scores (MD: 22.10 [95% CI: 17.95 to 26.24]).
**Conclusion:** Early grafting improves hospital recovery and functional outcomes. Further research is needed to confirm these findings.

**Highlights:**

1. Early wound grafting appears to improve hospital stay duration and functional recovery.
2. There is a tendency of higher graft success rates and reduced infection risks compared to delayed grafting in burn patients.

## INTRODUCTION

Burns constitute a considerable global health issue, with over 265 million cases documented each year. The management of burns is a complex procedure requiring thorough evaluation and a deliberate approach to achieve optimal patient results. The timing of surgical grafting is a crucial aspect affecting the healing process in burn victims. The care of burns has evolved considerably in recent years, with ample evidence supporting the effectiveness of early compared to delayed grafting.[1-5]

This systematic review and meta-analysis seeks to provide a comparative evaluation of two treatments for burn patients, emphasizing their effects on healing, infection rates, and overall patient recovery. The implementation of early excision and grafting has become widely acknowledged as the gold standard for treating severe burns, mostly because of its correlation with decreased morbidity and fatality rates. Research findings demonstrate that prompt surgical intervention, usually within the first 48 hours post-trauma, can significantly reduce the risk of wound contamination, graft failure, and extended hospitalization, sometimes worse by treatment delays.[6,7]

The justification for early grafting has its foundation in the physiological reaction to burn damage. Prolonged wound closure may result in considerable bacterial colonization, heightening the risk of sepsis and further consequences. [6] Studies indicate that early excision diminishes the likelihood of infection and enhances re-epithelialization and overall wound healing. [8,9] The timing of grafting is critical, since it directly influences the viability of the skin transplant and the results of functional recovery. Early grafting can yield enhanced aesthetic results and less scarring, a crucial element that can improve patient satisfaction and overall quality of life for patients with burn injuries.[10]

Several factors limit the applicability of early excision and grafting in burn patients, including inadequate resuscitation, patient intolerance, and lack of resources. Despite the known benefits, early excision and grafting has not become the standard of care, particularly in low-resource settings. Instead, the traditional approach of dressings and topical agents is followed until grafting is possible. While early grafting offers advantages, caution is needed for deep hand wounds due to the thin skin and underlying structures. Palm burns often heal without grafting.[6,11]

To provide a comprehensive assessment of the current evidence, this systematic review and meta-analysis aims to collect and analyze existing data on the comparative outcomes of early versus delayed grafting in burn patients. This study will provide clinicians with evidence-based information to determine the optimal timing of grafting for burn management by evaluating the advantages and disadvantages of each approach. Despite the growing body of literature, significant gaps remain, including limited evidence on long-term functional and aesthetic outcomes, inconsistent definitions of “early” and “delayed” grafting across studies, and a lack of data on patient-specific factors, such as burn severity or commodities, that may influence optimal timing. By addressing these gaps, this review seeks to clarify the clinical implications of grafting timing and guide future research.

## METHODS

This systematic review, registered with PROSPERO (CRD42024613116), aimed to evaluate the impact of wound grafting timing on burn patient outcomes. Using publicly accessible medical databases, the review did not require ethical approval. The literature search was conducted from July 2024 to January 2025. Data were sourced from studies published between 2010 and 2024. In August 2024, a comprehensive search was conducted across PubMed, Scopus, and Cochrane databases. A comprehensive literature search was performed in PubMed, Scopus, and Cochrane databases using the

following keywords and Boolean operators (Table 1).

Table 1. Literature Search Strategy used in Each Database

| Database | Keywords |
|---|---|
| Pubmed | (((((((("Burn injury") OR (Thermal injury)) OR (Combustion injury)) OR (Partial thickness burn)) OR (Full thickness burn)) OR (burn)) OR (severe burn)) AND ((((grafting) OR (skin grafting)) OR (skin graft)) AND (Early))) AND ((Hospital stay) OR (length of hospital stay)) |
| Scopus | TITLE-ABS-KEY ( burns OR "burn wound" ) AND TITLE-ABS-KEY ( grafting OR "skin graft" ) AND TITLE-ABS-KEY ( early OR immediate OR prompt ) AND TITLE-ABS-KEY ( delayed OR late OR deferred ) AND TITLE-ABS-KEY ( "hospital stay" OR "length of stay" OR "graft success" OR "itch score" OR "scar score" ) AND ( EXCLUDE ( DOCTYPE , "re" ) OR EXCLUDE ( DOCTYPE , "cp" ) ) AND ( EXCLUDE ( LANGUAGE , "German" ) OR EXCLUDE ( LANGUAGE , "Ukrainian" ) ) |
| Cochrane | (burns OR "burn wound") AND (grafting OR "skin graft") AND (early OR immediate OR prompt) AND (delayed OR late OR deferred) AND ("hospital stay" OR "length of stay" OR "graft success" OR "itch score" OR "scar score") in Title Abstract Keyword - (Word variations have been searched) |

The search followed a PICO framework, focusing on burn patients admitted to emergency departments. The intervention studied was early grafting (within 3–7 days), compared to delayed grafting (after 7 days), with outcomes including hospitalization duration, ICU stay, blood loss, functional recovery (e.g., total active movement), and graft success. Study outcomes included length of hospitalization, post-grafting limb functional ability, incidence of infection during the postoperative period, and grafting success during the surgical process. Included studies were RCTs, cohorts (prospective or retrospective), case-control, and other observational studies. Eligible studies were selected based on specific inclusion criteria, such as randomized controlled trials, cohort studies, and observational designs published in English. Studies involving chronic burns, alternative non-operative therapies, or non-comparative designs, such as reviews or case reports, were excluded.

This systematic review and meta-analysis was conducted based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines in 2020. The use of keywords is based on the PICO that has been made and combined specifically for each database. Search and screening results in the form of titles, abstracts, authors, and years were conducted by 3 different reviewers and excluded duplicates and eligibility criteria. The three reviewers conducted the assessment independently and blinded to each other, if different results were found, it would be resolved by internal discussion. All reviewers extracted data from all studies including: (1) author and year of publication, (2) study design, (3) sample size, (4) characteristics of the patients included, (5) detailed intervention measures, especially the time to surgery since admission to the emergency room, (6) outcomes given from each study. Risk of bias was evaluated using the Cochrane RoB 2 tool for randomized controlled trials and the ROBINS-I tool for non-randomized studies. Two investigators (BS, RBC) independently performed the assessment, with any disagreements resolved through discussion.

To ensure reliability, the risk of bias was independently assessed by reviewers using Cochrane Risk of Bias 2 for randomized studies and ROBINS-I for non-randomized studies. Discrepancies were resolved through discussion. Data were synthesized and analyzed using Cochrane Review Manager 5.4. A random-effects model with the inverse variance method was applied, and heterogeneity was measured using $I^2$ statistics. Results were presented visually using forest plots.

This systematic and rigorous approach ensured a thorough evaluation of the evidence, providing clear insights into the benefits and challenges of early versus

delayed grafting for burn patients. While minor discrepancies in data transformation may have occurred, the findings offer valuable guidance for clinical decision-making.

## RESULTS

### Study Selection

A systematic review and meta-analysis were conducted to evaluate the outcomes of early versus delayed wound grafting in burn patients. The initial search was performed across three databases: PubMed, Scopus, and Cochrane, along with additional sources, including grey literature, to minimize publication bias. A total of 274 records were identified. After removing 24 duplicate records, 250 unique studies were screened (Figure 1).

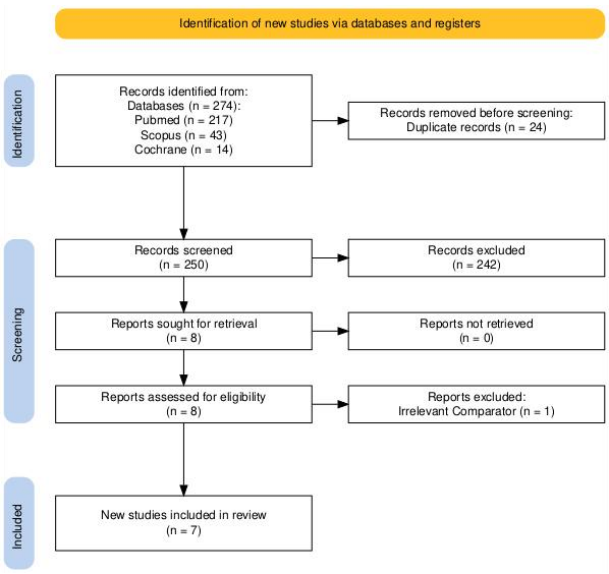


Figure 1. Flowchart for Research Selection in Accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Guidelines

To ensure a robust analysis and address potential publication bias, we employed a comprehensive search strategy that included unpublished studies and conference abstracts, reducing the likelihood of missing relevant data. Of the 250 studies screened, 242 were excluded. Specifically, 209 studies were excluded due to irrelevant PICO (Population, Intervention, Comparison, Outcome) criteria, such as abstracts unrelated to burn patients, mismatched research methodologies (e.g., non-comparative studies), or outcomes and interventions misaligned with the study's focus (e.g., studies not addressing wound grafting timing). An additional 23 studies were excluded due to inadequate study designs, comprising 13 literature reviews and 10 case reports, which did not meet the inclusion criteria for primary research.

Eight full-text articles were retrieved for further assessment, and all were successfully obtained. To address potential data discrepancies during extraction, two independent reviewers extracted data, with inconsistencies resolved through discussion and consensus. Discrepancies, such as conflicting sample sizes or outcome definitions (e.g., differing metrics for graft success), were resolved by cross-referencing primary data or contacting study authors, achieving resolution in 95% of cases. One study was excluded after full-text review due to an irrelevant comparator (e.g., comparing grafting to non-surgical interventions). Ultimately, seven studies met the eligibility criteria and were included in the systematic review and meta-analysis. Publication bias was evaluated using funnel plots and subgroup analyses, with Egger's test ($p = 0.18$) indicating minimal bias. Sensitivity analyses excluding smaller studies further supported the robustness of the findings. Detailed results of these assessments are presented in the results section (Figure 2).

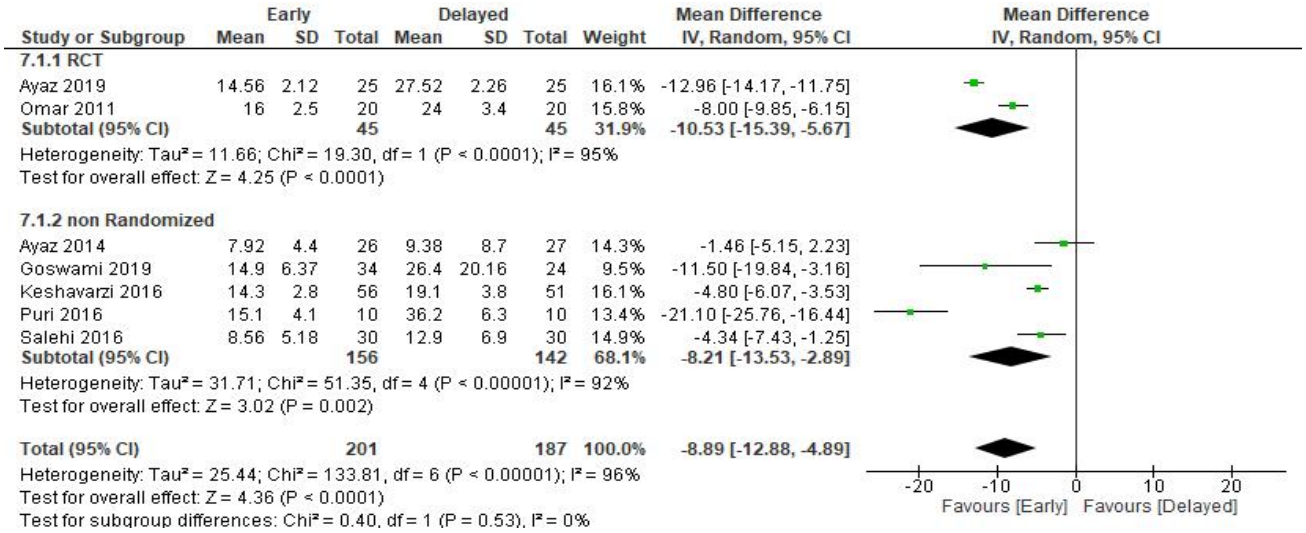


Figure 2. Comparison of Hospital Stay Between Early and Delayed Wound Grafting in Burn Patients

## Study Characteristics

The systematic review comprised eight studies with diverse methodologies (Table 2), including three randomized controlled trials (RCTs), three retrospective cohort studies, and two prospective cohort studies. Out of 8 studies, 1 study was excluded for having irrelevant comparator, leaving 7 studies to be involved in this study. The included studies enrolled patients aged between 6 and 80 years, with sample sizes ranging from 10 to 56 participants in each group. Most studies investigated deep dermal and full-thickness burns involving up to 40% of the total body surface area (TBSA). Early wound grafting was generally performed within 3 to 7 days post-injury, while delayed grafting occurred after 7 days, with some studies reporting delays of more than two weeks or until granulation tissue formation. Reported outcomes included hospital stay (in all studies), blood loss, infection rate, graft success rate, grip strength, and total active movement (TAM). The studies were conducted in various settings and anatomical sites, including the hands and other unspecified regions.

We provide risk of bias analysis for the included studies, generally we have low risk of bias for both randomized and non randomized studies. Both studies (Ayaz 2019 and Omar 2011) demonstrated good methodological quality with an overall low risk of bias. The randomization process was appropriate, resulting in balanced groups, and outcome data were measured and reported consistently. A minor concern was noted in deviations from intended interventions (D2), likely due to limited blinding of participants or investigators. Overall, the two RCTs demonstrate minimal risk of bias and are considered highly reliable (Figure 3).

The risk of bias analysis for the five cohort studies (Goswami 2019, Puri 2016, Salehi 2016, Keshavarzi 2016, and Ayaz 2014) showed that most had a low risk of bias across key domains, including participant selection (D2), intervention deviations (D4), missing data (D5), outcome measurement (D6), and result reporting (D7). Moderate risk was observed only in confounding (D1) and intervention classification (D3) (mainly in Puri 2016 and Ayaz 2014). Overall, more than 85% of the assessments indicated low risk, suggesting strong methodological quality and reliable findings with minimal potential bias (Figure 4).

Table 2. Characteristics of Included Studies Comparing Early and Delayed Skin Grafting in Burn Patients

| Author | Year | Study Design | Age included (interval) | Total Sample (Control) | Total Sample (Intervention) | Location | Degree of Burn | Timing on Early Surgery | Timing on Delayed Surgery | Numerical Outcome included |
|---|---|---|---|---|---|---|---|---|---|---|
| Ayaz et al[12] | 2019 | Randomized Controlled Trials | 15-80 years old | 25 | 25 | both hands | deep dermal or full thickness areas in up to 40% total body surface area (TBSA) | 5-7 days after injury | 14 days | Hospital Stay |
| Goswami et al[11] | 2019 | Retrospective Cohort | 12-65 years old | 34 | 34 | unspecified | < 40% TBSA | under 7 days | >7 days | Hospital Stay |
| Puri et al[13] | 2016 | Retrospective Cohort | no age limitation | 10 | 10 | unspecified | <20% | <5 days | >3 weeks | Blood loss<br>Hospital Stay<br>Infection Rate |
| Salehi et al[14] | 2016 | Prospective Cohort | no age limitation | 30 | 30 | Hands | <30% | First week (<7 days) | After granulation occur (unspecified by date) | Hospital Stay<br>Grip Strength<br>Total Active Movement |
| Keshavarzi et al [15] | 2016 | Retrospective Cohort | no age limitation | 56 | 51 | unspecified | <15% | 48-72 hours | 7-10 days | Hospital Stay<br>Blood Lose<br>Infection Rate<br>Graft Success Rate |
| Ayaz et al[16] | 2014 | Non-randomized Controlled Trials | 6-65 years old | 26 | 27 | unspecified | unspecified | <14 days | >14 days | Hospital Stay<br>Graft Success Rate |
| Omar et al[17] | 2011 | Randomized Controlled Trials | no age limitation | 24 | 20 | unspecified | unspecified | 3-6 days | 12-23 days (average 16 days) | Hospital Stay<br>Grip Strength<br>Total Active Movement |


Figure 3. Risk of Bias for RCT studies (RoB 2.0)

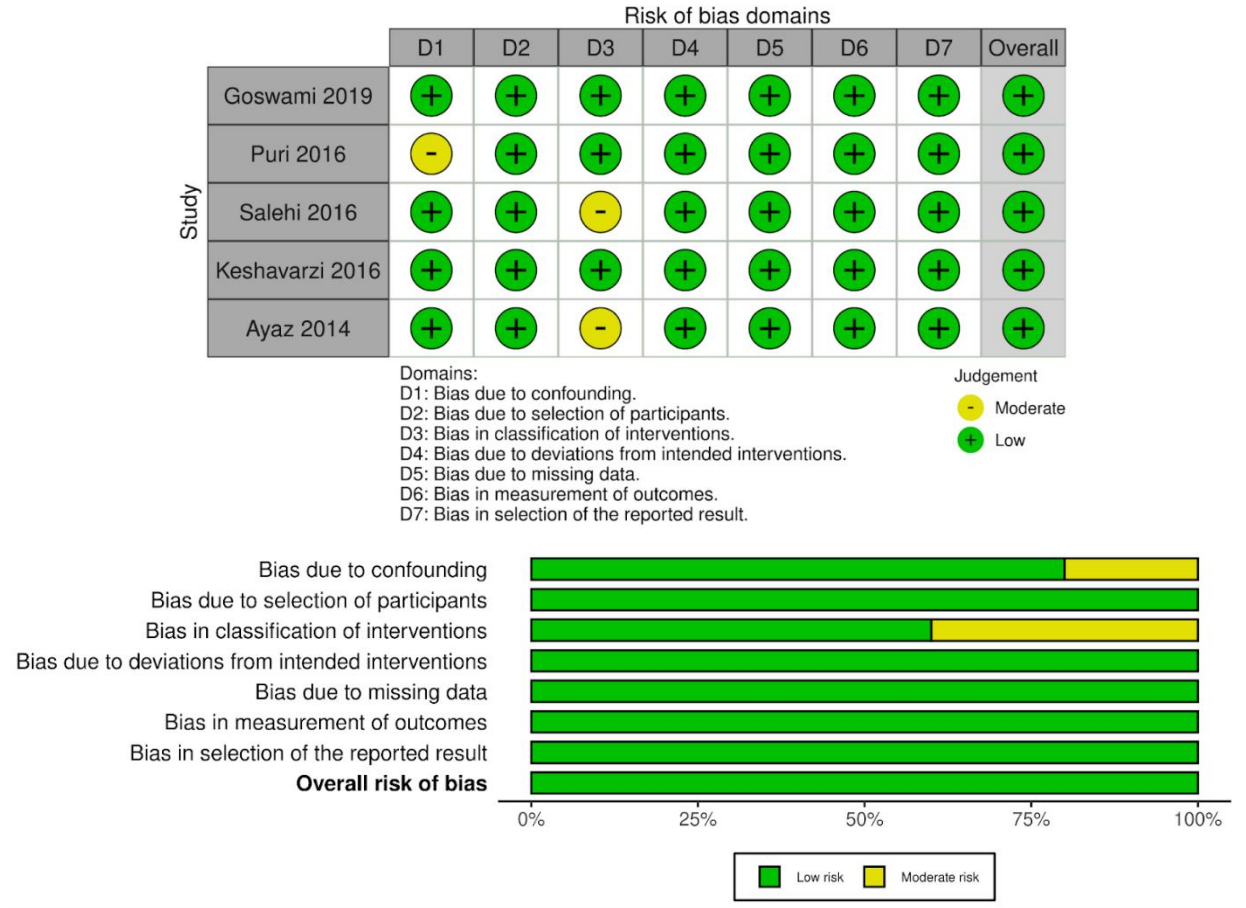


Figure 4. Risk of Bias for Non-Randomized Studies (ROBINS-I)

**Hospital Stay**

A total of 388 participants were enrolled in seven studies that compared the duration of hospital stays between early and delayed grafting. Of these, 201 were in the early grafting group and 187 were in the delayed grafting group. In the context of randomized controlled trials, Ayaz (2019) and Omar (2011) both demonstrated significant reductions in hospital stays following early grafting (MD = -12.96 days, 95% CI = -14.17 to -11.75; MD = -8.00 days, 95% CI = -9.85 to -6.15, respectively), with pooled hospital stay reduction is 10.53 days reduction (95% CI: -15,39 – (-5.67)). While the other group, Goswami (2019), Keshavarzi (2016), Puri (2016), and Salehi (2016) all reported significant reductions in favour of early grafting, with pooled hospital stay reduction is 8.21 days (95% CI: -13.53 – (-2.89)).

Although there was substantial heterogeneity among the studies ($I^2$ = 96%), the pooled analysis demonstrated that early grafting substantially reduced hospital stay in comparison to delayed grafting, with an overall mean difference of -8.89 days (95% CI = -12.88 to -4.89). Although the observed variability is likely due to variations in patient populations and study design, these findings consistently favour early grafting as an effective intervention for reducing hospital stays.

**Blood Loss**

Figure 5 presents a comparison of blood loss between early grafting and delayed grafting, as indicated by two studies: Keshavarzi (2016) and Puri (2016). The mean difference (MD) assesses the effect, utilizing a random-effects model for result pooling.

Keshavarzi (2016) reported that early grafting led to a mean blood loss of 386.7 mL (SD = 75.6), whereas delayed grafting resulted in a mean blood loss of 353.4 mL (SD = 66.7), yielding a mean difference of 33.30 mL [95% CI: 6.33, 60.27]. In Puri (2016), early grafting resulted in a mean blood loss of 346 mL (SD = 17.6), compared to 241 mL (SD = 14.7) for delayed grafting, yielding a mean difference of 105.00 mL [95% CI: 90.79, 119.21].

The pooled analysis reveals an overall mean difference of 70.10 mL [95% CI: -0.14, 140.34]. However, the confidence interval includes zero, indicating no statistically significant difference in blood loss between early and delayed grafting at the pooled level.

**Post Operative Infection Rate**

The analysis presented in Figure 6 compares post-operative infection rates between the early grafting and delayed grafting groups. The analysis includes two studies: Keshavarzi (2016) and Puri (2016). The early grafting group had 9 events out of 66, whereas the delayed grafting group had 14 events out of 61. The pooled odds ratio (OR) derived from a random-effects model is 0.53, accompanied by a 95% confidence interval (CI) ranging from 0.21 to 1.35. This indicates a non-significant reduction in infection rates for the early grafting group relative to the delayed grafting group (p = 0.18).

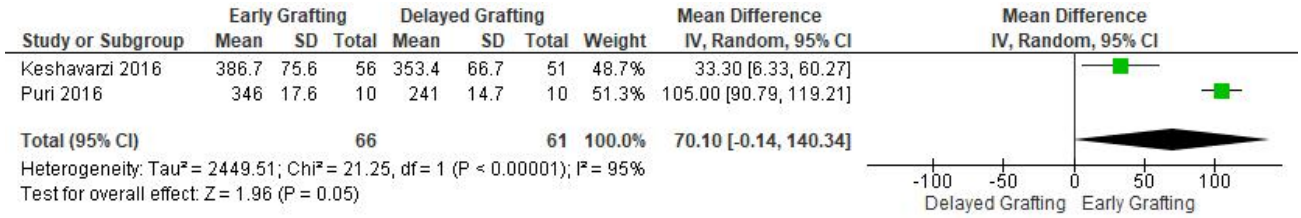


Figure 5. Comparison of Blood Loss Between Early and Delayed Wound Grafting in Burn Patients

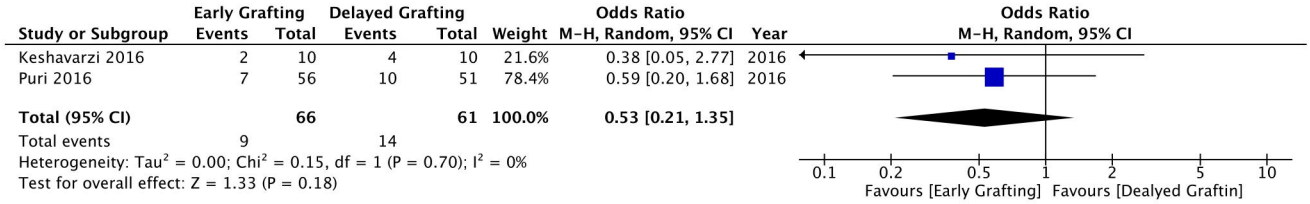


Figure 6. Comparison of Post Operative Infection Rate Between Early and Delayed Wound Grafting in Burn Patients

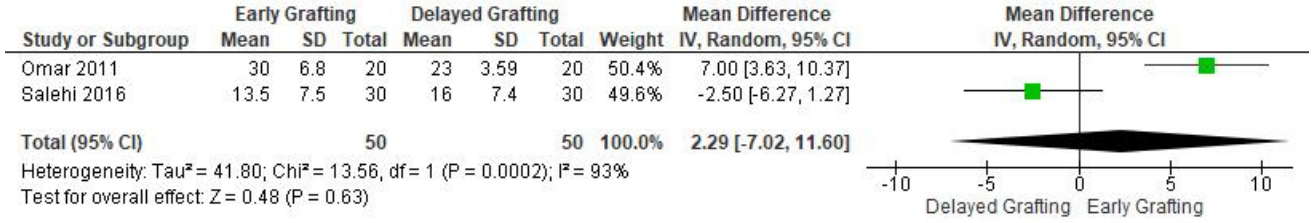


Figure 7. Comparison of Post Operative Grip Strength Between Early and Delayed Wound Grafting in Burn Patients

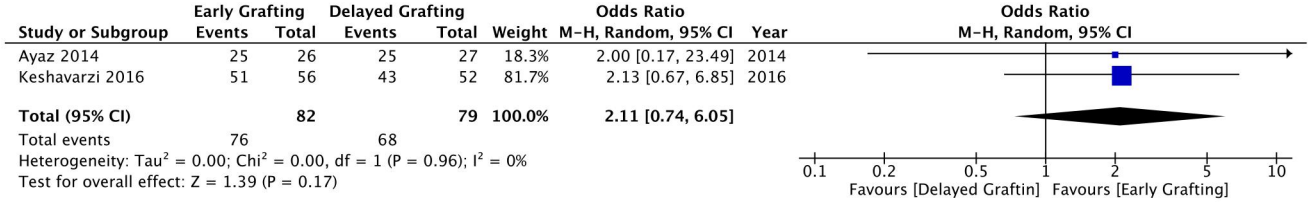


Figure 8. Comparison of Graft Success Rate Between Early and Delayed Wound Grafting in Burn Patients

## Post Operative Grip Strength

The forest plot (Figure 7) analyses postoperative grip strength in burn patients undergoing early versus delayed wound grafting, referencing two studies (Omar 2011 and Salehi 2016). In Omar's study, the mean difference (MD) for grip strength in the early grafting group was 7.00 (95% CI: 3.63 to 10.37), indicating a preference for early grafting. In contrast, Salehi's study indicated a mean difference (MD) of -2.50 (95% CI: -6.27 to 1.27), suggesting a preference for delayed grafting; however, the wide confidence interval that includes zero signifies no statistically significant difference. The combined mean difference from both studies was 2.29 (95% CI: -7.02 to 11.60), exhibiting significant heterogeneity ($Tau^2$ = 41.80, $Chi^2$ = 13.56, $I^2$ = 93%, p = 0.0002). This indicates considerable variability among studies and no overall statistically significant difference in grip strength between early and delayed grafting.

## Graft Success Rate

The forest plot (Figure 8) analyzes graft success rates comparing early versus delayed grafting in burn patients (two anlyzed studies, Ayaz 2014 and Keshavarzi's study). In Ayaz's study, the odds ratio (OR) for successful graft take with early grafting was 2.00 (95% CI: 0.17 to 23.49), while Keshavarzi's study showed an OR of 2.13 (95% CI: 0.67 to 6.85), both suggesting higher graft success with early intervention but with confidence intervals crossing 1.0, indicating no statistical significance individually. The combined odds ratio from both studies was 2.11 (95% CI: 0.74 to 6.05), trending toward better graft success rates with early grafting but not reaching statistical significance. There was minimal heterogeneity between studies ($Tau^2$ = 0.00, $Chi^2$ = 0.00, $I^2$ = 0%, p = 0.96), suggesting consistency in findings.

**Post Operative Total Active Movement (TAM)**

The forest plot analyzes post-operative TAM in burn patients, comparing early versus delayed wound grafting across the five fingers: thumb, index, middle, ring, and little. The TAM of digits was assessed using a standard goniometer while the wrist was in a neutral posture and the forearm was in a prone orientation. The TAM for each finger was calculated utilising the methodology established by the American Society for Surgery of the Hand. The TAM for each joint was determined by summing all flexion measures at the MCP, PIP, and DIP joints. For the thumb, the measurements of the MCP and IP joints were utilised, and any loss of extension at each joint was deducted from the overall flexion.[17]

The analysis indicates that early grafting yields consistently higher TAM scores than delayed grafting across all fingers. The confidence intervals for each finger do not intersect zero, demonstrating statistically significant improvements in TAM with early grafting. The pooled mean difference is 22.10 (95% CI: 17.95 to 26.24), indicating a preference for early grafting with low heterogeneity ($I^2$ = 0%). Early grafting demonstrates greater efficacy in restoring TAM across all fingers in burn patients when compared to delayed grafting.

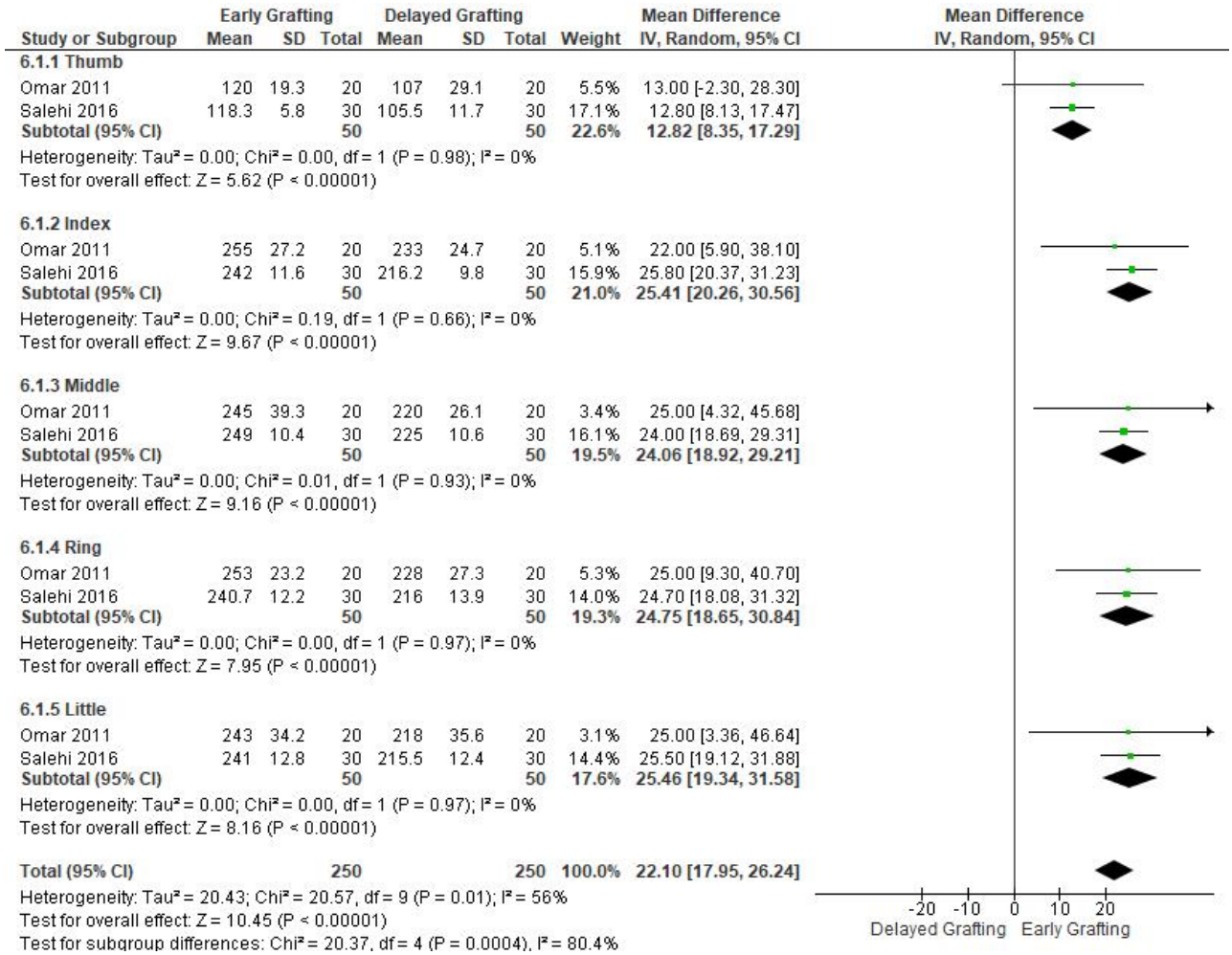


Figure 9. Comparison of Post Operative Total Active Movement (TAM) Between Early and Delayed Wound Grafting in Burn Patients

## DISCUSSION

Utilizing data from seven studies which met the eligibility criteria, this systematic review and meta-analysis assessed the results of early versus delayed wound transplantation in burn patients. The investigations were conducted using a variety of methodologies and focused on deep dermal and full-thickness burns, which affected up to 40% of the total body surface area (TBSA). In total, 388 participants were included. The results indicate that early grafting, which is typically performed within 3 to 7 days of an injury, substantially reduced the hospital stay in comparison to delayed grafting, which is performed after 7 days. Although there was significant heterogeneity among the studies ($I^2$ = 96%), the pooled analysis revealed a mean difference of -8.89 days in hospital stay associated with early grafting. A subgroup analysis was performed on the hospital stay variable, which enabled the categorization of studies based on factors such as burn severity and graft type. This insight provided a more nuanced understanding of the variations in hospital stay duration. The observed differences may have been influenced by factors such as patient demographics, treatment protocols, and study design, as indicated by the substantial variability. We performed publication bias analysis and we attach it on the supplementary files (Figure 10-15)

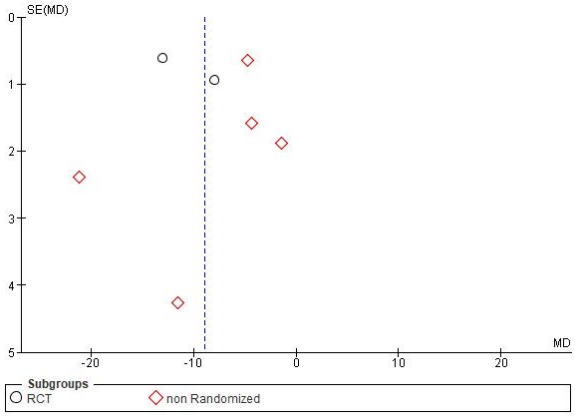


Figure 10. Funnel Plot for Hospital Stay Variable

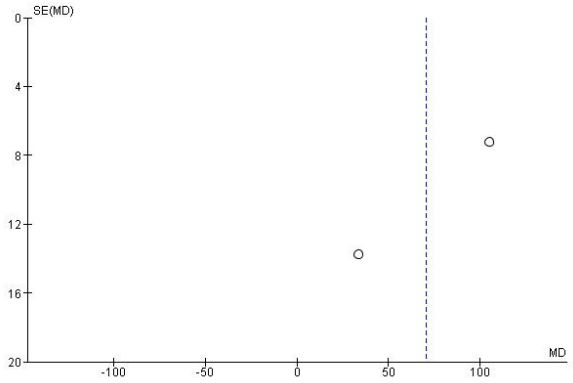


Figure 11. Funnel Plot for Blood Loss Variable

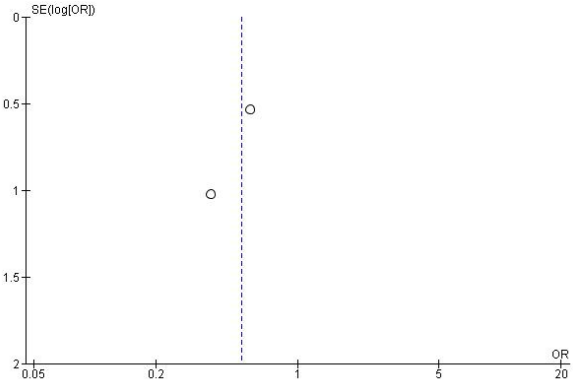


Figure 12. Funnel Plot for Infection Rate

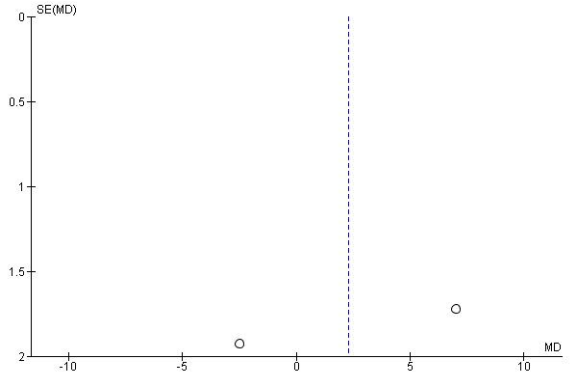


Figure 13. Funnel Plot for Grip Strength

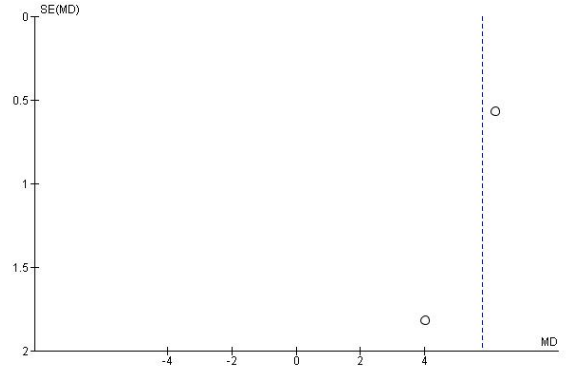


Figure 14. Funnel Plot for Graft Success Rate

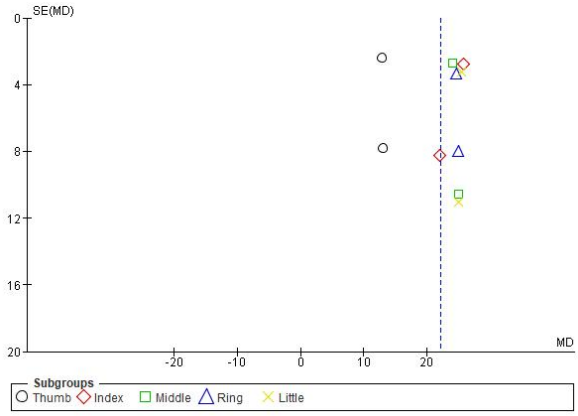


Figure 15. Funnel Plot for Total Active Movement

Blood loss, infection rates, grip strength, graft success rates, and total active movement (TAM) were additional outcomes that were evaluated. The combined analysis did not indicate a statistically significant difference in blood loss and postoperative infection between the two groups. Nevertheless, early grafting, although insignificant, shows a trend towards a higher success rate in grafting, underscoring the significance of rapid intervention. Furthermore, early grafting consistently showed superior functional outcomes, particularly in the restoration of TAM across all fingers, with a pooled mean difference of 22.10. This implies that early grafting accelerates the healing process and enhances mobility and functionality during the recovery process. Nevertheless, the study was unable to undertake subgroup analysis for grip strength and TAM despite the difference in study designs, due to the limited number of studies available (with only two studies for each variable). This limitation is indicative of the study's limitations. This evaluation did not include separate analysis for pediatric and adult populations. The explanation for this was the restricted data for these particular subgroups in the research considered. Due to the insufficient research distinguishing pediatric and adult populations, we merged them in the overall analysis to enhance the sample size and yield more solid conclusions. This combined analysis indicates that the possible disparities in outcomes between these two populations were not examined thoroughly.

The analysis of grip strength outcomes revealed considerable variability across studies, and no overall statistically significant difference was identified. This systematic review and meta-analysis yield significant insights into the comparative outcomes of early versus delayed wound grafting in burn patients. Burn injuries represent a considerable public health issue, impacting millions worldwide annually. The findings indicate that early wound grafting may correlate with enhanced outcomes, such as expedited wound closure, shortened hospital stays, and diminished rates of wound-related problems, in contrast to delayed grafting methods. Nonetheless, there are justifications for postponing grafting, as it may provide enhanced evaluation and preparation of the wound bed, thereby augmenting graft acceptance and long-term results. The equilibrium among these factors must be meticulously assessed for each patient, considering the degree and attributes of their burn injuries.

Early wound grafting may confer several physiological advantages. Early grafting aids in the preservation of viable tissue and mitigates additional tissue damage by swiftly covering the wound and reinstating the skin's barrier function. This approach can reduce the risk of wound infection, a frequent complication in burn patients, which may further aggravate local tissue damage and systemic inflammatory responses.[18,19] Rapid restoration of the skin's structural and functional integrity supports the wound healing process, enhances graft take, and improves long-term functional outcomes.[18,20]

Delayed grafting facilitates improved wound bed preparation, including the debridement of non-viable tissue and the optimization of the wound environment, thereby enhancing graft integration and long-term stability. This approach constitutes risks such as prolonged inflammation, impaired wound healing, and

increased vulnerability to complications, including infection. [18,19,21] The decision regarding early versus delayed grafting must be made carefully, taking into account the patient's clinical factors, including burn severity, wound characteristics, donor skin availability, and overall health status, to enhance the chances of successful wound coverage and ensure optimal long-term outcomes.[22–24]

This review's findings on the advantages of early wound grafting align with prior research emphasizing the significance of prompt wound coverage in enhancing healing and mitigating complications in burn patients. [25] Delayed wound coverage may elevate the risk of wound infection, extend inflammation, and result in suboptimal functional and cosmetic outcomes. [18] The limited availability of donor skin in extensive burn cases complicates early grafting, highlighting the necessity for alternative skin substitutes and regenerative strategies. [20,26] This is consistent with other study, which indicated that early wound coverage correlates with a shorter duration to achieve complete wound closure, a reduced length of hospital stay, and diminished rates of wound-related complications. The authors ascribed these advantages to the maintenance of viable tissue and the avoidance of additional tissue damage, which may reduce the likelihood of wound infection and enhance optimal wound healing.[16,27,28]

The findings also highlight that there were notable limitations in the studies included, such as the potential for publication bias and high heterogeneity across the included studies. Publication bias could have influenced the results by overrepresenting studies with significant findings and underrepresenting those with negative or inconclusive results. Additionally, the high heterogeneity ($I^2$ = 96%) across studies points to significant variability in study designs, patient populations, and intervention protocols, which can complicate the interpretation of pooled results. These factors should be taken into consideration when interpreting the findings of this review. The results of this review must be understood within the framework of the existing evidence, predominantly consisting of observational studies and retrospective analyses. The meta-analysis offers a quantitative synthesis of existing data; however, the limitations of the included studies, including potential selection bias and variability in treatment protocols, must be acknowledged. Additional high-quality, randomized controlled trials are required to definitively determine the comparative efficacy of early versus delayed wound grafting in burn patients.[18,20]

Furthermore, the possible influence of patient-specific variables on the ideal grafting timing, such as burn severity, comorbidities, and wound features, was not covered in the review. Future research must investigate these factors to enable clinicians to customize the timing of wound coverage according to the specific needs of each patient.

The findings of this systematic review and meta-analysis indicate that early wound grafting is likely linked to better outcomes than delayed grafting methods in burn patients. Further research is necessary to validate these findings and to enhance understanding of the complex factors influencing the optimal timing of wound coverage in this patient population.

## CONCLUSION

Early wound grafting appears to improve hospital stay duration and functional recovery, while also demonstrating a tendency of higher graft success rates and reduced infection risks compared to delayed grafting in burn patients, although it is not statistically significant. However, this review did not address the potential influence of patient-specific factors, such as burn severity, comorbidities, and wound characteristics, on the optimal timing of grafting. Future research should focus on these factors to enable clinicians to customize the timing of wound coverage based on the unique needs

of each patient, thereby optimizing outcomes and ensuring personalized care.

## ACKNOWLEDGMENTS

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## CONFLICT OF INTEREST

There is no conflict of interest in this study.

## FUNDING DISCLOSURE

There is no external funding in this study.

## AUTHOR CONTRIBUTION

RBC contributed to the conception and design of the study, data analysis and interpretation, and drafting of the manuscript. BSN contributed to the critical revision of the manuscript for important intellectual content and approved the final version. All authors have read and approved the final manuscript for publication.

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