

## Current Ulcer Care Practices Among Leprosy Patients - A Systematic Review & Meta Analysis

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Foot ulcers remain a major cause of morbidity among people affected by leprosy. Peripheral neuropathy leads to repeated unnoticed trauma to the feet, resulting in chronic ulceration. While off-loading the affected limb through absolute resting of is the most effective solution for ulcer healing, several other interventions are in practice owing, to the impracticalities associated with the absolute rest. This systematic review and meta-analysis examined such currently practiced interventions and assessed the effectiveness of available interventions for the management of leprosy-related foot ulcers. A comprehensive search identified studies published between 2005 and 2024, including randomized controlled trials (RCTs), cohort, cross-sectional, and retrospective studies. Twenty-one studies (n=957) from India, Brazil, Indonesia, and other countries met the inclusion criteria. Ulcer types included trophic, plantar, neuropathic, and chronic non-healing ulcers. Interventions evaluated comprised basic wound care, platelet-based and stem cell therapies, autologous grafts, surgical procedures, low-level laser therapy, topical agents, and traditional therapies. In these studies, the healing rates ranged from 20.4% to 100%, with an overall pooled healing proportion of 67.4% (95% CI: 51.5–81.8). Surgical interventions (100%), topical agents (74.3%), and platelet-based therapies (64.9%) demonstrated higher/ highest healing rates, while traditional therapies showed lower effectiveness (39.0%). The pooled risk ratio from RCTs was 2.12 (95% CI: 1.24–3.63), indicating two times better healing rates in intervention groups. Surgical and topical therapies were most effective, with platelet-based and stem cell therapies showing promising potential. However, rest and mechanical off-loading are essential for ulcer healing and should be integral to all treatment protocols. Findings underscore the need for standardized treatment protocols and robust multicentre trials to optimize ulcer care in leprosy.

**Key Words:** Leprosy, Wound Healing, Foot Ulcers, Surgery

### Introduction

Leprosy, or Hansen's disease, is an infectious condition caused by *Mycobacterium leprae*, primarily affecting the skin, peripheral nerves, eyes, and upper respiratory mucosa which poses long term consequences if left untreated (Thatoju

et al 2025b, Santacroce et al 2021). Despite the availability of effective multi-drug therapy (MDT) and more than 95% reduction in disease burden, the disease remains endemic in several low- and middle-income countries, with India, Brazil, and Indonesia accounting for a substantial proportion

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of global cases (WHO 2025, Dockwell et al 2022). Peripheral neuropathy a complication of leprosy results in loss of protective sensation, particularly in the hands and feet (Agrawal et al 2005). Repetitive, unperceived mechanical stress during weight-bearing leads to callus formation and subsequent tissue breakdown, most commonly on the plantar surface of the foot. Autonomic dysfunction and impaired microvasculature further compromise skin integrity, predisposing to chronic non-healing ulcers (Ebineshan et al 2020). These ulcers frequently progress from hyperkeratotic lesions to deep wounds complicated by secondary infection and in advanced cases progressing to osteomyelitis. Recalcitrant foot ulcers are one of the leading causes of prolonged morbidity, functional impairment, or limb amputation in persons affected by leprosy (Riyaz & Sehgal 2017). In addition, visible deformities and chronic wounds contribute to stigma, social isolation in the leprosy affected persons resulting in psychological distress, significantly affecting their quality of life (Cross 2007).

The World Health Organization (WHO) Global Leprosy Strategy 2021-2030 emphasizes early diagnosis, timely management of complications, and disability prevention as critical to achieving leprosy elimination goals (WHO 2021). An estimated 34% of the leprosy patients with loss of sensation develop plantar ulcers, and 7% develop during the disease course (Govindasamy et al 2023). Some studies have reported 76% of patients had ulcers even after completing MDT (Anandan et al (2016). Current management strategies range from basic wound care such as cleaning, debridement, infection control and dressings to advanced therapies, including platelet-rich fibrin (PRF), stem cell secretome gels, skin grafting, topical growth factors, and surgical corrections. However, rest and effective

off-loading of pressure remain the cornerstone of ulcer healing, with other interventions serving as adjuncts (Riyaz & Sehgal 2017). Inconsistent off-loading, limited access to or non-compliant usage of protective footwear and inadequate patient education often compromise outcomes. Moreover, repetitive use of systemic antibiotics for treating recurrent secondary infections on chronic foot ulcers without any guidance by the antimicrobial susceptibility testing (AST) raises concerns about emerging antimicrobial resistance (Agrawal et al 2005, WHO Antimicrobial resistance 2023).

Ulcer care practice remains diverse across the regions due to limited availability of healthcare infrastructure and resources in most of the endemic settings. High recurrence rates and poor long-term outcomes are frequently linked to inadequate preventive strategies and insufficient follow-up care (Upputuri et al 2020). Although individual interventions have been studied, comprehensive evidence comparing the effectiveness of all the currently available treatments remains limited.

Present systematic review and meta-analysis acknowledge the criticality of proper and timely management of foot ulcers in leprosy and aim to evaluate current ulcer management practices among persons affected by leprosy, focusing on pooled healing outcomes. By synthesizing data across diverse settings, this study seeks to examine effectiveness of various ulcer care strategies that are currently being undertaken. Evidence thus generated informs the most effective one that could potentially be integrated into the local health policies.

## Methods

The study protocol was registered on the PROSPERO International Prospective Register (ID: CRD420251010372), and the detailed protocol has been published (Thatoju et al 2025a).

### Inclusion Criteria

We included observational studies, randomized controlled trials (RCTs) - Clinical trials that focused on ulcer care practices among patients with leprosy. Only articles with full-text access were considered eligible. To capture recent advancements in ulcer management, we restricted the inclusion to studies published between 2005 and 2024. No restrictions were applied regarding the country of origin.

### Exclusion Criteria

We excluded articles with other study designs such as conference abstracts, letters, commentaries, theses, books, reviews, editorials, author responses, previous systematic reviews and meta-analyses, and animal studies. In addition, articles published in languages other than English were excluded due to limitations in translation resources.

### Search Strategy

A comprehensive search of relevant literature was conducted using various databases, including PubMed, Google Scholar, along with conference programs, dissertations and government reports. The search was conducted using the following key terms: "Leprosy," "Hansen's disease," "*Mycobacterium leprae*," "Leprosy ulcer," "Plantar ulcer," "Leprosy-related ulcer," "Ulcer care," "Wound management," "Debridement," "Topical therapy," "Foot care". Boolean operators such as AND and OR were used to combine these search terms and refine the search results. The search strategy was: ("Leprosy" OR "Hansen's disease" OR "*Mycobacterium leprae*") AND ("Leprosy ulcer" OR "Leptrotic ulcer" OR "Leprosy-related ulcer") AND ("Ulcer care" OR "Wound management" OR "Debridement" OR "Topical therapy" OR "Foot care").

### Study Selection Process

Three authors independently screened the titles and abstracts of the identified articles using the

web-based RevMan software (Review Manager, version 5.4). The full-text articles were searched for potentially eligible studies and assessed against the inclusion criteria. Disagreements were resolved by discussion and consensus among three reviewers. A PRISMA flowchart (Fig 1) was used to document the number of studies identified, screened, included and excluded at each stage of the review.

### Risk of Bias Assessment

The risk of bias was assessed on the basis of the study design of the included articles (S1-S2 Tables). For randomized controlled trials (RCTs) and clinical trials, the Cochrane Risk of Bias 2 (RoB 2) tool was used. This tool assesses bias in five key areas: Bias due to the randomization process, bias due to deviation from planned interventions, bias due to missing outcome data, bias in the measurement of the outcome, and bias in the selection of the reported outcome. Each area was assessed and categorized as low risk, some concern, or high risk of bias.

For other study designs, including cohort studies, case-control studies, cross-sectional studies, and descriptive studies, the Newcastle-Ottawa Scale (NOS) was applied as appropriate for each design. The NOS scale assesses the quality of studies based on three main areas: Selection of study groups, comparability of groups, and ascertainment of outcome (for cohort studies) or exposure (for case-control studies).

### Critical Appraisal/ Quality Assessment

In addition, the Joanna Briggs Institute (JBI) guidelines for critical appraisal were used for all study designs, to ensure methodological rigour and maintain the overall quality of the included studies (S3 Table). The JBI tool focuses on key aspects such as the appropriateness of sampling frame, sampling method, adequacy of sample size, clarity in describing study participants and settings, scope of data

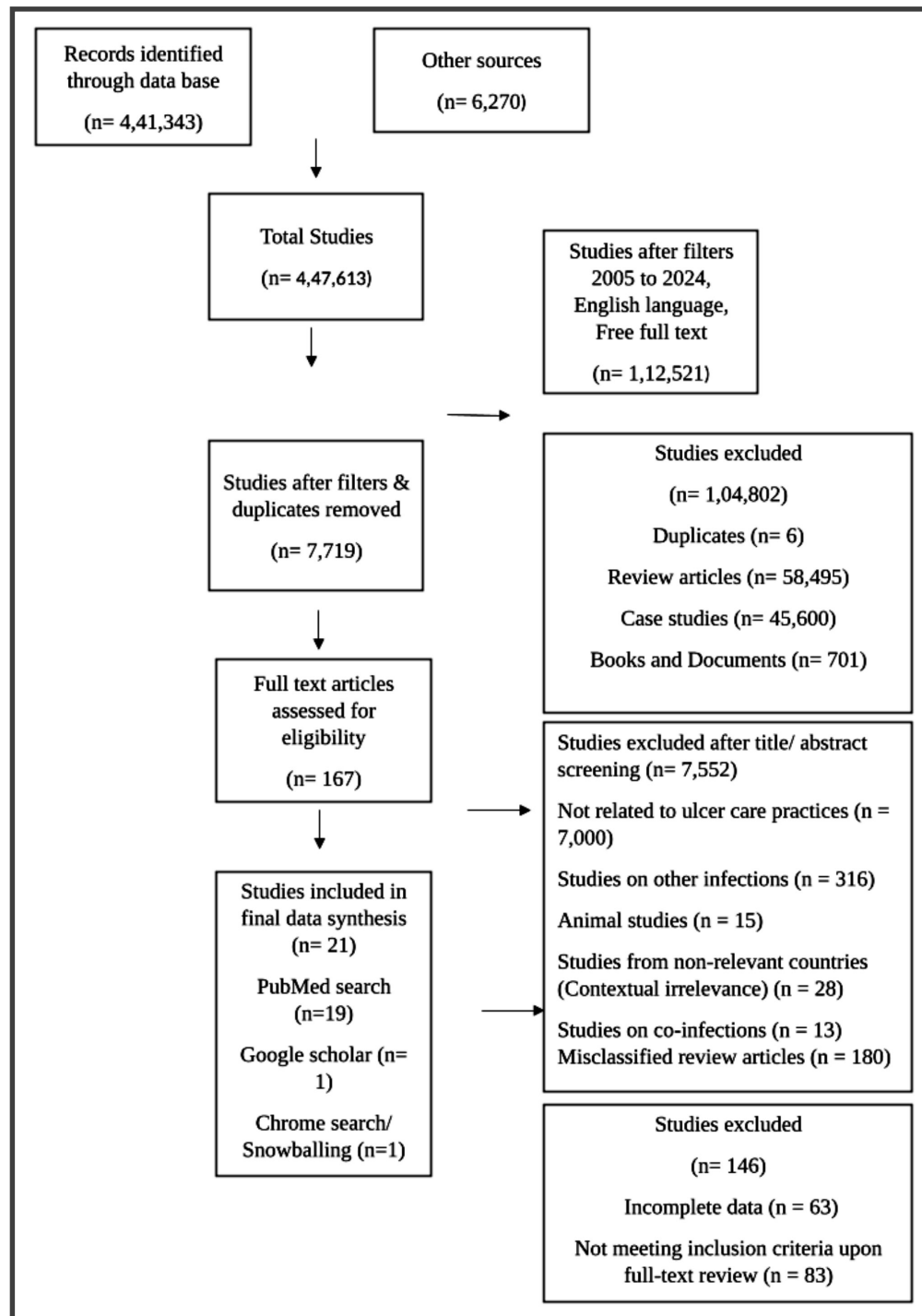


Fig. 1 : PRISMA flowchart of studies selection.

**Supplementary Table 1 (S1) : Risk of bias assessment of the included studies using the revised Cochrane risk-of-bias 2 tool**

| Author, yr             | Bias arising from the randomization process | Bias due to deviations from intended interventions | Bias due to missing outcome data | Bias due to measurement of the outcome | Bias in selection of the reported result | Overall bias  |
|------------------------|---------------------------------------------|----------------------------------------------------|----------------------------------|----------------------------------------|------------------------------------------|---------------|
| Saha et al 2020        | Low                                         | Unclear                                            | Low                              | Low                                    | Unclear                                  | Some concerns |
| Nunes et al 2024       | Unclear                                     | Unclear                                            | Low                              | Low                                    | Unclear                                  | Some concerns |
| Barreto & Salgado 2010 | Low                                         | Low                                                | Low                              | Low                                    | Low                                      | Low           |
| Rosa et al 2024        | Low                                         | Low                                                | Low                              | Low                                    | Low                                      | Low           |
| Alinda et al 2023      | Low                                         | Low                                                | Unclear                          | Low                                    | Low                                      | Some concerns |
| Napit et al 2024       | Low                                         | Low                                                | Low                              | Unclear                                | Low                                      | Some concerns |
| Singh & Pawar 2020     | Unclear                                     | Low                                                | Low                              | Unclear                                | Low                                      | Some concerns |

analysis, validity and reliability of condition measurement, appropriateness of statistical analysis, and management of response rates. This critical appraisal process helped to ensure the methodological quality and consistency of the various included studies. The evaluation was carried out independently by two authors (SN, PKT) and, in case of disagreement, the opinion of a third and fourth author (PKR, AS) was sought in order to reach a consensus.

#### **Statistical Analysis**

Data extraction was performed by creating a structured worksheet containing the following information for each study: Author, year, type of study, study site, type of ulcer, definition of ulcer, sample size, intervention, duration of intervention and outcome. Statistical analysis was performed using R Studio software (version 4.3.2). A forest plot was created for all included studies to estimate pooled prevalence and a random effects model was applied as the  $I^2$

statistic indicated substantial heterogeneity between studies. In addition, separate forest plots were created for RCTs and non-RCTs to present estimates for subgroups. For the forest plot of RCTs, the effect size was calculated using the risk ratio (RR) with the corresponding 95% confidence intervals. A subgroup analysis was performed to compare the pooled prevalence between different ulcer care practices. A funnel plot was created to assess publication bias and the Egger test was performed. Additionally, a Baujat plot was used to identify studies contributing most to heterogeneity. Meta-regression was conducted to explore the relationship between the duration of intervention and the pooled effect size. Furthermore, a sensitivity analysis was performed using the leave-one-out method to assess the robustness of the pooled results.

#### **Results**

##### **Study Selection and Characteristics**

A total of 21 studies published between 2005 and

2024 were included in this systematic review and meta-analysis (Table 1). The studies employed a range of designs, including randomized controlled trials (RCTs,  $n = 7$ ) and non-randomized studies ( $n = 14$ ), such as prospective cohorts, cross-

sectional, descriptive, retrospective reviews, and both blinded and unblinded comparative designs (e.g., observer-blinded, single-blinded, patient-blinded placebo-controlled, open-label, and controlled open studies). Geographically,

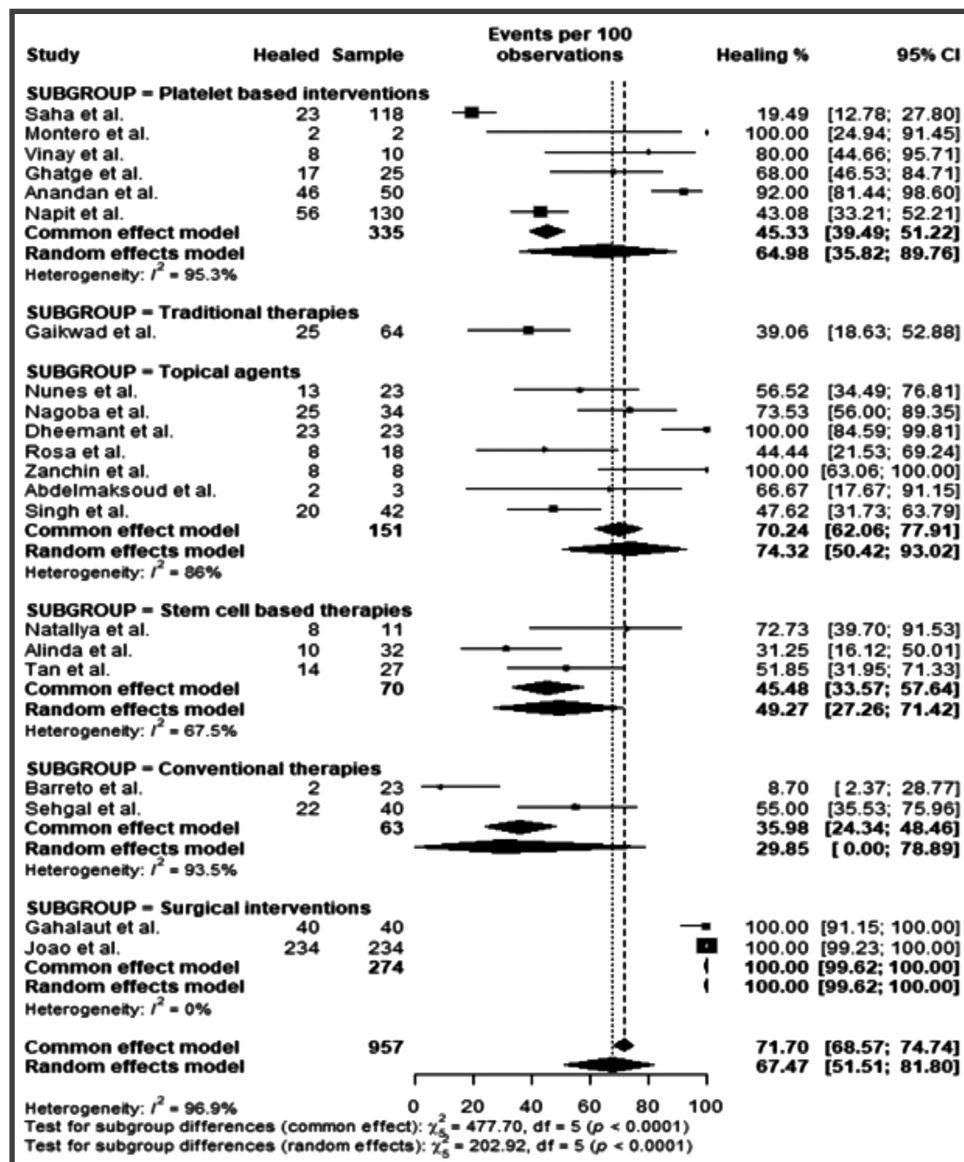


Fig 2 : Forest plot showing Pooled Healing Proportions Across Different Intervention Subgroups

most studies were conducted in India ( $n = 10$ ), followed by Brazil ( $n = 5$ ), Indonesia ( $n = 3$ ), and one study each from Nepal, Egypt, and Spain. Sample sizes varied from 2 to 234 participants, totalling 957 individuals across all studies.

The sample population studied comprised people affected by leprosy with chronic foot ulcers. While the definitions of ulcers varied slightly across studies, most emphasized key characteristics such as chronicity, ulcer

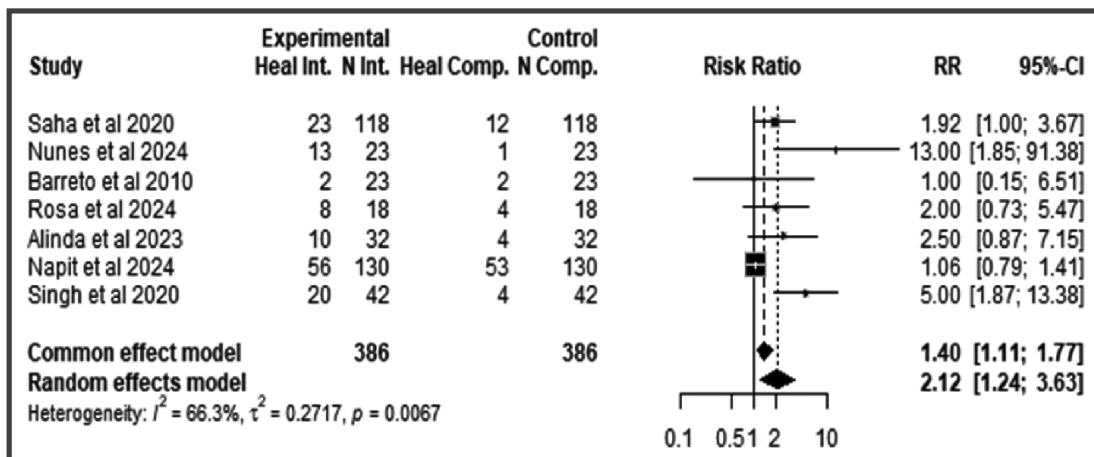


Fig 3 : Forest plot showing Pooled Healing Proportions (Risk Ratios) of RCT studies.

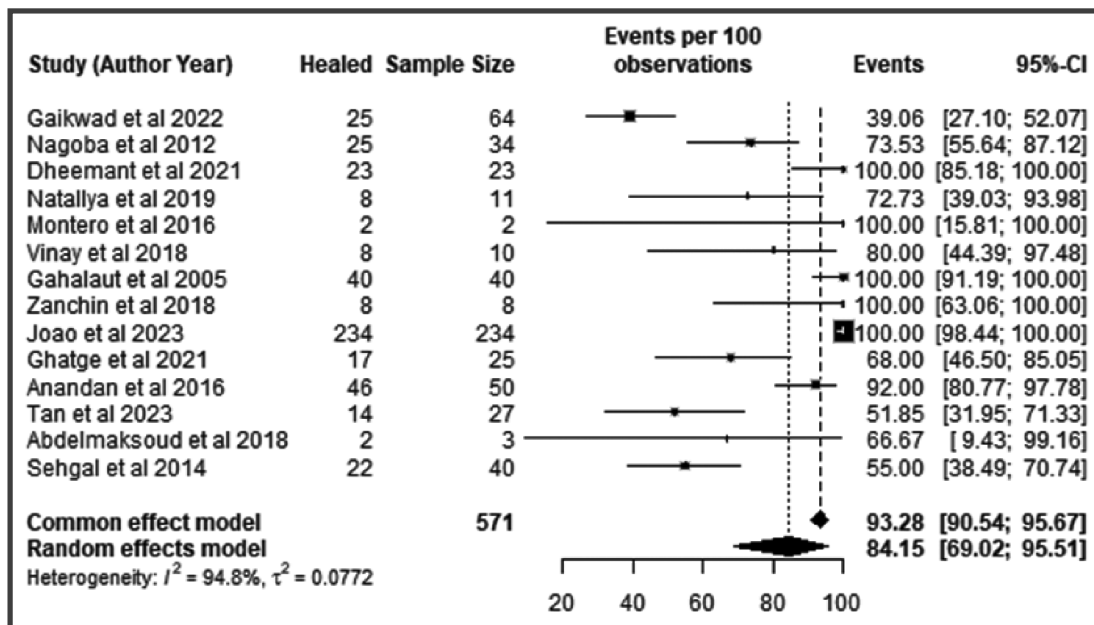


Fig 4 : Forest plot showing Pooled Healing Proportions of Non-RCT studies.

dimensions. The treatment interventions evaluated ranged from conventional treatments (dressings, antibiotics, ointment) and topical agents to innovative strategies such as platelet-based therapies (platelet-rich plasma/fibrin), stem cell-based therapies, autologous skin grafts, surgical procedures, and low-level laser therapy. Intervention durations ranged from 1 to 120 months.

The primary outcome assessed in nearly all studies was ulcer healing, with varied healing rates ranging from 20.37% to as high as 100%. Table 1 provides a comprehensive summary of the key characteristics, methodologies, and outcomes of the studies included in this systematic review.

#### Pooled Healing Proportions and Subgroup Analysis

The overall pooled ulcer healing proportion across all 21 studies was 67.4% (95% CI: 51.5%–81.8%), with significant heterogeneity observed ( $I^2 = 96.9\%$ ) (Fig 2). Subgroup analyses by intervention type revealed varying efficacy, notably, surgical interventions had the highest pooled healing proportion, estimated at 100% (95% CI: 99.6%–100.0%).

#### Meta-Analysis of Randomized Controlled Trials

Fig. 3 shows the forest plot for the meta-analysis of Risk Ratios of RCT studies. Seven RCTs were analysed to estimate pooled risk ratios (RRs). Using a random-effects model, the pooled RR was 2.12 (95% CI: 1.24–3.63), a two times more healing proportion in intervention groups compared to controls. Individual study RRs ranged from 1.00 (95% CI: 0.15–6.51) to 5.00 (95% CI: 1.87–13.38). The common-effect model

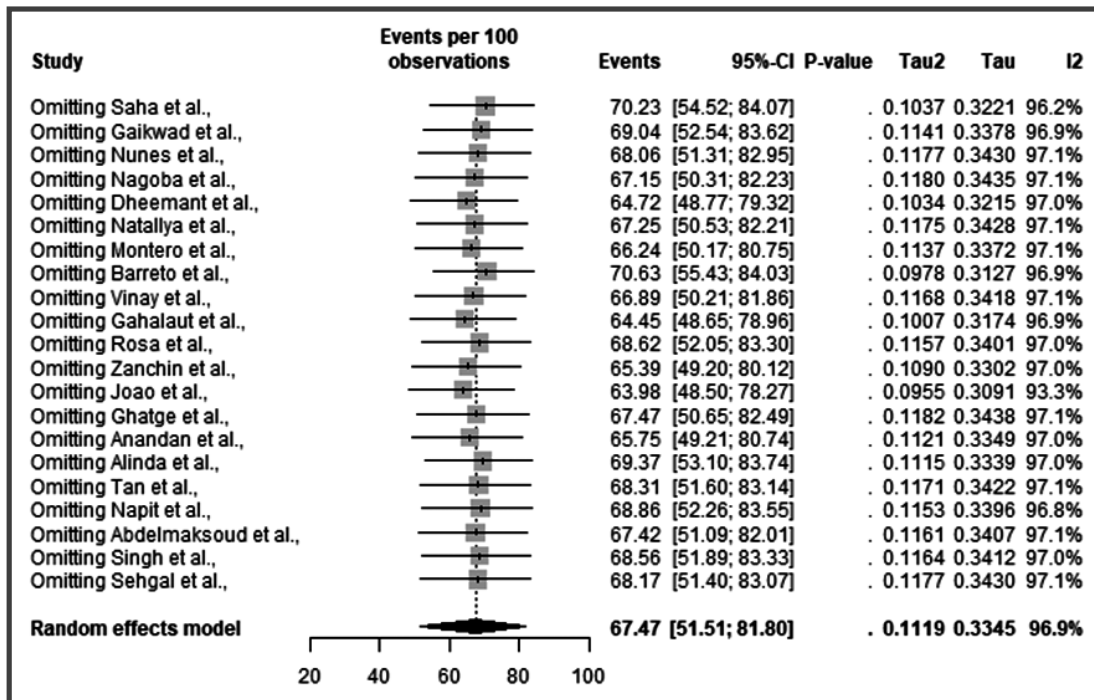


Fig 5 : Sensitivity Analysis (Leave-One-Out) with 95% Confidence Intervals: Assessing the Stability of the Pooled Estimate by Omitting One Study at a Time.

**Supplementary Table 2 (S2): Newcastle-Ottawa Scale (NOS) Assessment for Observational Studies**

| Study (Author, Year)     | Selection<br>(max 4 stars) | Comparability<br>(max 2 stars) | Outcome/<br>Exposure (max<br>3 stars) | Total Stars<br>(Quality) |
|--------------------------|----------------------------|--------------------------------|---------------------------------------|--------------------------|
| Gaikwad & Gaikwad 2022   | ★★                         | ★                              | ★★                                    | ★★★★★<br>(Moderate)      |
| Nagoba et al 2012        | ★★                         | ★                              | ★★                                    | ★★★★★<br>(Moderate)      |
| Natallya et al 2019      | ★★                         | -                              | ★★                                    | ★★★★<br>(Low)            |
| Conde-Montero et al 2016 | ★                          | -                              | ★                                     | ★★ (Low)                 |
| Keshavamurthy et al 2018 | ★★★                        | -                              | ★★★                                   | ★★★★★★<br>(Moderate)     |
| Gahalaut et al 2005      | ★★★                        | -                              | ★★★                                   | ★★★★★★<br>(Moderate)     |
| Zanchin et al 2018       | ★★★                        | -                              | ★                                     | ★★★★<br>(Low)            |
| Joao et al 2023          | ★★★                        | -                              | ★★★                                   | ★★★★★★<br>(Moderate)     |
| Ghatge et al 2021        | ★★★                        | -                              | ★★★                                   | ★★★★★★<br>(Moderate)     |
| Anandan et al 2016       | ★★★                        | -                              | ★★★                                   | ★★★★★★<br>(Moderate)     |
| Tan et al 2023           | ★★★                        | ★                              | ★★                                    | ★★★★★★<br>(Moderate)     |

yielded a slightly lower pooled RR of 1.40 (95% CI: 1.11–1.77). Moderate heterogeneity was noted ( $I^2 = 66.3\%$ ,  $p = 0.0067$ ).

#### **Meta-Analysis of Non-Randomized Studies**

The 14 non-RCTs demonstrated a pooled healing proportion of 84.1% (95% CI: 69.0%–95.5%) using the random-effects model (Fig. 4). Considerable heterogeneity was observed ( $I^2 = 94.8\%$ ). Healing rates ranged widely, from 39.1% (95% CI: 27.1%–52.0%) to 100% in five studies with CIs ranging from 15.8% to 100%.

#### **Sensitivity and Bias Analysis**

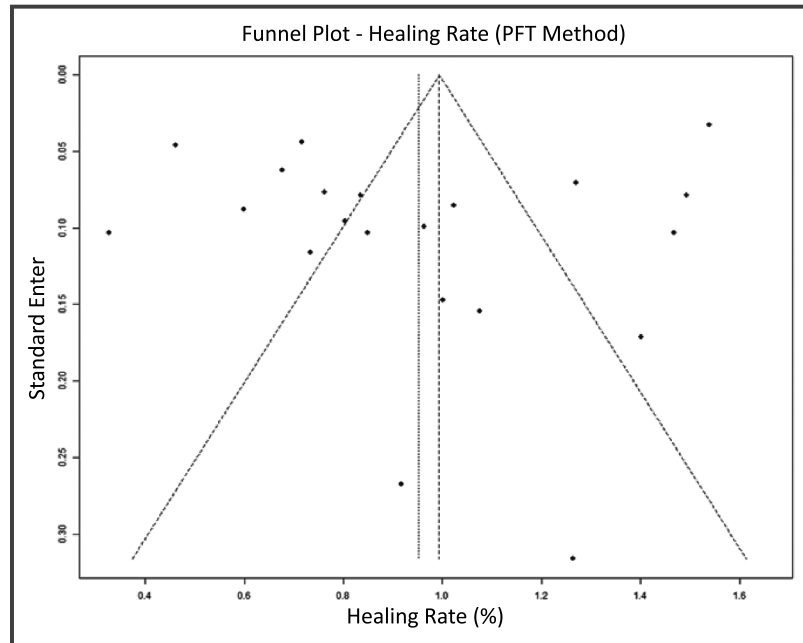
Sensitivity analysis demonstrated that the overall

pooled healing proportion remained stable (67.5%; 95% CI: 51.5%–81.8%) upon sequential exclusion of individual studies, indicating that no single study disproportionately influenced the meta-analytic estimate (Fig. 5).

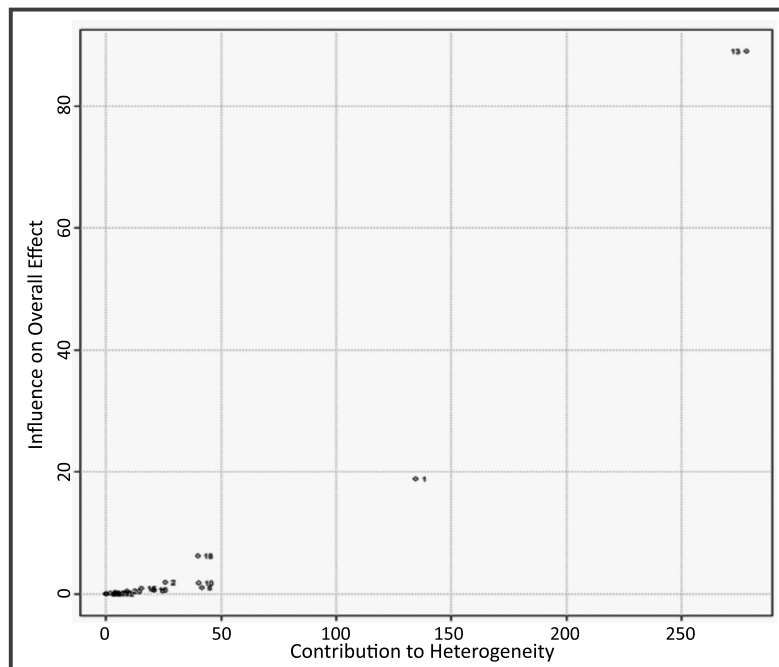
Assessment of publication bias revealed mild asymmetry in the funnel plot (Fig. 6). However, Egger's regression test did not indicate statistically significant small-study effects ( $t = -0.77$ ,  $p = 0.45$ ). The estimated bias coefficient was  $-2.05$  (SE = 2.66), suggesting minimal risk of publication bias. Baujat plot analysis identified three studies - João et al (2023), Saha et al (2020), and Napit et al

Supplementary Table 3 (S3) : JBI Quality scores of selected studies 1-Yes, 0-No, U-uncertain

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**Fig 6 : Funnel plot to analyse Publication bias.**



**Fig. 7 : Baujat plot illustrating the contribution of individual studies to heterogeneity. The numbers correspond to the study serial numbers listed in Table 1.**

Table 1 : Study Characteristics.

| Author            | Year | Type of Study                               | Study Site | Type of Ulcer     | Definition of ulcer                                                                                                                                                                                                   | Sample Size                                                          | Intervention                                                                                    | Duration of intervention | Outcome                                                                                    |
|-------------------|------|---------------------------------------------|------------|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|--------------------------|--------------------------------------------------------------------------------------------|
| Saha et al        | 2020 | Observer-blind, randomized controlled study | India      | Trophic Ulcer     | Clinically diagnosed trophic ulcers due to leprosy located on the plantar, medial, or lateral aspects of the foot (including all toe surfaces) with a wound area of less than 10 cm <sup>2</sup> .                    | 118<br>Allocation ratio: 1:1                                         | Group A: Platelet-rich plasma (PRP) and Total Contact cast<br>Group B: Total Contact Cast alone | 20 months                | Group A: Healing of Ulcer 39.29%<br>Group B: Healing of Ulcer 21.15%                       |
| Gaikwad & Gaikwad | 2022 | Non-randomized comparative clinical trial   | India      | Trophic Ulcer     | An ulcer that has persisted for one year or more and is not deep enough to affect the bones.                                                                                                                          | 64<br>Allocation ratio: 1:1                                          | Ayurveda and Antibiotics, Anti-inflammatory drugs,                                              | 4 months                 | Study group: Healing of Ulcer 76.84%<br>Control group: Healing of Ulcer 43.24%             |
| Nunes et al       | 2024 | Randomised Controlled Trail                 | Brazil     | Plantar Ulcer     | A plantar ulcer in individuals with a previous diagnosis of leprosy, with an ulcer size smaller than 24 cm <sup>2</sup> .                                                                                             | 23<br>Allocation ratio: 15 (Bio MemCp LP) and 8 (Standard treatment) | BioMem CpLP, hydrocolloid (Curatec) and silver sulfadiazine, hydrocolloid wound dressings       | 56 days                  | Healing of Ulcer BioMem CpLP: 88%<br>Hydrocolloid (Curatec): 6%<br>Silver Sulfadiazine: 6% |
| Nagoba et al      | 2012 | Prospective study                           | India      | Lepromatous Ulcer | A chronic ulcer ranging from 2–8 cm in diameter and 0.5–1 cm in depth, persisting for a prolonged period (1 month to 2 years) and not responding to conventional therapy, including antibiotics and local wound care. | 34                                                                   | Citric acid Ointment                                                                            | 84 months                | Healing of Ulcer 73.52%                                                                    |

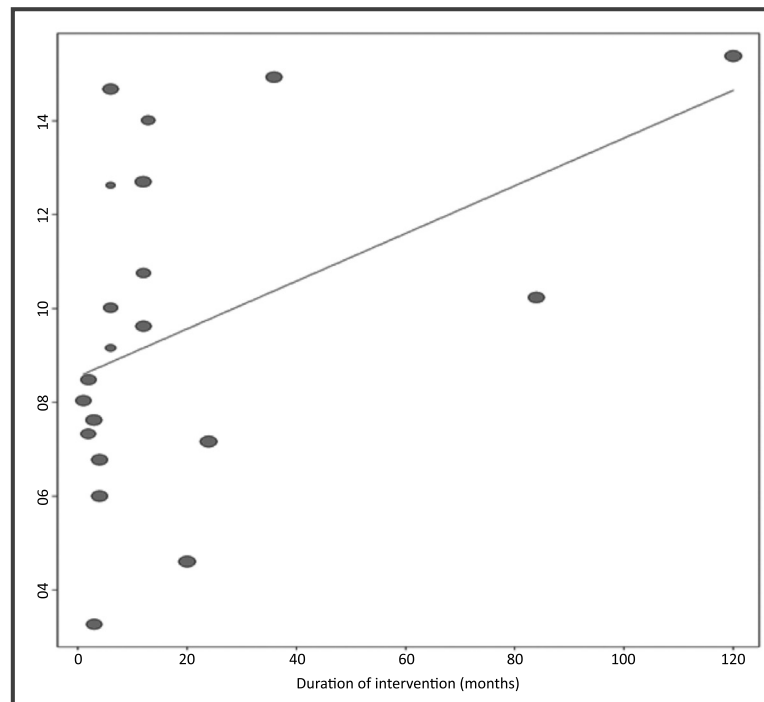
|                     |      |                           |           |                                   |                                                                                                                                                                                                                                                                                                                  |    |                                                                          |          |                                                                                                                      |
|---------------------|------|---------------------------|-----------|-----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|--------------------------------------------------------------------------|----------|----------------------------------------------------------------------------------------------------------------------|
| Dheemant et al      | 2021 | Cross sectional study     | India     | Chronic Non-healing Trophic Ulcer | A non-healing trophic ulcer secondary to Hansen's disease in individuals who have completed treatment, with a duration of more than six weeks and a size not exceeding 5 cm x 5 cm.                                                                                                                              | 23 | Autologous smashed follicular dermal graft and Epidermal cell suspension | 6 months | Healing of Ulcer 100%                                                                                                |
| Natallya et al      | 2019 | Descriptive study         | Indonesia | Plantar Ulcer                     | A chronic plantar ulcer resulting from leprosy for at least six weeks, with a maximum size of 9 cm <sup>2</sup> and a depth of no more than 0.5 cm. The ulcer lacks complications, showing no surrounding erythema, swelling, acute pain, warmth upon palpation, wound sinuses, or exposure of tendons or bones. | 11 | hAMSC secretome gel                                                      | 6 months | Healing of Ulcer 72.7%                                                                                               |
| Conde-Montero et al | 2016 | Prospective study         | Spain     | Plantar Ulcer                     | -                                                                                                                                                                                                                                                                                                                | 2  | Platelet-rich plasma (PRP)                                               | 6 months | Healing of Ulcer 100%                                                                                                |
| Barreto & Salgado   | 2010 | Randomised Clinical Trail | Brazil    | Neuropathic Ulcer                 | A neuropathic ulcer in individuals who have attended at least three weekly appointments at the dressing service of UREMIC and have completed specific multidrug therapy for <i>Mycobacterium leprae</i> .                                                                                                        | 23 | Allocation ratio: Laser therapy= 12 and Dressings =11                    | 3 months | Ulcer area: 3.8(5.7).<br>Ulcer depth: 4.1(3.9).<br>PUSH score: 7.9(5.3).<br>Healing of ulcer (Laser therapy): 20.37% |

|                            |      |                                         |        |                        |                                                                                                                                                                                                                                           |                                |                                                                                                                                    |           |                                                                                                              |
|----------------------------|------|-----------------------------------------|--------|------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|------------------------------------------------------------------------------------------------------------------------------------|-----------|--------------------------------------------------------------------------------------------------------------|
|                            |      |                                         |        |                        |                                                                                                                                                                                                                                           |                                | Ulcer area:<br>4.4(8.5).<br>Ulcer depth:<br>5.4(5.7).<br>PUSH score:<br>8.4(5.3)<br>Healing<br>of ulcer<br>(Dressings):<br>14.89%. |           |                                                                                                              |
| Keshava-<br>murty<br>et al | 2018 | Retro-<br>spective<br>Review            | India  | Trophic<br>Ulcer       | A non-healing trophic ulcer<br>in leprosy patients, defined<br>as the failure to show signs<br>of healing after 12 weeks of<br>treatment with complete<br>rest and sterile dressings.                                                     | 10                             | Platelet Rich<br>Fibrin (PRF)<br>dressings<br>and use of<br>microcellular<br>rubber<br>footwear                                    | 12 months | Healing of<br>Ulcer 80%                                                                                      |
| Gahalaut<br>et al          | 2005 | Prospective<br>study                    | India  | Plantar<br>Ulcer       | Plantar ulcers in leprosy<br>patients who had a<br>bacterial index $\leq 1$ , were<br>not in reaction, and had<br>either been released from<br>treatment or had completed<br>at least six months of<br>multidrug anti-leprosy<br>therapy. | 40                             | Local<br>superficial<br>flaps<br>(advance-<br>ment,<br>rotation,<br>trans-<br>position and<br>first toe web<br>flap)               | 36 months | Healing of<br>Ulcer 100%                                                                                     |
| Rosa et al                 | 2024 | Blinded<br>Randomised<br>Clinical Trail | Brazil | Lower<br>Limb<br>Ulcer | Skin wounds in the lower<br>limbs as sequelae of treated<br>and cured leprosy, with an<br>area between 3 and 75 cm <sup>2</sup> .                                                                                                         | 18<br>Allocation<br>Ratio: 1:1 | Humanitas<br>propolis<br>ointment<br>(ongoing),<br>Lanolin and<br>Vaseline                                                         | 2 months  | Healing<br>of Ulcer<br>(Humanitas<br>propolis<br>ointment)<br>84.33%,<br>(Lanolin and<br>Vaseline)<br>39.73% |

|               |      |                                                        |        |               |                                                                                                                                                                                                                                                                                                                            |     |                                                                                                               |            |                       |
|---------------|------|--------------------------------------------------------|--------|---------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|---------------------------------------------------------------------------------------------------------------|------------|-----------------------|
| Zanchin et al | 2018 | Open, Uncontrolled study                               | Brazil | Trophic Ulcer | National Pressure Ulcer Advisory Panel (NPUAP) Grade 1 (intact skin with non-blanching erythema): 3 ulcers (23%), Grade 2 (partial-thickness loss of skin with exposure of the dermis): 5 ulcers (38.5%), Grade 3 (full-thickness loss of skin) and IV (full-thickness loss of skin and loss of tissue): 5 ulcers (38.5%). | 8   | Poly-hexanide 0.2%                                                                                            | 13 months  | Healing of Ulcer 100% |
| Joao et al    | 2023 | Descriptive and Analytical retrospective study         | Brazil | Plantar Ulcer | Leprosy-associated chronic plantar ulcers not responsive to conventional dressings, with the presence of bony prominences in the lesion bed.                                                                                                                                                                               | 234 | Corrective resection of bone prominences and the primary closure of the lesion with Bipe diculated local flap | 120 months | Healing of Ulcer 100% |
| Ghatge et al  | 2021 | Non-Randomized and Non controlled Interventional study | India  | Trophic Ulcer | A Wagner's Grade 2 trophic ulcer secondary to leprosy, characterized by a deep ulcer extending to the ligament, tendon, joint capsule, or deep fascia but without abscess or osteomyelitis.                                                                                                                                | 25  | Platelet Rich Fibrin (PRF)                                                                                    | 12 months  | Healing of Ulcer 68%  |
| Anandan et al | 2016 | Prospective interventional study                       | India  | Trophic Ulcer | A Wagner's Grade 2 ulcer, characterized by a deep ulcer extending to                                                                                                                                                                                                                                                       | 50  | Platelet Rich Plasma (PRP)                                                                                    | 12 months  | Healing of Ulcer 92%  |

|                                                                                                                                                                                                          |      |                                                     |           |                    |                                                                                                                                                                           |     |                       |                                                                                                |                 |                                                      |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|-----------------------------------------------------|-----------|--------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|-----------------------|------------------------------------------------------------------------------------------------|-----------------|------------------------------------------------------|
| ligaments, tendons, joint capsule, or deep fascia but without abscess or osteomyelitis. The ulcer size is greater than 1 cm × 1 cm and less than 6 cm × 6 cm, with negative pus culture and sensitivity. |      |                                                     |           |                    |                                                                                                                                                                           |     |                       |                                                                                                |                 |                                                      |
| Alinda et al                                                                                                                                                                                             | 2023 | Single-blinded randomised controlled clinical trial | Indonesia | Plantar Ulcer      | A chronic plantar ulcer in leprosy patients, persisting for more than six weeks, with an ulcer depth of less than 0.5 cm and a maximum injury area of 9 cm <sup>2</sup> . | 32  | Allocation ratio: 1:1 | Topical adipose mesenchymal stem cell-conditioned medium and framycetin gauze                  | 4 months        | Healing of Ulcer ADMSC-CM: 62.5% FGD: 25%            |
| Tan et al                                                                                                                                                                                                | 2023 | Non-randomized controlled and open trial            | Indonesia | Trophic Ulcer      | A chronic ulcer of degrees 2 and 3, not recovering with routine therapy for at least one month. There were no minimum wound area criteria for participation in the study. | 27  |                       | Topical administration of secretome of human umbilical cord mesenchymal stem cells (SM-hUCMSC) | 1 month 2 weeks | Healing of Ulcer 52.31%                              |
| Napit et al                                                                                                                                                                                              | 2024 | Randomised in a single-blinded, controlled trial    | Nepal     | Chronic Foot Ulcer | A foot ulcer of at least six weeks duration, not infected (no pathogenic organism growth in ulcer swab culture), and with an area between 2 to 20 cm <sup>2</sup> .       | 130 | Allocation ratio: 1:1 | Leukocyte and Platelet-Rich Fibrin (L-PRF) and Normal Saline dressing                          | 24 months       | Healing of ulcer L-PRF: 86.2% Saline dressing: 81.5% |

|                         |      |                                                                                             |       |                  |                                                                                       |                                                                    |          |                                                                                  |
|-------------------------|------|---------------------------------------------------------------------------------------------|-------|------------------|---------------------------------------------------------------------------------------|--------------------------------------------------------------------|----------|----------------------------------------------------------------------------------|
| Abdelma-<br>ksoud et al | 2018 | Cross<br>sectional<br>study                                                                 | Egypt | Plantar<br>Ulcer | 3                                                                                     | 1% topical<br>propranolol<br>in liposomal<br>gel                   | 6 months | Healing of<br>Ulcer 66.6%                                                        |
| Singh &<br>Pawar        | 2020 | Randomized<br>patient-<br>blinded<br>placebo-<br>controlled<br>inter-<br>ventional<br>study | India | Trophic<br>Ulcer | 42<br>Allocation<br>ratio:<br>Topical<br>Insulin =<br>23; Saline<br>dressings<br>= 19 | Topical<br>Insulin<br>and Saline<br>dressings                      | 3 months | Healing of<br>Ulcer<br>Topical<br>Insulin: 87%<br>Saline<br>dressings:<br>21.05% |
| Sehgal<br>et al         | 2014 | Cross<br>sectional<br>study                                                                 | India | Trophic<br>Ulcer | 40                                                                                    | Phenytoin<br>sodium fine<br>powder zinc<br>oxide paste<br>dressing | 1 month  | Healing of<br>Ulcer 55%                                                          |



**Fig 8 : Meta Regression plot.**

(2024) as major contributors to between-study heterogeneity and influence on the overall effect size (Fig. 7). While these studies exhibited distinct methodological and population characteristics, their inclusion did not significantly alter the robustness of the meta-analytic findings.

#### **Meta-Regression**

Fig. 8 shows the Meta Regression plot between the duration of intervention (months) and the effect size (healing rate). A positive slope indicated that longer duration interventions were generally associated with better outcomes. However, the majority of studies had intervention durations of less than 20 months, with a few long-term studies (60–120 months) influencing the trend. Considerable variation remained among short-duration interventions, suggesting that treatment duration alone does not fully account for healing outcomes.

#### **Discussion**

Despite achieving elimination as a public health problem, leprosy continues to pose clinical and social challenges in India, contributing to nearly 60% of the global leprosy burden. Of the 9,124 newly detected global cases presenting with WHO grade 2 disability, 21% (1,888) were reported from India, indicating a substantial burden of disability at the time of diagnosis (WHO 2025). The risk of disability persists even after successful completion of MDT, with studies reporting a 1.28-fold increase in disability risk up to a decade post-MDT (Pilaka et al 2024). Chronic plantar ulcers are most common grade-2 disabilities in leprosy. These ulcers are often recurrent, prone to secondary infections, and severely diminish the quality of life of the affected persons (Nunes et al 2024). Despite their burden, there is a paucity of programmatic data on the prevalence, clinical

management, and outcomes of plantar ulcers in routine care. This systematic review and meta-analysis aimed to synthesize existing evidence on current ulcer care practices among people affected by leprosy, to inform clinical guidelines and policy strategies for disability prevention.

Leprosy-related neuropathy results in progressive deterioration and fragmentation of foot bones, resulting in the development of plantar bony prominences that play a central role in the onset and persistence of ulcers (Price 1964, Srinivasan & Mukherjee 1964, Hidalgo & Shaw 1986). Repetitive pressure and shear forces on insensitive feet promote tissue breakdown and delayed healing. This pathophysiological process underscores the critical importance of rest and mechanical off-loading, though not absolutely practical, still remain the cornerstone of ulcer management.

Among the various treatment interventions reported for foot ulcers, surgical interventions demonstrated the highest pooled healing proportions. This finding is consistent with existing literature highlighting the effectiveness of surgical methods in correcting anatomical deformities underlying chronic ulceration. Surgical procedures included skin grafting, and various local or regional flap reconstruction techniques (Lamberty & Healy 1994). However, despite better healing outcomes, recurrence remains a significant challenge, with earlier studies reporting recurrence rates ranging from 18.3% to 90% (Gahalaut et al 2005, Yan et al 2003, Batista et al 2019) often attributable to unresolved mechanical stress and persistent bony prominences. Importantly, surgery is not a universal solution for all leprosy-related ulcers. In routine clinical practice, surgical management is reserved for specific indications, including the presence of necrotic tissue, sequestra, osteomyelitis, septic arthritis or tenosynovitis,

excessive fibrous tissue, large ulcers, or ulcers located over bony prominences that require flap coverage to reduce recurrence risk (Virmond et al 2017). Even in such cases, surgical success is critically dependent on sustained post-operative rest, effective off-loading, and long-term self-care. Notably, although some studies included in this review reported data on ulcer recurrence, overall reporting was limited, restricting comprehensive assessment of long-term surgical effectiveness.

Innovative therapies, including platelet-rich plasma, stem cell-based therapies, and low-level laser therapy, demonstrated encouraging healing outcomes in the studies included. However, heterogeneity in intervention protocols, small sample sizes, and the absence of robust comparative studies limit firm conclusions regarding their effectiveness. These advanced therapies including surgical interventions should therefore be regarded as adjuncts to foundational ulcer care rather than standalone solutions. Without consistent and effective off-loading and mechanical rest, the benefit of adjunctive therapies over standard wound care measures is likely to be limited (Virmond et al 2017).

The meta-analysis of randomized controlled trials demonstrated that participants receiving structured interventions were more than twice as likely to achieve ulcer healing compared with controls, underscoring the importance of protocol-driven care. Moderate heterogeneity was observed across trials due to sample size, ulcer severity, and study quality. In contrast, non-randomized studies reported higher pooled healing proportions (84.1%) but with substantial heterogeneity ( $I^2 = 94.8\%$ ), likely reflecting methodological limitations, selection bias, and variability in patient populations. While these studies provide valuable insights, their findings should be interpreted cautiously.

Meta-regression analysis demonstrated a modest

positive association between intervention duration and ulcer healing rates, suggesting that prolonged-duration interventions may be beneficial in certain contexts. However, high healing rates reported in some short-duration interventions, particularly surgical studies, indicate that duration alone does not determine outcomes. Ulcer characteristics, patient adherence, off-loading practices, and the quality of post-intervention care are key factors, reinforcing the multifactorial nature of ulcer healing in leprosy and the need for individualized management strategies.

Overall, the findings of this review emphasise the clinical relevance of both conventional wound care practices and advanced therapeutic approaches in the management of chronic leprosy-related plantar ulcers. Interventions such as platelet-rich plasma, stem cell-based therapies, and low-level laser therapy, although evaluated in relatively few studies, showed promising results and warrant further investigation through well-designed clinical trials. While surgical interventions demonstrated the highest healing proportions among evaluated modalities, their role is best understood within a comprehensive management framework that prioritizes rest and off-loading as primary measures.

From a programmatic perspective, these findings support the availability of surgical services as part of comprehensive ulcer care for selected chronic, non-healing ulcers that do not respond to conservative, off-loading-based management. Expanding access to appropriate off-loading devices, rehabilitation services, and referral-level surgical care particularly in resource-limited and endemic settings may contribute to reducing disability and improving quality of life. A multidisciplinary approach that integrates early detection, patient education, wound care, strict off-loading, and surgical intervention when

indicated is essential for optimizing outcomes. The predominant studies from India and Brazil further highlight the need for high-quality studies from other endemic regions to enhance the generalizability of findings.

The findings align with existing WHO recommendations, which emphasize early detection, MDT, protective footwear, and self-care education as central components of disability prevention. While MDT effectively controls infection, it does not reverse established neuropathy or address chronic ulcers. This review suggests that strengthening ulcer care frameworks grounded on rest and mechanical off-loading and supplemented by selected evidence-based non-surgical interventions may improve healing outcomes. It will be even more effective to enable and enhance the access to surgical facilities, wherever it is possible. Such an approach supports strengthening of ulcer management within national leprosy programmes while maintaining prevention-focused strategies as the foundation of disability care.

#### **Strengths and Limitations:**

This review has several strengths, including the inclusion of a broad range of study designs, comprehensive subgroup and sensitivity analyses, and methodological rigor in addressing heterogeneity and publication bias. However, several limitations should be acknowledged. The variability in ulcer definitions, sample sizes, and follow-up periods poses challenges for comparability. Also, studies with small sample sizes and heterogeneous intervention protocols limit the precision of pooled estimates. The inclusion of non-randomized studies, while expanding the evidence base, also introduces potential biases that may affect the internal validity of the results. Protective footwear and Plaster of Paris (POP) casts were not analysed as stand-alone interventions, as they constitute

integral components of rest and mechanical off-loading rather than independent therapeutic modalities for chronic ulcers.

### Conclusion

This review supports the effectiveness of various interventions in promoting healing of chronic plantar ulcers in individuals affected by leprosy, with the highest efficacy noted in surgical approaches followed by traditional offloading techniques. The evidence underscores the importance of tailored, long-term strategies and highlights the clinical relevance of both conventional wound care and emerging advanced therapies. Interventions such as platelet-rich plasma, stem cell-based therapies, and low-level laser therapy, though evaluated in fewer studies, show promising potential as adjuncts to standard care. Further high-quality, multicentric trials are needed to optimize treatment protocols for probable integration into existing health systems and to support global efforts to reduce leprosy-related disability.

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