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Review Article

Efficacy and Safety of Mesenchymal Stem Cell Therapy in Chronic Limb-Threatening Ischemia: A Meta-analysis of Randomized Controlled Trials

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Abstract

Chronic Limb-Threatening Ischemia (CLTI) represents the terminal stage of peripheral artery disease, carrying substantial morbidity and mortality. Despite various therapeutic strategies, clinical outcomes remain unsatisfactory, highlighting the urgent need for novel treatments. While Mesenchymal Stem Cells (MSCs) show promise at the cellular level, human studies are limited, preventing generalizable conclusions at this time. This study aimed to systematically assess the efficacy and safety of MSCs implantation in CLTI. PRISMA 2020-guided meta-analysis of intervention. Various databases were searched using keywords based of the PICOS framework. The PICOS framework guided our approach: Patients (CLTI), Intervention (MSCs), Comparison (Placebo OR Control), Outcome (Amputation, Ulcer Healing Rate, Rest Pain Change, Ankle-Brachial Index, Adverse Effect), and Study (Randomized Controlled Trial [RCT]). Statistical analysis was performed using Review Manager (RevMan 5.4.1) and RStudio (R.4.4.3). An Independent Risk-of-Bias 2 (RoB2) risk of bias assessment was performed. Seven RCTs were included with a total of 270 patients. Meta-analysis showed that MSCs were more effective than the control group on suppressing the amputation rate (Odds Ratio [OR] = 0.40, 95% Confidence Interval [CI] = 0.17–0.95, p = 0.04). Ulcer healing rate was significantly higher in the MSCs therapy group compared to the control group (OR = 9.79, 95% CI = 2.59–36.98, p = 0.0008). Moreover, MSCs therapy markedly improved clinical outcomes, including rest pain score (Mean Difference [MD] = –1.88, 95% CI = –2.93 to –0.84, p = 0.0004) and ankle-brachial index (MD = 0.16, 95% CI = 0.09–0.22, p < 0.00001). Interestingly, MSCs therapy showed an excellent safety profile, with negligible gastrointestinal-hepatobiliary events and only 4% mild infections or musculoskeletal effects. This review shows that MSCs therapy offers a transformative approach for CLTI, significantly improving limb outcomes and perfusion while maintaining an excellent safety profile.

Keywords: Chronic Limb-Threatening Ischemia, Efficacy, Mesenchymal Stem Cell, Meta-Analysis, Safety.

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Introduction

The global rate of non-traumatic amputations is rising, mainly due to increasing cases of Peripheral Artery Disease (PAD), especially Chronic Limb-Threatening Ischemia (CLTI).[1] These conditions limit blood flow to the lower limbs and can lead to CLTI, which causes ongoing pain, non-healing wounds, or gangrene.[2] CLTI, also referred to as Critical Limb Ischemia (CLI), is the severe subset and end stage of PAD and is defined by severe pain at rest (lasting > 2 weeks), and/or non-healing ischemic skin lesions, and/or gangrene of the extremity due to inadequate blood supply.[3] Importantly, PAD affects about 200 million people worldwide. Notably, CLTI is the most severe form of PAD and develops in roughly 11% of PAD patients. Reflecting the growing burden of vascular disease, the prevalence of CLTI has shown an increasing trend, from 0.23% in 2014 to 0.32% in 2018.[4] In Indonesia, PAD, including CLTI, affects 5–8% of adults, and prevalence is increasing due to risk factors like diabetes, hypertension, and chronic kidney disease.[5] Globally, mortality from CLTI has steadily increased over the past decade. The five-year mortality rate has risen from approximately 35% in 2010 to around 50–60% in 2023.[6] Given this alarming trend, CLTI is now recognized as a critical vascular emergency requiring prompt, multidisciplinary intervention.

Current treatments for CLTI, such as wound care, Endovascular Revascularization (EVR), and bypass surgery, each have notable limitations. Conservative wound care only provides symptom relief without restoring proper blood flow, leaving patients at risk of infection, poor healing, and amputation.[7] EVR, while minimally invasive, often faces restenosis, recoil, and dissection, which limit long-term outcomes. Aihara et al. reported vessel patency rates declining to 67.8% at one year and 45.2% at five years, highlighting its limited durability.[8-9] EVR also struggles in severe occlusions where lesion crossing is difficult. Bypass surgery offers better long-term patency but carries greater risks of wound complications and mortality, especially in patients with multiple comorbidities, making it a challenging option for many CLTI cases.[10] Based on the currently available treatment, it only addresses tissue-level injury; however, according to pathophysiology, CLTI also progresses at the cellular level. Therefore, a precision and regenerative approach to reduce the morbidity was required.

Research on Mesenchymal Stem Cells (MSCs) has been ongoing for several decades, and the growing scientific interest in MSCs offers significant therapeutic potential for a wide range of diseases. MSCs possess unique biological properties, primarily mediated by the release of paracrine modulators, including cytokines, that regulate tissue regeneration in various pathological conditions.[11] Previous studies have shown promising improvements in MSCs-based therapies, which are generally considered safe and do not induce significant short-term adverse effects.[11] However, most clinical studies on the application of MSCs are still in the early stages, with relatively small sample sizes and heterogeneous study designs. This variability poses challenges in comparing results across studies and in assessing the overall efficacy of MSCs-based therapies.[12] Thus, the aim of this meta-analysis was to critically assess and synthesize evidence from randomized controlled trials on the efficacy, safety, and clinical applicability of mesenchymal stem cell-based therapies for treating patients with chronic limb-threatening ischemia.

Methods

Registration

This study was constructed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Guideline and registered with PROSPERO under the number [CRD420251184085].

Eligibility Criteria

The eligibility criteria were based on the PICOS framework and additional inclusion and exclusion criteria. Inclusion criteria were as follows PICOS: 1. Population (adult participants diagnosed with the relevant clinical condition), 2. Intervention (MSCs), 3. Comparator (placebo or standard of care) 4. Outcomes (at least amputation rate outcome and other predefined efficacy or safety endpoint) 5. Study design (Randomized Controlled Trial [RCT]) 5. Availability of sufficient quantitative data to calculate effect sizes (e.g., odds ratio, risk ratio, mean difference). Exclusion criteria included non-English studies, studies with inadequate, non-extractable, or insufficient quantitative data, and duplicate analyses of previously included data.

Screening

A comprehensive literature search was performed in PubMed, ScienceDirect, and Epistemonikos databases from inception (July 1, 2004) to October

1, 2025. The search combined MeSH terms and free-text keywords related to the population, intervention, and outcomes (("mesenchymal stem cell" OR "MSCs") AND ("critical limb ischemia" OR "chronic limb threatening ischemia" OR "CLI" OR "CLTI")). All retrieved records were imported into reference management software to remove duplicates. The remaining studies were screened in two stages: 1. Title and abstract screening, and 2. Full-text eligibility assessment. Each stage was independently conducted by eight reviewers. Any disagreements were resolved through discussion and deliberation among all authors to determine the feasibility of inclusion.

Data Extraction

Data extraction was performed independently by eight investigators (NA, AMS, MCAA, DWBA, LAS, HFU, MCA, KSL) using a standardized form. The following information was recorded from each included study: (1) Author and year of publication, (2) Study design and country, (3) Sample size and baseline characteristics, (4) Details of the intervention and control, (5) Follow-up duration, and (6) Reported outcomes and numerical data (mean ± SD, event counts, or effect estimates). Any disagreements were resolved through discussion under the guidance and consultation of the senior author (ADSN, YHH, ASM). When necessary, corresponding authors were contacted for missing or unclear data.

Data Synthesis/Analysis

Quantitative synthesis was conducted using a random-effects model to account for inter-study variability. For dichotomous outcomes, the Odds Ratio (OR) with 95% Confidence Intervals (CIs) was calculated. For continuous outcomes, Mean Differences (MDs) were used as appropriate. Heterogeneity among studies was evaluated using the I^2 statistic. Proportional meta-analysis performed with REM to estimate proportional results of adverse effects reported in studies with 95%CI. Heterogeneity was considered substantial if I^2 exceeded 50%. All analyses were performed using RevMan version 5.4.1 and R software (version 4.4.1) with the *meta* and *metafor* packages. Statistical significance was set at $p < 0.05$.

Risk of Bias

The methodological quality of the included RCTs was evaluated using the Cochrane Risk-of-Bias 2 (ROB-2) tool. Five domains were assessed. Each domain was rated as *low risk*, *some concerns*, or *high risk of bias*. All reviewers independently performed the assessments, and discrepancies were resolved by consensus. The overall risk-of-bias summary and traffic-light plots.

Results

Study Selection and Risk of Bias

A total of 124 records were identified through database searches, PubMed (n = 17), ScienceDirect (n = 39), and Epistemonikos (n = 68). After removal of five duplicates, 119 unique articles were screened based on title and abstract. Of these, 55 records were excluded due to irrelevance to the review question. The remaining 64 full-text articles were assessed for eligibility. During full-text evaluation, 57 studies were excluded for the following reasons: inappropriate study design (n = 14), ineligible population (n = 17), unsuitable comparison (n = 11), outcomes not relevant to the review (n = 4), and inaccessible full text (n = 11). Finally, seven studies fulfilled all inclusion criteria and were included in both the qualitative and quantitative syntheses.13–19 The study selection and data extraction process followed the PRISMA guidelines (Figure 1). These studies comprised randomized controlled trials evaluating the intervention of interest with comparable outcome measures. Sample sizes varied across studies.

The risk of bias was assessed using the Cochrane ROB-2 tool. The overall methodological quality of the included studies was considered acceptable, with most domains demonstrating low risk of bias. As illustrated in Figure 2, the majority of studies presented low risk in the domains of deviations from intended interventions, measurement of outcomes, and missing outcome data. A few studies raised some concerns in the domains of the randomization process and selection of the reported results, mainly due to insufficient description of allocation concealment or selective outcome reporting. The detailed per-study risk-of-bias judgments are shown in Figure 2. Overall, five of the seven studies were rated as low risk of bias, whereas two studies showed some concerns but no evidence of serious or critical risk. Consequently, the pooled evidence was judged to be of moderate-to-high internal validity.

Characteristics of Included Studies

A total of seven randomized controlled trials were included in this systematic review, encompassing studies conducted between 2008 and 2023 across Asia, North America, and South America. The included trials collectively involved 270 participants diagnosed with CLTI, allocated to intervention and control groups in varying proportions. All studies

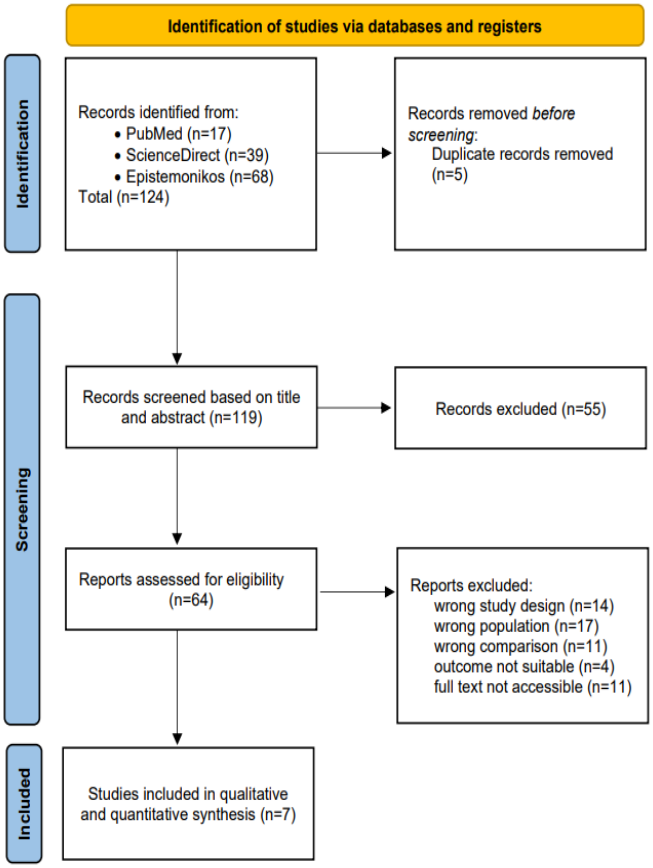

Figure 1. PRISMA flow chart.

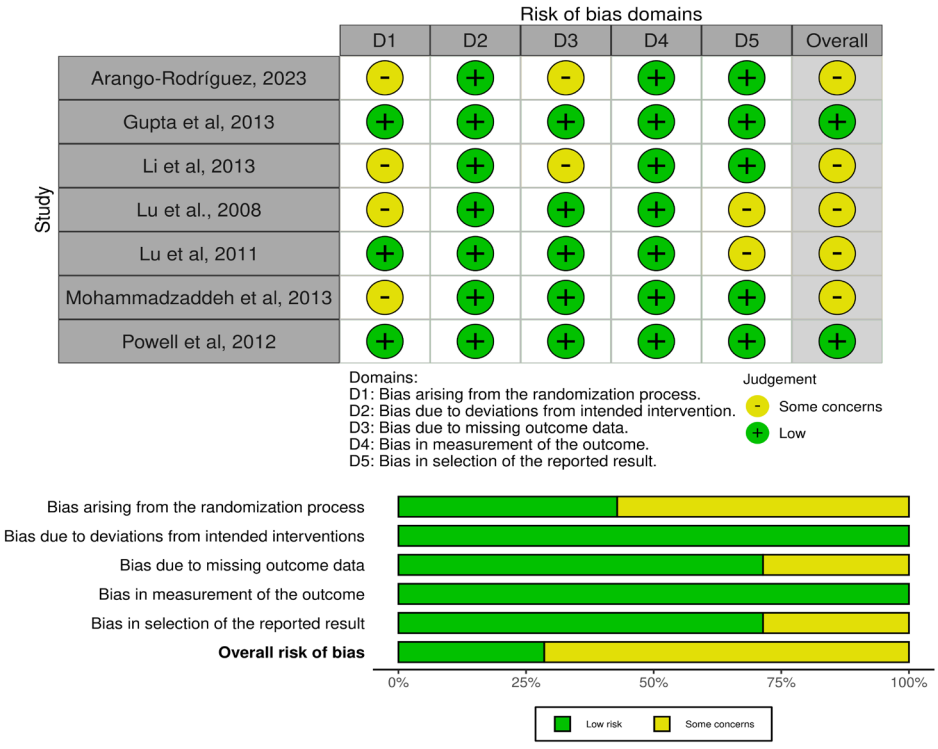

Figure 2. Summary and traffic plot of RoB2 for included studies.

adopted a parallel-group RCT design, investigating the efficacy of mesenchymal stem cell–based therapy or related cell-based interventions compared with standard or placebo control. The trials originated from China (3 studies), India (1), Iran (1), Colombia (1), and the United States (1), demonstrating broad geographical representation.

Sample sizes ranged from 17 to 72 participants, with intervention group sizes varying from 7 to 48 subjects. The mean or median ages of participants across studies were generally in the sixth to seventh decade of life (approximately 60–70 years), reflecting the typical demographic profile of CLTI. The proportion of males was predominant in most studies, with reported sex distributions roughly balanced in a few trials. Diabetes mellitus was a frequent comorbidity, with prevalence ranging from 0% to 100% across included studies, consistent with the established role of diabetes as a major etiologic factor for CLTI.

The follow-up duration ranged from 3 to 24 months, with most studies maintaining outcome assessments for at least 6–12 months after the intervention. Across all studies, the mode of administration was intramuscular or peri-adventitial injection, targeting ischemic limbs. Overall, the studies were relatively small-scale but methodologically homogeneous, each employing prospective randomization and parallel-group allocation. Despite the variation in cell sources and regional contexts, all studies shared comparable baseline characteristics between intervention and control groups in terms of age and diabetes prevalence, thereby supporting the validity of pooled analysis (Table 1).

Primary and Secondary Outcomes

This meta-analysis included seven randomized controlled trials evaluating the efficacy of MSC-based therapy in patients with CLTI. The primary outcome, amputation rate, showed a significant reduction in the MSC-treated group compared with control (OR = 0.40; 95% CI 0.17–0.95; p = 0.04; I^2 = 19%). This finding indicates a consistent and clinically meaningful decrease in limb loss following MSC therapy.

Table 1. Summary characteristics of included studies.

Author (Year)	Country	Study Design	Total Sample (n)	Intervention (n)	Control (n)	Diabetes (%)	Mean Age (years)	Route of Administration	Follow-up Duration
Gupta et al., 2013	India	RCT	20	10	10	0	46.7 (Intervention), 43 (Control)	Intramuscular	24 months
Lu et al., 2008	China	RCT	45	22	23	100	66.6 ± 6.5 (Intervention), 65.5 ± 9.6 (Control)	Multiple intramuscular & hypodermic injections	12 weeks
Lu et al., 2011	China	RCT	37	18	19	100	BMMSC: 63 ± 8; BMMNC: 65 ± 10	Intramuscular	6 months
Arango-Rodríguez et al., 2023	Colombia	RCT	17	7	10	24	78.3 (Intervention), 73.1 (Control)	Peri-adventitial injection	12 months
Powell et al., 2012	USA	RCT	72	48	24	50	69.2 ± 13.2 (Intervention), 67.3 ± 11.6 (Control)	Intramuscular	12 months
Min Li et al., 2013	China	RCT	58	29	29	43	61 ± 9 (Intervention), 63 ± 10 (Control)	Intramuscular	6 months
Mohammad-zadeh et al., 2013	Iran	RCT	21	7	14	100	63.5 ± 7.8 (Intervention), 64.2 ± 7.8 (Control)	Intramuscular	3 months

RCT: Randomized Controlled Trial; BMMSC: Bone Marrow Mesenchymal Stem Cells; BMMNC: Bone Marrow Mononuclear Cells.

For the secondary outcomes, the ulcer healing rate was markedly improved among MSC recipients (OR = 9.79; 95% CI 2.59–36.98; p = 0.0008; I^2 = 33%), supporting enhanced angiogenic and regenerative potential. MSC therapy also yielded significant improvement in rest pain level (MD = –1.88; 95% CI –2.93 to –0.84; p = 0.0004; I^2 = 85%) and Ankle–Brachial Index (ABI) (MD = 0.16; 95% CI 0.09–0.22; p < 0.00001; I^2 = 15%). Collectively, these results demonstrate that MSC-based therapy confers both clinical and functional benefits, effectively reducing the need for major amputation while promoting wound healing, pain relief, and improved peripheral perfusion in CLTI patients (Figure 3).

Adverse Effect

The investigation into gastrointestinal and hepatobiliary adverse events revealed an exceptionally high safety profile. In both categories, the pooled proportion of events was effectively zero and near zero, at 0.00 and 0.01 (95% CI: 0.00–0.05). This result stems from the fact that not many events were reported in any of the included randomized controlled trials. Consequently, the analysis demonstrated perfect homogeneity across the studies, with an I2 statistic below 25% for both categories (p=0.3506 for gastrointestinal and p=0.9948 for hepatobiliary), indicating complete consistency in the absence of these specific complications.

A similar, though not identical, trend was observed for infection-related adverse events. The pooled proportion was very low, at 0.04 (95% CI: 0.00–0.17). This suggests that the risk of infection associated with MSC therapy is minimal and uniformly low across different study contexts. Interestingly, the analysis of musculoskeletal adverse events yielded a similar pooled proportion of 0.04 (95% CI: 0.00–0.19). However, in stark contrast to the other categories, this analysis uncovered moderate and statistically significant heterogeneity among the studies (I2 = 82.1%, p<0.0001) (Figure 4). This significant result implies that the variability in the incidence of musculoskeletal events across trials is greater than what would be expected by chance alone. This finding suggests that underlying factors, such as differences in patient populations, specific MSC protocols, or follow-up procedures, may be influencing the risk of this particular adverse event.

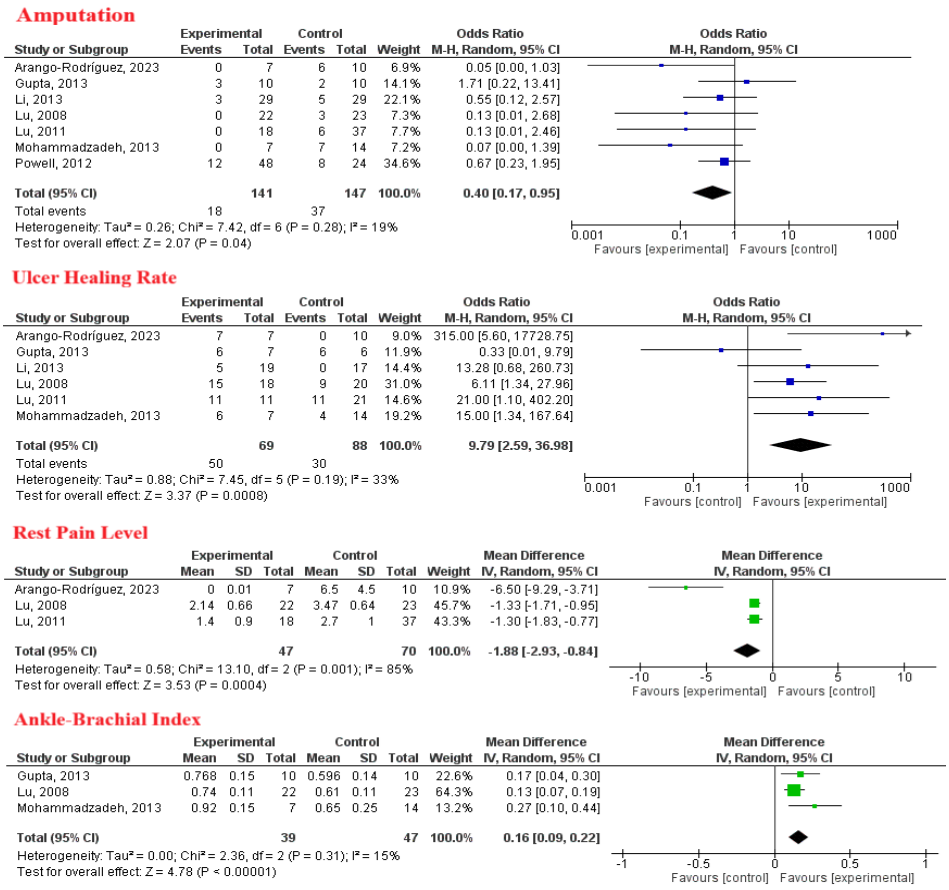

Figure 3. All efficacy parameter of MSCs compared with control in treating CLTI.

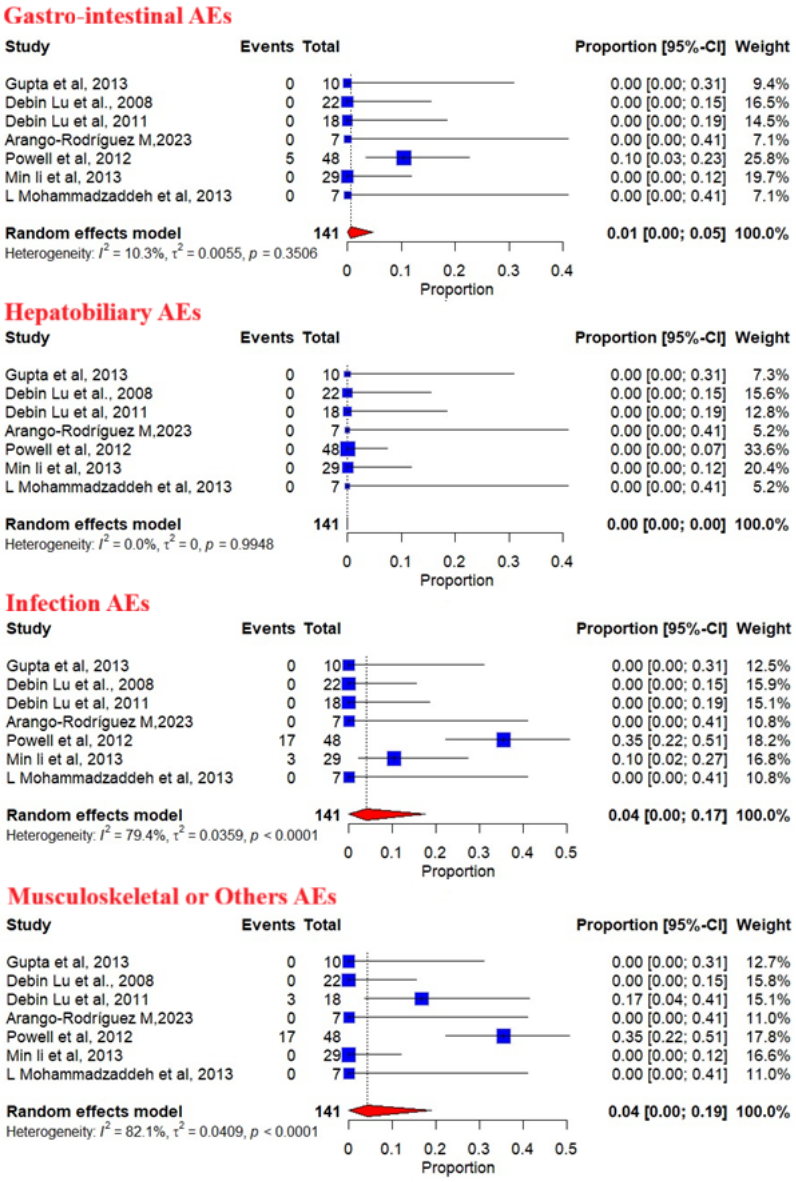

Figure 4. Proportional forest plot for adverse effect.

Discussion

Principal Finding

Patients with CLTI face a high risk of reduced quality of life and limb loss. Many remain unaware of their PAD until severe complications occur, including ischemia or sepsis. Although revascularization is the standard treatment, about 30% of patients are ineligible.[20] For those who cannot undergo revascularization, especially with sepsis or extensive tissue loss, amputation is often considered. However, amputation may not be suitable for all patients or families.[21] When amputation is declined, repeated revascularization and wound debridement are often necessary. This leads to higher costs and limited effectiveness.[22] MSCs have emerged as a less invasive and potentially more effective alternative.[15] Our study shows that MSCs can reduce amputation rates by up to 60% compared to controls. Stem cell therapies enhance blood flow at the transplant site through the processes of angiogenesis and neovascularization. They also release pro-angiogenic factors and modulate the immune response.[14] These mechanisms may help prevent amputations in patients with CLTI. MSCs, therefore, represent a promising therapeutic option tailored to the needs of this population.

Our study showed that the intervention group experienced a significantly lower amputation rate than the control group, indicating that MSCs may reduce limb loss risk, especially in patients ineligible for standard therapy. Comparable outcomes were

demonstrated in the 2019 systematic review and meta-analysis by Gao et al., where autologous stem cell therapy significantly reduced major amputation rates and improved perfusion indices in PAD patients.[23] Secondary outcomes, such as ulcer healing, resting pain, and ABI, also improved. These findings are consistent with the study of Xie et al. (2018) in a meta-analysis of RCTs, reported that cell therapy markedly improved ulcer healing, Transcutaneous Oxygen Tension (TcO_2) levels, and ABI in CLTI patients.[24] For outcomes with substantial heterogeneity, leave-one-out sensitivity analyses confirmed that the primary conclusions of this meta-analysis remain robust.

For patients unable to receive standard treatment, MSC therapy not only helps prevent amputation but also enhances physical function and quality of life. Additionally, MSC therapy is associated with reduced chronic pain and may mitigate the psychosocial impact of amputation.[25] These findings resonate with those discussed by Huerta et al. (2023), who emphasized the analgesic and neuroprotective mechanisms of MSCs in CLTI-related chronic pain.[26] Although there have not yet been systematic reviews or meta-analyses specifically addressing the safety of intramuscular MSC therapy for CLTI, multiple randomized controlled trials and clinical studies consistently demonstrate that intramuscular administration of mesenchymal stem cells for patients with CLTI is safe, with no serious adverse events, complications, or evidence of infection, immunological rejection, or tumor formation reported during both short-term and long-term follow-up periods.[18,27]

Mechanistic Insight

MSCs are specialized cells capable of migrating specifically to ischemic sites in response to signals secreted by immune and injured cells. They play key roles in angiogenesis, regeneration, and immunomodulation, and are considered as fundamental treatment in CLTI patients. The primary mechanism underlying MSCs therapeutic effects is paracrine activity, mainly through the secretion of various growth factors that promote vascularization and tissue repair.[28]

The secretome, a collection of bioactive substances secreted by MSCs, possesses antimicrobial, antifibrotic, and pro-regenerative properties, contributing to angiogenesis, proliferation, differentiation, immune modulation, and wound healing.[29] Several factors secreted by MSCs contribute to tissue regeneration in CLTI patients, including Insulin-like Growth Factor 1 (IGF-1), Vascular Endothelial Growth Factor (VEGF), basic Fibroblast Growth Factor (bFGF), Transforming Growth Factor-beta (TGF-β), von Willebrand Factor (vWF), and the angiogenic marker Cluster of Differentiation 31 (CD31), which collectively stimulate the angiogenesis process. Another mechanism by which MSCs alleviate injury is through tunneling nanotube formation, which allows the transfer of large molecules, such as mitochondria, to neighboring cells. Mitochondrial exchange occurs when MSCs transfer mitochondria to injured cells under oxygen-glucose deprivation/reoxygenation stress, thereby restoring aerobic respiration and protecting cells from apoptosis.[28]

Clinical Implementation

Mesenchymal stem cell implantation shows significant potential as an adjunctive therapy to conventional revascularization or as an alternative strategy for patients with CLTI who have no remaining treatment options. Recent preclinical and clinical studies have underscored the ability of MSCs to enhance tissue perfusion, stimulate angiogenesis, and accelerate ulcer healing through their paracrine and immunomodulatory mechanisms.[30] Previous investigations have emphasized that MSC-based regenerative therapy represents a promising biological alternative for *no-option* CLTI patients, as it promotes angiogenesis and facilitates wound healing in individuals who are either ineligible for or unresponsive to surgical or endovascular revascularization.[26]

Furthermore, a recent clinical cohort demonstrated that bone-marrow-derived MSC implantation achieved a 92.8% amputation-free survival rate over a two-year follow-up, accompanied by significant improvements in pain-free walking distance, ABI, tissue oxygenation, and ulcer healing. These findings reinforce the safety and effectiveness of MSC therapy as a safe and effective adjunct or stand-alone approach for limb preservation in advanced ischemic disease. Collectively, the evidence supports MSC implantation as a valuable regenerative intervention, either complementing revascularization procedures or serving as a viable alternative in patients lacking conventional treatment options, with the potential to improve limb salvage rates, functional recovery, and overall quality of life.[25]

A critical consideration in the clinical application of MSCs therapy for CLTI is the heterogeneity of dosing regimens and injection protocols across the included studies. Our analysis reveals a broad spectrum of cellular dosages, ranging from weight-

based administrations to high-dose absolute concentrations. For instance, Gupta et al. (2013) utilized a standardized dose of 2 million cells/kg, whereas Lu et al. (2008, 2011) reported significantly higher absolute doses ranging from 7.32×10^8 – 5.61×109 cells.[13,16-17] Other trials, such as those by Powell et al. (2012) employed a wide range of 35–295 x 10^6 cells.[18]

The administration techniques also varied, primarily favoring intramuscular delivery to ensure localized paracrine distribution. Notably, Mohammadzadeh et al. used an intensive protocol with 60 injection sites, each containing $1.5–2.0\times10^7$ cells, to maximize tissue coverage.[19] While most studies utilized intramuscular or hypodermic routes, Arango-Rodríguez introduced a peri-adventitial injection approach ($1.3x10^6$ cells/mL), highlighting the evolving nature of delivery strategies.[14] Despite this procedural diversity, the consistent improvements observed in ABI and ulcer healing across these trials suggest that MSCs maintain therapeutic potency across various delivery volumes and concentrations. However, the lack of a standardized "optimal dose" remains a notable gap in the literature, necessitating future dose-response trials to refine the efficacy-to-safety ratio in advanced limb ischemia.

Study Limitation

This meta-analysis possesses several inherent limitations that warrant careful interpretation. First, the aggregate sample size across the seven included RCTs remains relatively modest (n = 270), reflecting the nascent stage of cellular therapy in vascular regenerative medicine. While the observed clinical improvements were statistically significant, these findings should be validated in larger, multicenter Phase III trials to establish more definitive therapeutic benchmarks. Second, substantial methodological heterogeneity was identified regarding MSC sources, dosages, and delivery routes. Such variability precludes the establishment of a standardized "gold standard" protocol and likely contributes to the observed statistical variance in safety reporting, particularly for musculoskeletal adverse events (I^2 = 82.1%). Third, follow-up durations varied across studies (3–24 months), underscoring the need for longer longitudinal data to evaluate the long-term durability of microvascular perfusion.

Furthermore, we acknowledge that our literature search was restricted to English-language publications indexed in PubMed, ScienceDirect, and Epistemonikos. The exclusion of broader databases, such as Embase and Web of Science, and international trial registries, such as ClinicalTrials.gov. introduces a risk of geographic and publication bias, which may lead to the omission of localized RCTs or unpublished negative outcomes. However, since the primary databases used in this study index the highest-impact cardiovascular literature, we believe this subset represents the current core evidence. Future investigations should aim for a broader multi-database and linguistic scope to incorporate emerging regional data. Despite these constraints, this study provides a comprehensive synthesis of high-level evidence, offering a critical foundation for integrating MSCs into the clinical management of "no-option" CLTI patients.

Conclusion

This meta-analysis aimed to evaluate the efficacy and safety of mesenchymal stem cell therapy in patients with chronic limb-threatening ischemia. The results demonstrated that MSC therapy significantly improved key clinical outcomes, including a reduced risk of major amputation, enhanced ulcer healing, increased ABI, and greater relief of rest pain compared to control or placebo. Importantly, MSC implantation exhibited an excellent safety profile, with only mild and transient adverse events reported.

Collectively, these findings suggest that MSC therapy is a promising, biologically rational approach for CLTI management, offering meaningful improvements in limb salvage and microvascular perfusion. Nevertheless, the choice of therapy should be tailored according to disease severity, patient comorbidities, and institutional expertise.

Further high-quality randomized controlled trials with standardized MSC sources, delivery routes, and long-term follow-up are warranted to confirm the durability of benefit and establish optimized clinical protocols. In this evolving era of regenerative cardiovascular interventions, our results underscore the potential of stem cell–based therapy to transform outcomes for patients otherwise facing limited treatment options.

List of Abbreviations

ABI	Ankle-Brachial Index
bFGF	Basic Fibroblast Growth Factor
BMMSC	Bone Marrow Mesenchymal Stem Cells
BMMNC	Bone Marrow Mononuclear Cells
CD31	Cluster of Differentiation 31
CLTI	Chronic limb-threatening ischemia
CLI	Critical limb ischemia
CI	Confidence interval

EVR	Endovascular revascularization
IGF-1	Insulin-like Growth Factor 1
MD	Mean Difference
MSCs	Mesenchymal stem cells
OR	Odds Ratio
PAD	Peripheral artery disease
RCT	Randomized controlled trial
RoB2	Risk-of-Bias 2
TcO_2	Transcutaneous Oxygen Tension
TGF-β	Transforming Growth Factor-Beta
VEGF	Vascular Endothelial Growth Factor
vWF	von Willebrand factor

Ethical Clearance

Not applicable.

Publication Approval

All authors have reviewed and approved the final version of the manuscript and consent to its publication in the Indonesian Journal of Cardiology.

Authors' Contributions

Concept and design: NA, AMS. Analysis and interpretation: NA, AMS. Data collection: MCAA DWBA, LAS, HFU, MCA, KSL. Writing the article: NA, AMS, MCAA, DWBA, LAS, HFU, MCA, KSL. Critical revision of the article: ADSN, YHH, ASM. Final approval of the article: all authors.

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Conflict of Interest

None.

Availability of Data and Materials

Not applicable.

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Copyright/Permissions for Figures

No copyright materials were used.

Generative AI and AI-Assisted Technologies in the Writing Process

Generative AI tools were utilized to support the preparation of this manuscript. ChatGPT (OpenAI) and Gemini AI was used to help refine wording, improve clarity, and correct grammar and spelling. All content was critically reviewed and edited by the authors to ensure accuracy, originality, and adherence to ethical standards.

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