The Effectiveness of Silver Nanoparticles in Burn and Diabetic Wound Healing: A Systematic Review and Meta-Analysis of Clinical Trials

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Abstract

Burn wounds and diabetic wounds continue to present significant public health challenges worldwide due to prolonged healing durations and heightened infection risks. Silver-based wound dressings, particularly silver nanoparticles (AgNPs), have emerged as potential alternatives to conventional therapeutic approaches owing to their well-documented antimicrobial and anti-inflammatory properties. However, the evidence regarding their efficacy in promoting wound healing remains inconsistent across studies. This systematic review and meta-analysis aimed to evaluate the therapeutic efficacy of AgNPs in the management of burn and diabetic wounds. A comprehensive literature search was conducted across multiple databases, including PubMed, Scopus, EMBASE, and The Cochrane Library, following PRISMA guidelines. Randomized controlled trials (RCTs) that assessed the therapeutic outcomes of AgNPs compared to conventional wound treatments were included. Primary outcomes of interest included wound healing time and the proportion of wounds achieving full epithelialization. Statistical analyses were conducted using STATA software. Seventeen RCTs were included in this meta-analysis. In the case of burn wounds, AgNPs demonstrated a trend toward rapid wound healing (mean difference [MD] = -1.57 days; 95% CI: -3.27 to 0.12; p = 0.07), although statistical significance was not reached. There was also no significant improvement observed in complete wound closure (relative risk [RR] = 0.98; 95% CI: 0.80-1.21). Despite this, the data suggest a potential advantage in reducing healing duration, though further studies are necessary to validate clinical relevance. For diabetic wounds, AgNPs did not result in statistically significant reduction in healing time compared to control interventions (MD = 3.17 days; 95% CI: -2.47 to 8.80; p = 0.27), nor was there a marked improvement in the proportion of wounds that achieved full healing (RR = 1.18; 95% CI: 0.94-1.47; p = 0.15). The current evidence indicates that the utility of AgNPs in accelerating wound healing in diabetic patients may be limited. AgNPs were found to exhibit therapeutic effects comparable to those of conventional treatments. Although statistical significance was not achieved, the consistent trend toward reduced healing time underscores their potential clinical value. Future research should prioritize the implementation of standardized treatment protocols and consistent timing of outcome measurements to strengthen the reliability of evidence.

Keywords**:** *Silver nanoparticle, Burn wound, Diabetic wound, Wound healing*

1. Introduction

Wound healing is a fundamental physiological process that restores the structural and functional integrity of the skin following injury. Despite advancements in wound care, both burn wounds and diabetic ulcers remain persistent global health challenges due to their prolonged healing durations and heightened vulnerability to microbial infection. Burn injuries, which affect approximately 11 million individuals annually and contribute to an estimated 180,000 deaths worldwide, are particularly prevalent in resource-limited regions such as Southeast Asia and the Middle East (James et al., 2020). The clinical presentation of burn wounds varies significantly, ranging from superficial skin damage to full-thickness tissue damage, frequently necessitating specialized treatment to prevent complications such as infections, fluid imbalances, and scarring. Similarly, diabetic foot ulcers (DFU) represent a major complication of diabetes mellitus, a metabolic disorder affecting nearly 500 million individuals globally. Among diabetic individuals, chronic

non-healing wounds develop in approximately 20% of cases, substantially increasing the risk of lower limb amputation (Armstrong et al., 2017). The persistence of these wounds is primarily attributed to compromised immune responses, inadequate circulation, and sustained hyperglycemia, all of which contribute to delayed healing and increased susceptibility to bacterial infections. In light of these multifactorial challenges, the development of effective wound management strategies is imperative for improving clinical outcomes and alleviating healthcare system burdens.

Traditional wound care regimens often incorporate silver-based agents, such as silver nitrate and silver sulfadiazine (SSD), which have been extensively utilized for their broad-spectrum antimicrobial activity. However, these agents require frequent reapplication and are associated with adverse effects, including cytotoxicity and formation of pseudo-eschar (Lansdown, 2002). In contrast, AgNPs, a product of recent nanotechnology developments, offer improved antimicrobial efficacy through the sustained release of silver ions (Ag+), along with reduced cytotoxicity and prolonged wound coverage (Oves et al., 2018; Shanmuganathan et al., 2019).

Mechanistically, AgNPs exert broad-spectrum antimicrobial effects by releasing Ag^{+}, which binds to thiol groups in proteins, phosphorus in DNA, and sulfur-containing proteins in the bacterial membrane. These molecular interactions disrupt vital bacterial processes, including enzymatic activity and DNA replication. AgNPs also adhere to and penetrate bacterial cell walls, impairing mitochondrial electron transport, inducing the generation of reactive oxygen species (ROS), and contributing to intracellular acidification. This resultant oxidative stress inhibits bacterial growth and ultimately causes cell death under both aerobic and anaerobic conditions. In addition to their antimicrobial effects, AgNPs have been shown to enhance fibroblast migration, angiogenesis, re-epithelialization, and granulation tissue formation, which are all critical phases of the wound healing process (Morones et al., 2005).

Several studies have investigated the therapeutic efficacy of AgNP-based dressings in wound management. A randomized controlled trial (RCT) conducted by Aggarwala et al. (2021) found that Acticoat® dressings significantly reduced healing time in partial-thickness burn wounds compared to alternative dressings, including Biobrane®, Aquacel Ag®, and Mepilex Ag®. Similarly, Adhya et al. (2015) reported that AgNP dressings significantly shortened wound healing duration in burn patients compared to SSD-treated groups. In the context of DFU management, studies by Essa et al. (2021) and Tsang et al. (2017) demonstrated that AgNPs enhanced wound closure rates and significantly reduced ulcer dimensions compared to traditional treatments. Collectively, these findings suggest the potential of AgNPs to treat both burn and diabetic wounds by mitigating infection risks and facilitating accelerated tissue regeneration.

Although AgNPs have shown promising potential in accelerating wound healing, current treatment outcomes for both diabetic and burn wounds remain suboptimal, and existing studies present inconsistent findings. While some previous research, including some meta-analyses, has compared AgNPs with antibiotics primarily in the context of infection control, few studies have rigorously evaluated their direct impact on wound healing outcomes. Moreover, there is a lack of standardized comparisons between AgNP-based treatments and conventional wound care across both wound types. These gaps highlight the need for further comprehensive investigation. Accordingly, this systematic review and meta-analysis was undertaken to synthesize available clinical evidence and statistically assess the effectiveness of AgNPs in promoting wound healing in diabetic and burn wounds, with the goal of informing future clinical applications and treatment guidelines.

2. Objectives

To study the effectiveness of AgNPs in burn wound healing and diabetic wound healing.

3. Materials and Methods

This study was conducted as a systematic review and meta-analysis to evaluate the effectiveness of silver nanoparticles (AgNPs) in promoting wound healing in burn and diabetic wounds. The methodology adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.

3.1 Eligibility criteria

Eligible studies included RCTs focusing on human studies that assessed the effectiveness of AgNPs in patients with burn wounds or diabetic wounds, specifically those with wounds covering less than 40% of the total body surface area (TBSA). To ensure reliability and accessibility, only peer-reviewed studies published in English were considered. Studies were excluded if they addressed donor site wound healing, lacked a control group, or employed AgNPs as a secondary rather than a primary treatment. Additionally, studies that failed to provide sufficient data for statistical analysis were excluded to preserve consistency and analytical validity in this systematic review and meta-analysis.

3.2 Data search and Literature search

This systematic review and meta-analysis followed the PRISMA guidelines. A comprehensive literature search was conducted across multiple electronic databases, including PubMed, Scopus, EMBASE, and the Cochrane Library. The search included studies from their earliest available publication date until January 2024. In addition, the reference lists of relevant articles were screened to identify additional eligible studies.

The search strategy incorporated a combination of Medical Subject Headings (MeSH) terms and keywords related to AgNPs, burn wounds, diabetic wounds, and wound healing. Boolean operators (AND/OR) were applied to refine the search results. Retrieved records were screened for relevance, and duplicates were removed prior to the eligibility assessment and data extraction stages.

3.3 Data extraction

Data extraction was independently conducted by two reviewers using a standardized data collection form. Extracted data encompassed study characteristics (e.g., author, year of publication, and country), patient demographics (mean age, wound type, wound severity), details of the wound (cause of burn, depth of burn, percent of total body surface area affected, location of the wound), and intervention details (type of AgNPs application and treatment duration).

Primary outcomes assessed were the time to complete wound healing and the proportion of wounds achieving full closure. Any discrepancies in data extraction were resolved through discussion or consultation with a third reviewer.

3.4 Quality assessment and risk of bias

The methodological quality of the included studies was assessed using the Cochrane Risk of Bias (RoB) tool for RCTs. Each study was systematically evaluated for potential sources of bias, including selection, performance, detection, attrition, and reporting bias. Based on the assessment, studies were categorized as having a low, high, or uncertain risk of bias.

Publication bias was assessed through the use of a funnel plot, which allows visual evaluation of the distribution symmetry among the included studies. A symmetrical funnel plot indicates minimal bias, thereby suggesting the validity of the meta-analysis results. Conversely, asymmetric distribution patterns may suggest potential publication bias or influencing factors such as small sample sizes, study variability, random chance, or selective reporting. Any observed asymmetry was critically appraised and taken into account when interpreting the findings, in order to ensure analytical rigor and an accurate conclusion.

3.5 Statistical analysis

The meta-analysis was conducted using STATA version 17 to evaluate the clinical efficacy of AgNPs in promoting wound healing. Pooled effect sizes were estimated using both fixed-effect and random-effect models, selected based on the degree of statistical heterogeneity across studies. Additionally, descriptive statistics were used to summarize the general characteristics of the included studies, including study protocol, sample size, and participant demographics.

For continuous outcomes, standardized mean differences (SMDs) with 95% confidence intervals (CIs) were calculated, while for dichotomous outcomes, relative risks (RRs) with 95% CIs were applied. Statistical heterogeneity across studies was assessed using Cochrane's Q-test and the I^2 statistic, with an I^2 value of >50% considered indicative of substantial heterogeneity. In cases of significant heterogeneity (I^2 >50% or p-value <0.1), a random-effects model was employed; otherwise, a fixed-effects model was used.

4. Results and Discussion

4.1 Result

4.1.1 Search results

A PRISMA flowchart illustrating the study selection process is shown in Figure 1. Initially, 3,108 articles were retrieved, and 1,201 duplicates were removed. Following title and abstract screening, 1,825 studies were excluded based on predefined criteria. Full-text assessment was conducted for 52 articles, of which 35 were excluded due to ineligible interventions, comparisons, outcomes, duplicate publications, or language restrictions. Ultimately, 17 RCTs fulfilled the inclusion criteria and were included in the final meta-analysis, providing comprehensive data on the effects of AgNPs on wound healing.

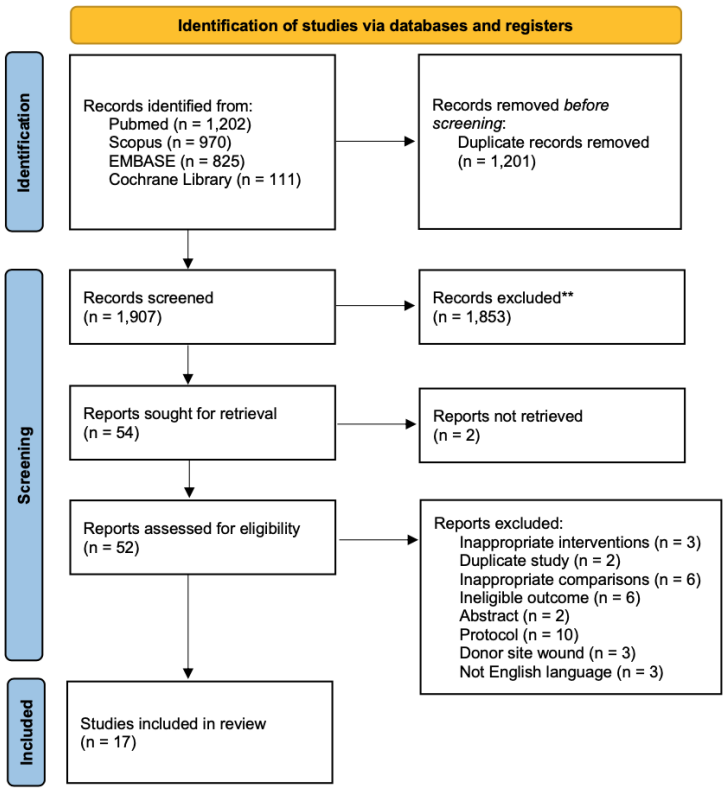


Figure 1 PRISMA flow diagram for studies included and excluded from the systematic review. (Page et al., 2021)

4.1.2 Characteristics of eligible studies

The 17 randomized controlled trials (RCTs) included in this review were published between 1998 and 2023, with the majority conducted in Asian countries (notably China, India, and Thailand) and several originating from Western countries such as Australia, Belgium, and New Zealand. Sample sizes ranged from 31 to 166 participants, primarily focusing on adults aged 26-63 years, although some studies included pediatric burn cases. The studies assessed AgNPs in burn and diabetic wounds, comparing various

formulations such as AgNP creams, Acticoat®, and nanosilver dressings to standard treatments like SSD, conventional wound dressings, and advanced wound care products (e.g., Aquacel® and Biobrane®).

4.1.3 Meta-analysis results

- The effect of AgNPs on the healing time of Burn wounds.

A total of eleven RCTs with diverse sample sizes were included in the analysis to evaluate the effect of AgNPs on wound healing duration. The pooled mean difference was -1.57 (95% CI: -3.27 to 0.12), indicating a potential reduction in healing time in the AgNP-treated group compared to the control group. However, statistical significance was not achieved ($p = 0.07$). The heterogeneity test revealed a high degree of variability across studies ($I^2 = 79.87\%$, $p = 0.00$), indicating that AgNPs did not significantly reduce healing time compared to other wound treatments (see Figure 2a).

- The Effect of AgNPs on the Proportion of Wounds with Complete Healing of Burn Wounds

Three RCTs with a total of 230 patients were included in this analysis to evaluate the effect of AgNPs on the rate of wounds achieving complete healing. The pooled RR was 0.98 (95% CI: 0.80-1.21), indicating no significant enhancement in the likelihood of complete wound healing with AgNP treatment compared to control interventions. The heterogeneity test showed low variability across studies ($I^2 = 5.32\%$, $p = 0.35$). The results suggest that AgNPs did not markedly improve wound healing rates relative to standard treatments. (see Figure 2b).

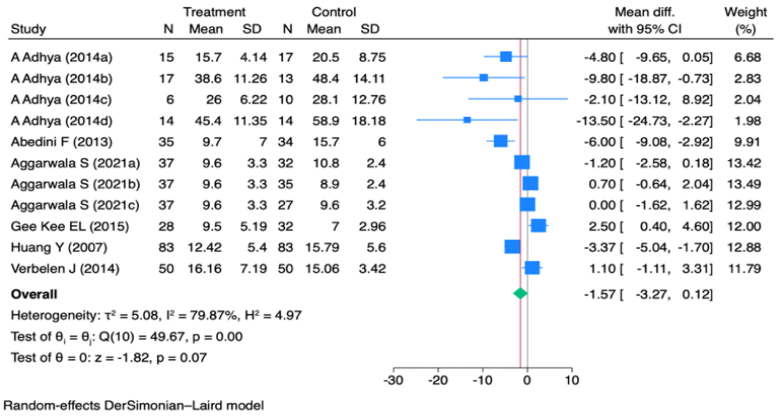
- The effect of AgNPs on the healing time of Diabetic wounds.

Four RCTs, comprising a total of 407 patients, were included in this analysis. The meta-analysis results revealed a mean difference (MD) of 3.17 days (95% CI: -2.47 to 8.80; $p = 0.27$), indicating no statistically significant difference in healing time between AgNPs and conventional treatments. The heterogeneity test indicated a high level of variability ($I^2 = 99.91\%$, $p = 0.00$), necessitating the use of a random-effects model. While AgNPs demonstrated a trend toward faster wound healing, the wide confidence interval highlights potential variability in the treatment effect across studies (see Figure 2c).

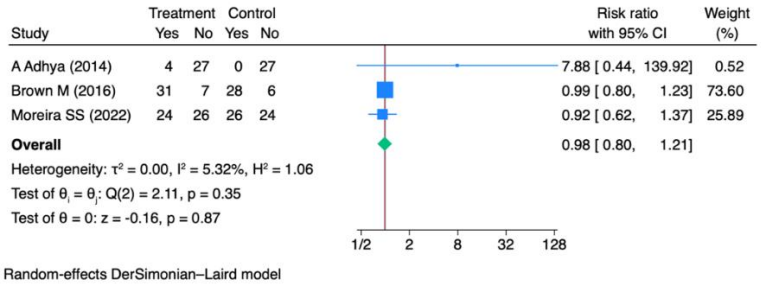
- The effect of AgNPs on the proportion of wounds with complete healing of Diabetic wounds.

Five RCTs, involving 467 patients, were analyzed to determine the effect of AgNPs on the proportion of wounds achieving complete healing. The pooled risk ratio (RR) for complete wound healing in the AgNPs group compared to the control group was 1.18 (95% CI: 0.94-1.47, $p = 0.15$), indicating no statistically significant improvement in complete wound healing associated with AgNPs treatment. Individual studies reported a broad range of effect estimates, with RR values varying from 0.92 to 23.05. The heterogeneity analysis demonstrated moderate variability among studies ($I^2 = 65.42\%$, $p = 0.02$) (see Figure 2d).

(a)



(b)



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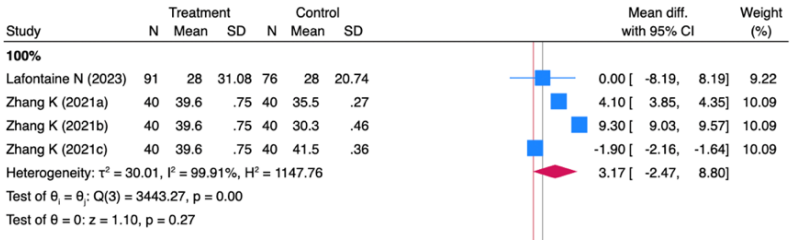

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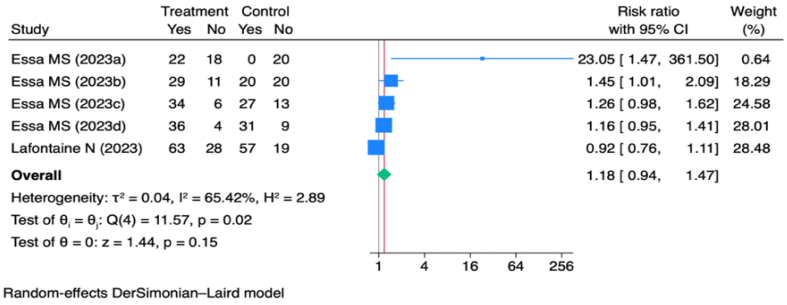

Figure 2 Figure 2: Forest plot showing the effect of AgNPs on (a) healing time in burn wounds (b) proportion of wounds with complete healing in burn wound (c) healing time in diabetic wound (d) proportion of wounds with complete healing in diabetic wounds.

■ This square represents the individual studies' effect (sometimes known as a "blob"). The size of the "blob" varies to reflect the weight a particular study has in the overall analysis (larger "blobs" have more weight).
— The black line represents the CIs of a study; the smaller "blobs," which have less weight, generally have larger CIs than the larger "blobs."
◆ The diamond represents the overall or summary effect. The outer edges of the diamond represent the CIs.

4.1.4 Risk of bias assessment

The risk of bias assessment revealed methodological limitations that may compromise the trustworthiness of the findings. Several studies raised concerns regarding deviations from the intended interventions, selective outcome reporting, and missing data. Although randomization was generally well-executed, cumulative issues across multiple domains led to an overall high risk of bias in several studies. Additionally, variability in intervention reporting further contributed to inconsistencies. These sources of bias may have influenced the pooled estimates by either overestimating or underestimating the treatment effects. The findings should, therefore, be interpreted with careful consideration of the potential impact of these biases on the overall results.

4.1.5 Publication bias

- Publication Bias on Diabetic Wounds

The funnel plot revealed visible asymmetry, characterized by a relative scarcity of smaller studies on the left of the mean effect size. This pattern suggests the presence of potential publication bias or small-study effects, indicating that studies with non-significant or less favorable results may be underreported in the literature, potentially overestimating the pooled effect size.

- Publication Bias on Burn Wounds

The funnel plot analysis revealed an overall symmetrical distribution, suggesting minimal publication bias. However, variations in study sizes indicate the possibility of small-study effects, wherein smaller studies tend to report more pronounced treatment outcomes. While this pattern does not invalidate the findings, it underscores the importance of interpreting the pooled findings with caution.

4.2 Discussion

This meta-analysis initially identified 3,108 records through comprehensive database searches. After the removal of duplicates and subsequent screening, 54 full-text articles were assessed for eligibility. Following the application of inclusion and exclusion criteria, 17 RCTs were included in the final meta-analysis to evaluate the effectiveness of AgNPs in wound healing.

Based on the results of this meta-analysis, burn wounds treated with AgNPs demonstrated a trend toward faster healing, with a mean difference of -1.57 days compared to conventional treatment. However, this difference was not statistically significant, and no meaningful improvement was observed in the proportion of wounds achieving complete closure. The substantial heterogeneity across studies may be attributed to several factors. Differences in wound size likely influence the healing process and overall treatment outcomes. Variability in the forms of AgNPs used, such as creams, gels, or dressings, may have influenced the bioavailability and chemical interactions of the active agent. Differences in application methods and frequency, particularly in cases with high exudate, along with variation in treatment duration, further complicate cross-study comparisons. Patient-related factors such as age, underlying health conditions, immune function, and nutritional status also play a critical role in wound healing. In addition, impaired tissue perfusion and elevated oxidative stress in some individuals may have delayed recovery and contribute to variability in treatment responses (Lee et al., 2004; Hall et al., 2017).

In diabetic wounds, results from the meta-analysis indicated that AgNPs had no significant effect on healing time or complete wound closure when compared to conventional treatments. While these findings are consistent with those in burn wounds in terms of high heterogeneity, diabetic wounds involve additional

condition-specific factors that may further contribute to the variability. These include differences in wound characteristics, such as variations in depth, chronicity, and severity, along with the lack of standardized grading systems, which complicate comparisons across studies. Furthermore, patient-related factors such as poor glycemic control, vascular insufficiency, immune dysfunction, and the presence of infection may influence treatment outcomes. The complex biological impairments commonly seen in diabetic wounds, including delayed angiogenesis and reduced cellular activity, are also likely to contribute to the inconsistency observed across studies (Park et al., 2011; Burgess et al., 2021).

Although overall outcomes may appear comparable to conventional treatments at the study endpoint, this may not fully capture the therapeutic value of AgNPs. Wound healing is a complex process, especially in patients with metabolic disorders or extensive tissue damage, where early-phase interventions can play a critical role. Several studies have emphasized the potential benefits of AgNPs during the initial stages of healing, a period characterized by heightened inflammation and increased risk of infection. AgNPs have been widely used in medical treatments due to their antimicrobial activity, ability to combat drug-resistant pathogens, and anti-inflammatory effects (Aminov et al., 2009).

The results of this meta-analysis suggest that AgNPs are as effective as conventional treatments and may be considered a viable clinical option when appropriate. To obtain more conclusive evidence, future studies should measure outcomes at multiple time points and establish consistent timing for evaluating complete wound closure in order to better understand healing rates and treatment responses. In addition, employing clear study designs, standardized AgNP formulations, and well-defined control groups would help reduce variability and improve the reliability of the findings. These improvements would enhance confidence in clinical decision-making and support more effective integration of AgNPs into clinical practice.

This meta-analysis has several limitations that should be acknowledged. Many of the included studies had relatively small sample sizes, which may have reduced the statistical power and increased the likelihood of random error. The risk of publication bias was also evident, particularly in diabetic wound studies, where funnel plot asymmetry suggested that smaller studies with negative or non-significant findings may be underreported. Additionally, the limited number of studies in certain subgroups restricted the ability to perform meaningful sensitivity analyses to assess the robustness of the pooled estimates.

5. Conclusion

This meta-analysis indicates that AgNPs are comparable in effectiveness to conventional treatments in promoting wound healing for both burn and diabetic wounds. Given their therapeutic potential, AgNPs may serve as a supportive option in clinical wound management when used appropriately. To further define their role and enhance clinical application, well-designed studies with standardized protocols are warranted.

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