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ORIGINAL ARTICLE

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Efficacy and safety of hyperbaric oxygen therapy in the management of diabetic foot ulcers: A systematic review and meta-analysis

Lihua Tao[1] | **Xiao Yuan**[2]

[1]Department of Endocrinology, Linping Campus, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China

[2]Department of Endocrinology, The First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, China

Correspondence
Xiao Yuan, Department of Endocrinology, The First Affiliated Hospital of Zhejiang Chinese Medical University, Youdian Road 54, Hangzhou, Zhejiang 310006, China.
Email: yx1218yuanxiao@126.com

Abstract

Diabetic foot ulcers (DFUs) represent a major health concern for diabetic patients, often leading to debilitating complications. Hyperbaric oxygen therapy (HBOT) has been posited as an adjunctive therapeutic strategy to augment the healing rates of these ulcers. This systematic review and meta-analysis sought to critically evaluate the efficacy and safety of HBOT in the context of DFUs management. A rigorous search, adhering to PRISMA guidelines, was conducted across multiple electronic databases. Randomized controlled trials (RCTs) assessing the impact of HBOT on DFUs were included. Outcome measures were complete ulcer healing, major and minor amputation rates and adverse reactions. The analysis employed both fixed and random-effects models, contingent on the heterogeneity levels detected. Seven studies met the inclusion criteria. HBOT was found to significantly improve the complete healing rates of DFUs with a risk ratio (RR) of 3.59 (95% CI: 1.56–8.29, $p < 0.001$). However, HBOT's impact on both major and minor amputation rates did not yield statistically significant results. The sensitivity analysis underscored the robustness of the principal outcomes, and the publication bias assessment suggested the absence of any significant bias. Hyperbaric oxygen therapy stands out as a potent therapeutic tool in promoting the complete healing of diabetic foot ulcers, offering a promising adjunct to standard care protocols, while ensuring patient safety.

KEYWORDS

amputation, diabetic foot ulcers, hyperbaric oxygen therapy, randomized controlled trials, wound healing

Key Messages

- Significance of the Problem: Diabetic foot ulcers (DFUs) are a serious health issue for diabetic patients, frequently resulting in severe complications.
- Role of HBOT: Hyperbaric oxygen therapy (HBOT) has been suggested as a supplemental treatment to enhance the healing rates of DFUs.

- Methodology: Utilizing the PRISMA guidelines, a systematic review and meta-analysis were conducted by examining randomized controlled trials (RCTs) from various electronic databases. The main outcomes evaluated were complete ulcer healing, amputation rates and any adverse reactions associated with HBOT.
- Primary Findings: HBOT notably improved the complete healing rates of DFUs, with a risk ratio of 3.59. However, the therapy's influence on major and minor amputation rates was not statistically significant.
- Conclusions: HBOT appears as an effective and safe adjunctive therapy for DFUs, emphasizing its potential as a valuable tool in diabetic foot care management.

1 | INTRODUCTION

Diabetic foot ulcers (DFU) are among the most common complications of diabetes mellitus, affecting an estimated 6.4% of the global diabetic population, with Asia contributing to this global percentage with a prevalence rate of approximately 5.5%. These ulcerations are not only highly incident but also notorious for their elevated rates of recurrence, reaching upwards of 50% within 3 years post-treatment.[1,2] Three pivotal factors chiefly contribute to the onset of DFU: peripheral neuropathy, peripheral arterial disease and localized tissue infection. DFUs are typically categorized into three primary types depending on the presence of ischemia or neuropathy: ischemic, neuropathic and neuroischemic.[3] Ischemic ulcers arise from vascular insufficiencies that result in poor distal limb perfusion, leading to decreased skin temperature, claudication (a clinical manifestation commonly seen in vascular insufficiencies) and ultimately unhealing ulcers or dry gangrene.[4] This symptom is an important diagnostic indicator for ischemic type DFUs as it reflects the severity of peripheral arterial disease affecting limb perfusion. By contrast, neuropathic ulcers occur due to sensory abnormalities caused by peripheral nerve damage; however, they are more prone to healing due to unimpaired blood supply. Neuroischemic ulcers are a confluence of both neuropathic and ischemic symptoms and are more commonly observed in China than the singular ischemic variant.[5,6]

A cornerstone feature shared among these diverse DFUs is tissue hypoxia, which significantly impairs the healing cascade. Some patients may eventually require amputation or may succumb to fatal complications. This underscores the exigency for robust preventative and therapeutic strategies for DFU due to its considerable impact on the patients' quality of life.[7] Among the plethora of treatments, the mainstay interventions for DFU primarily include optimal glycaemic control to slow progression and localized wound care strategies aimed at infection control and promoting revascularization. Current treatment modalities encompass glycaemic control, microcirculation enhancement, neurotrophic support, infection management, local wound debridement, offloading, foot care, hyperbaric oxygen therapy (HBOT) and negative pressure wound therapy, among others. HBOT, as an adjunctive therapy, boasts nearly half a century of clinical utilization.[8] The cutaneous wound healing in diabetic patients is a complex and meticulously orchestrated process involving three overlapping phases: inflammation, proliferation and remodelling. Acute injuries trigger vascular damage, creating a hypoxic milieu around the wound, further exacerbated by the high metabolic demands of recruited inflammatory cells.[9] Though acute hypoxia may stimulate cellular proliferation and tissue repair, chronic hypoxia can conversely inhibit angiogenesis, re-epithelialization and extracellular matrix (ECM) synthesis, thus compromising the healing trajectory.[10]

Recent advances in DFU pathophysiology have demonstrated that impaired angiogenesis plays a pivotal role in the progression of DFUs. Enhancing tissue oxygenation emerges as a critical therapeutic strategy. HBOT has been found to modulate various growth factors like VEGF, EGF, PDGF, CXCL10, IL-1α, FGF-2 and SDF-1, thereby promoting angiogenesis and arteriogenesis.[11,12] Moreover, HBOT has shown its efficacy in activating fibroblasts and endothelial cells through signalling pathways like HIF-1α and NF-κB, thus accelerating the healing process.[13] Although HBOT is increasingly popular and theoretically advantageous, its clinical efficacy remains contentious. While some studies suggest that HBOT can facilitate wound healing and reduce amputation rates in DFUs, others argue that the differences in healing rates are not statistically significant. Consequently, this study aims to conduct a meta-analysis by collecting randomized controlled trials (RCTs) on the application of HBOT in DFUs, systematically assessing its efficacy and safety in the treatment of this condition.

2 | MATERIALS AND METHODS

2.1 | Search strategy

In accordance with the stringent criteria set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, meticulous rigour was exercised throughout the systematic review and the subsequent articulation of the findings.[14] To exhaustively canvass the existing scientific literature, a rigorous search was conducted on 26 July 2023 across four established electronic databases—PubMed, Embase, Web of Science and the Cochrane Library—without imposing any temporal constraints. The search algorithm was strategically engineered to include an array of pertinent key terms—namely, diabetic foot ulcers, hyperbaric oxygen therapy, HBOT, wound healing, amputation and randomized controlled trials. These terms were judiciously chosen to encapsulate the comprehensive breadth of the PICO schema, thereby ensuring a thorough accumulation of relevant scholarly articles for this meta-analytical investigation. The language criterion was intentionally left unrestricted. Moreover, reference lists from eligible articles were manually vetted to identify potential additional entries that may contribute to the meta-analysis.

2.2 | Eligibility criteria

Inclusion criteria: (1) Population (P): Patients with a confirmed diagnosis of DFUs; (2) Intervention (I): The experimental group should be undergoing HBOT, either as a standalone treatment or in combination with other foundational treatment modalities; (3) Comparison (C): The control group should be managed with standard care protocols, which may include regular glycaemic, lipid and blood pressure control; vasodilatory treatment; antiplatelet aggregation; peripheral nerve nutrition; and routine wound care. The control group may also receive treatment with high-pressure air in combination with these therapies. For those with superimposed wound infections, concomitant administration of antibiotics, to which the bacteria are sensitive, should be included; (4) Outcome (O): Primary and secondary outcomes include complete wound healing rate, efficacy rate, rates of major and minor amputations, reduction in ulcer surface area and any adverse reactions; (5) Study Type (S): Randomized Controlled Trials (RCTs).

The exclusion criteria were as follows: (1) Studies where the intervention group did not specifically receive HBOT; (2) Studies presenting incomplete, ambiguous or conflicting outcome metrics; (3) Manuscripts of suboptimal quality, lacking raw data or empirical evidence; (4) Case reports, commentaries, expert opinion and narrative reviews.

2.3 | Data extraction

In accord with rigorous meta-analytic protocols, the processes of literature screening and data extraction will be independently executed by two evaluators, subject to inter-rater cross-verification. Should divergences arise during this procedural stage, the engaged reviewers are to convene for deliberative resolution; if consensus remains elusive, the arbitration of a third-party evaluator may be invoked. The data sets to be culled comprise a range of variables, including foundational details of the included studies (such as geographic locale, authorship and publication date), study characteristics (including research design, study population and inclusion criteria), as well as outcome measurements (pertaining to outcome indicators and measurement methodologies). If pertinent data are absent from published reports, the principal investigators of the original studies will be contacted via electronic correspondence to solicit unreported data.

2.4 | Quality assessment

In compliance with established meta-analytic standards, the integrity of the studies incorporated into the analysis was scrutinized using the Cochrane Collaboration's risk of bias assessment tool.[15] This evaluation was conducted independently by a duo of reviewers across several domains, encompassing generation of randomized sequences, concealment of allocation procedures, blinding mechanisms for study participants and personnel, completeness of outcome data, susceptibility to selective reporting and other conceivable biases. Each domain underwent risk categorization as either low, unclear or high. Any discordance between the evaluators was reconciled through consultative discourse, and in cases where consensus was unattainable, a third-party reviewer was enlisted for arbitration.

2.5 | Statistical analyses

To assess the level of inter-study variability, chi-square tests were employed in conjunction with the I^2 statistic for quantification of heterogeneity. A nonsignificant level of heterogeneity was deduced when the I^2 statistic was below 50% and accompanied by a p-value $\geq$0.10. Under these conditions, a fixed-effects model was applied for the

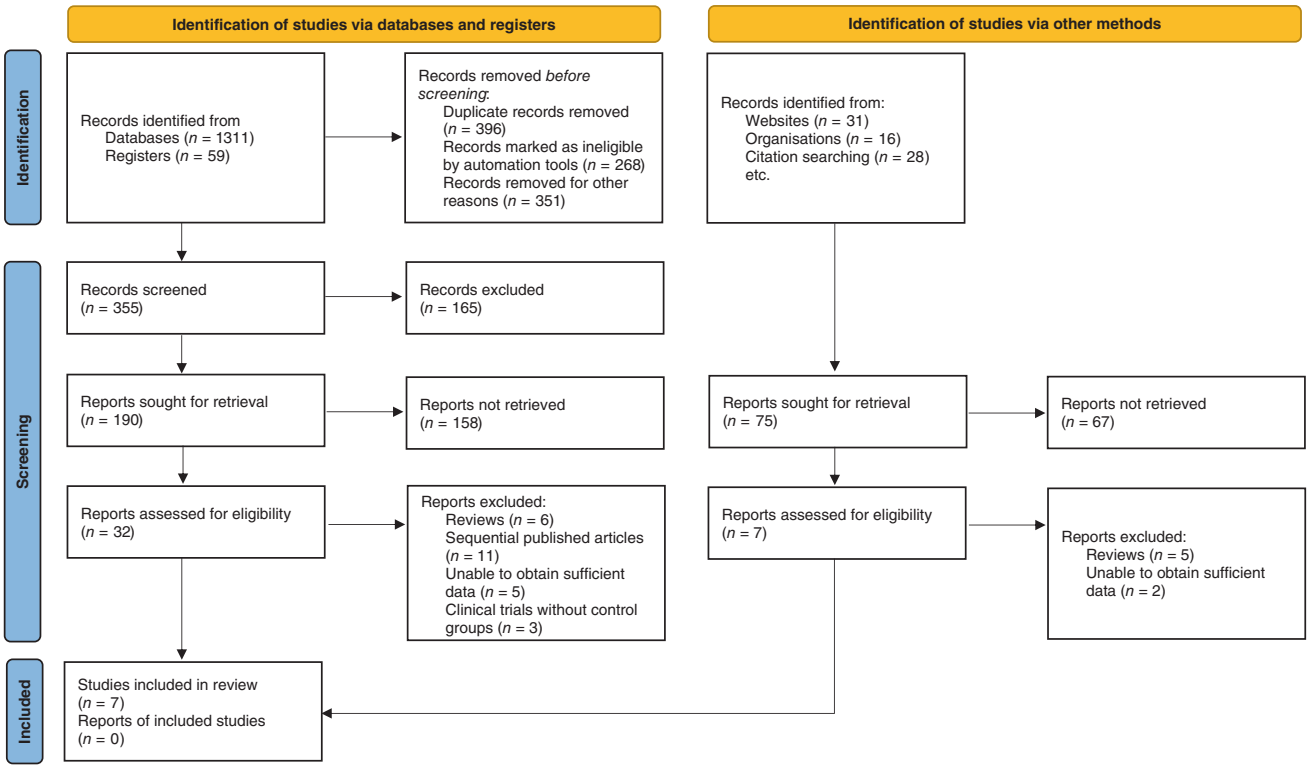

FIGURE 1 Selection process of included studies.

derivation of the pooled effect size. Conversely, a significant level of heterogeneity was indicated by an I^2 statistic of 50% or greater or a p-value <0.10; in these instances, a random-effects model was implemented for aggregation of effect sizes. To evaluate the stability and reliability of our meta-analytic findings, a sensitivity analysis was executed. This involved the iterative removal of each individual study, followed by re-estimation of the aggregated effect size. To scrutinize the presence of publication bias, we assessed the symmetry of funnel plots. A symmetrical distribution of data points around the apex of the funnel plot would suggest a diminished propensity for results to be affected by publication bias. As an adjunct, Egger's linear regression test served as a quantitative approach to detect any publication bias. All statistical tests were two-sided, and a p-value threshold of <0.05 was established for statistical significance. Statistical analyses were performed using Stata version 17 (StataCorp, College Station, TX, USA).

3 | RESULTS

3.1 | Search results and study selection

Upon conducting an initial search in multiple electronic databases, a total of 1445 pertinent articles were identified. Following the elimination of duplicate entries and careful review of both titles and abstracts, the corpus was whittled down in strict accordance with predefined inclusion and exclusion criteria, resulting in a subset of 39 relevant studies. After a more in-depth evaluation, an additional 32 articles were excluded, culminating in the final inclusion of seven studies.[16–22] The systematic methodology employed for literature selection and the corresponding results are graphically depicted in Figure 1.

3.2 | Study characteristics

The meta-analysis incorporates studies from different countries spanning from 2003 to 2020. All included studies utilized a RCT design. The studies primarily investigated the effects of HBOT in conjunction with standard care, as compared to various control conditions, which ranged from standard care alone to standard care supplemented with specific atmospheric pressure air. The pressure applied during HBOT sessions varied between 2 and 3 ATA, with session durations ranging from 60 to 120 min. The number of total sessions varied across studies, with a range from 20 up to 45. Wagner grades, utilized to classify the severity of the foot ulcers in the patients, primarily varied between grades 1 and 4, though some studies did not specify this. Key outcome measures

TABLE 1 Baseline characteristics of studies included in the meta-analysis.

Author	Year	Country	Study design	Pressure (ATA)	Duration (min)	Total sessions	Wagner grade	Intervention group	Control group	Outcome measures	Wagner grade
Kumar	2020	India	RCT	2.4	90	36	2–4	Standard Care + HBOT	Standard Care +0.3ATA Air	Complete healing, major amputations, minor amputations	2–4
Salama	2019	Egypt	RCT	2.5	60	20–40	2–3	Standard Care + HBOT	Standard Care	Complete healing, major amputations, minor amputations, ulcer reduction	2–3
Chen	2017	China	RCT	2.5	120	20	Not available	Standard Care + HBOT	Standard Care	Complete healing, major amputations	Not available
Fedorko	2016	USA	RCT	2.4	90	30	2–4	Standard Care + HBOT	Standard Care +1.2ATA Air	Complete healing, major amputations, minor amputations, adverse reactions, ulcer reduction	2–4
Löndahl	2010	Sweden	RCT	2.5	85	40	2–4	Standard Care + HBOT	Standard Care +2.5ATA Air	Complete healing, major amputations	2–4
Duzgun	2008	USA	RCT	2–3	90	30–45	2–4	Standard Care + HBOT	Standard Care	Complete healing, major amputations, minor amputations	2–4
Abidia	2003	UK	RCT	2.4	90	30	1–2	Standard Care + HBOT	Standard Care	Complete healing, major amputations, minor amputations	1–2

Abbreviation: ATA, atmospheres absolute.

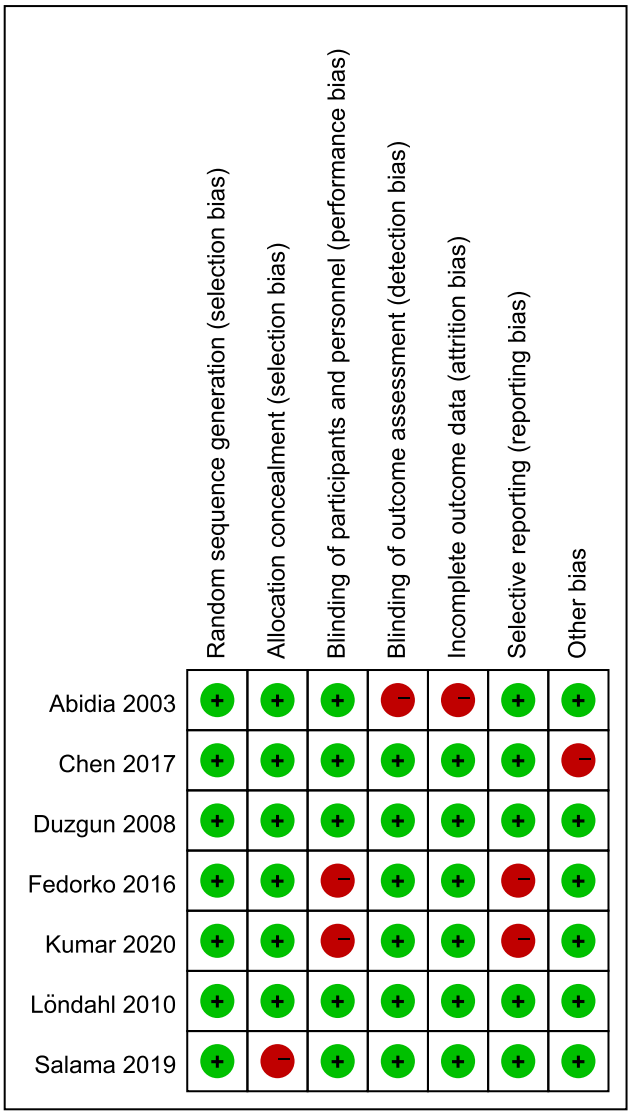

FIGURE 2 Quality assessment of included studies using Cochrane Collaboration's tool criteria. Red in figure indicates high risk, and green means low risk.

across the studies included complete ulcer healing, major and minor amputations, ulcer size reduction and, in certain studies, adverse reactions, offering a holistic view of HBOT's potential benefits and challenges in foot ulcer treatment (Table 1).

3.3 | Results of quality assessment

The risk of bias was thoroughly assessed in the seven incorporated studies. Two of the studies displayed an all-encompassing low risk of bias, reflecting a strong methodological foundation. However, a notable 29% of these studies showcased a high risk in the domain related to the blinding of participants and staff. Such findings hint at the potential influence of performance bias on their reported outcomes. Additionally, a consistent 29% of the selected randomized controlled trials manifested a significant risk pertaining to selective reporting bias. This suggests the potential influence of selective or noncomprehensive outcome reporting on the aggregated findings of these studies (Figure 2).

3.4 | Meta-analysis on complete healing rates of diabetic foot ulcers

Our meta-analysis encompassed a total of 7 studies focusing on the complete healing rates of diabetic foot ulcers. Upon assessment for heterogeneity among the included studies, we identified a pronounced variation, with an I^2 value of 65.3% and a p-value of 0.008. This evident heterogeneity necessitated the employment of the random-effects model for deriving the combined effect size. The resultant analysis highlighted a statistically significant difference between the studied groups. The risk ratio (RR) stood at 3.59, accompanied by a 95% confidence interval (CI) ranging from 1.56 to 8.29, and a significant p-value of <0.001 (Figure 3). This delineates the substantial impact of the investigated intervention on promoting complete healing in patients with diabetic foot ulcers.

3.5 | Meta-analysis on major amputation rates

The major amputation rate, defined as any amputation level proximal to the ankle joint, was a pivotal endpoint addressed in this meta-analysis. Across the seven studies reporting this outcome, there was no significant heterogeneity identified, with an I^2 value of 41% and a p-value of 0.132. Due to the absence of considerable heterogeneity, a fixed-effects model was employed to derive the combined effect size. The calculated RR was 0.54, with a 95% CI spanning from 0.18 to 1.63. Notably, the difference observed did not reach statistical significance, given the p-value of 0.31 (Figure 4). This consolidated result suggests that there is not ample evidence to conclusively advocate that the adjunctive use of hyperbaric oxygen therapy can effectively reduce the incidence of major amputation events in the studied population.

3.6 | Meta-analysis on minor amputation rates

Minor amputation rate, which refers to amputations at or below the level of the ankle joint, was critically examined

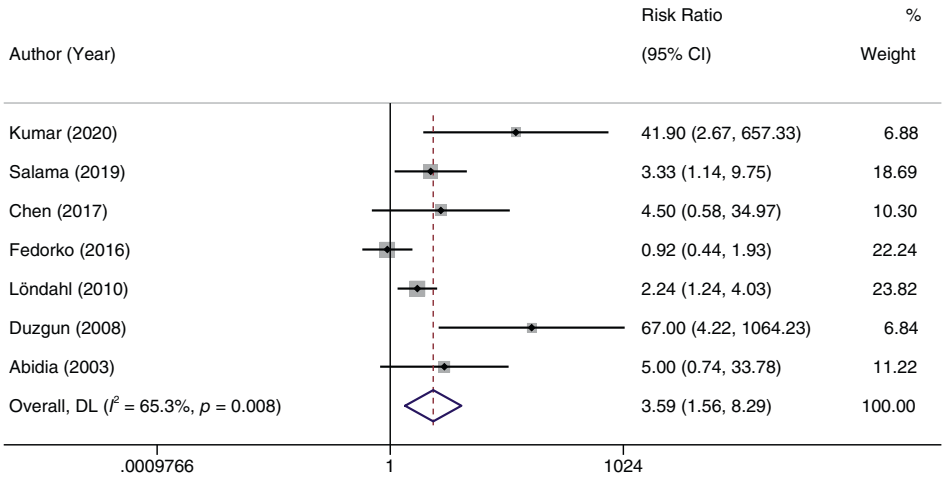

FIGURE 3 Forest plots on complete healing rates of diabetic foot ulcers.

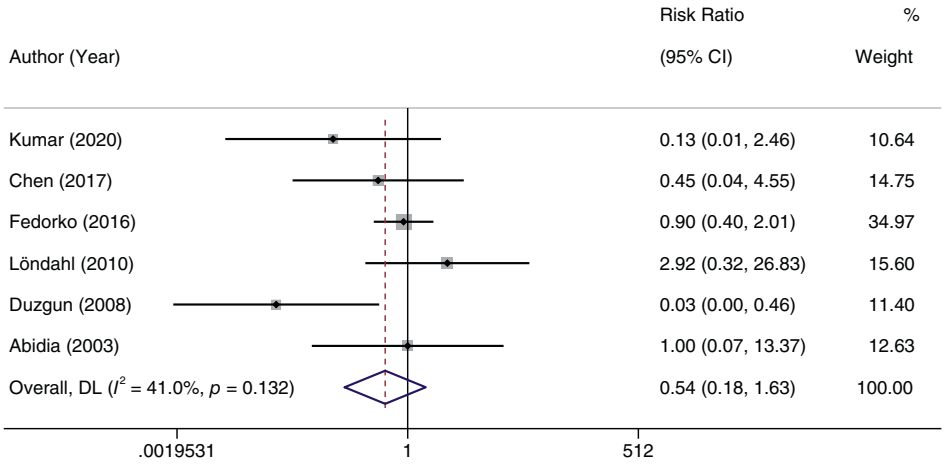

FIGURE 4 Forest plots on major amputation rates of diabetic foot ulcers.

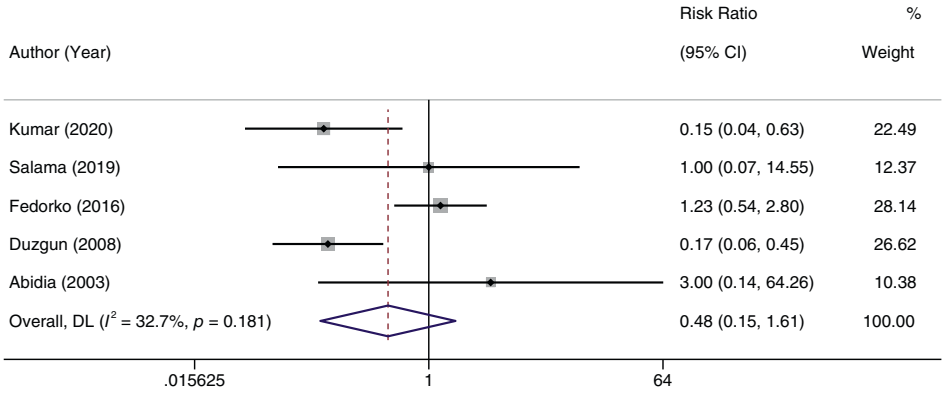

FIGURE 5 Forest plots on minor amputation rates of diabetic foot ulcers.

in our meta-analysis. Out of the data pool, five studies reported on this specific outcome. The meta-analytic findings highlighted that the heterogeneity across these studies was not substantial, as evidenced by an I^2 value of 32.7% and a p-value of 0.181. Employing a fixed-effects model for the consolidated analysis yielded a RR of 0.48 with a 95% CI ranging from 0.15 to 1.61. This outcome, with a p-value of 0.26, was statistically nonsignificant (Figure 5). Therefore, in terms of enhancing minor amputation rates, the current evidence does not robustly support the hypothesis that adding hyperbaric oxygen therapy to standard care is superior to standard care alone.

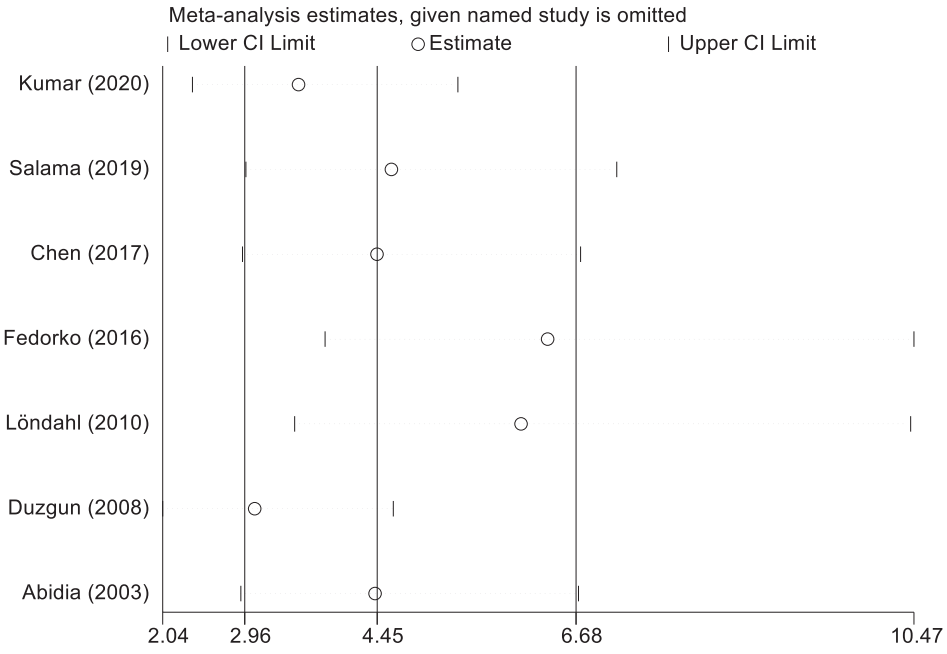

FIGURE 6 Sensitivity analysis on complete healing rates of diabetic foot ulcers.

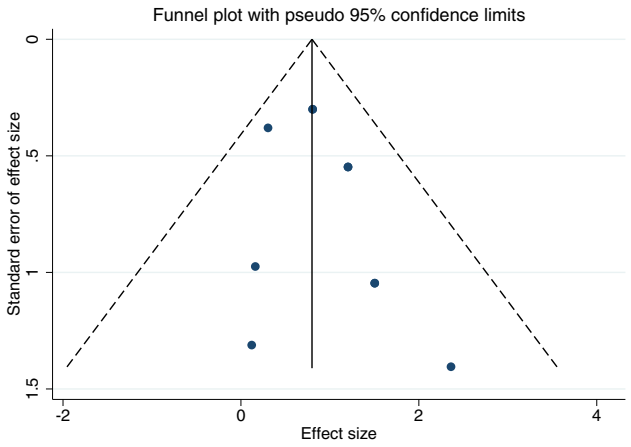

FIGURE 7 Funnel plot for publication bias in all included studies.

3.7 | Sensitivity analysis

Given the discernible heterogeneity observed in the meta-analysis concerning the complete healing rates of diabetic foot ulcers, we conducted a sensitivity analysis to validate the reliability and consistency of the combined results. By systematically omitting one study at a time and re-evaluating the amalgamated effect sizes for the remaining dataset, we aimed to test the resilience of our conclusions. This meticulous approach to sensitivity assessment confirmed that the aggregate outcomes were consistently stable, even with the removal of any particular study. It becomes clear, therefore, that no singular study disproportionately swayed the comprehensive results. The sustained stability across these assessments not only reinforces the validity of our principal outcomes but also solidifies the inferences made from this meta-analysis, as depicted in Figure 6.

3.8 | Publication bias

Funnel plots derived from the incorporated studies exhibited symmetrical distribution, suggesting an absence of significant publication bias as illustrated in Figure 7. Moreover, results from the Egger's linear regression test corroborated the lack of substantial publication bias across various parameters (all p-values >0.05), reinforcing the reliability of the findings from this meta-analysis.

4 | DISCUSSION

Diabetic foot disease has emerged as a predominant factor contributing to morbidity and mortality in patients with diabetes mellitus. The heightened rates of major amputations, alongside substantial relapse rates, have posed significant challenges for both patients and healthcare professionals. Recognizing potential precursor symptoms of DFUs and initiating intensified monitoring and proactive care measures are vital.

Such preventative therapeutic interventions have the potential to minimize the incidence of severe DFUs, subsequently optimizing patient prognosis.[23] HBOT has long been employed as an adjunctive treatment for diabetic

wounds. Its modus operandi encompasses increasing tissue oxygenation, enhancing perfusion, mitigating oedema and suppressing inflammation. Such therapeutic actions further stimulate fibroblast proliferation, collagen synthesis and angiogenesis, collectively fostering wound healing.[8,24] In the present study, we meticulously explored the efficacy of HBOT in the management of DFUs. Our findings underscored a notable enhancement in complete ulcer healing rates in patients subjected to HBOT compared to those receiving standard care. Additionally, while our analysis highlighted a favourable safety profile for HBOT, the presence of specific adverse effects like barotrauma necessitates careful patient screening and monitoring during treatment sessions. The novel insight of our research lies in the comprehensive evaluation of HBOT's therapeutic potential, emphasizing its clinical utility in advancing the standard of care for DFU patients and potentially reducing amputation rates and associated morbidity.

Wound healing is intrinsically a multifaceted process, with oxygen playing an instrumental role. Chronic wounds often demonstrate a marked decline in oxygen levels, and augmenting oxygen content in wound tissues can expedite healing while concurrently reducing bacterial colonization. HBOT facilitates patients to inhale 100% oxygen at pressures exceeding atmospheric levels, boosting intracellular oxygen content and thus maximizing tissue oxygenation.[25] However, when evaluating major and minor amputation rates, the aggregated effects between the HBOT group and control were not statistically significant. Most of the studies in our review alluded to minimal adverse reactions, indicating that HBOT for diabetic foot ulcers is relatively safe. An isolated study mentioned barotrauma and visual alterations,[19,26] yet there was not any statistically significant difference in adverse event rates between the HBOT and control groups. The most frequently reported adverse effect of HBOT remains barotrauma of the middle ear, arising from pressure fluctuations during treatment sessions. Appraising patients for any medical history that might impact the Eustachian tube patency, inspecting its status and regulating pressurization speeds are pivotal in averting barotrauma. While reports linking visual changes post-HBOT are limited, the precise aetiology behind these alterations remains elusive and might be intertwined with diabetic retinopathy.

Transcutaneous oxygen tension serves as a pivotal reference parameter for the administration of HBOT in DFUs. The European Underwater and Baromedical Society's 2017 consensus recommended HBOT for diabetic foot ulcers graded Wagner 3 and above, ensuring a transcutaneous oxygen tension >100 mmHg during treatment. However, while HBOT can elevate arterial blood oxygen tension, oxygen delivery to wounds could be hindered due to macrovascular diseases. Conversely, tissue hypoxia induced by microvascular diseases or oedema could potentially be alleviated by HBOT, which increases tissue oxygen tension, thus enhancing wound healing. Therefore, an exhaustive pre-HBOT evaluation is imperative.[10] Typically, patients undergo treatment in a hyperbaric chamber where they inhale 100% oxygen under increased atmospheric pressures, often between 2.0 and 2.5 ATA, for durations spanning 60–120 min daily, with a standard therapeutic course ranging from 15 to 30 sessions.

However, there remains an absence of a universally adopted protocol for HBOT in treating DFUs. Most studies have encompassed Wagner-graded 2–4 DFU patients, excluding the measurement of transcutaneous oxygen tension. Not adhering rigorously to expert consensus recommendations—incorporating HBOT only for Wagner 3 and above or those meeting transcutaneous oxygen tension therapeutic thresholds—might render certain included patients nonresponsive to HBOT benefits. Hence, prior to clinical application, it becomes indispensable to thoroughly assess the severity of diabetic foot ulcers, determine pertinent metrics and classify them based on Wagner grading. Strict adherence to HBOT indications, curtailing unnecessary treatments, remains pivotal for the widespread clinical adoption of HBOT in DFU management.

Several limitations can influence the results and interpretations of research studies. Firstly, the sample size of some studies may be inadequate, reducing the statistical power and potentially leading to inaccurate conclusions. Secondly, selection bias, where participants are not randomly selected, can skew results. Additionally, differences in study protocols and methodologies can result in inconsistent outcomes. Finally, the reliance on self-reported data in some studies may introduce inaccuracies due to recall bias or misrepresentation. It is essential to consider these constraints when generalizing study findings. Furthermore, the absence of long-term follow-up limits understanding of sustained outcomes. In light of the findings, future research should focus on delineating the patient subsets most amenable to HBOT and establishing standardized protocols. Large-scale, randomized controlled trials are imperative to validate HBOT's efficacy within these refined parameters. Additionally, mechanistic studies are needed to elucidate HBOT's role in wound biochemistry, which may inform more targeted and economically viable therapeutic strategies.

5 | CONCLUSIONS

In conclusion, the findings from this systematic review suggest that hyperbaric oxygen therapy significantly

enhances the complete healing rates of diabetic foot ulcers, promoting effective wound resolution, while also demonstrating commendable safety profiles.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Xiao Yuan https://orcid.org/0009-0002-2645-2286

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