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Application of hyperbaric oxygen therapy in diabetic foot ulcers: A meta-analysis

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Abstract

Hyperbaric oxygen therapy (HBOT) has been used in patients with diabetic foot ulcers (DFU) for many years, but its clinical efficacy is still controversial. Therefore, this study explored the efficacy of HBOT applied to DFU by means of meta-analysis. PubMed, Cochrane Library, Embase, CNKI and Wanfang databases were searched, from database inception to October 2023, and published randomised controlled trials (RCTs) of HBOT in DFU were collected. Two investigators independently screened the collected literature, extracted relevant data and assessed the quality of the literature. Review Manager 5.4 software was applied for data analysis. Twenty-nine RCTs with 1764 patients were included. According to the combined results, when compared with conventional treatment, HBOT significantly increased the complete healing rate of DFUs (46.76% vs. 24.46%, odds ratio [OR]: 2.83, 95% CI: 2.29–3.51, $p < 0.00001$) and decreased the amputation rate (26.03% vs. 45.00%, OR: 0.41, 95% CI: 0.18–0.95, $p = 0.04$), but the incidence of adverse events was significantly higher in patients (17.37% vs. 8.27%, OR: 2.49, 95% CI: 1.35–4.57, $p = 0.003$), whereas there was no significant difference in the mortality (6.96% vs. 12.71%, OR: 0.52, 95% CI: 0.21–1.28, $p = 0.16$). Our results suggest that HBOT is effective in increasing the complete healing rate and decreasing the amputation rate in patients with DFUs, but increases the incidence of adverse events, while it has no significant effect on mortality.

KEYWORDS

diabetic foot ulcers, hyperbaric oxygen therapy, meta-analysis, wound healing

Key Messages

- Explore the application of hyperbaric oxygen therapy (HBOT) in diabetic foot ulcers (DFU).
- HBOT significantly increased the complete healing rate of patients with DFU.
- HBOT significantly decreased the amputation rate of patients with DFU.

1 | INTRODUCTION

Diabetes mellitus is a common chronic clinical disease, now classified as type I and type II diabetes, and its incidence is increasing year by year.[1] Diabetic foot ulcer (DFU) is one of the common serious complications in diabetic patients.[2] The pathogenesis of diabetic foot is still unclear, and the existing theory is that the patient is in a long-term hyperglycemic state, the formation of thrombus after lower limb vascular sclerosis, the occlusion of lower limb blood vessels, resulting in local ischemia and hypoxia, peripheral nerve trophic disorder and infection of the lower limbs, ulcer formation, and the three interact with each other and influence each other.[3] Early diabetic foot is mainly manifested as lower limb skin sensory abnormality and temperature decrease, and later gradually develops into foot ulcer and gangrene, which can lead to amputation or even death in serious cases, and cause a great burden to the society and the patient's family.[4,5]

Over the years, diabetic foot treatments have included the administration of improved microcirculation, proper control of blood glucose levels, regular local debridement and dressing changes, anti-infection, nerve nutrition and amputation.[6] In recent years, some adjunctive treatments such as hyperbaric oxygen have been shown to not only improve the healing rate of diabetic foot wounds, but also reduce amputation rates.[7] Hyperbaric oxygen therapy (HBOT) involves breathing pure oxygen in a hyperbaric chamber at more than one atmosphere of pressure, which passively raises oxygen tension in arteries and tissues.[8] It has been found that hyperbaric oxygen improves vascular blood flow in the lower limbs of patients, promotes local blood and oxygen supply, improves neuropathy in the tissues surrounding the diabetic foot, enhances tissue metabolism, reduces inflammatory exudation and reduces or eliminates oedema, thus accelerating ulcer healing.[9] In 2015, Kranke et al. concluded that healing of DFUs significantly improved after HBOT.[10] However, HBOT reduced amputation rates but was ineffective in improving wound healing as reported in Brouwer et al.[11] At this stage, the efficacy of HBOT for DFU is still controversial. We therefore conducted this study exploring the application of HBOT for DFU, and assessed its clinical efficacy and safety via meta-analysis, with a view to providing a reference basis for clinical decision-making.

2 | MATERIALS AND METHODS

2.1 | Literature search

PubMed, Cochrane Library, Embase, CNKI and Wanfang databases were searched, from database inception to October 2023, and published randomised controlled trials (RCTs) of HBOT in DFU were collected. The search keywords: diabetic foot, chronic wound, diabetic foot ulcers, diabetic ulcer, hyperbaric oxygen therapy, hyperbaric oxygen. More relevant literature was also searched using manual searching and literature backtracking methods.

2.2 | Selection criteria

Screening was performed by two researchers who independently read all of the titles, abstracts and body text of each document; disagreements were resolved through discussion, and if agreement still could not be reached, a third researcher made the judgement. The inclusion criteria for this study were (1) published RCTs of HBOT applied to DFUs; (2) the study subjects were patients with DFUs who met the WHO diagnostic criteria for diabetes mellitus, regardless of the type of diabetes mellitus, gender, age and ethnicity; (3) the intervention was HBOT, and conventional treatment was used in the control group; and (4) the primary outcome metrics were the rate of complete healing of ulcers, and the secondary outcome metrics were the rate of amputation, the incidence of adverse event rate and mortality rate. Exclusion criteria: (1) repetitive publications or repetitive cases; (2) reviews, meta-analyses, conference abstracts, case reports and studies of animal testing; (3) studies with incomplete or unavailable full-text data.

2.3 | Data extraction

Data and information were extracted independently by two researchers, and disagreement was resolved by discussion, and if agreement still could not be reached, a third researcher made the judgement. The extracted data included (1): general information: author's name, country, year of publication, sample size, patient's age, gender, Wagner grading, HBOT time, pressure and frequency; (2) outcome indicators: ulcer complete healing rate, amputation rate, adverse event rate, lethality rate.

2.4 | Quality assessment

Using the Cochrane Risk Assessment for Bias tool in the Cochrane Handbook, the results of the evaluation were checked by two investigators after independently evaluating the quality of the included literature, with a third investigator deciding when disagreements arose. Evaluated items included: method of random allocation, allocation scheme concealment, blinded evaluation, completeness of outcome information, selective outcome reporting, other sources of bias.

2.5 | Statistical analysis

RevMan 5.4 software was applied for data analysis. Heterogeneity test was assessed using I^2; if $I^2 > 50\%$, heterogeneity was indicated to be significant and a random-effects model was applied; otherwise, a fixed-effects model was applied. The complete healing rate, amputation rate, adverse event rate and mortality rate were count data, so they were expressed using odds ratio (OR) and 95% confidence interval (CI). Sensitivity analyses were performed to observe the effect of individual studies on the combined effect sizes by excluding literature one by one to determine their stability. Funnel plots were applied for qualitative judgement of publication bias.

3 | RESULTS

3.1 | Study selection

A total of 895 relevant literatures were retrieved through the computer search until October 2023. All retrieved literature was imported into Endnote literature management software, 193 duplicates were removed by software and manually, 586 studies not related to the topic were excluded by further reading of titles and abstracts, 116 were left over, 87 were excluded by careful reading of the full text and 29 literature that met the criteria were finally included.[12–40] Among them, 12 were in English and 17 were in Chinese, and the process of literature screening is shown in Figure 1.

3.2 | Characteristics of included studies and quality assessment

Twenty-nine RCTs were finally included and their basic characteristics are shown in Table 1. The total number was 1764, with 877 patients in the HBOT group and 887 patients in the conventional treatment group. The sample size of the studies ranged from 16 to 120, and most of the Wagner grading grades were between 1 and 4. The risk of bias summary is shown in

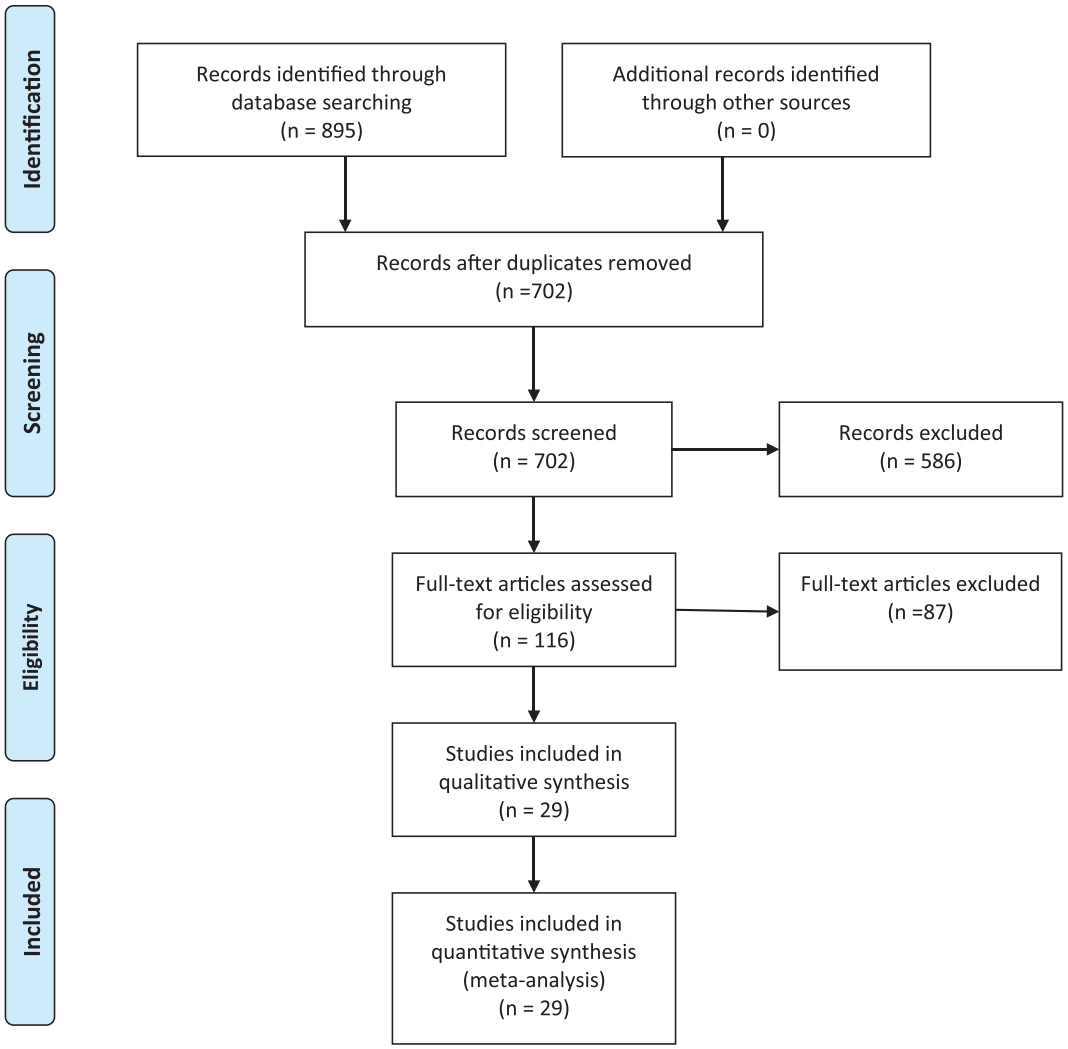

FIGURE 1 Flow chart of study selection process.

TABLE 1 Characteristics of the included studies.

Author	Year	Country	Number of patients		Age (years)		Gender (male/female)		Wagner grading	HBOT intervention	Outcome index
			HBOT	Control	HBOT	Control	HBOT	Control			
Abidia	2003	UK	8	8	72.0 ± 12.6	70.0 ± 6.6	5/3	3/5	1–2	90 min, 0.24 MPa, 5 days/week	①②
Chaudhary	2013	India	20	20	43.8 ± 9.4	45 ± 7.5	10/10	11/9	3–4	60 min, 0.24 MPa, 5 days/week	①
Chen	2017	China	20	18	64.3 ± 13.0	60.8 ± 7.2	10/10	11/7	1–3	120 min, 0.25 MPa, 5 days/week	①②
Chen	2021	China	47	47	62.3 ± 3.5	62.2 ± 3.8	26/21	27/20	1–4	60 min, 0.2 MPa, once/day	①
Doctor	1992	India	18	18	59.8 ± 6.5	60.4 ± 5.6	11/7	12/6	1–3	90 min, 2.5 ATA, 5 days/week	②
Dong	2019	China	34	34	48.79 ± 3.62	48.52 ± 3.44	23/11	21/13	NR	60 min, 2.2 ATA, once/day	①
Duzgun	2008	Turkey	50	50	58.10 ± 11.03	63.3 ± 9.15	37/13	27/23	2–4	120 min, 2–3 ATA, 5 days/week	①②
Faglia	1996	Italy	35	33	61.7 ± 10.4	65.6 ± 9.1	27/8	21/12	2–4	90 min, 2.2–2.5 ATA, 5 days/week	②③
Fedorko	2016	Canada	49	54	61 ± 12	62 ± 12	31/18	38/16	2–4	90 min, 2.44 ATA, 5 days/week	①②③
Huang	2019	China	25	25	60.12 ± 3.97	59.18 ± 4.16	17/8	15/10	1–3	60 min, 2.2 ATA, once/day	①
Jin	2017	China	29	31	61.25 ± 8.12	63.12 ± 9.01	19/10	20/11	NR	NR, 2.0 ATA, NR	①
Kalani	2002	Sweden	17	21	64 ± 14	65 ± 11	12/5	18/3	NR	90 min, 2.5 ATA, 5 days/week	①②③④
Ke	2013	China	30	30	58.72 ± 9.56	58.30 ± 10.62	NR	NR	1–3	60 min, 1.8 ATA, once/day	①
Kessker	2003	France	14	13	60.2 ± 9.7	67.6 ± 10.5	10/4	9/4	1–3	90 min, 2.5 ATA, 5 days/week	①③
Kong	2006	China	34	34	63.7 ± 2.2	62.0 ± 2.2	21/13	22/12	0–5	60 min, 2.0 ATA, once/day	①
Kumar	2020	India	28	26	56.2	59.8	12/3	10/5	NR	45 min, 3 ATA, 2 days/week	①②
Li	2001	China	18	18	55 (45–65)	55 (45–65)	NR	NR	NR	60 min, NR, once/day	①

TABLE 1 (Continued)

Author	Year	Country	Number of patients		Age (years)		Gender (male/female)		Wagner grading	HBOT intervention	Outcome index
			HBOT	Control	HBOT	Control	HBOT	Control			
Liu	2012	China	26	23	54.6 ± 9.2	54.6 ± 9.2	NR	NR	1–4	60 min, 2.0 ATA, once/day	①
Liu	2023	China	37	37	54.32 ± 2.22	54.29 ± 2.18	21/16	20/17	NR	60 min, 2.5 ATA, once/day	①
Londahl	2010	Sweden	38	37	69 (37–95)	68 (28–86)	38/11	38/7	2–4	85 min, 2.5 ATA, 5 days/week	①②③④
Qiu	2015	China	30	30	61.4 ± 15.1	59.7 ± 16.7	16/14	17/13	0–1	60 min, 2.2 ATA, once/day	①
Salama	2019	Egypt	15	15	55.1 ± 7.5	57.7 ± 6.7	12/3	10/5	2–3	60 min, 2.5 ATA, 5 das/week	①②
Santenma	2018	Netherlands	60	60	67.6 ± 10.0	70.6 ± 11.2	51/9	46/14	2–4	60 min, 2.4 ATA, 5 days/week	①②③④
Wei	2012	China	52	44	56.8 ± 7.9	57.1 ± 8.0	NR	NR	0–3	NR	①
Wu	2020	China	21	22	60.4	60.4	NR	NR	1–3	60 min, 2.2 ATA, once/day	①
Ye	2017	China	33	30	65.3	64.6	16/17	14/16	0–1	60 min, 2.0 ATA, once/day	①
Yuan	2019	China	36	36	53.0 ± 13.1	56.0 ± 12.5	19/17	21/15	NR	60 min, 2.0 ATA, once/day	①
Zhang	2005	China	33	33	60.0 ± 3.0	61.0 ± 3.0	16/17	15/18	0–4	50 min, 2.0 ATA, once/day	①
Zhou	2018	China	30	30	55.5 ± 5.7	53.5 ± 6.2	17/13	18/12	NR	120 min, 2.0 ATA, once/day	①

Note: ① Complete ulcer healing; ② Amputation; ③ Adverse events; ④ Mortality rate.
Abbreviation: NR, not report.

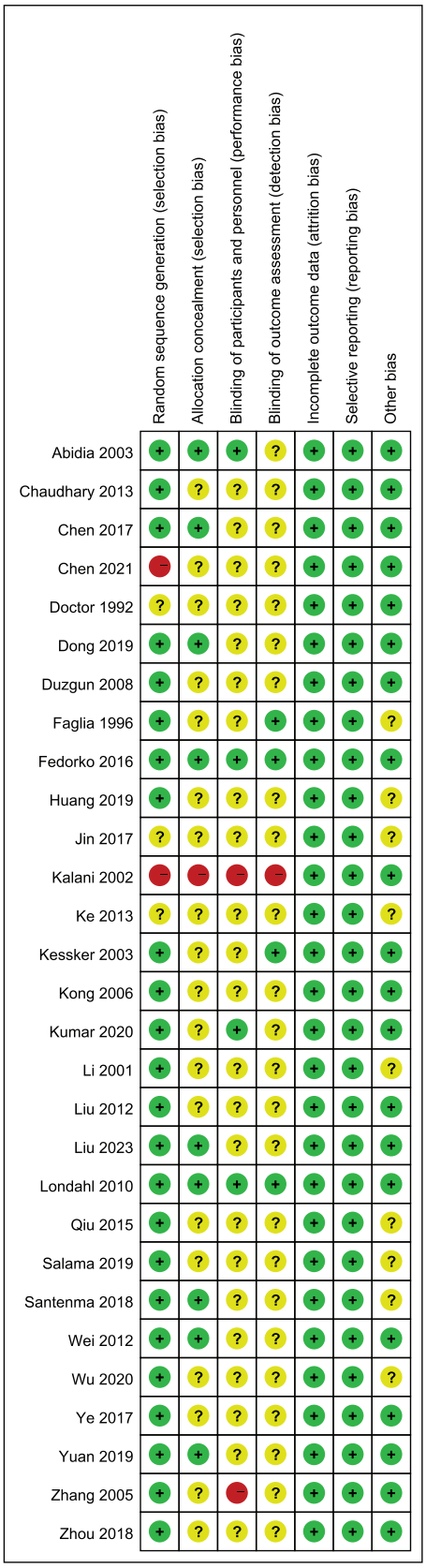

FIGURE 2 The risk of bias summary of the included studies.

Figure 2, where two studies were assessed as high risk using an incorrect randomisation method, and two studies stated that the assessment was of high quality with triple blinding of investigators, subjects and medical assessors. Most of the remaining unclear risks were from unmentioned allocation concealment, blinding and others.

3.3 | Complete ulcer healing

Twenty-seven RCTs reported complete ulcer healing rates, 834 in the HBOT group and 826 in the conventional treatment group. Heterogeneity test showed mild heterogeneity ($p = 0.02$, $I^2 = 39\%$) and a fixed-effects model was applied. The results revealed HBOT significantly increased the complete healing rate of DFUs compared to conventional treatment (46.76% vs. 24.46%, OR: 2.83, 95% CI: 2.29–3.51, $p < 0.00001$) (Figure 3).

3.4 | Amputation rate

Amputation rates were reported in 11 RCTs, 338 in the HBOT group and 340 in the conventional treatment group. Heterogeneity test showed large heterogeneity ($p < 0.00001$, $I^2 = 76\%$), so a random-effects model was applied. The results revealed HBOT reduced the amputation rate in patients compared to conventional treatment (26.03% vs. 45.00%, OR: 0.41, 95% CI: 0.18–0.95, $p = 0.04$) (Figure 4).

3.5 | Adverse events

Adverse events were reported in six RCTs, 213 in the HBOT group and 218 in the conventional treatment group. Heterogeneity test showed no heterogeneity ($p = 0.46$, $I^2 = 0\%$), so a fixed-effects model was applied. The results revealed the incidence of adverse events was significantly higher in HBOT compared to conventional treatment (17.37% vs. 8.27%, OR: 2.49, 95% CI: 1.35–4.57, $p = 0.003$) (Figure 5).

3.6 | Mortality rate

Only three RCTs reported patient mortality, 115 in the HBOT group and 118 in the conventional treatment group. Heterogeneity test showed no heterogeneity in the included studies ($p = 0.46$, $I^2 = 0\%$), so a fixed-effects model was applied. The results revealed there was no difference in the effect of HBOT versus conventional treatment on patient mortality (6.96% vs. 12.71%, OR: 0.52, 95% CI: 0.21–1.28, $p = 0.16$) (Figure 6).

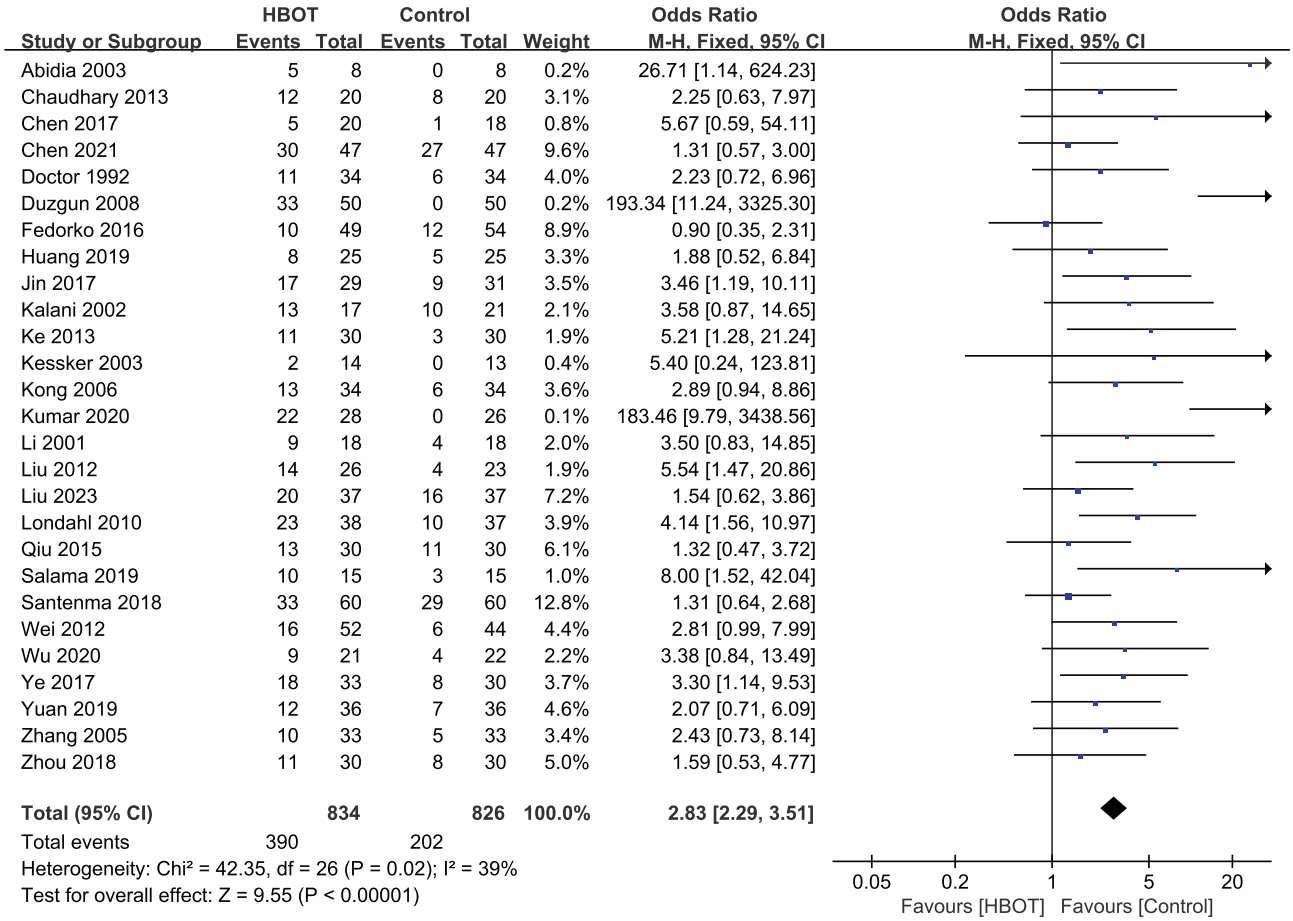

FIGURE 3 The forest plots of complete ulcer healing rate.

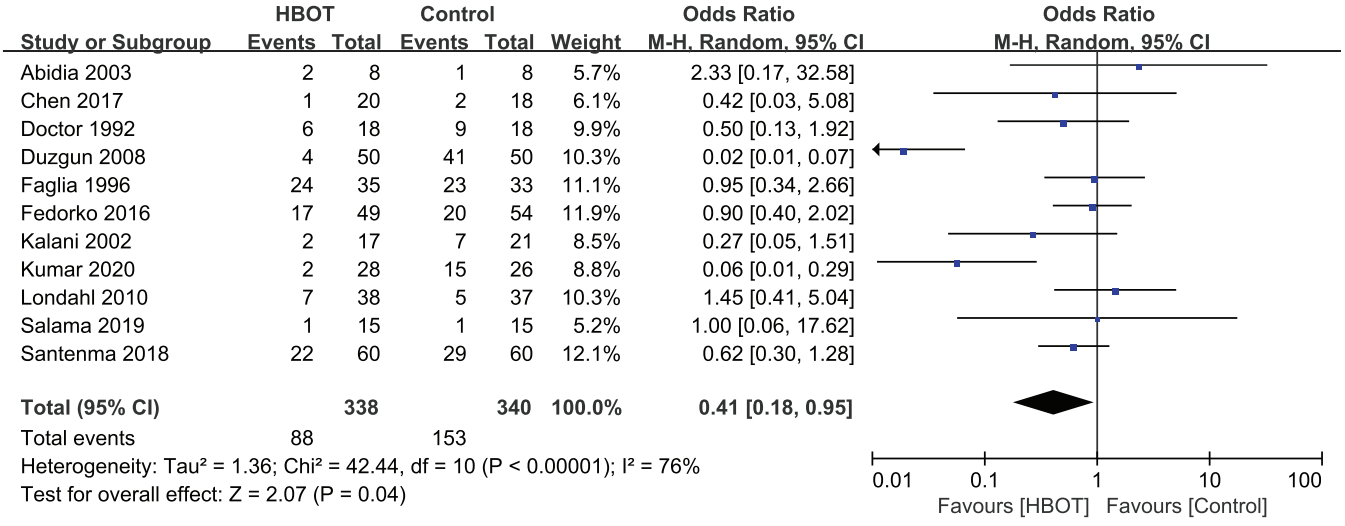

FIGURE 4 The forest plots of amputation rate.

3.7 | Publication bias and sensitivity analysis

A funnel plot of the literature incorporating the rate of complete ulcer healing was plotted, and the results are shown in Figure 7, suggesting a low likelihood of publication bias among the studies. Higher heterogeneity was suggested in the amputation results, and after excluding them one by one, it was found that two results, Duzgun et al. and Kumar et al., had a greater impact on the

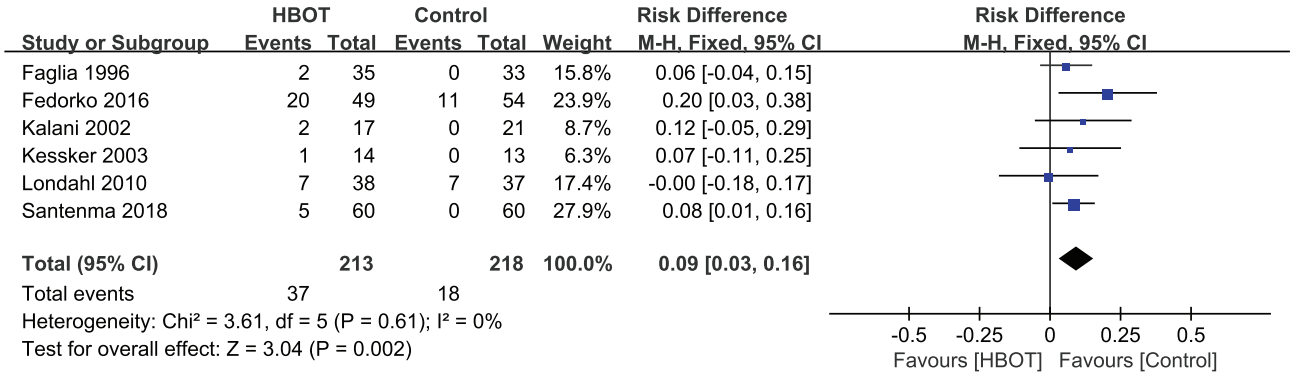

FIGURE 5 The forest plots of adverse events.

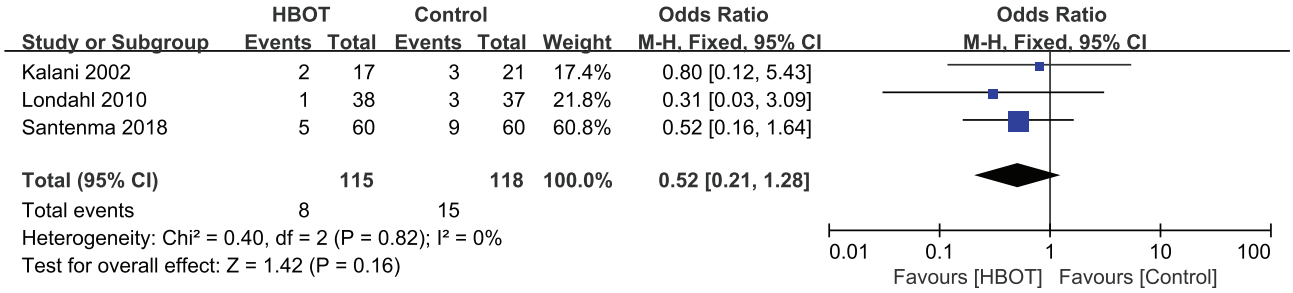

FIGURE 6 The forest plots of mortality rate.

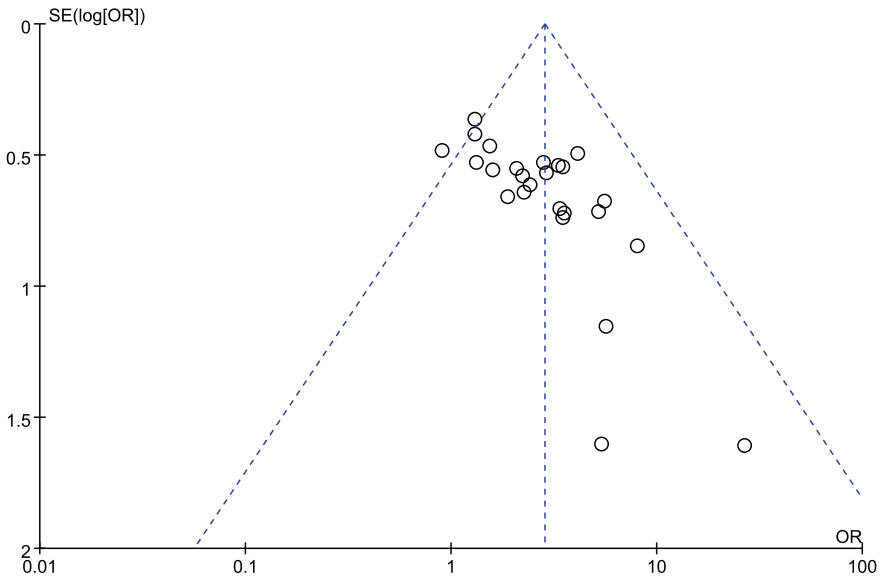

FIGURE 7 Funnel plot for publication bias of complete ulcer healing rate.

heterogeneity, and the heterogeneity was reduced to 0% after the exclusion, suggesting that the results were unstable in the amputation results.

4 | DISCUSSION

DFU is an ischaemic, hypoxic lesion of the foot that becomes infected and ulcerated due to prolonged high blood sugar levels in diabetics.[41] DFU have a high risk of amputation, a long duration of disease and great difficulty in healing. They are a major complication of diabetes and affect the walking function of the patient, and even have the risk of lifelong disability, which poses a serious threat to the patient's quality of life and physical and mental health.[5,42,43] High amputation rate and high recurrence rate cause great trouble to DFU patients and medical workers. More intensive monitoring and active

care of DFU should be initiated when a possible pre-ulcer is detected, and treatment should be individualised as early as possible, this preventive treatment may reduce the incidence of more severe DFU and improve the prognosis of the patient to a certain extent.[44] HBOT has been used for a long time as an adjunctive therapy for diabetic wounds, promoting healing by increasing tissue oxygen levels, enhancing perfusion, reducing oedema, inhibiting inflammation and promoting fibroblast proliferation, collagen synthesis and angiogenesis.[9,45,46]

In this study, the information and data of 29 RCTs totalling 1764 patients were summarised and analysed, and the results revealed HBOT can effectively improve the rate of complete healing of DFU and reduce the rate of amputation, but it will increase the incidence of adverse reactions, whereas it has no significant effect on the mortality rate. Wound healing is a complex process in which oxygen plays a crucial role.[47] In chronic wounds, oxygen levels are decreased, and by increasing oxygen levels in the wound tissue it is possible to accelerate wound healing and reduce bacterial colonisation.[19] Patients in the HBOT group inhaled 100% oxygen above normal atmospheric pressure, which increased the amount of oxygen in the body's cells and maximised tissue oxygenation.[20,48] Londahl's et al.[16] and Sharma's et al.[42] all reported higher rates of complete ulcer healing in patients with DFU receiving HBOT than conventional treatment, consistent with our findings. In Margolis's et al. study, which included 6259 patients with diabetes mellitus, adequate arterial perfusion of the foot and foot ulcers extending to the dermis, the results showed that amputation was not prevented by the use of HBOT, which is in contrast to the findings of our study.[49] However, only two articles in our study concluded that the difference in amputation rates was statistically significant, with Duzgun et al.'s study concluding that HBOT significantly reduced the rate of major amputations, and two RCTs, Duzgun et al. and Kumar et al., concluding that HBOT significantly improved the rate of minor amputations.[15,22] The reason for the difference may be the high heterogeneity of the included relevant studies, making this result less stable, and more homogeneous RCTs need to be included for analysis.

Most of the studies included in this study did not mention the occurrence of significant adverse effects and concluded that HBOT for DFU has few side effects and is safe. However, our results show that HBOT increases adverse effects in patients, the more common of which is middle ear pneumatic pressure injury.[42] When patients are treated in the hyperbaric oxygen pressurisation chamber, the changes in air pressure caused by pressurisation and decompression result in an imbalance of pressure inside and outside the middle ear drum chamber, at which time the mouth of the eustachian tube cannot be opened or is difficult to open, leading to difficulties in regulating the pressure, and an imbalance of pressure between the inside and outside of the drum chamber is likely to induce middle ear pneumatic pressure injury. However, studies have shown that the occurrence of middle ear pneumatic injuries can be prevented if the operation is regular and the speed of pressurisation is strictly controlled.[50] This provides a direction for future patients with DFU to reduce the Brownian response when receiving HBOT. The present study showed that no significant difference was observed between HBOT and conventional therapy in treating the incidence of death in patients with DFU, which is in agreement with Sharma's et al.[42] findings.

This meta-analysis included studies from multiple countries and regions, which increases the generalisation of the findings. However, this meta-analysis has some limitations: (1) although the included studies clearly stated the specific grouping method of the randomised controlled studies, the allocation of concealment and implementation of blinding were not mentioned in more studies, and it is more difficult to implement blinding for this treatment measure, which may lead to an unclear risk of bias; (2) the included studies differed in the intervention time, hyperbaric oxygen pressure and the number of interventions, which may be a source of heterogeneity; (3) the results of the amputation rate were less stable, and more high-quality clinical studies are needed to further validate this conclusion.

5 | CONCLUSIONS

In conclusion, HBOT could effectively increase the complete healing rate of DFU and reduce the amputation rate, but it would increase the incidence of adverse reactions, while it had no significant effect on mortality. Due to the limitation of the quality and quantity of the included literature, more high-quality RCTs are still needed to evaluate the effectiveness and safety of HBOT as an adjunctive treatment for DFU at a later stage.

CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

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

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