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Review Article

Efficacy of hyperbaric oxygen therapy for diabetic foot ulcers: An updated systematic review and meta-analysis

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SUMMARY

The present systematic review and meta-analysis was performed to evaluate the efficacy of hyperbaric oxygen therapy (HBOT) in the treatment of diabetic foot ulcers (DFUs). Relevant articles were retrieved from PubMed, the Cochrane Library, EMBASE and other databases through November 2020. A total of 20 randomized clinical trials and 1263 trials were included in the meta-analysis. For each trial, the average difference, odds ratio and 95% confidence interval were calculated to evaluate the efficacy. Hyperbaric oxygen therapy increased the healing rate of diabetic foot ulcers (relative risk, 1.901; 95% CI = 1.484 −2.435, $p < 0.0001$), shortened the healing time (MD = −19.360; 95% CI = −28.753~-9.966, $p < 0.001$), and reduced the incidence of major amputation (relative risk, 0.518, 95% CI = 0.323−0.830, $P < 0.01$). In summary, our meta-analysis confirmed that hyperbaric oxygen therapy offers great benefits in the treatment of DFU and the reduction of amputation. In addition, larger and well-designed randomized controlled trials need to be planned and conducted to verify this conclusion.

1. Introduction

Diabetic foot ulcer (DFU) is a severe diabetic complication that has the potential to cause high morbidity and impose considerable treatment costs.[1,2] Additionally, the rate of DFU development in characters with diabetic neuropathy is increased.[3] Complex wounds represent a major challenge for clinicians and wound care specialists.[4] Hyperbaric oxygen is a therapy that promotes fibroblast proliferation, enhances immune function, and stimulates angiogenesis.[5,6] Hyperbaric oxygen therapy has been recommended and used in wound ulcers. However, the method lacks adequate scientific validation of efficacy or safety.[7] On the other hand, A. R. Berendt et al argued that hyperbaric oxygen for DFU is not effective.[8] Boulton suggested that it is important to focus on estimating the quality of life of patients and the final outcome to assess their utility.[9] Consequently, we performed this meta-analysis to confirm the efficiency of hyperbaric oxygen therapy for DFU.

2. Materials and methods

2.1. Trials and search formula

We searched all relevant studies from the PubMed, Cochrane, Excerpta Medica Database (EMBASE), China National Knowledge Infrastructure (CNKI) and Wanfang Data Information Service platform databases to retrieve valid trials. To confirm the efficiency of hyperbaric oxygen therapy for diabetic ulcers, we employed a search formula that contained both keywords and medical subject heading (MESH) terms, such as “diabetic foot,” “foot ulcer,” “leg ulcer,” “hyperbaric oxygenation,” and “hyperbaric oxygen therapies”. The retrieval time was from the establishment of the database to November 2020. The study retrieval process is presented in Fig. 1.

2.2. Inclusion criteria

Following our search formula, studies were retrieved based on the following criteria: (1) patients with diabetic foot ulcer (no limit on grade); (2) the case group was treated with hyperbaric oxygen therapy; (3) the control group received conventional treatment or placebo treatment; (4) randomized controlled trial; (5) outcomes

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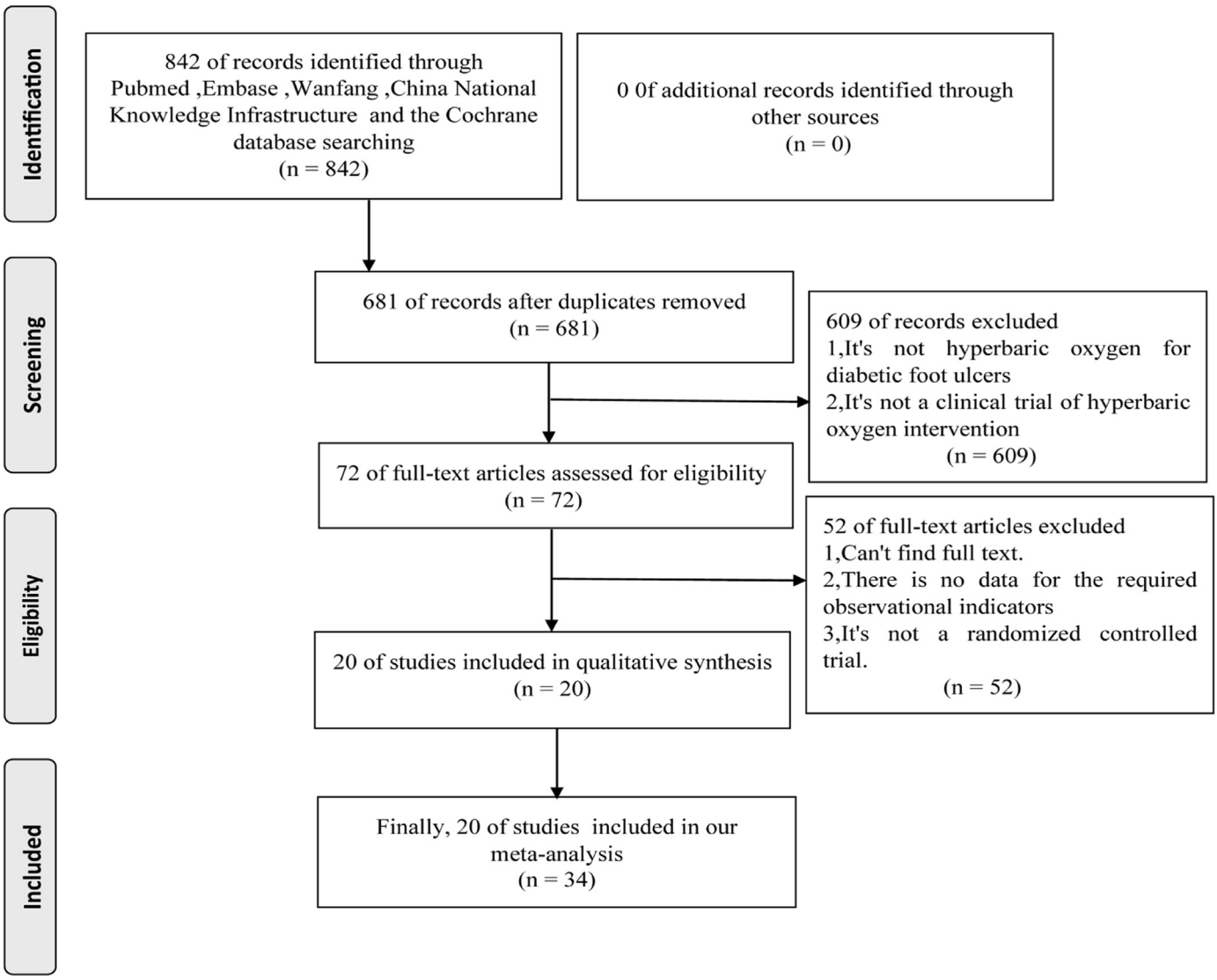

Fig. 1. RISMA diagram.

included wound healing time, wound healing rate, granulation tissue formation time, amputation rate, or incidence of adverse events; and (6) articles were in English or Chinese.

2.3. Exclusion criteria

Articles were excluded for the following criteria: (1) research subjects without diabetic foot ulcer patients; (2) nonrandomized controlled trials; and (3) research with incomplete or unavailable data.

2.4. Data extraction

Data from all relevant studies were extracted and input into data abstraction forms independently by two researchers. During the screening, the articles with different opinions were discussed with other authors. All of the following valid data are listed in Table 1: the first author, country, study subject, Wagner grading, course of disease, number of control groups and case groups, treatment measures, treatment time, follow-up time, and observation index.

2.5. Quality evaluation

The quality of the enrolled studies was assessed according to the RCT risk assessment tool. The risk of tool is recommended in the Cochrane Manual 5.1.0 and assesses selective bias, implementation bias, measurement bias, follow-up bias, reporting bias and so on. The quality of the overall studies was divided into three levels: low bias (the possibility of bias was small, and 4 or more items met the criteria of low risk of bias); moderate bias (there was a moderate probability of bias, 2 or 3 items met the criteria of low risk of bias); and high bias (there was a high probability of bias, 1 or more items met the high risk criteria or only 1 or none items met the low risk criteria). The quality of all selected studies is shown in Fig. 2.

2.6. Statistical analysis

We employed STATA16.0 software to perform our meta-analysis. The risk ratio was used for the combined statistical analysis for the dichotomous variables. The continuous variables calculated the weighted mean difference for combining statistics. Both variables were assessed with the 95% confidence interval (CI). The statistical

Table 1
Characteristics of included studies.

Include in the literature	Study site	Subject	Wagner grading	Course of disease	N/n	Treatment time	Follow-up time	Observation Index
M. Londahl[10]	Sweden	Chronic foot ulcer	2–3	Median ulcer duration was 11.8 and 10.3 months (HBOT vs Placebo)	37/38	8–10 weeks	12 months	③
A. Abidia[11]	United Kingdom	Diabetic foot ulcer	1–2	Control group: average 9 months; experimental group: average 6 months.	8/8	6 weeks	12 months	③④⑤
Xinyan Niu[12]	China	Diabetic foot ulcer	Unspecified	Unspecified	30/30	Unspecified	None	③
Ludwik Fedorko[13]	The United States	Diabetic foot ulcer	2–4	Control group: 336–528 days; experimental group: 227–235 days.	54/49	12 weeks	12 weeks	③④⑤⑥
MAGNUS LONDAHL[14]	Sweden	Diabetic foot ulcer	2–4	The median duration of ulcers was 10 months	37/38	8–10 weeks	12 months	③④⑤⑥
Katrien T.B[15]	Netherlands	Diabetic foot ulcer	2–4	Control group: average 6 months; experimental group: average 5.6 months.	81/39	8 weeks	12 months	③④
Ying Dong[16]	China	Diabetic foot ulcer	Unspecified	Control Group: the longest course of ulcer was 2 years, the shortest course was 20 days, the average was (0.87 ± 0.42) years; experimental group: the longest course was 3 years, the shortest course was 24 days, the average was (1.12 ± 0.51) years.	34/34	2 months	None	③
Yaoping Huang[17]	China	Diabetic foot ulcer	1–3	The course of ulcer was 22 d–3 years in control group and 18 d –2.7 years in experimental group.	25/25	52 days	None	③
Zhengyu Zhang[18]	China	Diabetic foot ulcer	0–5	In control group, the course of disease ranged from 10 to 189 days, with an average of (50.3 ± 12.5) days, and in experimental group, from 10 to 210 days, with an average of (48.2 ± 13.8) days	33/33	34–36 days	None	③
Shaozhi Deng[19]	China	Diabetic foot ulcer	0–5	Control group: 34–76 days; experimental group: 29–85 days.	42/43	122 days	None	②③
Shunyong Li[20]	China	Diabetic foot ulcer	Unspecified	The duration of the disease is 2 months and 10 days	18/18	30 days	None	②③
Lei Kong[21]	China	Diabetic foot	0–5	Unspecified	34/34	40–61 days	None	③
Xia Yuan[22]	China	Diabetic foot ulcer	1–5	Unspecified	36/36	30 days	None	③
Jie Liu[23]	China	Diabetic foot ulcer	1–4	The average duration of diabetic foot was (55.3 ± 12.2) days	23/26	2 months	None	③
Shimaa E[24]	Egypt	Diabetic foot ulcer	2–3	Control group: 15.5 ± 1.4 weeks; experimental group: 16.5 ± 1.5 weeks.	15/15	2 months	8 weeks	③
Chen-Yu Chen[25]	China	Diabetic foot ulcer	1–3	Control group: 34.9 ± 33.6 days; experimental group: 59.1 ± 48.8 days.	18/20	4 weeks	2 weeks	③
Arife Polat Duzgun[26]	Turkey	Diabetic foot ulcer	2–4	>4 weeks	50/50	20–30 days	92.12 weeks	③
Ezio FAGLIA[27]	Italy	Diabetic foot ulcer	2–4	Unspecified	33/35	Unspecified	None	④⑤⑥
Atit Kumar[28]	India	Diabetic foot ulcer	2–4	The treatment group was 8 ± 2.1 months (3 ± 40), while the control group was 9 ± 2.9 months (3 ± 39)	26/28	6 weeks	1 year	②
Nilesh[29]	India	Diabetic foot ulcer	Unspecified	Unspecified	15/15	2 weeks	2 years	④⑤

①Granulation time; ②Wound healing time; ③Wound healing rate; ④Major Amputation; ⑤Minor Amputation; ⑥Incidence of adverse events.

heterogeneity among the included studies in the meta-analysis was analyzed using the $\chi 2$ test. The test level was set at $\alpha = 0.10$, and the heterogeneity was quantitatively evaluated by I^2. In this study, $P > 0.10$ and $I^2<50\%$ indicated no statistical heterogeneity among the studies, and the fixed-effect model was used for pooled analysis. In contrast, $P \leq 0.10$ or $I^2 \geq 50\%$ suggested statistical heterogeneity among studies, and a random effects model was used for analysis. In the forest map, $P \leq 0.05$ indicated a statistically significant difference. When the heterogeneity was large, references were removed one by one to observe the heterogeneity changes, to determine the source of heterogeneity, or to perform further analysis through subgroups.

2.7. Sensitivity analysis

If necessary, we performed sensitivity analyses. The influence of individual studies on the combined effect size was observed to judge its stability.

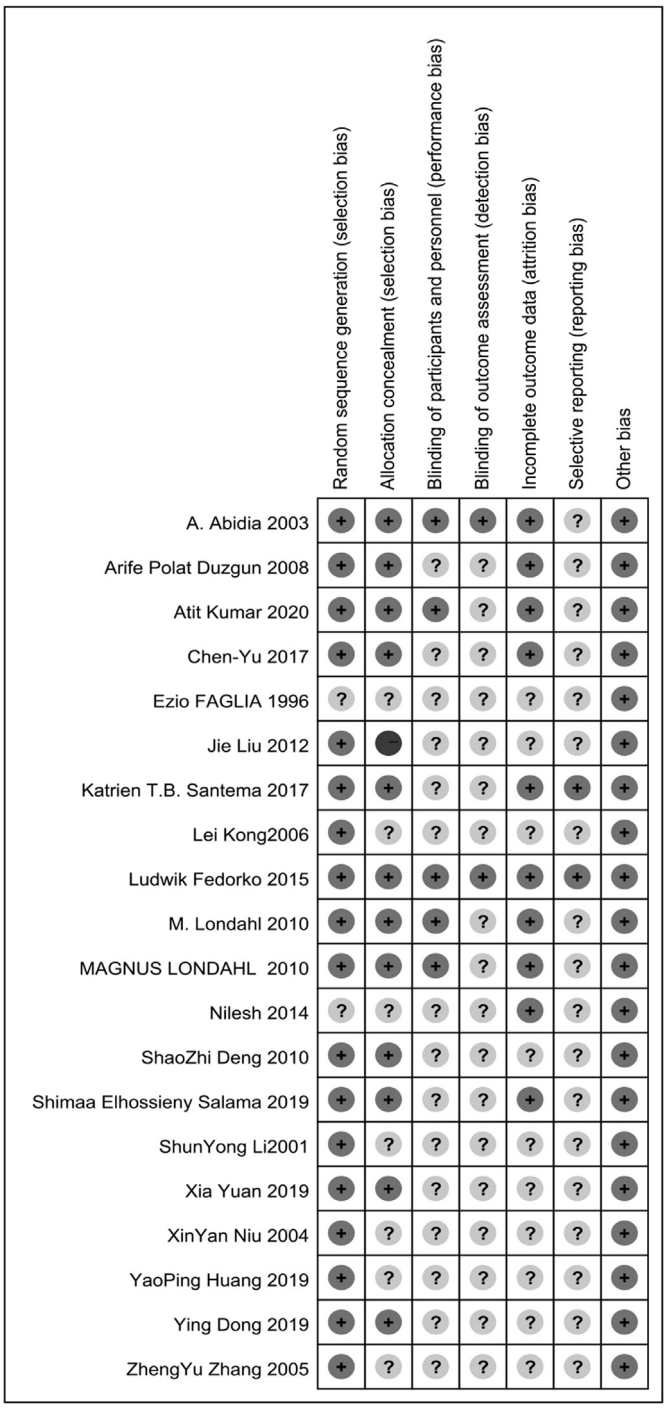

Fig. 2. Risk of bias (%) within studies according to the Cochrane risk of bias assessment for randomized trials.

3. Results

3.1. Characteristics of retrieved studies

The characteristics of the included studies are summarized in Table 1. A total of 1263 patients were eventually included in 20 studies, including 614 in the experimental group and 649 in the control group.

3.2. Quality assessment of the studies

The assessment of the risk of bias for the retrieved trials is displayed in Fig. 3. All studies reported randomized controls,[10–29] 13 studies randomly assigned methods, 5 studies were randomized by computer, 4 studies used sealed envelopes to randomly group participants, 3 studies randomly grouped participants using a random number table, 1 study was ranked as having a high risk of bias based on the order of admission, and the remaining 7 studies were judged as unclear. Five trials reported that the investigator and subjects were double-blinded. One study reported that the investigator and subjects were double-blinded, but the hyperbaric medicine technician was not. Two studies claimed researchers, subjects and medical evaluators were triple blinded. Two studies reported outcome evaluator blindness. However, the statuses of other studies were unclear.

Follow-up bias. Mlondahl et al had 2 patients who worsened and were lost to follow-up. Katrien TBY had 2 control groups, and 3 experimental group patients had no follow-up. In total, 10 studies reported follow-up time. The others did not mention follow-up, so the judgment was unclear.

Reporting bias. Three studies reported the clinical trial registration information, and the clinical trial registration numbers were NCT00621608, NCT00953186 and NTR3944.

3.3. Results of the meta-analysis

Healing time. Three trials reported wound healing time. However, incomplete data from Li et al prevented the inclusion of this study in the analysis. The combined effect size of the remaining two trials showed no significant heterogeneity among the trials ($I^2 = 0\%$; $P = 0.463$). Pooled analysis using the fixed-effect model showed that the difference was statistically significant (MD = −19.360; 95% CI = −28.753~ −9.966; $P < 0.001$; Fig. 4). The results revealed that HBOT reduced the healing time of DFU compared with the control group.

Healing rates. The wound healing rate was reported in 17 studies. Healing was defined as ulcers that were completely covered by epithelial regeneration. The combined effect size results were presented ($I^2 = 39.7\%$, $P = 0.047$). The heterogeneity among the studies was large. We used the random effects model to merge the effects ($I^2 = 29.7\%$, $P = 0.120$). Pooled analysis using the random-effects model demonstrated that the difference was statistically significant (RR = 1.901; 95% CI = 1.484–2.435, $P < 0.0001$; Fig. 5). The results showed that HBOT improved the healing rate.

3.3.1. Major and minor amputation

Major Amputation. The most serious complication (major amputations, defined as amputations above the ankle joint) was assessed in 6 trials, and the combined effect size results demonstrated that there was no significant heterogeneity among studies ($I^2 = 42.4\%$, $P = 0.123$). The pooled results from the fixed-effects model showed that the difference was statistically significant (RR = 0.518, 95% CI = 0.323–0.830, $P < 0.01$; Fig. 6), and the results demonstrated that HBOT therapy reduced the risk of major amputation.

Minor Amputation. Five trials provided data on minor amputations distal to the ankle joint. There was no evidence to suggest statistical heterogeneity ($I^2 = 0.0\%$, $P = 0.854$). Pooled analysis using the random-effects model demonstrated that the difference was statistically significant (RR = 1.444; 95% CI = 0.992–2.102, $P = 0.055$; Fig. 7). The results showed that there was no significant difference in the risk of minor amputation between HBOT and conventional therapy. Finally, we found that there was no difference in total amputation rate between HBOT and conventional

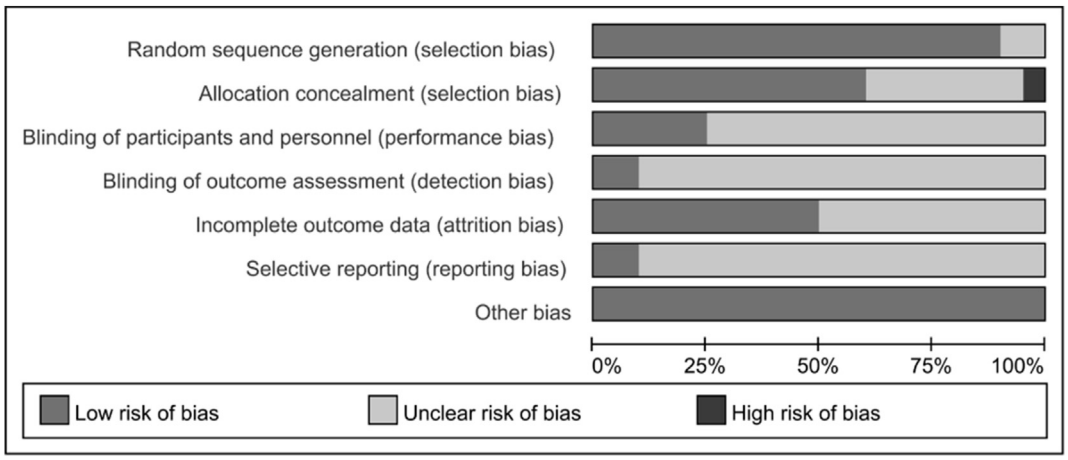

Fig. 3. The assessment of the risk of bias for the retrieved trials.

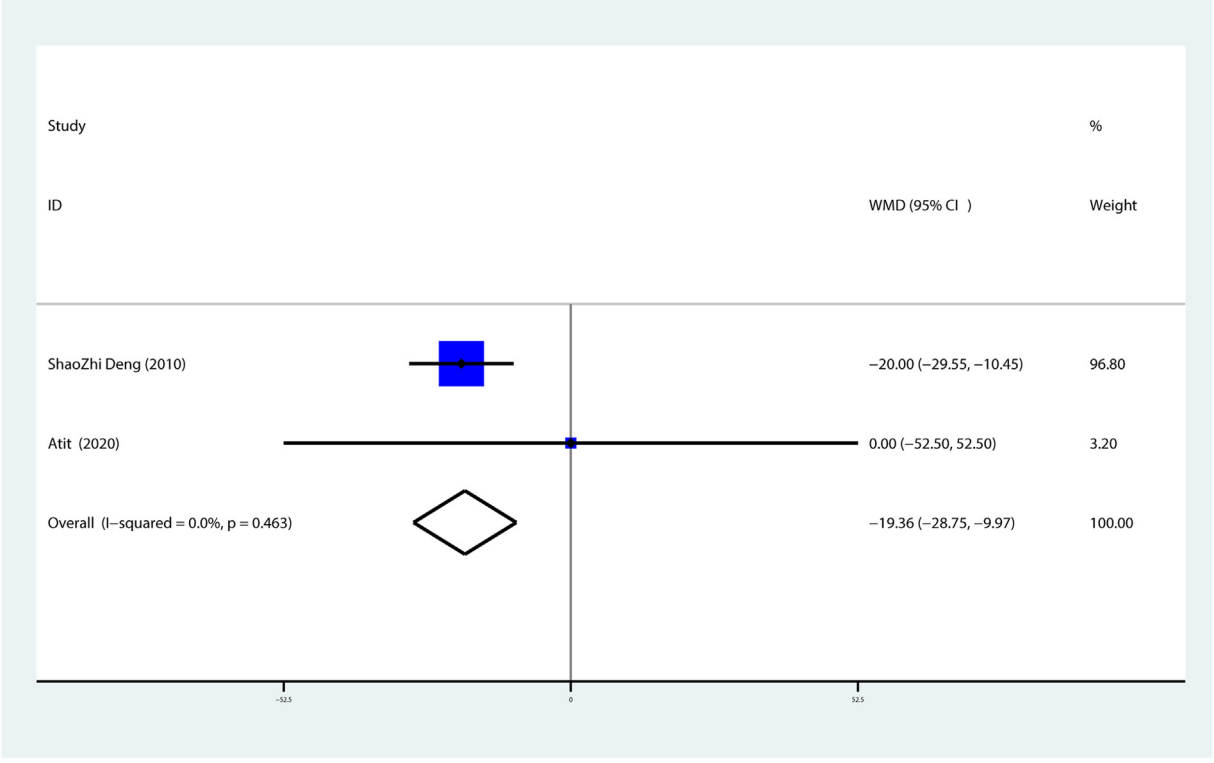

Fig. 4. Forest plot of the meta-analysis on healing time.

therapy (36.2% vs 35.7%).

Adverse reactions. Three studies included adverse reactions, and the combined effect size results demonstrated that there was no significant heterogeneity among studies (I^2 = 39.7%, P = 0.456). Pooled analysis using a fixed-effect model revealed no statistically significant difference (RR = 1.324; 95% CI = 0.834–2.101; P = 0.234, Fig. 8).

Quality of life. Three studies mentioned measures of quality of life in patients. A. Abidia reported that hyperbaric oxygen did not improve the quality of life. Dong Ying and Yaoping Huang's research shows that hyperbaric oxygen therapy can improve the quality of life. In the study by A. Abidia, quality of life was measured using the generic form SF-36 and Hospital Anxiety and Depression Scale. No significant difference was noted between the experimental group and the control group. The quality of life of the hyperbaric oxygen group was not improved. Ying Dong used the Hamilton Anxiety Rating Scale to compare the anxiety of the two groups, and the result was that the hyperbaric oxygen group relieved patient anxiety. Yaoping Huang compared pain grade and pain relief in the hyperbaric oxygen group to the control group, and the difference was statistically significant.

Sensitivity Analysis and Publication bias. We used STATA 16.0 to perform some sensitivity analyses. Regarding the healing rate of DFU, the result was stable. The sensitivity analysis funnel diagram is shown in Fig. 9. We assessed publication bias based on the P-value of Begg test. The P values of the Begg test were more than 0.05, and their 95% CIs of intercept included zero in the Begg publication bias plots. This result indicated that the meta-analysis funnel plots were

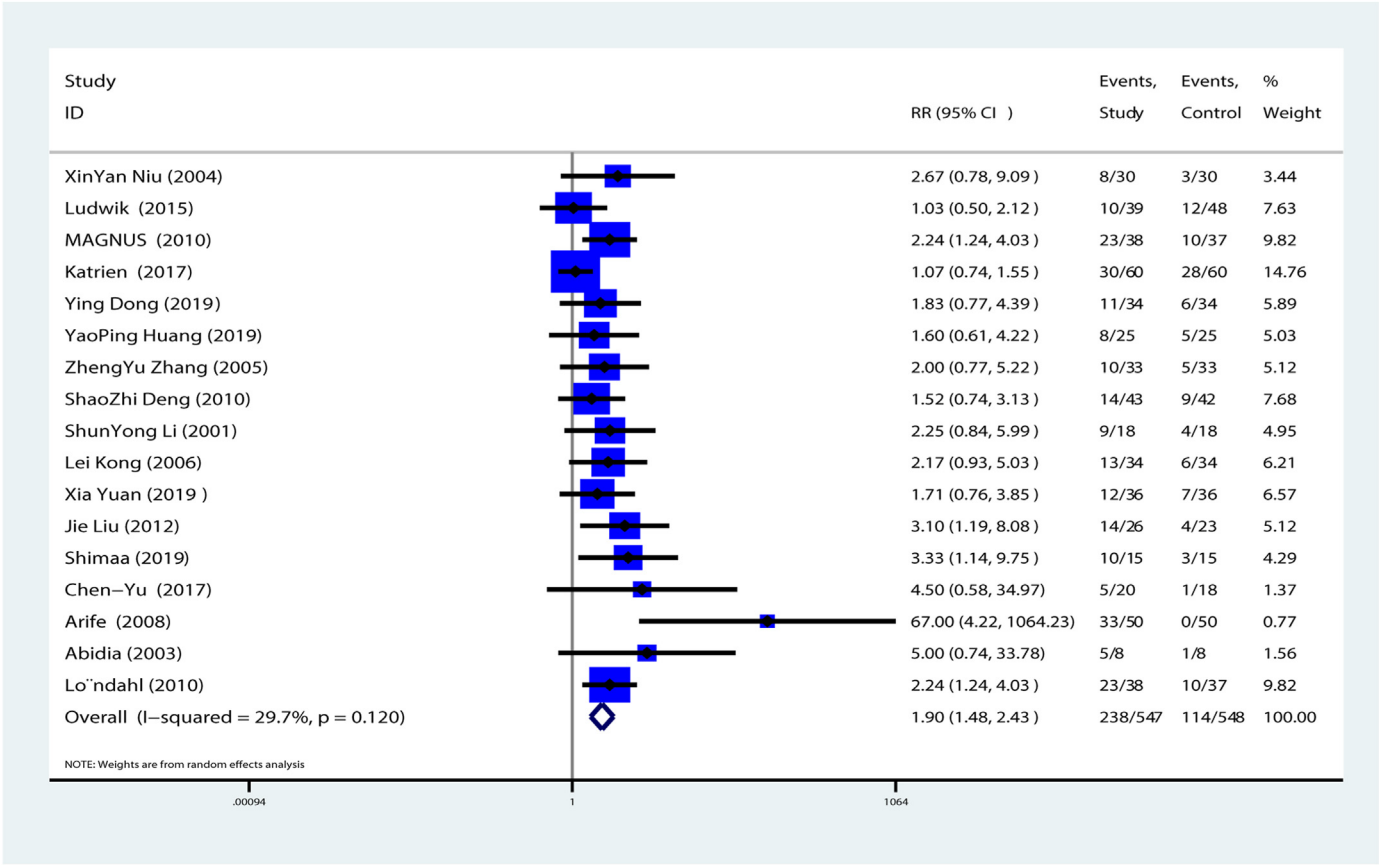

Fig. 5. Forest plot of the meta-analysis on healing rate.

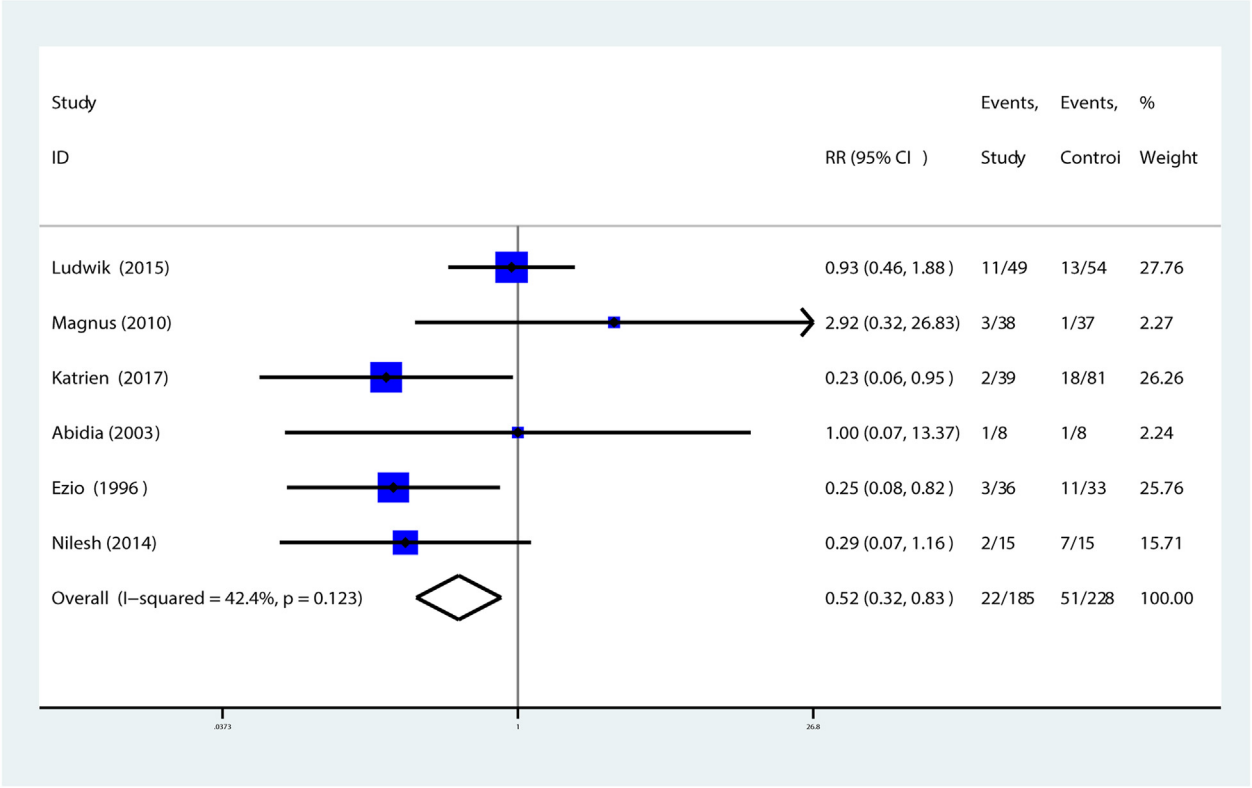

Fig. 6. Forest plot of the meta-analysis on major amputation.

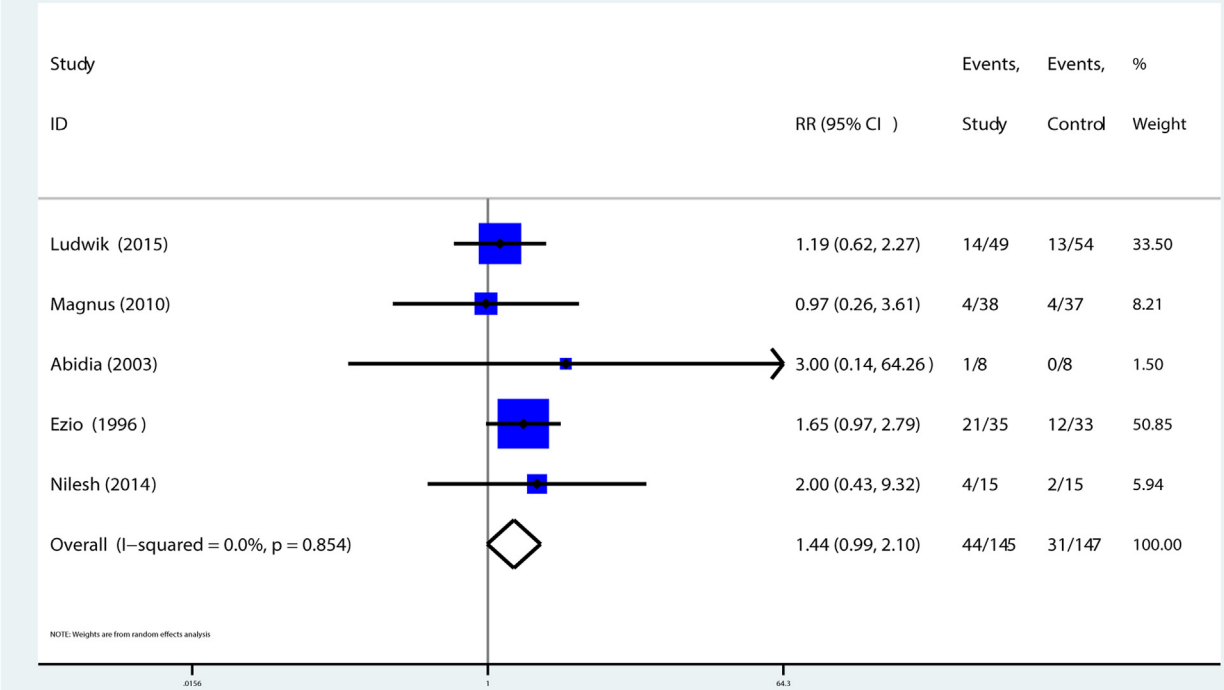

Fig. 7. Forest plot of the meta-analysis on minor amputation.

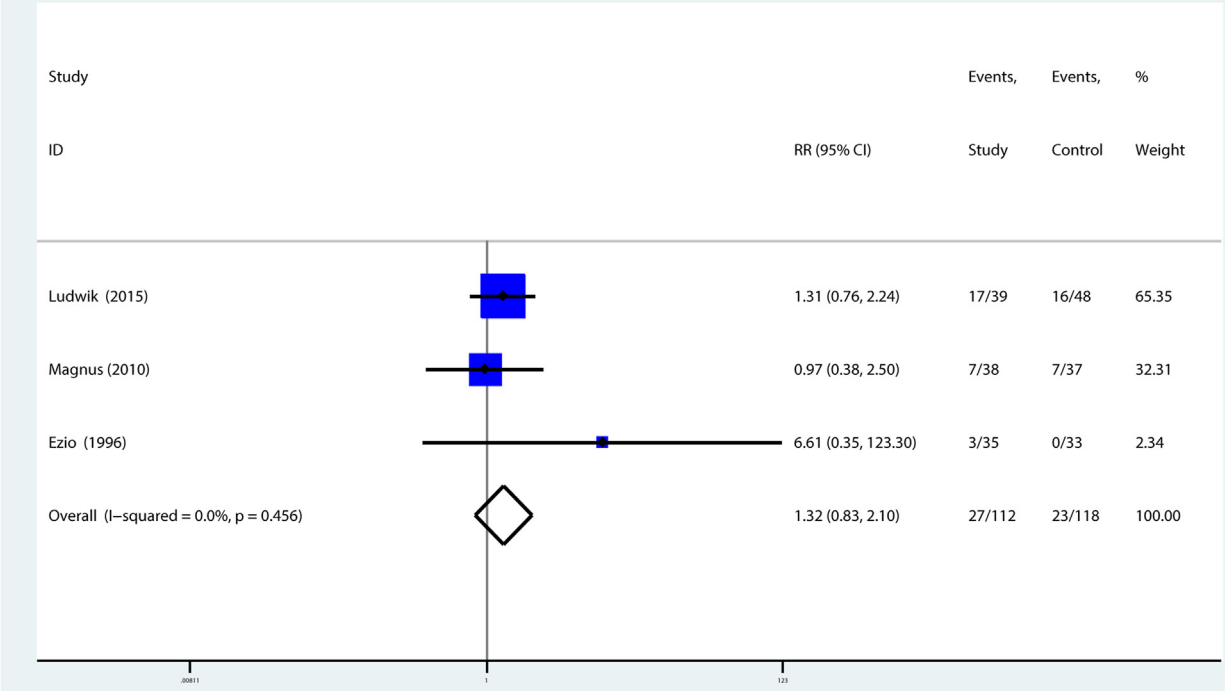

Fig. 8. Forest plot of the meta-analysis on adverse reactions.

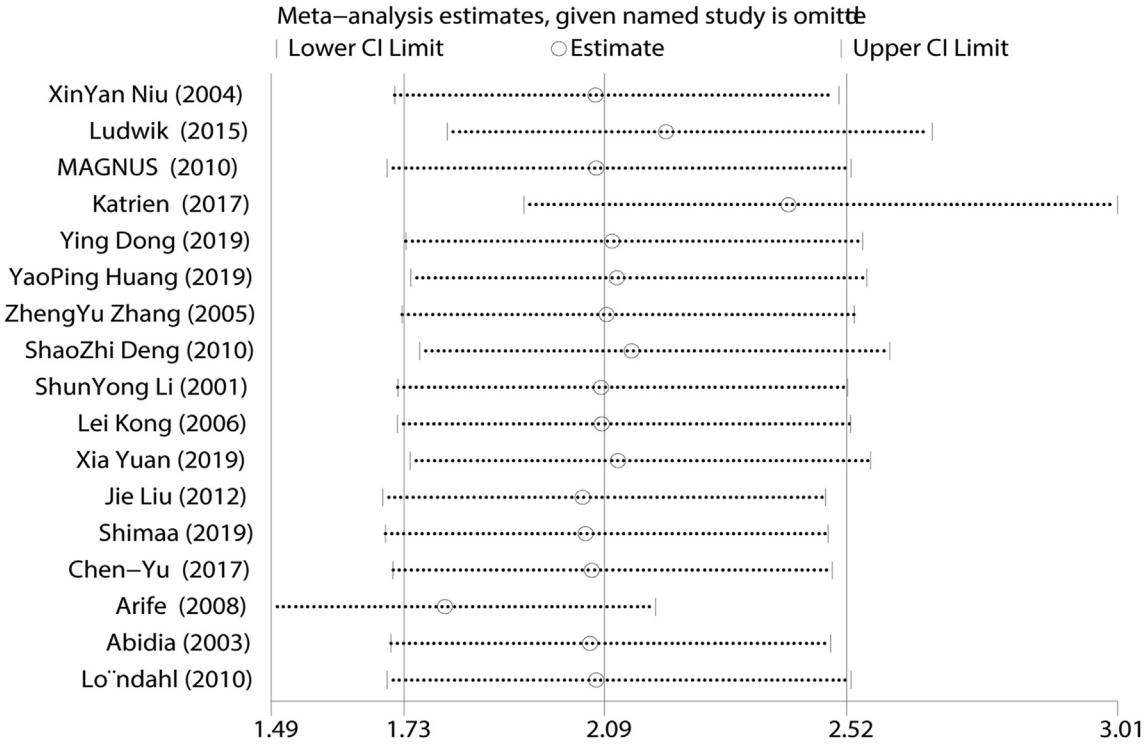

Fig. 9. Plot of the sensitivity analysis on healing rate.

Table 2
The publication bias consequences.

Study subject	RR(95%I)	P	Test for hetergeneity		Analysis model
			I2%	P	
Minor Amputaion	0.160(‘-41.741–2.062)	0.806	0	0.854	Random model
Major Amputaion	‘-0.363(‘-4.231–3.504)	0.807	42.4	0.123	Fixed model
Adverse rate	1.324(0.834–2.101)	0.234	0	0.456	Fixed model
Healing rate	2.416(1.941–3.008)	0	29.7	0.12	Random model
Healing time	19.360(9.966–28.753)	0	0	0.463	Fixed model

symmetrical without publication bias. The publication bias consequences were listed in Table 2. In conclusion, there was no publication bias between the major amputation and minor amputation of DFU. The funnel plot of healing rate revealed an apparent asymmetry that suggested the presence of a potential publication bias, a language bias, inflated estimates by a flawed methodologic design in smaller studies, and a lack of publication of small trials with opposite results. Begg's funnel plots are shown in Fig. 10, Fig. 11 and Fig. 12.

4. Discussion

Diabetic foot ulcer is the main cause of amputation and disability in many diabetic patients. Even with the best care and treatment, ulcers cannot be cured completely. Since the 1990s, scientists have found that hyperbaric oxygen is effective in treating diabetic foot ulcers.[1,3,30] However, there is a lack of sufficient experimental studies to confirm the effectiveness of the therapy. Consequently, we updated this meta-analysis to confirm the efficiency of HBOT for diabetic foot ulcers. In addition, this meta-analysis differs from previous meta-analyses in that our research was restricted to RCTs. We not only analyzed the clinical outcomes of HBOT in the treatment of diabetic foot ulcers but also summarized the quality of life of the included studies.

We included 20 prospective randomized trials in this article. Our study confirmed that HBOT has a beneficial effect on healing DFUs and can reduce the healing time. With respect to amputation, our findings indicate that HBOT may decrease amputations. No significant relationship was noted between hyperbaric oxygen and the adverse reactions of the patients who had diabetic foot ulcers. Regarding the cost, we could not assess the cost given that none of the trials included reported the burden of the therapy.

Most similar meta-analyses are consistent with our results, but there is some controversy as to whether HBOT can reduce the rate of amputation and whether it can improve the quality of life. The study conducted by Robin J[31] et al showed that there was no difference in the quality of life between the HBOT group and the control group. This finding is different from our research results. The difference can be explained by the different characteristics of the two studies. We also conducted two other trials to prove that hyperbaric oxygen therapy can improve the quality of life of patients receiving HBOT. Rakesh Sharma[32] et al conducted a meta-analysis of 14 controlled trials (including 12 RCTs and 2 non-randomized controlled trials) and proved that HBOT is effective for large amputations and can reduce adverse events, but has no effect on the rate of small amputations. R M Stoekenbroek[33] et al conducted a similar meta-analysis and proved that there is insufficient evidence that HBOT can reduce the amputation of diabetic

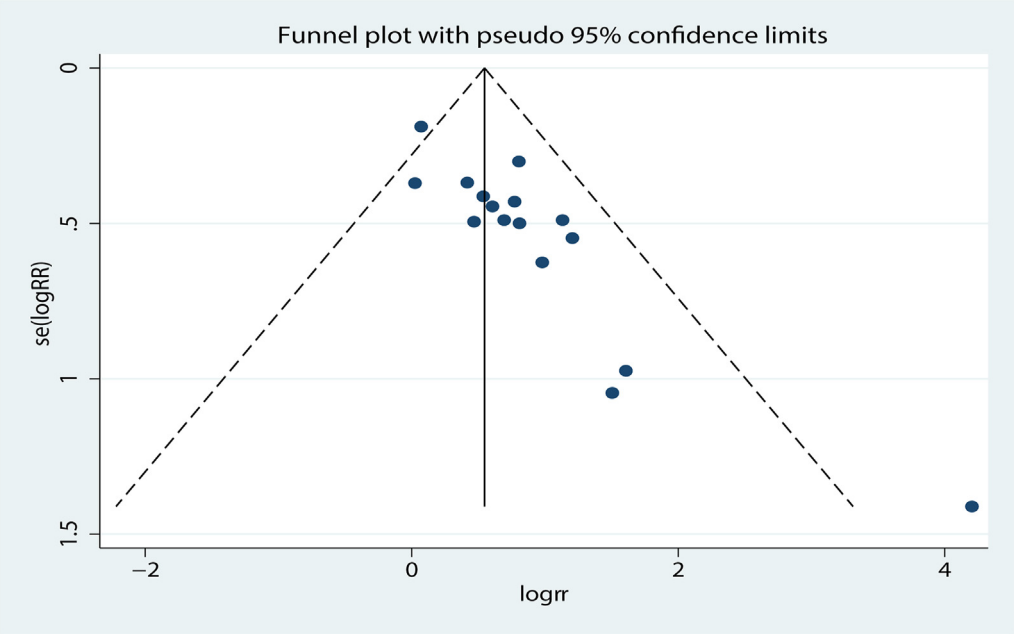

Fig. 10. Funnel chart of publication bias on healing rate.

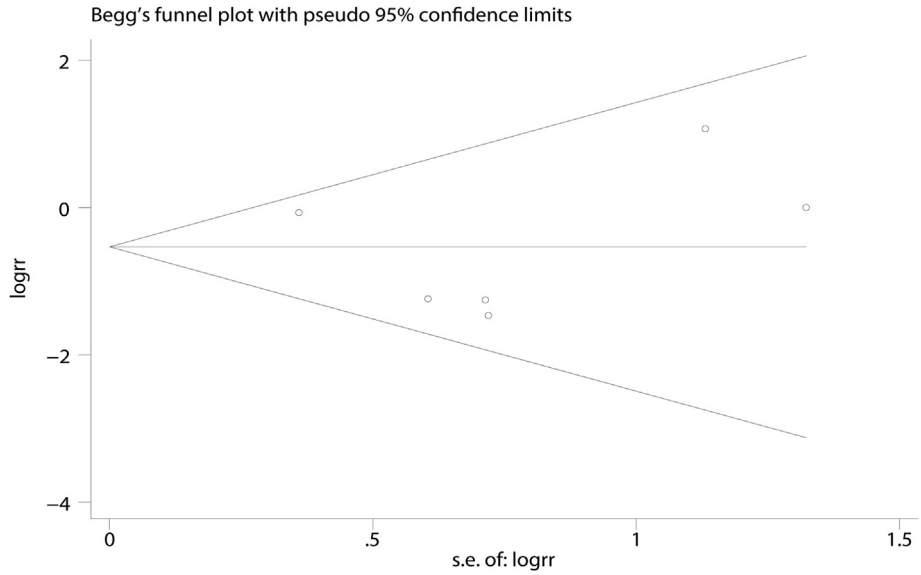

Fig. 11. Funnel chart of publication bias on major amputation.

ulcers. This difference may be due to the inclusion of non-English articles. The study performed by Di Zhao[34] et al displayed that compared with standard treatment (ST), HBOT has no difference in the incidence of ulcers, the risk of amputation, and adverse events. But it proves that HBOT reduces the ulcer wound area larger than ST. J. Golledge[35] et al believed that HBOT can improve the healing of diabetes foot ulcers and reduce large and small amputations. O'Reilly[36] et al conducted a study which was included in observational studies. It showed HBOT significantly reduced the risk of major amputation (RR = 0.39, 95% CI: 0.21–0.73), which is consistent with our findings. But research designed in this way is obviously biased.

In contrast to previous studies, our meta-analysis comprised more sample sizes of the cases and controls. In addition, to eliminate the bias of the meta-analysis, we recruited studies published in the Chinese literature. Finally, we only included RCT trials. These factors can improve the credibility of our study. Consequently, our research offers a more convincing evaluation compared with previous studies.

However, this article also has a multitude of limitations. First, the low number of participants for adverse reactions might result in inadequate statistical power to investigate the efficiency of HBOT. Next, significant heterogeneity was noted in the findings reported. Therefore, we performed subgroup analyses and sensitivity analysis to determine the cause of the heterogeneity. Therefore, our results should be cited with caution.

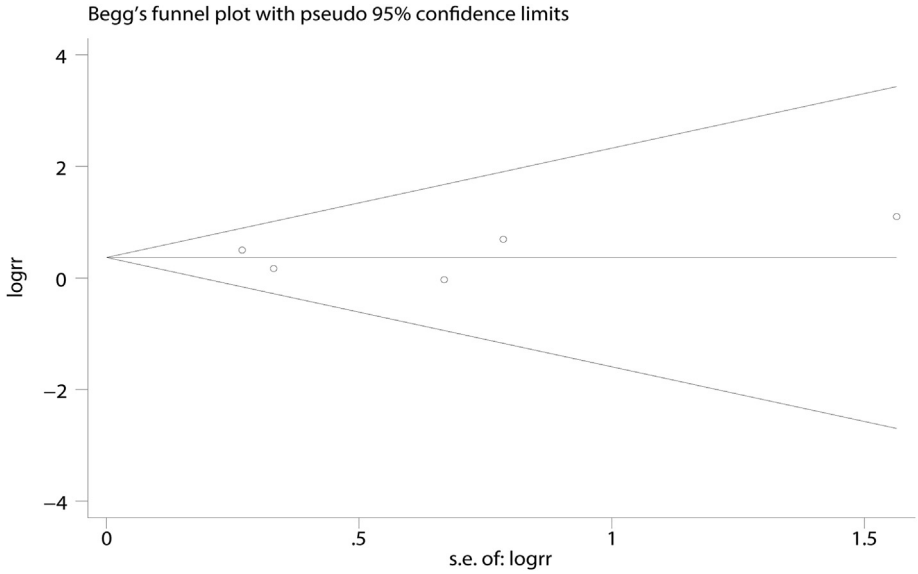

Fig. 12. Funnel chart of publication bias on minor amputation.

5. Conclusion

To sum up, this meta-analysis suggests that HBOT has a substantial benefit in healing DFU and decreasing amputation. Given these limitations, a larger number of trials are needed to evaluate the efficacy and burden of HBOT for healing DFU.

Declaration of competing interest

All authors have claimed no conflict of interest.

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