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ARTICLE

Could hyperbaric oxygen be an effective therapy option for pathological scars? A systematic review and meta-analysis

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ABSTRACT

Background: Hyperbaric oxygen (HBO) therapy involves breathing pure oxygen or a high oxygen concentration above atmospheric (ATM) pressure in an enclosed chamber. Studies on pathological scars have demonstrated that HBO can inhibit the formation of pathological scars.

Objective: To evaluate the efficacy of HBO in the treatment of pathological scars *via* meta-analysis.

Methods: Searches were run on various databases, including the Cochrane, Embase, PubMed, Web of Science, and CNKI databases. A comparative study was conducted on patients with pathological scars treated with or without HBO. We used RevMan 5.4 software to determine the recurrence rate, treatment satisfaction, and Vancouver Scar Scale(VSS) score in the pathological scar.

Results: A total of 543 publications were identified; after screening, four were selected for review, including one randomized controlled trial (RCT), one controlled clinical trial (CCT), and two retrospective cohort studies. Meta-analysis results showed that HBO treatment reduced the pathological scar recurrence rate after surgery and radiotherapy (OR = 0.26, 95% CI: 0.13–0.52, $p = 0.0001$). Patients had higher satisfaction after HBO therapy (OR = 4.45, 95% CI: 1.49–13.30, $p = 0.007$). The Vancouver scar scale (VSS) score of patients with pathological scars was significantly improved in the HBO group (SMD: −3.82, 95% CI: −6.07to −0.49, $p = 0.02$).

Conclusions: HBO treatment decreased the recurrence rate of pathological scars after surgery and radiotherapy, increased patient satisfaction, and reduced the VSS score, thus providing a new way to treat pathological scar hyperplasia. However, evaluation of the longer-term effects of HBO treatment requires further comprehensive studies, including more RCTs.

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Introduction

The wound healing process involves numerous biological processes, including hemostasis inflammation, cell proliferation, and scar formation remodeling. Pathological scars, including keloids and hypertrophic scars, and hypertrophic scars tend to soften over time, but keloids propend to expand beyond the original wounds. These mainly occur after surgery, burns, and trauma and are characterized by continuous local inflammation and excessive collagen deposition [1,2]. In addition, excessive development of pathological scarring often causes pain, pruritus, contracture, and other dysfunction, which are detrimental to physical and mental health [3–6]. Multiple studies on pathological scar formation have been conducted for decades. Scholars have recently identified many therapeutic strategies for preventing or reducing excessive scarring, such as surgery, radiotherapy, steroid injection, pressure therapy, cryotherapy, and laser therapy and so on [7,8]. However, most treatments remain clinically unsatisfactory; owing to the poor efficacy of conventional approaches, new therapeutic strategies are critically needed [9–11].

HBO therapy involves inhalation of pure oxygen or a high oxygen concentration in an environment maintained above one ATM and is widely used to accelerate the recovery of wounds [12] and provide more effective healing by reducing the development of scars [13]. A Cochrane review found that HBO can promote local wound blood supply, thereby alleviating radiation tissue injury [14]. The animal experiment demonstrated that HBO can activate the apoptosis pathway and inhibit pathological scar formation [15]. Zhou *et al*'s study found that HBO therapy can reduce glial scar formation after spinal cord injury by inhibiting the AKT and NF-kB pathways.

We found that HBO may affect pathological scar formation. However, the specific efficacy of HBO therapy on pathological scars has not yet been reported. Therefore, we hoped to identify the effectiveness of HBO treatment for pathological scars. Herein, a meta-analysis was used to examine the recurrence rate (the proportion of keloids that reappeared at the site of the lesion) after treatment, satisfaction and the VSS score on scar appearance of patients with pathological scars treated with HBO or non-HBO. The patients' satisfaction score about current health status on a scale of 1–10 before and after the whole course of treatment. The progression of the VSS score was defined as changes in the scar scores before and after therapy (Table 1). This study was the first to analyze the effectiveness of HBO in pathological scars and sought to provide a scientific basis for clinical treatment.

Methods

The meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

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Table 1. Vancouver scar scale.

Pigmentation	Vascularity	Pliability	Height (mm)
0 Normal	Normal	Normal	Normal
1 Hypopigmentation	Pink	Supple	<2
2 Hyperpigmentation	Pink to red	Yielding	2–5
3	Red	Firm	>5
4	Red to purple	Banding	
5	Purple	Contracture	

Data sources and search strategies

An investigation of eligible articles using the Cochrane, Embase, PubMed, and Web of Science databases for all studies published before January of 2021 was conducted. The search terms were: "Cicatrix [Mesh]", "Keloid [Mesh]", "Scar", "Cicatrices", "Hyperbaric oxygen therapy", and "Hyperbaric oxygen treatment". No language limits were applied to the search parameters. Titles, abstracts, and full texts of relevant research were included. In addition, other applicable articles were manually searched.

Inclusion and exclusion criteria

Inclusion criteria: (1) subjects: patients with keloids or hypertrophic scars; (2) type of intervention and comparison: HBO treatment alone compared with other treatments or HBO treatment after conventional treatment; (3) outcome measures: recurrence after surgery and radiotherapy, satisfaction, and VSS score; and (4) study with complete general information (e.g. author, publication year, patient clinical information, experimental protocol and outcome). The exclusion criteria: (1) animal research, reviews, case reports, conference documents and another non-clinically controlled study; (2) not including HBO therapy; and (3) the evaluation index of the study did not include the above outcomes or was unable to extract data.

Selection of relevant studies

Xie evaluated the eligibility of all studies searched using the predetermined selection criteria. The abstracts of all studies were reviewed to exclude articles based on the exclusion criteria. Full-text reviews were performed to determine whether the remaining studies satisfied the inclusion criteria.

Data extractions

Xie and Chen independently extracted the outcomes from the included studies. The predictor variables were HBO treatment or non-HBO treatment. The primary outcomes were recurrence rate, satisfaction, and progression of VSS score. Researchers screened the data by reading the titles and abstracts of the full text. Author name, publication date, study type, the mean age of patients, sex, scar type, sample size, intervention measures, and outcome were obtained.

Assessment of risk of bias

The Cochrane Collaboration tool [16] was used to help assess the risk of bias in the included studies: (1) Random sequence generation (selection bias). How were the participants randomized to groups? (2) Allocation concealment (selection bias). Was the group allocation of participants unknown to the recruiting trialist? (3) Blinding (performance and detection bias). Was a reliable method of blinding therapy employed? (4) Blinding of participants and personnel (performance bias). Can we be confident participants and trial personnel were unaware of allocation? (5) Blinding of outcome assessors (detection bias). Were those measuring outcomes unaware of allocation? (6) Incomplete outcome data (attrition bias). Were missing data a potential source of bias? (7) Selective reporting (reporting bias). Were planned outcomes missing in the trial report?

Statistical analysis

Review Manager (RevMan) software version 5.3 was utilized in all statistical analyses following Prisma's guidelines for meta-analysis. Odds ratio (OR) and standardized mean difference (SMD) were used as the effect endpoints for the counting and measurement data. All effect sizes were expressed at 95% confidence intervals (CIs) to evaluate the efficacy of HBO in the scars treatment. Heterogeneity test: $p \geq 0.1$ and $I^2 \leq 50\%$ indicated homogeneity between studies and used a fixed-effect model. $p < 0.1$ or $I^2 > 50\%$ indicated statistical heterogeneity between studies, using the effects model.

Results

Literature screening and data extraction

A total of 543 records were obtained from the Cochrane, Embase, PubMed, Web of Science, and CNKI databases, of which 149 duplicates were deleted. The screening process consisting of a review of the titles and abstracts excluded 370 studies, as they did not meet the inclusion criteria. A total of 24 articles were reviewed for eligibility by accessing the full text. Four articles were finally included for meta-analysis after excluding five animal experiments, seven case reports, one review, and seven studies that did not involve related data (Figure 1). The primary characteristics of the study were listed in Table 2. Among the four studies, we identified 117 patients with hypertrophic scars and 330 patients with keloids. Two studies on keloids reported recurrence rates and progress in VSS scores after treatment. Two other studies on hypertrophic scars reported objective satisfaction. These articles were published between 2018 and 2020. The follow-up time of the study ranged from 1 to 48 months.

Risk of bias

The four studies [17–20] did not provide a method for random sequence generation and were judged as unclear risks. Song's study [20] was assigned a high allocation of hidden risk according to the date of hospitalization. The studies of Chen and Chang [18,19] did not report assigned hidden risk and were therefore classified as assigned hidden risk unclear. Guo's study [17] used the random number table for allocation, and it was assessed to have a low risk. Two studies [17,18] were unblinded and may affect the study results, thus evaluated as high risk. The blinding of participants and personnel was not described in the studies of Chen and Song [19,20]. Three studies [18–20] were evaluated as having a low risk for blinding of outcome assessment. We found no blinding assessment in Guo's study [17], and the risk was considered as an uncertain risk. All four trials had a low risk of incomplete outcome data, selection reports, and other biases (Figure 2).

Results of the meta-analysis

A total of 447 patients were enrolled in the meta-analysis. Subgroup analysis was performed based on different outcome indicators.

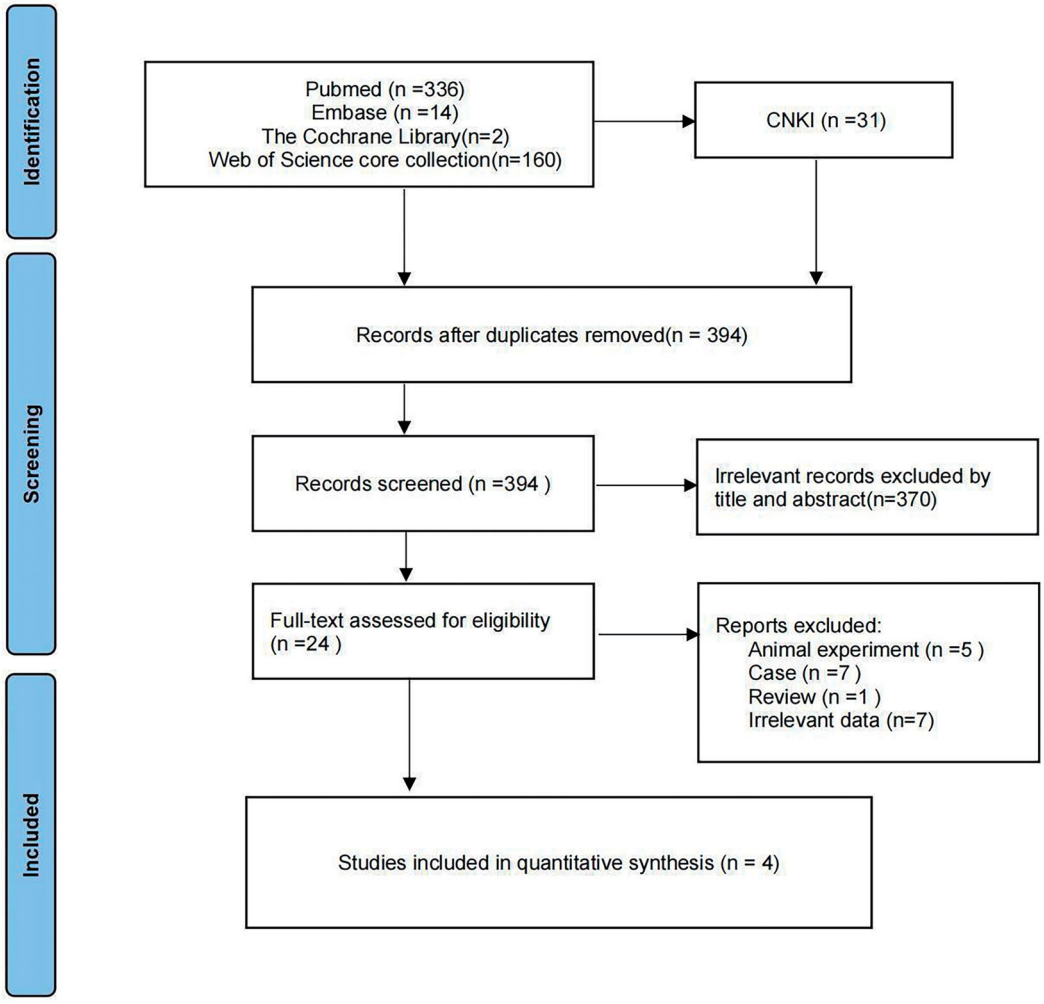

Figure 1. Flow diagram of the systematic review of the literature.

Table 2. Clinical data of included studies.

Author(Y)	Guo (2019) [17]	Chang (2020) [18]	Chen (2018) [19]	Song (2018) [20]
Study design	CCT	Retrospective cohort study	Retrospective cohort study	RCT
Outcome measurements	VSS, recurrence	Satisfaction	Satisfaction	VSS, recurrence
Age (Y, $\bar{X}\pm s$)	31.95 ± 9.76	2–24	37.0 ± 9.2	26.10 ± 0.58
HBO/Non-HBO	31.66 ± 9.05		49.4 ± 17.4	28.06 ± 0.92
Sex (M/F)	20/22	82/-	15/3	33/101
	22/26		15/2	32/74
Disease	Keloid	Hypertrophic scars	Hypertrophic scars	Keloid
Follow-up (mo)	12	5–48	1	20.5/
Treatment (Arm1)	Surgery, radiotherapy; HBO	HBO	HBO	Surgery, radiotherapy; HBO

Recurrence rate

We conducted a pooled analysis to identify whether treatment with HBO would result in a lower pathological scars recurrence rate after surgery and radiotherapy compared with non-HBO [17,20] (Figure 3A). A fixed-model meta-analysis involving 330 patients yielded a pooled relative risk for recurrence of 0.26. HBO treatment reduced the rate of pathological scars recurrence (95% CI: 0.13–0.52, $p = 0.0001$), and the difference was statistically significant.

VSS score

We explored the VSS scores of HBO therapeutic implementations on pathological scars. Two studies [17,20] provided useful data regarding significant decreases in scars' VSS scores. These brought together 57 HBO therapy cases and 74 non-HBO therapy cases. There was high heterogeneity between studies ($p < 0.00001$, $I^2 = 96\%$). For this combined analysis, we used a random effect term of the group. The VSS score was significantly lower in the HBO group than in the non-HBO group (SMD: −3.28, 95% CI: −6.07 to −0.49, $p = 0.02$) (Figure 3B), which showed a significant improvement in scar appearance.

Satisfaction

Finally, two trials included utilized satisfaction as the primary outcome [18,19]. A heterogeneity test showed no heterogeneity among the trials ($p = 0.61$, $I^2 = 0\%$). The satisfaction was

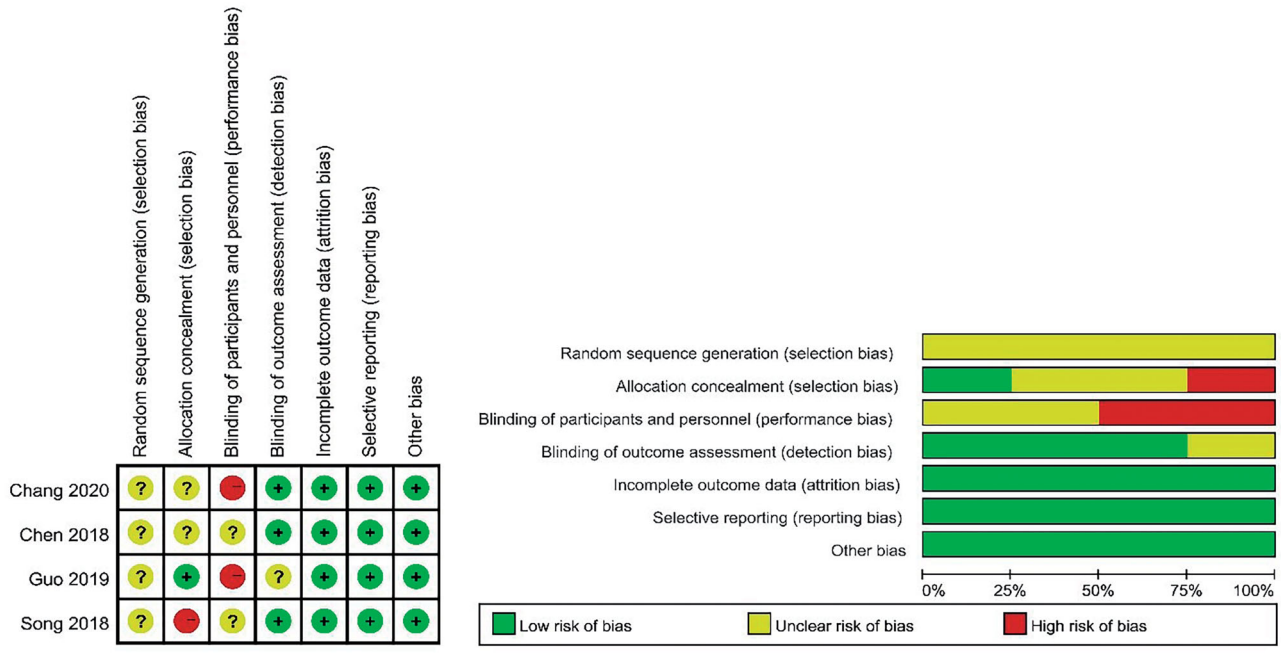

Figure 2. Review authors' judgments about each methodological quality item for each included study. +, low risk; −, high risk; ?, unclear risk.

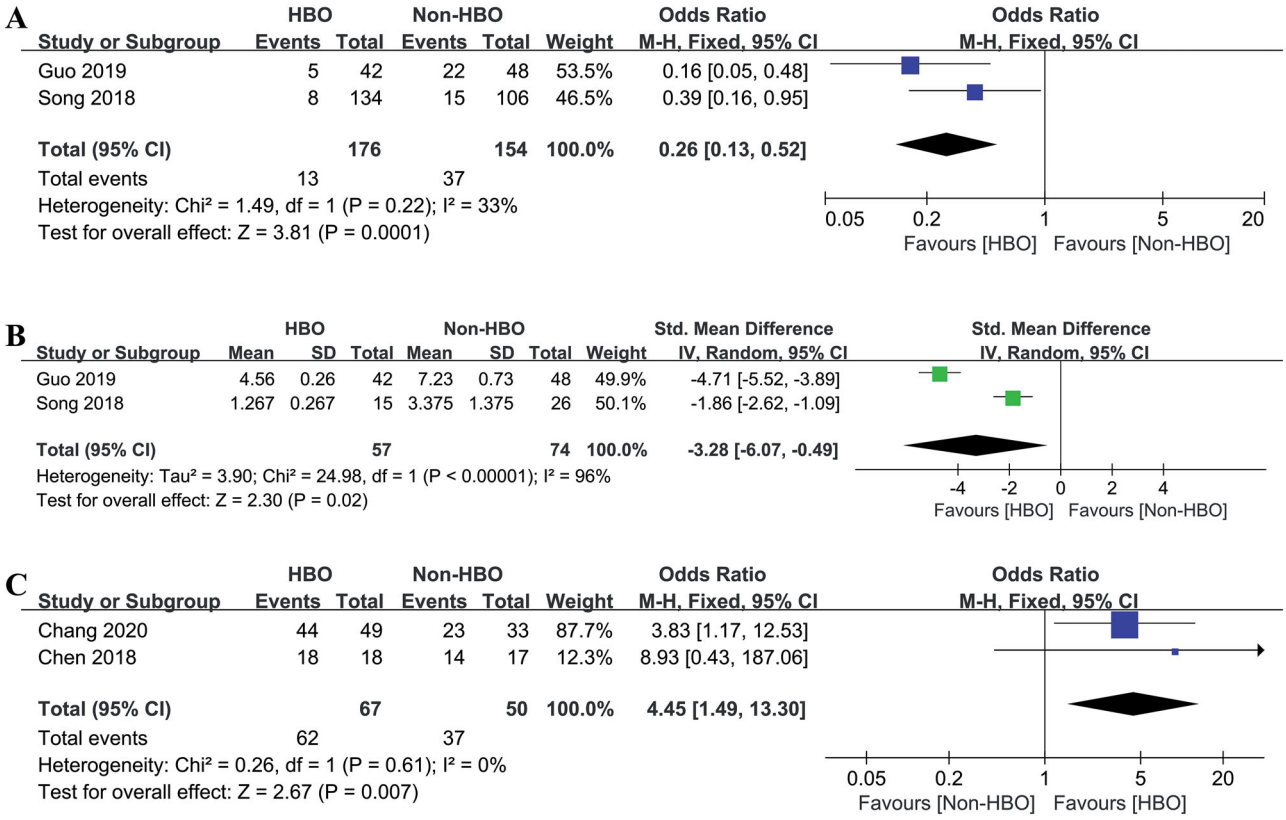

Figure 3. (A) Forest plot to compare the recurrence rate between the group treated with HBO and non-HBO. (B) Forest plot to compare the satisfaction between the group treated with HBO and non-HBO. (C) Forest plot to compare the VSS score between the group treated with HBO and non-HBO.

significantly higher in the HBO group than in the non-HBO group (OR = 4.45, 95% CI: 1.49–13.30, $p = 0.007$) (Figure 3C).

Through analysis, we found that the efficacy of HBO therapy was significant in the treatment of pathological scars, including ameliorating the appearance of the scars, reducing the recurrence rate after treatment and improving patient satisfaction.

Discussion

Pathological scars are characterized by excessive growth caused by cell proliferation and collagen synthesis during the wound healing process. The current study focused on the molecular mechanism of scar formation and antiscar strategies [21].

However, an effective treatment method for pathological scars has not been found so far [22]. Hypoxia is a critical feature of the pathological scar microenvironment. However, oxygen is essential for many intracellular and extracellular antioxidant mechanisms. Overgrowth of dense fibrous tissue causes scar tissue hypoxia, and a lack of protective antioxidant function prolongs the inflammatory period [23]. HBO therapy is frequently used in plastic surgery to treat skin flap transplantation and chronic wounds improves the skin flap survival rate and promotes the healing of burn wounds [24]. In HBO therapy, pure oxygen at a pressure >1 ATM is inhaled. By distributing the oxygen along a pressure gradient, the quantity of oxygen that dissolves in the interstitial fluid and plasma will rise to a level exceeding the dissociation of oxygenated hemoglobin, which can deliver a much higher oxygen partial pressure to the pathological scar tissues [25–27]. Recent studies confirmed that HBO therapy could reduce inflammation, release symptoms of itching, and pain in keloid patients, and restrain the formation of extracellular matrix (ECM) [28–30]. The expression level of HIF-1α was higher in keloid tissue than in the normal skin tissue, and it was significantly reduced after HBO therapy. The oxygen dissolved in the blood inhibited the collagen synthesis and excessive ECM synthesis by suppressing HIF-1α activation [31–34]. Furthermore, some studies have shown that HBO can inhibit scar growth by downregulating VEGF expression and reducing blood perfusion [35]. However, the actual effectiveness and mechanism of HBO treatment in pathological scars is unclear. As the first meta-analysis to analyze the effectiveness of HBO in pathological scars, the purpose of this study was to provide a new method of evaluating the effect of HBO. The meta-analysis based on these studies showed that HBO significantly ameliorated the appearance of the pathological scars, reduced the recurrence rate after surgery and radiotherapy and increased patient satisfaction.

There were significant improvements in evaluation indicators from pre- to post-HBO treatment, which indicated that it was considered meaningful to investigate the effects of HBO on pathological scars. In summary, our meta-analysis compared the efficacy of HBO and non-HBO in pathological scars. However, further evaluation is necessary to determine the efficacy of HBO due to insufficient high-quality evidence. The articles and data contained in this meta-analysis were limited. Most reports did not describe the blinding method and allocation hiding in the random method, which may cause a high risk of deviation. Therefore, more studies are required to determine the mechanism by which HBO treatment improves pathological scarring. In addition to large-sample, high-quality RCTs are needed to assess the efficacy and adverse effects of prophylaxis with HBO therapy.

Conclusion

Overall, this meta-analysis showed that HBO therapy may be a good therapeutic strategy in the treatment of patients with pathological scars. This therapy can decrease recurrence, increase patient satisfaction and ameliorate appearance. Future large-scale and long-term studies with sufficient follow-up will clarify the effectiveness of HBO therapy for pathological scars.

Acknowledgment

The authors Xie and Chen both contributed equally to the study design and acquisition of the data. Xie drafted the manuscript, performed a quality evaluation of the study and conducted mathematical models. Results analysis and interpretation were undertaken by Xie and Chen. Both authors Xie and Chen have read and approved the final manuscript.

Disclosure statement

The authors indicated no potential conflicts of interest. This study was exempt from institutional review board approval.

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