Original Article

Efficacy and safety of recombinant human granulocyte-macrophage colony-stimulating factor hydrogel in treating second- or third-degree burn wounds in children: a systematic review and meta-analysis

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Background: The efficacy and safety of recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF) hydrogel in adults with deep partial-thickness burns have been confirmed. However, the clinical safety and efficacy analysis of rhGM-CSF in pediatrics is lacking, and the results are questionable. Therefore, a meta-analysis was conducted to evaluate the efficacy and safety of rhGM-CSF hydrogel in children with second- or third-degree burn injury to provide evidence-based medicine for clinical application.

Methods: Articles on rhGM-CSF hydrogel for the treatment of pediatric burn wounds were retrieved from PubMed, Embase, WOS, Cochrane Central Registry of Controlled Trials, Chinese Biomedical Literature Database (CBM), China Science and Technology Journal Database (CSTJ), China National Knowledge Infrastructure (CNKI) and Wanfang from the inception of the databases to March 2024. Two reviewers screened articles and extracted the following data: general characteristics, intervention and treatment course, outcome measure. The meta-analysis was conducted using Revman 5.4 software.

Results: Eight reports (336 patients: experimental 175, control 161) were ultimately included in the meta-analysis, which showed that the experimental group (rhGM-CSF hydrogel ± other therapy) was superior to the control group (treatments without rhGM-CSF hydrogel) in terms of the wound healing rates at day 7 [mean difference (MD) =13.63, 95% confidence interval (CI): 7.25 to 20.00, P<0.001], day 14 (MD =15.59, 95% CI: 12.50 to 18.69, P<0.001), and day 21 (MD =7.47, 95% CI: 7.36 to 7.58, P<0.001), and the wound healing time (MD =–3.10, 95% CI: –3.50 to –2.71, P<0.001), and the differences were statistically significant. For the risks of bias, one study had a "high risk" in allocation sequence concealment, and the others were classified as "low risk" and "unclear risk".

Conclusions: rhGM-CSF hydrogel is significantly effective in improving the wound healing rate and shortening the wound healing time in children with second- or third-degree burns.

Keywords: Recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF); burns; children; meta-analysis

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Introduction

Burns in children are a leading cause of disability and can also lead to a variety of emotional and physical problems (1,2). Therefore, the early symptomatic management of burn wounds is crucial for reducing the disability rate and preventing emotional and psychological abnormalities in children. Granulocyte/macrophage colony-stimulating factor (GM-CSF) was initially developed as a hematopoietic growth factor to facilitate the differentiation of bone marrow precursor cells into granulocytes and macrophages; however, it plays a limited role in steady-state myelopoiesis. When the body is in an inflammatory state, GM-CSF is produced in large amounts to regulate the local inflammatory response (3). In addition to inducing the proliferation and maturation of granulocytes and monocytes/macrophages (3), GM-CSF also regulates the functions of vascular endothelial cells and fibroblasts (4,5) and plays a key role in tissue repair. Although the efficacy and safety of recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF) hydrogel in adults with deep partial-thickness burns have been confirmed by clinical trials (6,7), the clinical safety and efficacy analysis of rhGM-CSF in pediatrics is lacking, and the results are questionable. In the present study, a meta-analysis was conducted to evaluate the efficacy and safety of rhGM-CSF hydrogel in children with second- or third-degree burn injury to provide evidence-based medicine for clinical application. We present this article in accordance with the PRISMA reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-24-259/rc).

Highlight box

Key findings

- Recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF) hydrogel alone or in combination with other treatments can effectively improve the wound healing rate and shorten the wound healing time in children with second- or third-degree burns.

What is known and what is new?

- In clinical settings, topical GM-CSF has shown dramatic efficacy and safety in treating burn wounds in adults. Burns are one of the most common unintentional injuries in children and can lead to serious physical and mental abnormalities.
- This meta-analysis indicated that rhGM-CSF hydrogel has favorable efficacy and safety in treating pediatric burn wounds, which can shorten the healing time by about 3.10 days, reduce wound pain, without serious adverse events.

What is the implication, and what should change now?

- rhGM-CSF hydrogel could be a favorable alternative in the treatment of second- or third-degree burns in children.

Methods

Inclusion and exclusion criteria

Inclusion criteria

The inclusion criteria were as follows: (I) literature type: randomized controlled trials (RCTs); (II) subjects: children with second- or third-degree burns; (III) interventions (experimental group): rhGM-CSF hydrogel monotherapy or combination therapy, with no restrictions on the frequency, dose, or duration of medication; (IV) control measures (control group): other treatments without the use of rhGM-CSF hydrogel; and (V) outcome measures (including at least one of the following indicators): the wound healing rate, the wound healing time, the wound pain score, and adverse events (AEs).

Exclusion criteria

The exclusion criteria were as follows (I) publications in languages other than English or Chinese; (II) studies of patients with nutritional and/or metabolic diseases; and/or (III) studies of patients with dysfunction of liver and kidneys.

Literature search

The English search terms "rhGM-CSF", "GM-CSF", "granulocyte-macrophage colony-stimulating factor", "children", "pediatrics", and "burn" were searched in the PubMed, Embase, WOS, and the Cochrane Central Register of Controlled Trials databases. The Chinese search terms [see Supplementary file (Appendix 1)] were searched in Chinese Biomedical Literature Database (CBM), China Science and Technology Journal Database (CSTJ), China National Knowledge Infrastructure (CNKI), and Wanfang Database. The search period included literature published from the inception of the databases to March 2024. The literature screening was performed by two researchers independently, and a third investigator arbitrated any disagreements. The following data from each study was extracted: (I) general characteristic data (authors, publication year, sample size and age range); (II) intervention and treatment course data; and (III) outcome measure data.

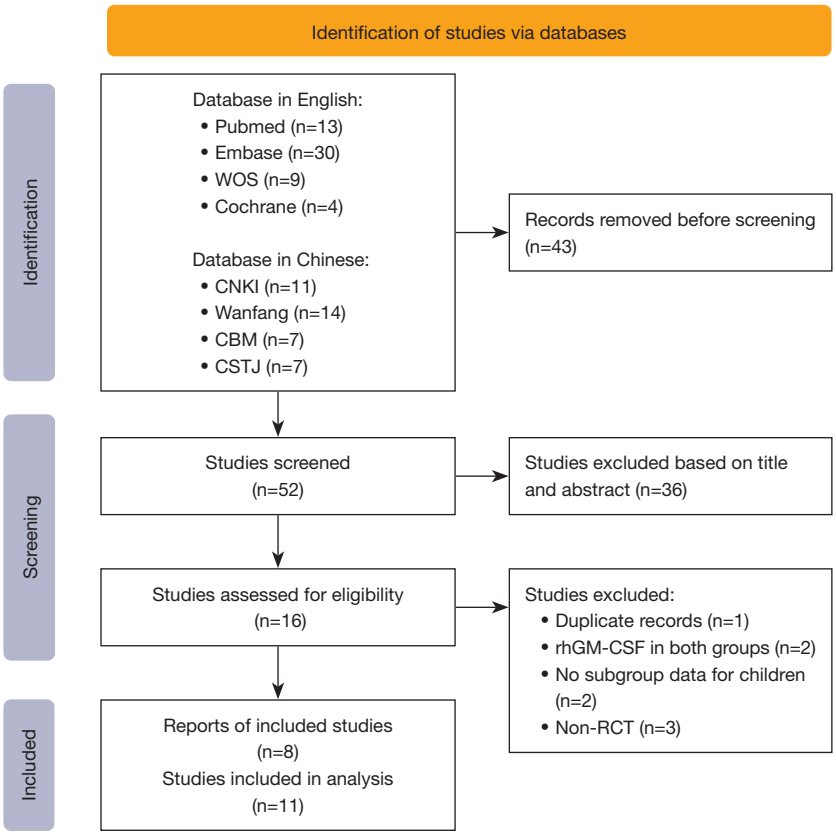

Figure 1 Flowchart of literature search and screening. rhGM-CSF, recombinant human granulocyte-macrophage colony-stimulating factor; RCT, randomized controlled trial.

Quality evaluation and assessment of risk of bias of the included studies

The studies were assessed using the Cochrane risk of bias tool in terms of random sequence generation, allocation sequence concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. The studies were classified as having a "low risk", "unclear risk", or "high risk" of bias. A risk of bias graph was generated.

Statistical analysis

The statistical analysis was performed using Revman 5.4 software. The count data are presented as the relative risk, the measure data are presented as weighted mean difference, and all the effect measures are expressed as 95% confidence intervals (CIs). The chi-square (χ^2) test combined with the Cochran *Q* test and the I^2 statistic were used to evaluate the heterogeneity; a P>0.1 and I^2<50% suggested that there was no significant heterogeneity, and the results were analyzed by a fixed-effects model. Conversely, a P≤0.1 and I^2≥50% suggested heterogeneity between the trial results, and the results were analyzed using a random-effects model. For all the tests a P value of <0.05 was considered statistically significant.

Results

Results of the literature search

The literature searching and screening flowchart is shown in *Figure 1*. A total of 95 relevant articles were found through the database search, and eight articles (8-15) entered the final analysis.

Characteristics of the included studies

The basic characteristics of the included literature are shown in *Table 1*.

Table 1 The basic characteristics of the included literature

Studies	Age range (years)	Number of patients in the experimental group/ control group (n)	Interventions		Treatment course (days)	Outcome measures
			Experimental group	Control group		
Chen *et al.*, 2016 (8)	0.2–5	6/8	rhGM-CSF hydrogel + petroleum jelly gauze	Silver sulfadiazine + petroleum jelly gauze	NA	② ③
		8/7	rhGM-CSF hydrogel + calcium alginate + adhesive dressing	Calcium alginate + adhesive dressing		
		6/4	rhGM-CSF hydrogel + petroleum jelly gauze	Silver sulfadiazine + petroleum jelly gauze		
		4/5	rhGM-CSF hydrogel + calcium alginate + adhesive dressing	Calcium alginate + adhesive dressing		
Zhou *et al.*, 2016 (9)	2–8	40/40	rhGM-CSF hydrogel	Silver sulfadiazine cream	20	① ②
Yu *et al.*, 2015 (10)	2–7	15/15	rhGM-CSF hydrogel	Petroleum jelly	21	① ②
Wang *et al.*, 2014 (11)	1–5	15/15	rhGM-CSF hydrogel	Hydrogel matrix	14	① ④
Yan *et al.*, 2013 (12)	1.5 (mean age)	20/5	rhGM-CSF hydrogel	Normal saline	Till complete re-epithelialization	②
Li *et al.*, 2012 (13)	1.5–6	10/10	rhGM-CSF hydrogel	Vaseline gauze	21	①
Jiaao *et al.*, 2011 (14)	5.3 (mean age)	15/15	rhGM-CSF hydrogel	Hydrogel matrix	NA	②
Luo *et al.*, 2024 (15)	0–3	36/36	rhGM-CSF hydrogel + medical collagen sponge	Medical collagen sponge	NA	②

①, wound healing rate; ②, wound healing time; ③, wound pain score; ④, adverse events. rhGM-CSF, recombinant human granulocyte-macrophage colony-stimulating factor; NA, not available.

Assessment of literature quality

The risks of bias were assessed using the Cochrane tool. All the eight included reports specified the method used to generate random sequences (*Figure 2*). However, one study had a "high risk" in allocation sequence concealment, and the other seven articles had an "unclear risk" in allocation sequence concealment, the blinding of participants and personnel, and the blinding of the outcome assessment. All the eight articles were classified as "low risk" in terms of incomplete outcome data, selective reporting, and other sources of bias.

Results of meta-analysis

Wound healing rate

The wound healing rate was presented at 7, 14, and 21 days according to the classification and description of the results in the original literature: (I) the 7-day wound healing rate was reported in two articles (10,11), and there was no significant heterogeneity between these two studies (P=0.53, I^2 =0%); the fixed-effects model showed that the wound healing rate of the experimental group was higher than that of the control group [mean difference (MD) =13.63, 95% CI: 7.25 to 20.00, P<0.001] (*Figure 3*); (II) the 14-day wound healing rate was reported in three articles (9-11), and there was no significant heterogeneity among these studies (P>0.99 , I^2=0%); the fixed-effects model showed that the wound healing rate of the experimental group was higher compare to the control group (MD =15.59, 95% CI: 12.50 to 18.69, P<0.001) (*Figure 4*); (III) the 21-day wound healing rate was reported in two articles (9,10), and significant heterogeneity was found between these two studies (P<0.001, I^2=93%); the random-

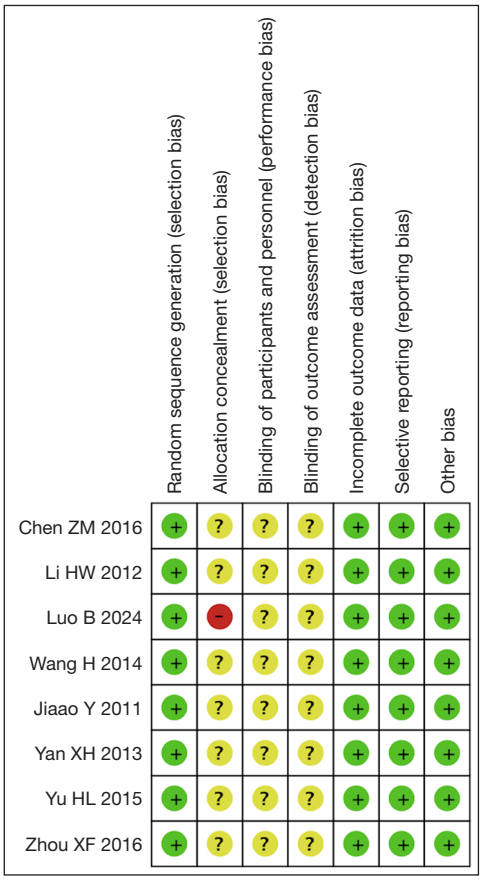

Figure 2 Risk of bias assessment of the included studies. Red, high risk of bias; yellow, unclear risk of bias; green, low risk of bias.

effects model showed that the wound healing rate of the experimental group was significantly higher than the control group (MD =7.47, 95% CI: 7.36 to 7.58, P<0.001) (*Figure 5*).

Wound healing time

The wound healing time was reported in six articles (8-10,12,14,15), among which significant heterogeneity was found (P<0.001, I^2=88%); the random-effects model showed that the wound healing time of the experimental group was significantly shorter than that of the control group (MD =–3.10, 95% CI: –3.50 to –2.71, P<0.001) (*Figure 6*).

Wound pain score

The wound pain scores were calculated in one study (8), and the results showed that the pain scores in the early stage (3.0±1.6) and middle/late stages (2.2±1.2) in the rhGM-CSF hydrogel + petroleum jelly gauze group were significantly lower than those in the silver sulfadiazine + petroleum jelly gauze group [(8.3±2.2) and (6.4±2.6), respectively]; similarly, the pain score in the middle/late stages was significantly lower in the rhGM-CSF hydrogel + calcium alginate + adhesive dressing group than in the calcium alginate + adhesive dressing group [(1.8±1.0) *vs.* (2.2±1.2)].

AEs

Only one article (11) assessed the safety profile using AEs,

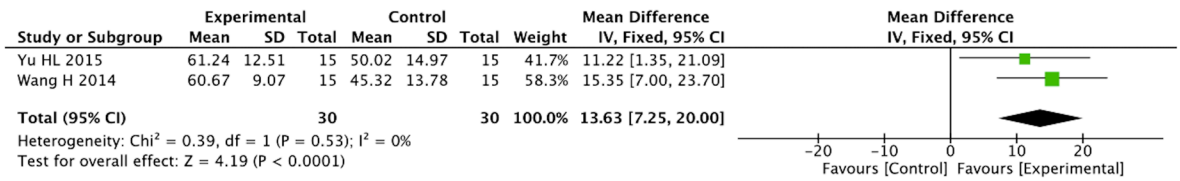

Figure 3 The wound healing rates of the experimental group and the control group at day 7. SD, standard deviation; IV, inverse variance; CI, confidence interval.

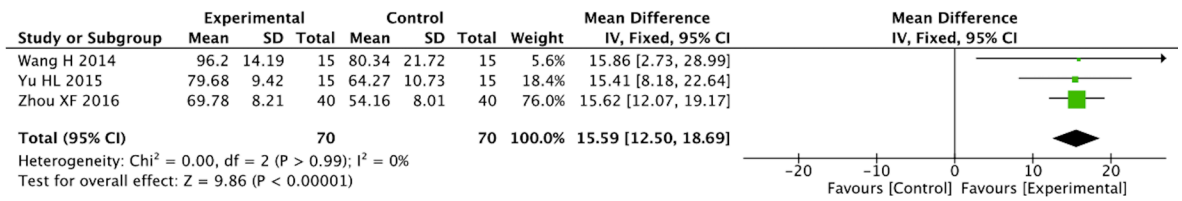

Figure 4 The wound healing rates of the experimental group and the control group at day 14. SD, standard deviation; IV, inverse variance; CI, confidence interval.

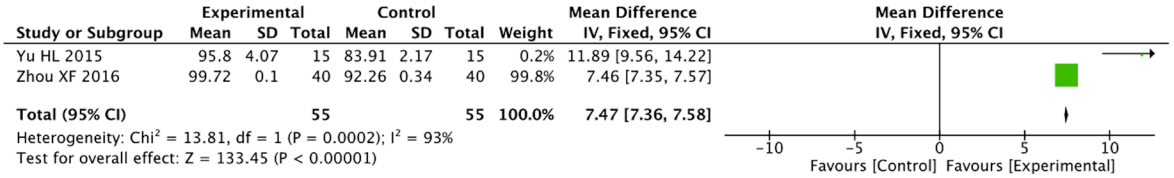

Figure 5 The wound healing rates of the experimental group and the control group at day 21. SD, standard deviation; IV, inverse variance; CI, confidence interval.

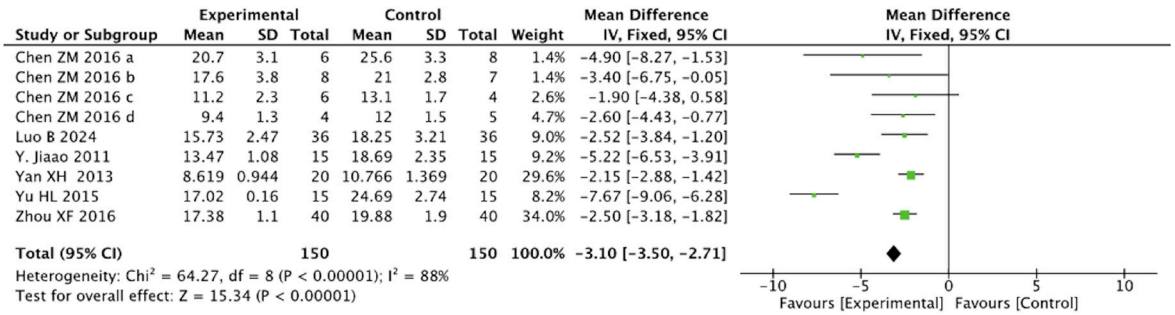

Figure 6 Wound healing times of the experimental group and the control group. SD, standard deviation; IV, inverse variance; CI, confidence interval.

including ulcers, fever, local allergies, and skin flushing (grade 1: highly safe, without AEs; grade 2: safe, with mild AEs that do not require treatment). In the experimental group, 11 children had grade 1 AEs and four had grade 2 AEs; in the control group, three children had grade 1 AEs and 12 had grade 2 AEs. Thus, the safety profile of the experimental group was superior to that of the control group.

Discussion

The incidence of burn injury, for which the elderly and children comprise high-risk groups, is increasing year by year. In hospitalized children with accidental injuries, burn injury ranks 2nd among the causes of injury (16). For pediatric burn victims, wound healing may require long-term scar treatment and surgical repair to avoid complications during their growth and development and to reduce the impact on the quality of life of the children and their family (17,18). Wound healing is a complex pathophysiological process, during which neutrophils and macrophages play key roles as immune cells (19). GM-CSF is a cytokine that regulates the functions of granulocytes and macrophages, and it can promote macrophage differentiation during the inflammatory phase of wound healing and enhance the innate immune function of neutrophils and macrophages (20,21). During the proliferative phase, GM-CSF facilitates angiogenesis and re-epithelialization, promotes the growth of granulation tissue, and shortens healing time (4,22). In addition, GM-CSF promotes the release of matrix metalloproteinases from fibroblasts (23), which may help avoid scarring by regulating the recombination of the extracellular matrix during the remodeling phase.

Topical GM-CSF has shown dramatic efficacy in treating burn wounds in clinical settings. Li *et al.* (24) screened seven RCTs involving a total of 982 patients (Mean age: 19–40 years) with deep second-degree burns, and their meta-analysis revealed that the average burn wound healing time was 4.77 days earlier in the rhGM-CSF group compared to standard wound care alone. A more recent network meta-analysis (25) compared the burn wound healing time of 11 different topical treatments, including rhGM-CSF, epidermal growth factor, fibroblast growth factor, and silver sulfadiazine, and found that rhGM-CSF was the best choice for shortening the healing time. In several guidelines and consensuses, GM-CSF is strongly recommended for the treatment of deep second-degree burns based on high-quality evidence (26,27).

Based on the significant efficacy and safety of rhGM-

CSF hydrogel in treating deep second-degree burns in phase III (6) and phase IV (7) trials, our present study aimed to analyze the efficacy and safety of rhGM-CSF hydrogel in pediatric victims with second- and third-degree burns. A total of six Chinese-language articles and two English-language articles entered the final analysis (8-15). Four studies (9-11,13) calculated and compared the wound healing rate at different time points. Our analysis showed that the wound healing rate of the experimental group using rhGM-CSF hydrogel alone or in combination with other drugs was significantly higher at days 7, 14, and 21 when compared with the control group. In terms of the wound healing time, six articles (8-10,12,14,15) showed that rhGM-CSF hydrogel monotherapy or combination therapy could shorten wound healing time by about 3.10 days on average compared with other treatments (including silver sulfadiazine, petroleum jelly, normal saline, hydrogel matrix, medical collagen sponge). In addition, wound pain scores and AEs were evaluated by one article each (8,11), each of which independently concluded that rhGM-CSF hydrogel reduced wound pain and adverse effects; however, no valid analysis could be performed due to the limited number of included studies.

The risk of bias of the eight reports included in our meta-analysis was as follows: (I) random allocation method: low risk for all studies; (II) allocation concealment: high risk in one study and unclear risk in the remaining seven studies; (III) blinding: unclear risk for participants, personnel, and outcome assessment; (IV) incomplete outcome data: low risk for all studies; (V) selective reporting: low risk for all studies; and (VI) other sources of bias: low risk for all studies. The unclear risk of bias for blinding in the included studies might have led to some bias in the results of the studies, which could have affected the quality of our meta-analysis.

In the present study, a comprehensive and systematic search was carried out in Chinese- and English-language databases, and the relevant literature was independently searched and screened by two researchers to minimize the proportion of missed studies. Eight RCTs entered the final analysis, and conclusions with higher statistical power were obtained based on a larger sample. However, our current study had certain limitations. First, the sample sizes of the included studies were small, and there might be a cognitive effect. Second, the span of publication years could have introduced variability in the treatment interventions and could have affected the estimation of the treatment efficacy. Third, the conclusions in some studies were uncertain due to incomplete data. Finally, only Chinese- and English-language articles were included in the meta-analysis, and the exclusion of articles published in other languages might have led to publication bias.

Conclusions

In summary, rhGM-CSF hydrogel alone or in combination with other treatments has favorable efficacy and safety in the healing of second- and third-degree burn wounds in children, as it can shorten the healing time, reduce wound pain, and prevent AEs. However, the sample sizes of all the included studies were small, and more large-sample, high-quality RCTs are warranted for further exploration and validation.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-24-259/rc

Peer Review File: Available at https://tp.amegroups.com/article/view/10.21037/tp-24-259/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-24-259/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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