Original Article

Clinical efficacy and safety between high-intensity focused ultrasound and uterine artery embolization for cesarean scar pregnancy: a systematic review and a meta-analysis

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Background: It was reported that high-intensity focused ultrasound (HIFU) of cesarean scar pregnancy (CSP) can locally inactivate pregnancy tissue. Uterine artery embolization (UAE) can achieve good results for CSP too. To investigate the clinical efficacy and safety of HIFU and UAE in the treatment of cesarean scar pregnancy (CSP), we conducted this research.

Methods: Multiple databases were used to search for relevant studies and articles related to HIFU, UAE, and CSP. The selected literature were retrospectively evaluated using Review Manager 5.2. In addition, forest plots, sensitivity analysis, and bias analysis were conducted for the included literature.

Results: Finally, 8 related studies met the inclusion criteria. There were no significant differences in postoperative adverse reactions and hospitalization time between the HIFU group and the UAE group. However, the normalization time of serum beta human chorionic gonadotropin (B-HCG) in the HIFU group was higher than that in the UAE group [MD =1.16, 95% confidence interval (CI), 0.09, 2.22, P=0.03, I^2=93%], and the hospitalization cost in the HIFU group was significantly lower than that in the UAE group (MD =−8.81, 95% CI, −12.64, −4.97, P<0.00001, I^2=99%).

Discussion: Our results show that HIFU and UAE have the same curative effect in the treatment of CSP, but HIFU has lower cost and fewer complications. These results supported that compared with UAE, HIFU is a better choice for CSP patients with long gestational age, large gestational sac diameter and high HCG level.

Keywords: High-intensity focused ultrasound (HIFU); uterine artery embolization (UAE); cesarean scar pregnancy (CSP)

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Introduction

Cesarean scar pregnancy (CSP) refers to an ectopic pregnancy in which the pregnancy sac or embryo sac is implanted on the scar site of a previous cesarean section. It results in a difficult, abnormal pregnancy. In recent years, the incidence of CSP in China has shown an increasing trend year by year. The exact etiology and pathogenesis of the disease are still unclear (1,2). The clinical manifestations are mainly irregular vaginal bleeding, which may be accompanied by abdominal pain. However, 36.8% of patients are asymptomatic and can be diagnosed by auxiliary examinations such as ultrasound and endoscopy. The risk factors for infertility and recurrence of CSP after previous CSP include age, antenatal BMI of pregnant women, history of vaginal delivery, and baby weight.

High-intensity focused ultrasound (HIFU) uses the physical characteristics of ultrasound, such as tissue penetration and focusability, to focus low-energy ultrasound to target tissues in the body, and uses the high temperature generated by high-intensity ultrasound at the focal point. This results in coagulative necrosis of the diseased tissue, in order to achieve the purpose of non-invasive treatment (3-5). In clinical practice, HIFU technology is mainly used to treat solid tumors of the abdomen, soft tissue and bone tumors of the limbs, and soft tissue tumors on the body surface. Studies have shown that HIFU treatment of CSP can locally inactivate pregnancy tissue. It is a safe and effective non-invasive technique and its efficacy has been widely verified in the treatment of benign gynecological diseases such as adenomyosis and uterine fibroids. It is also used in the treatment of CSP assisted uterine evacuation (6,7).

Uterine artery embolization (UAE) has been used in the treatment of obstetric and gynecological diseases such as uterine fibroids and postpartum hemorrhage since the 1990s (8-10). In recent years, with the development of interventional therapy technology, it has become minimally invasive, safe, and effective. UAE is widely used by domestic and foreign physicians to treat CSP, and can effectively control vaginal bleeding and reduce the risk of hysterectomy (11,12). At the same time, infusion of methotrexate in the uterine artery can increase the local drug concentration, improve the germ-killing effect, and quickly and effectively stop bleeding, providing necessary conditions for future uterine treatment to preserve the patient's uterus and fertility (13-15). And uterine artery embolization treatment of cervical pregnancy can achieve good results, and less intraoperative blood loss, less complications, high safety.

In order to investigate the clinical efficacy and safety of HIFU and UAE in the treatment of CSP, this meta-analysis was conducted to better understand their overall diagnostic performance and help maximize the clinical utility of these 2 kinds of diagnostic approaches. In this research, we presented the following article in accordance with the PRISMA reporting checklist (available at https://dx.doi.org/10.21037/apm-21-839).

Methods

Literature search strategy

We searched for related articles published from January 2005 to March 2020, in order to provide a theoretical basis for choosing the better diagnostic method. The Cochrane Library, PubMed, EMBASE, MEDLINE, Central, and Web of Science were searched with the following keywords: (I) high intensity focused ultrasound; (II) uterine artery embolization; (III) cesarean scar pregnancy. Search terms were combined using the Boolean operator "AND" with the aim of obtaining different articles that included 2 or more of the terms used for the search. No restrictions regarding the publication language were used in the literature retrieval step. Reference lists of retrieved articles were screened manually to ensure sensitivity of the search strategy and to identify additional relevant studies.

Study selection

A full-text review of online publications determined after the preliminary selection of studies was conducted, and the included studies had to meet the following inclusion criteria:

(I) HIFU was used;
(II) UAE was used;
(III) CSP patients.

We systematically excluded the studies that did not meet the inclusion criteria according to the following exclusion criteria:

(I) Research involving other health problems;
(II) Patients received other diagnostic techniques;
(III) Lack of research on the existing data.

Data extraction and quality assessment

Two reviewers extracted data from full length articles

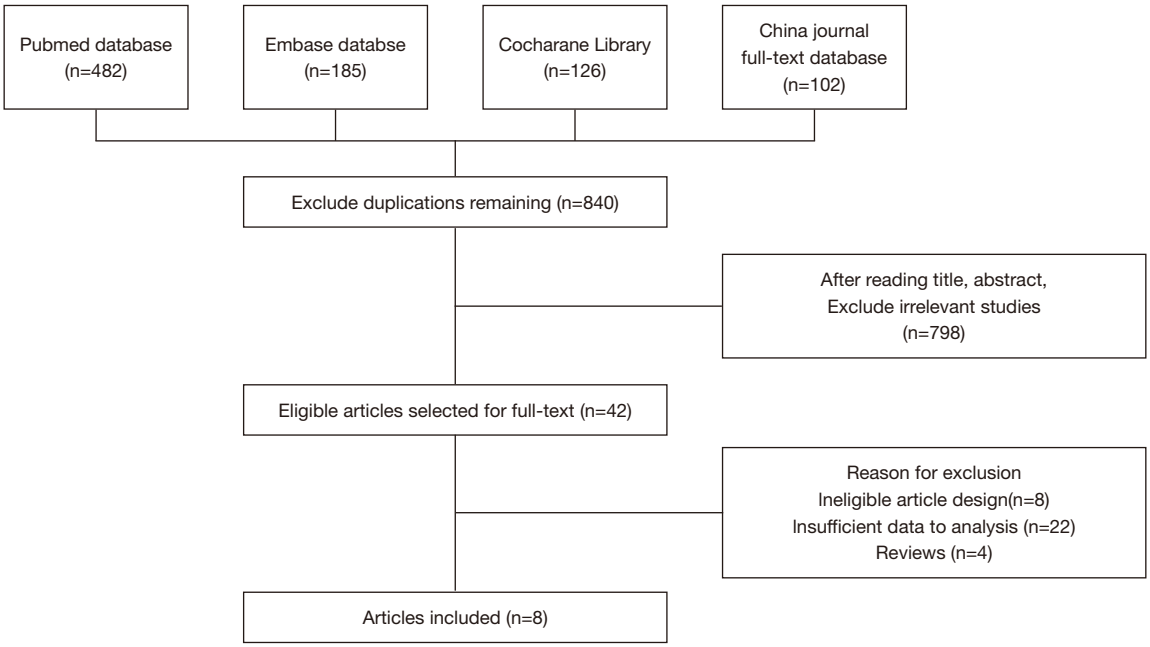

Figure 1 Flow diagram of the study selection.

independently. The collected data for each study included publication date, first author, country, number of patients recruited and randomized per study, age (years), and recruitment period. We also extracted the data of the following indicators: adverse reactions, serum beta human chorionic gonadotropin (B-HCG) normalization time, length of hospital stay, and treatment costs. We evaluated the quality of the involved trials using the Cochrane Collaboration's tool for assessing risk of bias. The risk of each domain was rated as high risk, unclear risk, or low risk according to the match level between the information extracted and the evaluation criteria.

It is worth noting that the authors tried to be fair in the quality assessment process, but the scores may have risen or fallen slightly. The manuscript met the applicable EQUATOR criteria.

Statistical analysis

For dichotomous variables, the odds ratio and 95% confidence interval (CI) were derived for each outcome. For continuous variables, we calculated the weighted mean difference and 95% CI.

The chi-squared test (Cochrane's Q test) and I^2 statistical test were used to analyze the heterogeneity between studies. Statistical heterogeneity was measured using the chi-squared test on the Q statistic, which was quantified by I^2 values, assuming that I^2 values of 25%, 50%, and 75% were nominally assigned as low, moderate, and high estimates, respectively. If the I^2 value was greater than 50%, there was moderate heterogeneity between studies. The effect size of each study was calculated using the DerSimonian and Laird random-effect model.

Publication bias was analyzed using a funnel plot and quantified with rank correlation. To assess the effect of an individual study on the pooled estimate, we performed a sensitivity analysis by omitting each study in turn. Data synthesis and statistical analysis were carried out using Review Manager Version 5.2 software.

Results

Search process

A total of 840 articles were identified by searching the electronic databases. After careful reading, 42 papers met the preliminary standard. After further screening, 34 articles were excluded due to ineligible research design and insufficient data and article types. Finally, 8 articles were selected and these papers were included in this meta-analysis. *Figure 1* (flow chart) describes the process of study identification and inclusion, and the reasons for exclusion.

Table 1 Characteristics of studies included in the meta-analysis

Study	Year	Language	Country	Age (mean)	No. in HIFU group	No. in UAE group	Years of onset
Chen *et al*.	2018	English	China	35±6.5	68	67	January 2007 to April 2016
Chu *et al*.	2018	Chinese	China	30.7±4.2	102	90	January 2014 to June 2016
Dai *et al*.	2017	Chinese	China	29.76±3.6	90	62	January 2014 to May 2016
Hong *et al*.	2017	English	China	32.37±4.3	85	67	September 2014 to January 2016
Lin *et al*.	2020	Chinese	China	30.85±6.95	55	61	October 2015 to October 2017
Wang *et al*.	2020	Chinese	China	30.85±6.95	96	46	January 2013 to June 2018
Xiao *et al*.	2016	English	China	31.36±4.28	31	45	October 2012 to September 2014
Zhu *et al*.	2016	English	China	31.95±5.05	76	46	January 2014 to December 2014

HIFU, high-intensity focused ultrasound; UAE, uterine artery embolization.

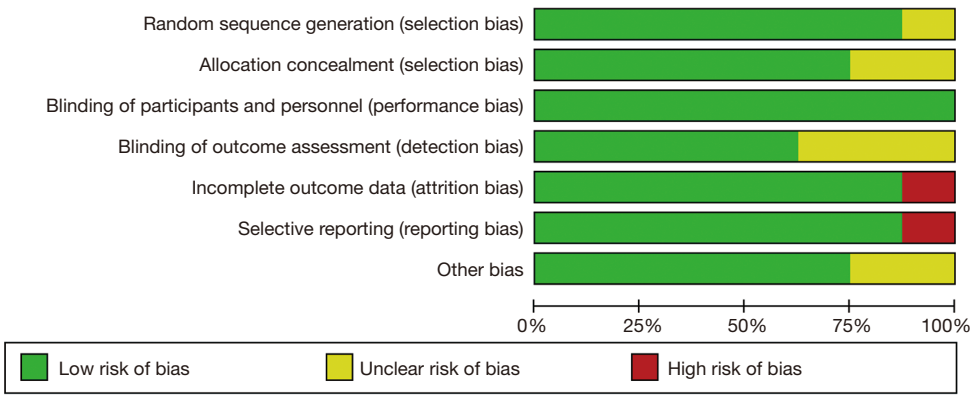

Figure 2 Risk of bias summary, with high risk of bias (red), low risk of bias (green), and unclear risk of bias (yellow).

Characteristics of included studies

Table 1 summarizes the types of studies reported and the total number of patients associated with each group (16-25). The content included author, year of publication, country, language, age, group, sample size, and recruitment time. The analysis included 4,665 patients. From 2007 to 2018, all the 8 articles were published. The sample size ranged from 76 to 192. There were 603 cases in the HIFU group and 484 cases in the UAE group.

Results of the quality assessment

We used the Cochrane risk bias assessment tool to evaluate the quality of the included trials and the Review Manager 5.2 software to analyze the data. The risk of bias in this study is shown in *Figure 2*, with little bias between the HIFU and UAE groups. *Figure 3* shows the details of the quality assessment in this study. As shown in *Figure 3*, the overall risk of all 8 papers was low.

Results of the heterogeneity test

Figure 4 shows the forest plot of the number of adverse reactions after treatment in the HIFU and UAE groups. Seven studies were included in the comparison, and the analysis showed no difference between the two groups (OR =0.72, 95% CI, 0.22, 2.29, P=0.57, I^2=86%).

Figure 5 shows the forest plot of the normalization time of serum B-HCG after treatment of CSP in the HIFU and UAE groups. Four studies were included in this comparison. The data obtained showed differences between the two groups. The normalization time of serum B-HCG in the HIFU group was higher than that in the UAE group (MD =1.16, 95% CI, 0.09, 2.22, P=0.03, I^2=93%).

Figure 6 shows a forest plot of the length of hospital stay

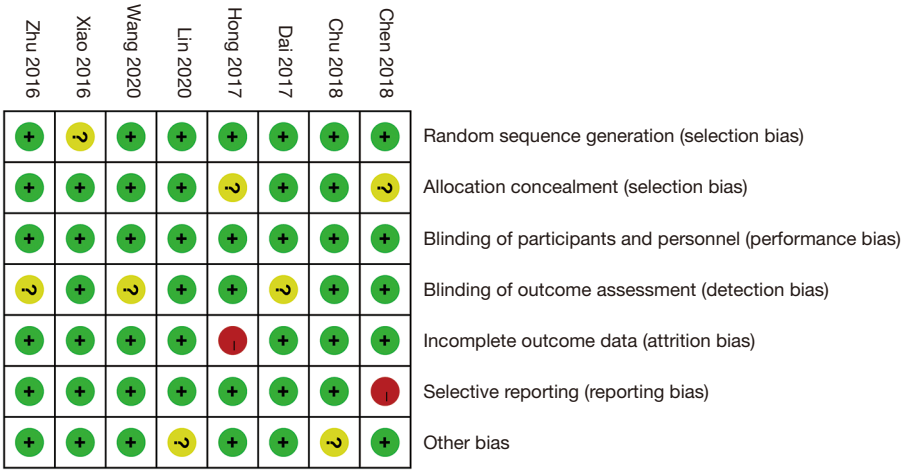

Figure 3 Quality assessment of the included studies. Green represented low risk, red represented high risk and yellow represented unclear risk.

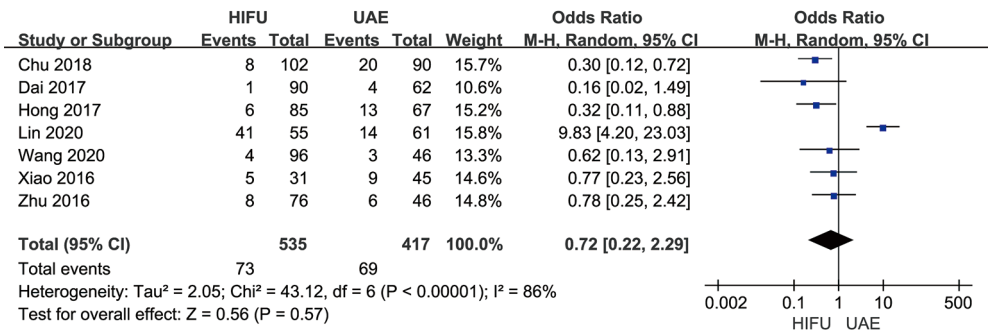

Figure 4 Forest plot of the incidence of adverse reactions after treatment of CSP in the two groups. CSP, cesarean scar pregnancy.

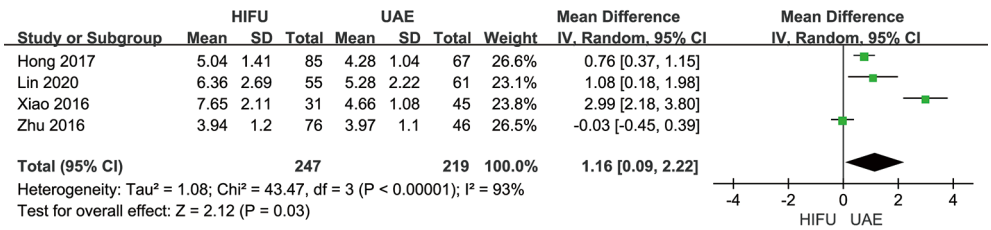

Figure 5 Forest plot of the normalization time of serum B-HCG after CSP treatment in the two groups. B-HCG, beta human chorionic gonadotropin; CSP, cesarean scar pregnancy.

in the HIFU and UAE groups. Six studies were included in the comparison, and the analysis showed no difference between the two groups (MD =–0.21, 95% CI, –0.64, 0.22, P=0.34, I^2=67%).

Figure 7 shows a forest plot of hospitalization expenses in the HIFU and UAE groups. Four studies were included in the comparison. The results showed that there was a difference between the two groups. The hospitalization cost in the HIFU group was significantly lower than that in the UAE group (MD =–8.81, 95% CI, –12.64, –4.97, P<0.00001, I^2=99%).

Results of the sensitivity analysis and publication bias

Sensitivity analysis was conducted in order to evaluate the

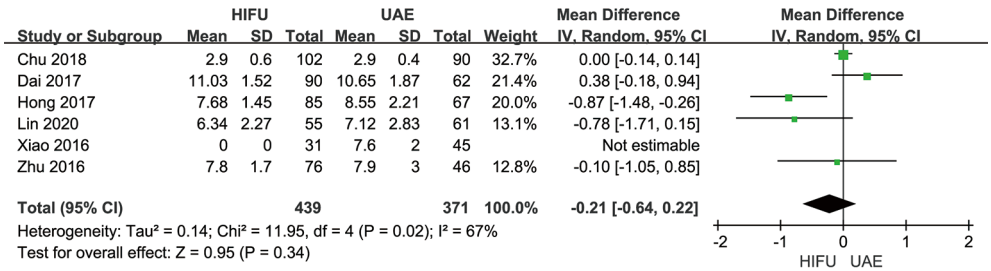

Figure 6 Forest plot of the length of hospital stay after treatment of CSP in the two groups. CSP.

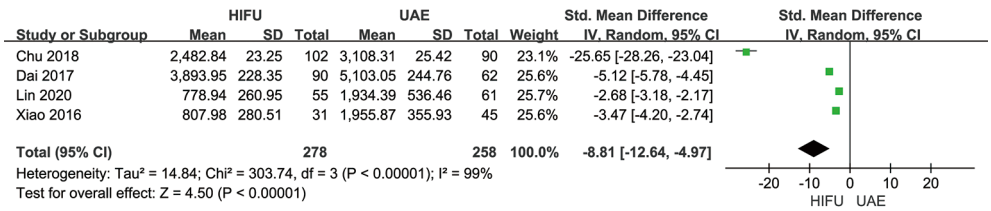

Figure 7 Forest plot of the hospitalization expenses of the two groups for treatment of CSP. CSP, cesarean scar pregnancy.

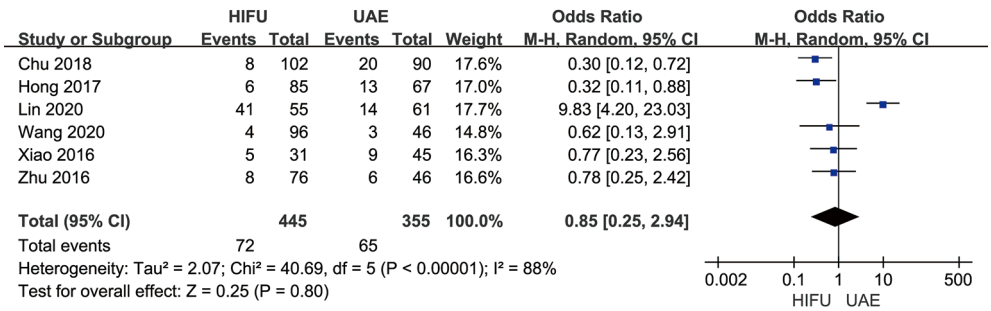

Figure 8 Sensitivity analysis of the incidence of adverse reactions after treatment of CSP in the two groups. CSP, cesarean scar pregnancy.

stability of the analysis results. Excluding a relative outlier, the sensitivity of the value changed from 86% to 88% in the heterogeneity part. The results showed that this heterogeneity was mainly due to Dai *et al.*'s research in 2017 (22). The forest plot without Dai *et al.*'s article is shown in *Figure 8*.

A funnel plot for publication bias was generated. Seven studies were included in the plot. The publication bias was estimated by the visual symmetry of the funnel plot. The symmetrical funnel plot indicated that there was no significant publication bias in this study (*Figure 9*).

Discussion

We identified 8 studies that met the inclusion criteria to evaluate the efficacy and safety of HIFU and UAE in the treatment of CSP (24,25). Meta-analysis of these studies showed that both HIFU and UAE were effective in the treatment of CSP, but HIFU cost less, was safer, was more effective, and was more suitable as an adjuvant therapy for CSP.

CSP refers to ectopic pregnancy in which the fertilized egg is implanted in the previous cesarean scar. It is rare and can lead to placenta accreta, uterine rupture, and even maternal death. It is a potential long-term serious complication after cesarean section (26-28). In the recent 10 years, with the deepening understanding of the disease, the experience and efficacy of clinical diagnosis and treatment have constantly accumulated and improved.

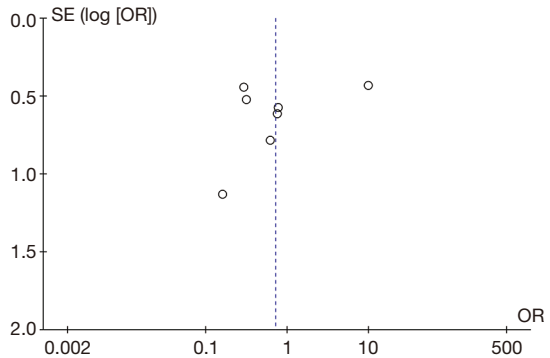

Figure 9 Funnel plot of publication bias.

Due to the variety of clinical features and manifestations of CSP, there is currently no unified treatment standard. The main treatment methods include HIFU, UAE, and local puncture, amongst others (29,30).

HIFU is a new clinical treatment technology which has developed in recent years. It is a non-invasive ablation therapy. It focuses the ultrasound on the target area in the organism to form a high-intensity ultrasound convergence area. The biological thermal effect produced by ultrasound results in coagulative necrosis of the tissue in this area under the effect of high temperature, so as to achieve the purpose of treatment (31-33). The advantages are that it is non-invasive, accurate, repeatable. The effect of high-intensity focused ultrasound combined with hysteroscopy in the treatment of re-pregnancy at the scar site after cesarean section is quite significant, which can shorten the operation time and increase the patient's uterine retention rate. UAE is a modern medical image-guided technology for the treatment of uterine fibroids, and is a type of vascular invasive surgery (34,35). The operation mainly uses modern medical equipment such as computed tomography, ultrasound, nuclear magnetic resonance, laparoscopy, and X-ray to make the diagnosis, and then carries out directional surgery on the lesion tissue to achieve the purpose of treatment. UAE has many advantages, and it is one of the main methods used to treat CSP because of the characteristics of rapid blood transfusion, less trauma, more selective retreatment, and fertility preservation.

HIFU and UAE have the same curative effect in the treatment of CSP, however, HIFU causes fewer adverse reactions and postoperative complications, so it is more suitable as an adjuvant treatment for CSP (36-38). In addition, there are some limitations in this article. Firstly, the probability of re-pregnancy after surgery was not compared and should be evaluated in further studies. Secondly, the sample countries could have included more areas, which should be included in future work.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://dx.doi.org/10.21037/apm-21-839

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-839). 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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