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Therapeutic use of hematopoietic mesenchymal stem cells in osteoarthritis: a meta-analysis study

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Abstract

Millions of people worldwide suffer from osteoarthritis, which is a major health problem. The accessible medicines are used in changing the side effects of osteoarthritis however missing illness alterations, not with-standing drug after-effects, and care expenses without adequacy of side effects help. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. We look for relevant articles in all articles published between December 30, 2007, and December 30, 2022, in the Cochrane Library, PubMed, Embase, Wanfang Database, CNKI, and Web of Science databases. With an average follow-up of 18.33 months, this study included 364 patients with knee joint osteoarthritis from 12 completely published articles. Data from seven studies using the Visual Analog Scale (VAS) score. In Bone Marrow Mesenchymal Stem Cells (BM-MSCs), the baseline score on the Visual Analogue Scale decreased. These results suggested that there was no significant relationship between the BM-MSCs at three months (Weighted Mean Difference (WMD) = 1.07, 95% CI: − 2.44, − 0.39, p= 0.074); and the greatest decrease in VAS score compared to the control at 18.33 months, WMD = 6.04, 95 percent CI: − 10.34, − 0.38, p = 0.017.

In clinical applications, intra-articular injection of BM-MSCs has advantages for treating OA because it reduces pain index, improves knee movement, and increases cartilage volume.

Keywords: BM-MSCs, Osteoarthritis, PRISMA

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Introduction

Osteoarthritis (OA) is the leading global problem that affects millions of people. The accessible medicines are used in changing the side effects of osteoarthritis however missing illness alterations notwithstanding drug aftereffects and careful expenses without adequacy of side effect help.

Osteoarthritis is characterized by progressive and irreversible cartilage damage as its primary pathological feature. Due to the decreased vascularity of the cartilage, the volume of the knee articular cartilage that needs to be repaired is fundamentally inadequate [19, 20]. This results in a lack of systemic regulation as well as an ineffective healing and tending response.

Numerous studies [15, 16] have documented significant complications associated with total knee replacement surgery. Twenty percent of patients who have additional issues following total knee replacement experience knee pain [17]. Significant reports showed pulmonary embolism and tissue infection, both of which necessitated hospital readmission, in 2% of patients who had total knee replacements [18]. Hemopoietic mesenchymal stem cells have been actively considered and researched as replacement regenerative and joint preservation management as a result of the health and economic effects of OA.

Friedenstein first mentioned hematopoietic mesenchymal stem cells (MSCs) in the 1970s [12], and Hillard Lazarus first tried them as a cellular pharmaceutical on a human trial in 1995 [13]. They have since evolved into the global platform for the most clinically studied and experimental cell therapy [14]. Because of their anti-inflammatory and immunomodulatory properties, MSCs are able to repair cartilage [15] and lessen knee pain, inflammation, and inflammation-related inflammation.

Because of their ease of harvesting under local anesthesia, safety, and potential to differentiate to connective tissue, mesenchymal stem cells (MSCs) are increasingly being considered a treatment option for osteoarthritis [16, 17]. In addition, the expression of a variety of growth factors and cytokines by MSCs has been associated with paracrine anti-inflammatory and immunomodulatory properties [18, 5, 19] [20]. The paracrine effect, reduction of immune response, and stimulation of local tissue restoration with the possession of MSCs would be advantageous to progress the intra-articular situation as a disease-modifying treatment because the pathophysiology of osteoarthritis is created on both degeneration and inflammation [21]. Clinical trial research articles on the intra-articular injection of MSCs for knee osteoarthritis have described positive cartilage renewal, effective significant pain relief, and functional recovery [22].

BMSCs serve two functions in BM: First, there is the well-known job of maintaining a supportive microenvironment for hematopoiesis. Based on their subendothelial location, the

second is connected to the advancement, stabilization, and preservation of the sinusoids [23]. Additionally, BMSCs target sinusoidal walls, and when hematopoietic development is observed in vivo, it occurs prior to the beginning of hematopoiesis [24]. In addition, BMSCs rank highly but do not differentiate into osteogenic progenitors [25]. These data represent an intriguing path for clinical studies and research into the exclusive, dual arrangement of stem/progenitor cells that functionally interrelate in the regulation of hematopoiesis and bone physiology [26] in light of the developing role of osteogenic cells in providing a niche for HSCs. Through a meta-analysis study, the primary objective of this study is to investigate the therapeutic use of hematopoietic mesenchymal stem cells in osteoarthritis.

Method

Study design

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines, which are in line with the systematic review and meta-analysis [27]. In addition to extracting and cross-checking the relevant data, two researchers independently reviewed the literature. A third researcher made a decision about observing data extraction in the event of disagreements.

Study search strategy

For relevant articles, we use the terms "stem cells," "osteoarthritis," "mesenchymal stem cell," "hematopoietic bone marrow," "degenerative arthritis," "polyarthritides," and "progenitor cell" as search terms in PubMed, Embase, "Wanfang Database," "CNKI," "Web of Science," "Cochrane Library," and "ClinicalTrials.gov."

Inclusion criteria

The following inclusion criteria which included in this study:

1. Individuals with knee osteoarthritis of any age or gender.
2. Management of patients using BM-MSCs that can be combined with other treatments.
3. In the intraarticular knee joint, only stem cells are used.
4. The minimum used one of the following indicators in the published article:
    - Visual Analogue Scale (VAS) score,
    - Western Ontario and McMaster Universities (WOMAC) subscale, and
    - incidence of adverse events.
5. All articles must be distributed in English.

Exclusion criteria

1. Animals were used in every study.
2. all review articles, case studies, retrospective studies, articles without full text, and conference papers.
3. Articles that didn't meet the inclusion criteria

Data screening and extraction

In order to further filter out the final applicant literature, the screening articles were read and extracted independently by two researchers. Additionally, the studies of the designated literature were cited. Contact the corresponding author to verify the results or to approximate the misplaced standard deviation in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [14] if some data are missing from the randomized controlled trials. The third reviewer was responsible for data extraction in the event of conflicts. The risk of bias was evaluated simultaneously across all randomized controlled trials.

Risk of bias assessment

Two researchers independently directed the estimation, which was then cross-checked. The third researcher would be consulted to resolve any disagreements. The study was valued using the Cochrane Risk of Bias, which has three levels:

1. Low chance of bias
2. Some concerns
3. Bias at a high risk

Outcome measures

The value of minimal clinically important differences are:

- VAS for pain (0-10 cm) was 1.02
- WOMAC pain score (0-20) as 1.79
- WOMAC physical function score (0-68) as 5.13
- WOMAC stiffness score (0-8) as 0.65

Data production

We created a meta-analysis for the studies that were sufficiently comparable in terms of the intervention, differences, populations, and outcomes. Before beginning any analysis, study descriptions were cross-tabulated and established for any clinical potential effect modifiers. An explanation synthesis was carried out when there was clinical heterogeneity or when the data from the original research studies were insufficient to carry out a meta-analysis.

Statistical analysis

The RevMan 5.3 software was used to make it work (Cochrane Collaboration, 2014). The chi-square test showed that the study was heterogeneous if I2 was greater than 50%. The relative risk (RR) and 95% confidence interval (CI) were used to communicate the listing results. The weighted mean difference (WMD) and 95% confidence interval (CI) were used to extract the measurement results. A funnel plot is used to evaluate bias in published papers.

Results

Article Search

After excluding duplicates and titles that did not match the results, 3114 relevant articles were retrieved in total. In addition, 12 randomized controlled trials were included in our study, which was assessed using strict inclusion and exclusion criteria (Figure 1).

Description of characteristics study

This study suggested that 12 manuscripts containing 364 patients with knee OA were fully published from December 30, 2007, to December 30, 2022, with an average follow-up of 18.33 months. Figure 1 depicts the study selection PRISMA flowchart.

Patients who participated in this study ranged in age from 34 to 60 years on average. The method of transplantation therapy was intra-articular injection (I.A.), and there were 184 male patients to 180 female patients. transplanted BM-MSCs without dose uniformity in the included studies (table 1).

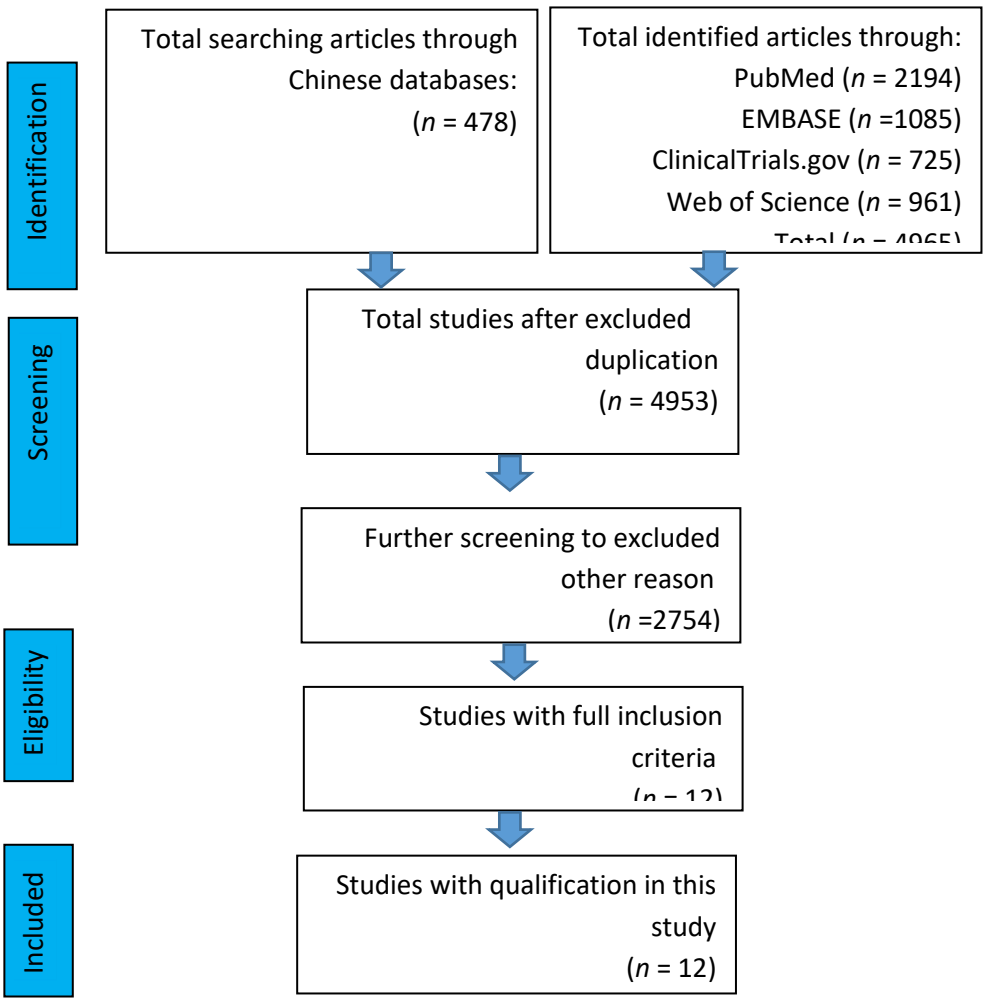

Figure 1.

Eligibility of studies for inclusion in the meta-analysis

Table 1.

Study characteristics

Study No.	Author(s) and year of publication	Sample size	M/F	Transplant route	Follow up (months)	Out come
1	Nejadnik H, et al 2010 [28]	36	15/21	IA	18	Better score in both VAS and WOMAC
2	Wong KL, et al 2020 [29]	28	16/12	IA	10	Better score in both VAS and WOMAC
3	Liang H, et al 2015 [30]	60	28/32	IA	18	VAS scale score from (6.7±1.3) points to (2.0±0.3) points
4	Vega A, et al 2015 [31]	30	10/20	IA	12	Better score in both VAS and WOMAC
5	Emadedin M, et al 2015 [32]	18	10/8	IA	30	Decreased visual analog scale (VAS), total WOMAC score decreased in these patients at months 6; P < 0.008), Mean WOMAC stiffness sub-scores were (31.2 vs. 10.6; P < 0.05)
6	Shapiro SA, et al 2017 [33]	25	15/10	IA	6	VAS pain scores in both knees decreased significantly from baseline at 1 week, 3 months, and 6 months (P ≤ .019)
7	Lamo- Espinosa JM, 2016 [34]	30	10/20	IA	60	Some improvement according to the WOMAC pain and physical function subscores
8	Wong KL, et al 2013 [35]	28	16/12	IA	12	Better score in both VAS and WOMAC
9	Aurelio V, et al 2015 [36]	30	12/18	IA	12	Better score in both VAS and WOMAC
10	Chahal J, et al 2019 [37]	14	9/5	IA	12	Significant overall improvements in WOMAC stiffness relative to baseline
11	Wakitani S, et al 2011 [38]	40	28/12	IA	18	Better score in both VAS and WOMAC
12	Shapiro SA, et al 2017 [39]	25	15/10	IA	12	VAS pain scores in both knees decreased significantly from baseline at 1 week, 3 months, and 6 months (P ≤ .019 for all)
Total		364	184/180		Average 18.33	

Quality Assessment

Figure 2 illustrates the included studies' methodological quality. There was no significant risk of bias in any of the included studies, so they were all included in the analysis.

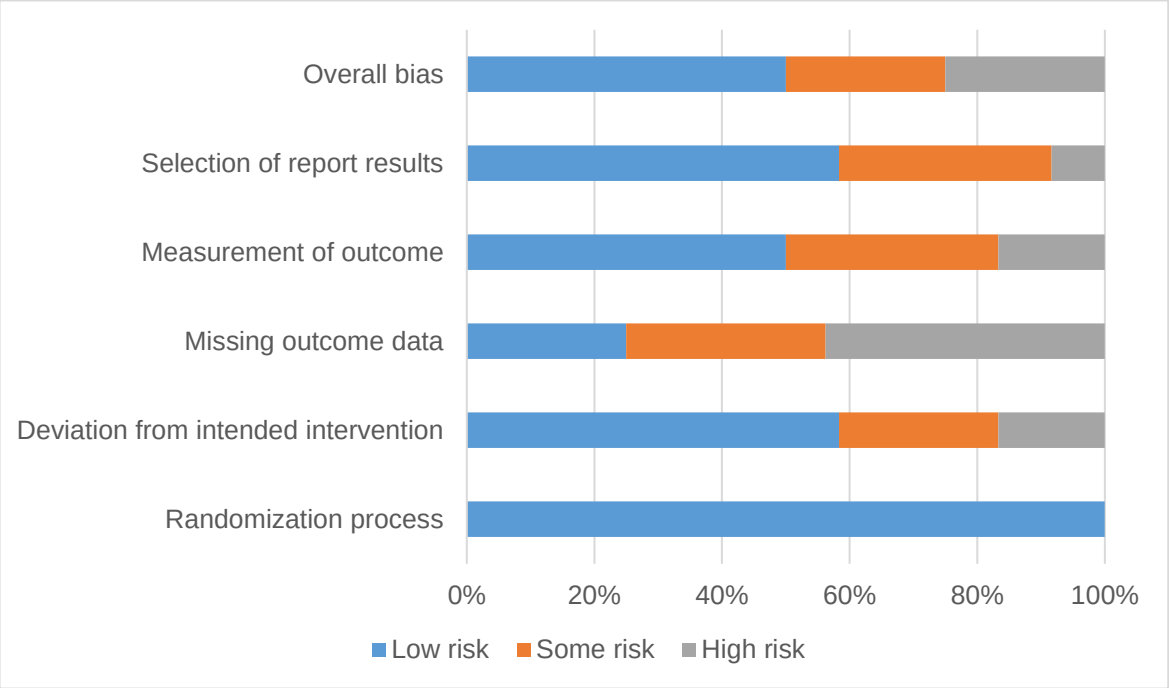

Figure 2. Quality Assessment is divided into three categories (low, some, and high risk)

Visual Analog Scale (VAS) score

The VAS data were reported in eleven of the included studies [28-39]. In both the MSC and control groups, the VAS score decreased from the initial value. At three months, the aggregated data suggested that there was no significant association between MSCs (WMD = 1.07, 95 percent CI: − 2.44, − 0.39, p = 0.074); and a lower VAS score than the control at 18.33 months, WMD = 6.04, 95 percent CI: − 10.34, − 0.38, p = 0.017; (Fig. 3).

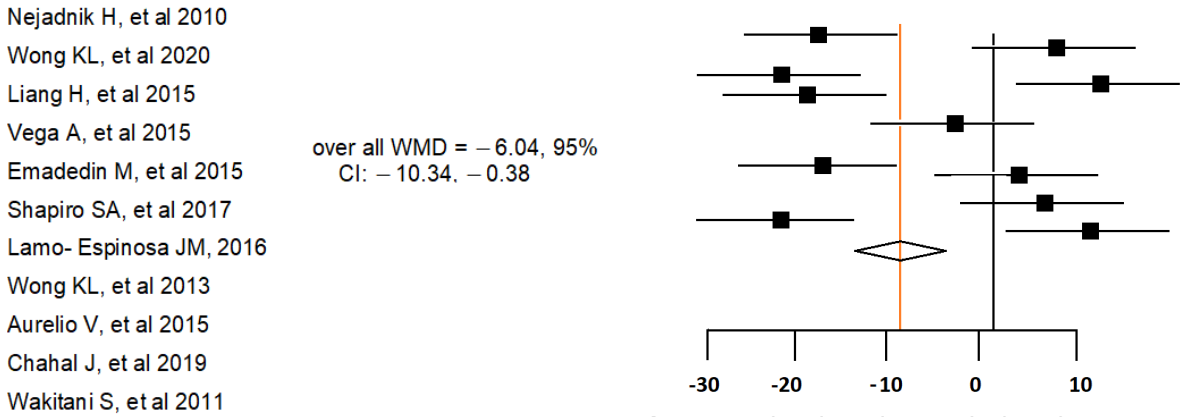

Figure 3. Visual Analog Scale (VAS) score

WOMAC pain score

In four of our studies, 33-36, patients with OA treated with BM-MSCs had lower WOMAC pain scores. Through a 12-month follow-up, this difference was evident: WMD = − 16.52, 95%CI: − 29.41, − 0.62, p = 0.032) (Fig. 4).

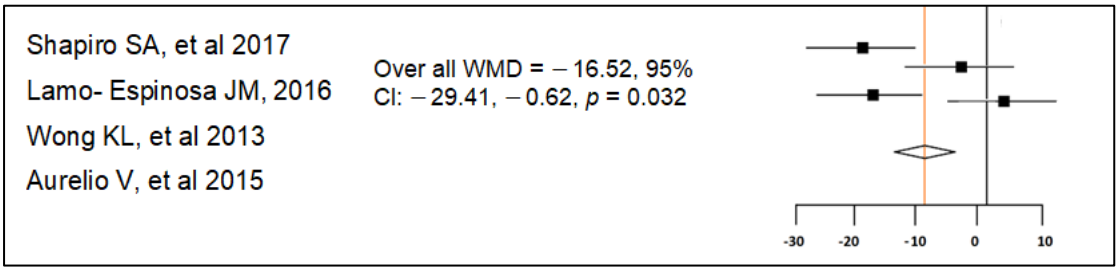

Figure 4.

WOMAC pain score

Publications Bias

The Funnel plot and the Egger regression test were used to look for publication bias, and the meta-analysis of the efficacy and safety of BM-MSCs in the treatment of knee osteoarthritis showed no publication bias (p=0.387), as shown in Figure 5. There was minimal publication bias because all of the studies were evenly distributed along the axes and within the 95% confidence interval.

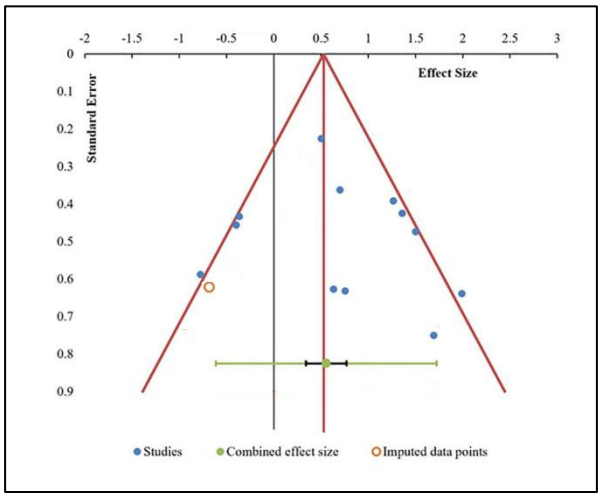

Figure 5.

Assessment of VAS for publication bias with funnel plot for all six studies included in this study.

Meta-regression

The meta-regression of BM-MSCs and OA ratings was evaluated solely for the VAS score, as shown in Table 2, due to the limited number of studies that provided complete results for multivariate meta-regression for demographic and clinical findings.

Table 2.

Meta-regression of BM-MSCs and OA grades.

Studies	Patients (%)	Grade I OA s (%)	Grades II–III OA (%)	Grade IV OA (%)
Fully recovered	65	60	36	20
Much improved	27	26	40	40
Slightly improved	6	11	14	25
No change	2	3	10	15
Worse	0	0	0	0

Discussion

Differentiation, plasticity, immunomodulatory, immune evasive, antimicrobial, and anti-inflammatory properties are all found in BM-MSCs. With the assistance of growth factors, cytokines, chemokines, and bioactive micromolecules released by BM-MSCs, BM-MSCs employ neo-angiogenesis and anti-apoptosis principles [40]. When treating knee osteoarthritis, the selection of BM-MSCs is crucial to achieving functional results [41-44]. the process of separating BM-MSCs from bone marrow aspirate concentrate (BMAC), harvesting them, preparing them, and characterizing them. The quantity and quality of the delivered BM-MSCs are crucial to the functional and structural benefits of BM-MSCs [40].

This meta-analysis looks at how well BM-MSCs therapy works for people with knee OA. Our findings, which were based on twelve studies, had a greater power to evaluate the impact of BM-MSCs on the treatment of knee OA patients. Results from our review recommended that the utilization of BM-MSCs fundamentally decreased the agony and further developed firmness and capability in the long haul. Similar to the findings of previous studies [45-48], this one suggested that BM-MSCs therapy could be used as a potential treatment for knee OA.

The WOMAC pain score at the end of one year was significantly lower in the BM-MSCs group (WMD = 16.52, 95 percent confidence interval) than in any other group. −29.41, −0.62, p = 0.032) [34]. Even though results from other studies varied [40, 49], they

suggested that BM-MSCs treatment did not alleviate pain (WMD = 1.33, 95% CI: − 3.08, 0.41; p = 0.13). The other researchers demonstrated that BM-MSC treatment resulted in an additional improvement of 7.65 (95% CI, 3.04 to 12.26); IKDC scores of 7.61 (95 percent CI, 1.44 to 13.79; p = 0.001) Lysholm scores (p = 0.016) and 0.64 (95% CI, 0.10 to 1.19; for Tegner scores (p = 0.021). The cell-recipient group had significantly higher MOCART scores in magnetic resonance imaging scans taken one year after surgery [40, 50]. In a pooled analysis, the MSCs/MST group performed statistically significantly better than the MST alone group in terms of postoperative international knee documentation committee subjective knee form (IKDC score) after two years of follow-up (trend estimate through ATM, 0.27; 95% CI: 0.006 to 0.54) [38-41]. At the conclusion of the study's follow-up, the MSCs/MST group also produced a MOCART score that was statistically significantly higher (Mean Difference, 16.42; 95% CI: 4.44 to 28.40) [40, 51].

Previous research [52] on the well-being of BM-MSCs among clinicians and patients confirmed that there were no major adverse events, with the exception of some patients who experienced temporary joint pain and swelling. With a mean follow-up of one year, the articles' sources found no serious adverse events. Our metanalysis study, which demonstrated that BM-MSCs were safe at this 12-month follow-up, supports the evidence.

Conclusion

All of the current treatments for osteoarthritis focus on relieving symptoms rather than preventing the disease. The progression of the disease cannot be stopped by current conservative treatments, and surgical management in the form of joint replacement comes with a number of serious complications. The pre-clinical and clinical trials have shown that intra-articular injection of BM-MSCs helps treat osteoarthritis by lowering the pain index, improving knee function, and significantly increasing the capacity of cartilage.

Abbreviations

Not applicable

Declarations

Ethics approval and consent to participate

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Authors' contributions

NG.Y.: assortment and gathering of data, and manuscript typing; P.L., and D.L.H.: formation, layout, collection of data, analysis, and paper writing; F. G. A., and A.N.A: construction of results, analysis; and paper typing; all authors, analysis results, and match proof manuscript.

Competing Interests

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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Not applicable

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