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The effect of vitamin D on recurrence of uterine fibroids: A randomized, double-blind, placebo-controlled pilot study

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ABSTRACT

Background: and purpose: A deficiency of vitamin D has been suggested as one of the principal risk factors for uterine fibroids (UFs). We aimed to investigate the effect of vitamin D supplementation on the recurrence of UFs.
Materials and methods: In a randomized, double-blind, placebo-controlled pilot study, women who had undergone hysteroscopic myomectomy from November 2017 to June 2020 were randomly given either vitamin D (1000 IU tablet; n = 55), or placebo (n = 54) daily for 12 months. Both groups were followed and compared in regard of the primary outcomes of the study, which were recurrence rates, size, and numbers of UFs based on three-dimensional transvaginal ultrasound investigation (3D-TVS). Data analysis was performed by the intention-to-treat (ITT) approach.
Results: The mean age of the study participants was 37.9 ± 6.5 years. The two groups did not differ significantly in terms of demographic and pre-intervention clinical characteristics. The administration of vitamin D supplements for one year reduced recurrence rates of UFs by 50% ($p = 0.17$). Vitamin D also reduced the size of recurrent UFs in the intervention group compared to controls (−7.7 mm), the difference was statistically different ($p < 0.001$). No adverse effect of vitamin D was reported in the present study.
Conclusion: Based on these results, vitamin D appears to be a promising and safe agent in the prevention of recurrence and reduction of the size of recurrent UFs, although further well-designed and appropriately powered studies are required to demonstrate a significant difference in the size and number of recurrent UFs.

1. Introduction

Uterine fibroids (UFs) or leiomyomas are the most common benign uterine tumors in women of reproductive age [1]. The prevalence of UFs is approximately 50–68.6% [2]. UFs are frequently associated with significant morbidity, especially when they are in a submucosal location [3]. Women with UFs may experience menstrual disorders, heavy and prolonged menstrual bleeding, anemia, pelvic pain, and infertility [4,5]; these are the most common reasons for performing a hysterectomy [4,6,7].

Myomectomy is a surgical option to preserve the uterus [8]. Minimally invasive surgical techniques (MIST), including laparoscopic myomectomy (LM), and hysteroscopic myomectomy, are currently the preferred modalities to treat UFs [9–11]. However, UFs may recur after MIST, as they do sometimes after open surgery [10,12]. Cumulative post-LM recurrence rates were 15.3%, 43.8%, 62.1%, and 84.4%, at postoperative years 1, 3, 5, and 8, respectively [9]. Age, UF size, the number of tumors, sex hormones, surgical technique, and postoperative parity are risk factors for the recurrence of UFs [9,13]. Nevertheless, risk factors for postoperative recurrence remain uncertain [9].

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Recent human and animal studies have suggested that the deficiency of essential minerals and vitamins may play a key role in the emergence of UF [14–17]. Vitamin D deficiency has been proposed as one of the main risk factors for UFs [18–20]. Expression levels of the vitamin D receptor (VDR) in UFs were lower than those in the myometrium [21]. Moreover, women with sufficient levels of vitamin D were less likely to develop UFs; the adjusted odds ratio was 0.68 [19].

Vitamin D has been described as a strong anti-tumor agent that inhibits the proliferation of leiomyoma cells *in vitro* [21]. Moreover, the size of UFs was found to be reduced by vitamin D *in vivo* in animal models [22]. These observations support the potential role of vitamin D, 1α, 25 (OH) 2D3 or its potent analogs in the non-surgical treatment of UFs [21]. Further research is needed to clarify the role of vitamin D on the growth and recurrence of UFs. Given the absence of any randomized, controlled prospective investigation on the subject, the present study was designed to evaluate the effect of vitamin D on the recurrence of UFs.

2. Materials and methods

2.1. Study design and participants

A randomized, double-blind, placebo-controlled clinical pilot study was performed at Hazrat-e Rasool Hospital affiliated to Iran University of Medical Sciences, Tehran, Iran, from November 2017 to June 2020. The main purpose of the study was to determine the effect of 12 months' treatment with vitamin D on the size and number of recurrent UFs. In accordance with Hertzog's recommendations [23], the sample size was 40 patients per group; 30% were added to compensate for potential loss to follow-up. The final estimated sample size was 55 patients in each group; the study power was 80% and the two-sided alpha error 0.05.

Patients who fulfilled the following inclusion criteria were eligible for the study: 1) age 30–45 years; 2) body mass index (BMI) 18.5–24.9 kg/m^2; 3) uterine submucosal fibroids (types 0, 1, 2) [24]; 4) no underlying disease such as hypertension (HTN), cardiovascular, respiratory, renal, hematologic, hepatic, neurologic, or psychological condition; 5) no use of hormonal drugs in the preceding three months and during the study period; 6) no history of taking vitamin D supplements in the past six months; 7) a vitamin D3 insufficiency (25-hydroxyvitamin D [25OHD]); vitamin D3 levels were determined by the enzyme-linked immunosorbent assay (ELISA) method (IDS Company, England) and a vitamin D insufficiency was defined as a serum 25-OH-D3 level of 20–30 ng/mL [25]; 8) normal thyroid function tests and lipid profile; 9) no disease other than UFs (polycystic ovary syndrome (PCO), endometriosis, tumor, etc.) detected during surgery or by clinical or paraclinical methods.

All patients underwent hysteroscopic myomectomy by an experienced team of gynecological surgeons. The cervix was dilated with a Hegar dilator (9 mm). A 26F continuous-flow bipolar resectoscope (Karl Storz, Tuttlingen, Germany) with a telescope of 4 mm, and a 12 fore-oblique equipped with a U-shaped cutting loop was inserted into the uterine cavity under direct visualization with a video camera. Using an automated fluid pump (Hamou Endomat; Karl Storz) with an inflow pressure of 80–100 mm Hg, the uterine cavity was irrigated with saline solution (0.9% sodium chloride). The leaking fluid from the vagina was extracted with plastic draping. An 80- to 100-W electrosurgical cutting device (Autocon II 400; Karl Storz) was used. The intrauterine portion of the submucosal myoma was resected from the maximum bulging region to the endometrial surface by slicing.

After the first menstruation following the hysteroscopic myomectomy, all patients underwent a three-dimensional transvaginal ultrasound (3D-TVS) investigation. Women whose ultrasound investigation revealed no UF were enrolled in the study by a convenient sampling method. All of the 3D-TVS examinations were performed at the radiology department using a GE Voluson S6 ultrasound device equipped with a RAB2-6 3D endocavitary probe (5–9 MHz). All of the ultrasound examinations were performed by the same radiologist to avoid bias. Patients with any gynecological disease other than UF (PCOs, endometriosis, tumor, etc.) identified by clinical or paraclinical methods during the follow-up period, patients who were unwilling to continue their participation, had adverse drug reactions, hypersensitivity or toxicity reactions to vitamin D, became pregnant, or had participated in an investigational program with interventions outside of routine clinical practice, were excluded from the study (Fig. 1).

2.2. Intervention, randomization, and blinding of study participants

The study was performed in a double-blind manner. The investigator, statistician, and radiologist were blinded to the group allocation of patients. Enrolled patients (n = 109) were randomly assigned to one of the two groups through a computer-generated random table using a block size of 4 (i.e., ABAB, AABB, and all other possible restricted permutations). A nurse who was not involved in the research project was asked to prepare the coded envelopes using sequential numbers, and the researcher allocated the patients to one of the two groups based on the envelopes. The first group received vitamin D3 1000 IU tablet [Poura Teb Pharmaceutical Co.] daily for 12 months; the second group received placebo starch tablets. Placebo agents were provided by Golesorkh Pharmaceutical Co. Ltd. Placebo tablets were identical in smell, taste, appearance, size, and the package with vitamin D3 1000 IU tablets. The dosage of vitamin D3 was selected on the basis of a previously published study [26]. Both groups were given advice about 10–30 min of midday sunlight exposure and were asked to exercise regularly for twenty to 30 min a day, swim once or twice a month, and perform simple activities of daily living.

2.3. Outcomes, measurements, and follow up

The primary endpoint of the study was the rate of recurrence of UFs following 12 months treatment with vitamin D or placebo. The size and number of recurrent UFs, as measured by 3D-TVS were defined as secondary endpoints. TVS has a sensitivity of 89.2–90.9% and a specificity of 99.6–100% in the detection of UFs [27].

General parameters including age, gravidity, parity, weight, height, BMI, family history of uterine fibroids, postoperative contraceptive methods, reasons for hysteroscopic myomectomy, exposure to sunlight, tobacco, alcohol, and caffeine consumption, physical activity, diet, and stress were registered. The data were either obtained directly from the patients or extracted from their medical records. The numbers, size and location of UFs on the 3D-TVS were taken into account. Specifically, three perpendicular diameters (sagittal, longitudinal, and transverse, in millimeters) of each fibroid were measured. The size and location of the largest fibroid were considered in patients with more than one fibroid.

Self-reported history of daily sun exposure in minutes, tobacco, alcohol, and caffeine consumption (number of times), and physical activity (minutes) were recorded at each monthly investigation. In order to ensure no major differences in diet, patients were asked preoperatively to fill the Food Frequency Questionnaire (FFQ) validated in Iran [28]. Perceived stress was measured before surgery using the Persian validated version [29] of the Perceived Stress Scale (PSS) developed by Cohen. All patients were followed for twelve months. The study participants were contacted every four weeks by the main investigator to confirm their compliance with medication and record side effects. All study participants who were outpatients reported every four months for checkups, assessment of their medication compliance, and recording of adverse effects. Before and after intervention a blood sample was collected and serum levels of vitamin D were measured in a single laboratory. At the end of the intervention, all patients underwent a 3D-TVS investigation, and the presence, size, and numbers of UFs were recorded.

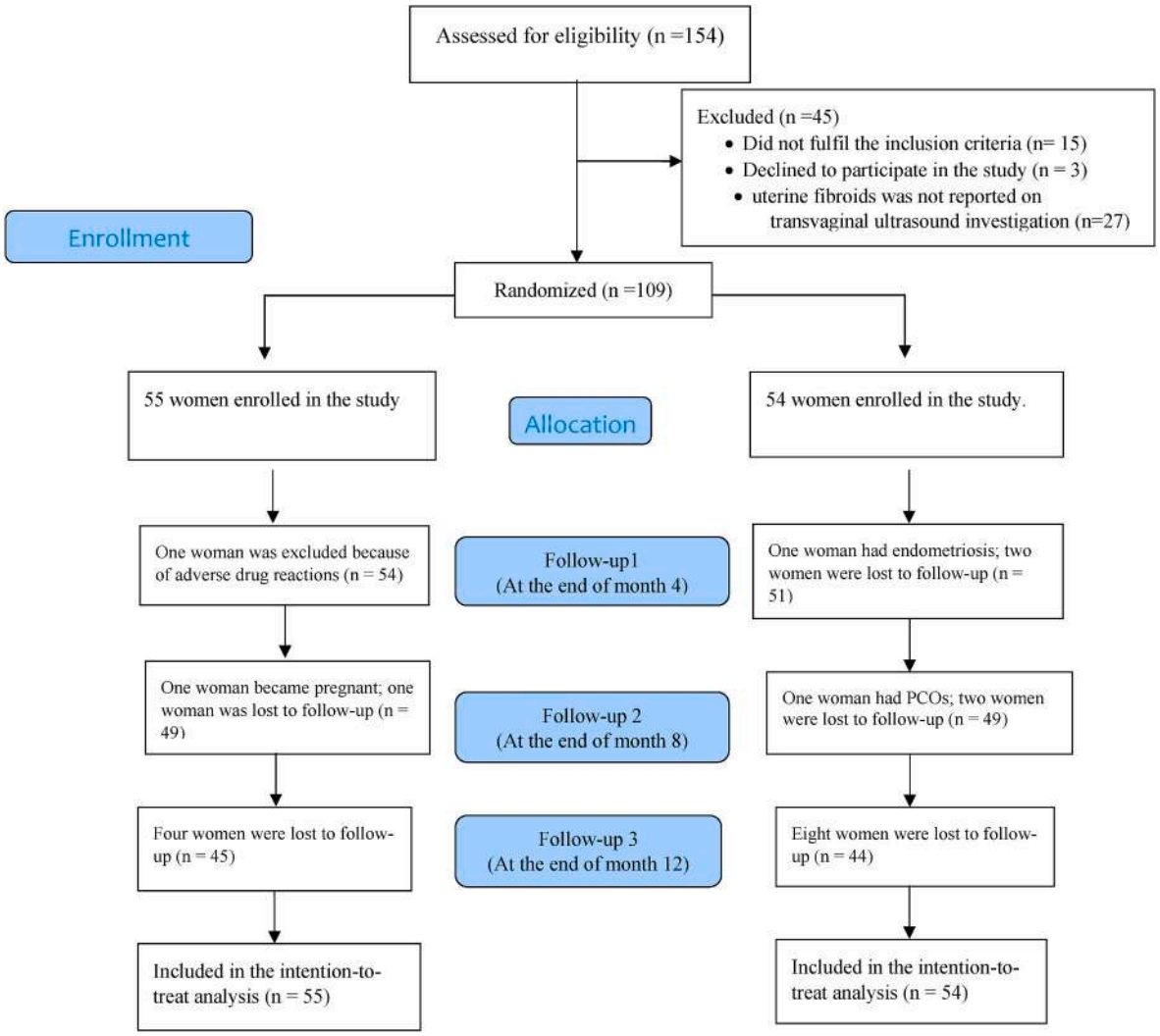

Fig. 1. CONSORT flow diagram for efficacy trial of vitamin D on recurrent uterine fibroids.

2.4. Ethical statement

All steps of the study were performed in accordance with the Declaration of Helsinki (ethical principles for medical research involving human subjects), and the regulations of the ethics committee of Iran University of Medical Sciences (approval number IR.IUMS.REC 1396.30623). The study was registered at the Iranian Registry of Clinical Trials (IRCT20150909023949N3, https://www.irct.ir/trial/27844). The objectives of the trial were explained to patients who were scheduled to undergo hysteroscopic myomectomy, and their written informed consent was obtained. The patients were free to discontinue their participation at any time. All personal data were treated confidentially and only reported in collective form.

2.5. Statistical analysis

All data were entered into the statistical software program IBM SPSS Statistics for Windows, version 21.0 (IBM Corp. 2012. Armonk, NY: IBM Corp). Qualitative variables were described by frequency (percentage) and comparison between groups was performed with Chi-square analysis followed by the Fisher's exact test. The one-sample Kolmogorov-Smirnov test was used to test the normal distribution of quantitative data. Data were also tested for normality using the Q-Q plot and were found to be normally distributed. Student's t-test was used for comparison between groups. Data analysis was performed by the intention-to-treat (ITT) approach and all patients who participated in the study were considered for the analysis. Missing data of patients lost to follow-up were imputed according to the preceding records. The level of significance was set to 0.05.

3. Results

Of 154 patients who were assessed for eligibility, 109 were included in the study (55 cases in the intervention group and 54 in the control group). Of all eligible cases, eight and nine women dropped out from the intervention and control groups, respectively (Fig. 1). The mean age of the study participants was 37.9 ± 6.5 years. Before intervention, the two groups showed no significant difference in terms of age, gravidity, parity, weight, height, BMI, family history of uterine fibroids, reasons for hysteroscopic myomectomy, sun exposure, tobacco, alcohol and caffeine consumption, physical activity, diet, stress, number, size, and location of fibroids. Pre-intervention serum levels of 25-hydroxyvitamin D3 in intervention and control groups were 23.6 ± 7.8 and 24.3 ± 8.1 respectively. The results of Student's t-test indicated this difference was not statistically significant. Demographic and pre-intervention clinical characteristics of patients are summarized in Table 1.

The two groups did not differ significantly in terms of BMI, contraceptive methods, sun exposure, tobacco, alcohol, and caffeine consumption at postoperative visits or at the end of the study. Post-12 month serum levels of 25-hydroxyvitamin D3 in intervention and

Table 1
Demographic and pre-intervention clinical characteristics of the two groups[a].

Variables		Intervention group (n = 55)	Control group (n = 54)	*p value*[b]
Age, y		37.6 ± 6.7	38.1 ± 6.4	0.63
Gravidity		3.0 ± 1.8	3.3 ± 2.1	0.51
Parity		2.1 ± 1.1	1.9 ± 0.9	0.2
BMI, kg/m^2		22.95 ± 3	23.45 ± 3.38	0.97
Family history of uterine fibroids,	Yes	14 (25.4)	16 (29.6)	0.13
	No	41 (74.6)	38 (70.4)	
Reason for hysteroscopic myomectomy	AUB	29 (52.7)	34 (64)	0.09
	Infertility	5 (9.1)	5 (9.2)	
	Pelvic pain	9 (16.4)	4 (7.4)	
	Abortion	12 (21.8)	11 (20.4)	
Postoperative contraceptive methods	Copper IUDs	10 (18.2)	13 (24.1)	0.34
	Condom	27 (49.1)	19 (35.2)	
	Withdrawal	18 (32.7)	22 (40.7)	
Pre-intervention serum levels of 25-hydroxyvitamin D3, ng/ml		23.6 ± 7.8	24.3 ± 8.1	0.68
Numbers of UFs	1	40 (72.7)	41 (75.9)	0.11
	2	9 (16.4)	6 (11.1)	
	3	6 (10.9)	7 (13)	
Size of the largest UF, mm		29.19 ± 11.1	30.51 ± 10.9	0.73
Location of the largest UFs	Anterior	17 (30.9)	10 (18.5)	0.19
	Posterior	12 (21.8)	16 (29.6)	
	Lateral	14 (21.5)	19 (35.2)	
	Fundal	12 (21.8)	9 (16.7)	

Abbreviation: n: number, y: year, BMI: body mass index, AUB: abnormal uterine bleeding, UFs: uterine fibroid, IUD: intrauterine device, SD: standard deviation.
[a] Continuous values are presented as means ± SD, and categorical variables as numbers (%).
[b] The p-value was calculated by the $\chi 2$ test (for categorical variables) or the Student's t-test (for continuous variables) in order to determine differences between groups.

control groups were 41.7 ± 15.3 and 26.9 ± 10.6 respectively. The results of Student's t-test indicated this difference was significant ($p < 0.001$).

The overall recurrence rate for UFs, without considering the study arms, was 16.8% (15/89). The results showed that 9.1% and 18.5% of patients in the intervention and control groups, respectively had a recurrence of UFs. This difference was not statistically significant. The serum levels of 25-hydroxyvitamin D3 were significantly lower in those women who had a recurrence of leiomyoma than in those who did not. Recurrent UFs in the intervention group were smaller than those in controls, and this difference was statistically significant. Post-intervention serum levels of 25-hydroxy vitamin D3 based on the recurrence of UFs are presented in Table 2.

No adverse effect of vitamin D was reported in the present study.

4. Discussion

Despite numerous publications on uterine fibroids, the role of vitamin D3 in the regulation of uterine fibroids has been scarcely investigated [19,20,30]. Recent studies have suggested that vitamin D is a potent regulator of the growth of UFs in the human uterus [30–33]. In this randomized, double-blind, placebo-controlled pilot study, we investigated the effect of vitamin D on the recurrence of UFs one year after hysteroscopic myomectomy. The recurrence rate of UFs in the present study in general, without considering the study arms, was 16.8% (15/89). The administration of vitamin D for twelve months was associated with a 50% lower recurrence rate of UFs. Furthermore, vitamin D was associated with a reduced size of recurrent UFs compared to controls, and the difference was statistically different. Our findings support previous *in vitro* and *in vivo* studies, which supported a role of vitamin D

Table 2
Comparison of levels of 25-hydroxy vitamin D3 and uterine fibroids in the intervention and control groups.

Variable		Intervention group (n = 55)	Control group (n = 54)	*p value*
		n (%)		
Post-12 month serum levels of 25-hydroxy vitamin D3, ng/ml		41.73 ± 15.3	26.87 ± 10.6	[a]<0.001
Recurrence of UFs	Yes	5 (9.1)	10 (18.5)	[b]0.17
	No	50 (90.9)	44 (82.5)	
Post-12 month serum levels of 25-hydroxy vitamin D3 based on the recurrence of UFs	Yes	27.2 ± 6.6	18.3 ± 3.1	[a]0.02[e]
	No	43.2 ± 10.9	29.9 ± 7.8	[a]<0.001[f]
[d]Size of UF, mm (mean ± SD)		13.5 ± 5.8	21.2 ± 6.9	[a]p < 0.001
[d]Numbers of UFs	1	5 (9.1)	7 (13)	[c]0.15
	2	0	3 (5.5)	

Abbreviation: n: number, UFs: uterine fibroid, SD: standard deviation.
Continuous values are presented as means ± SD, and categorical variables as numbers (%).
**Percentages were calculated according to the total recurrences of UFs.
[a] Student's t-test.
[b] $\chi 2$ test.
[c] Fisher's exact test.
[d] If there was more than one UF, the largest UF was considered.
[e] p value is for intervention group.
[f] p value is for control group.

supplementation in the development of UFs [19–21,30,32].

Patients in our intervention group experienced a significant increase in serum 25-OH-D3 levels after 12 months of supplementation. In line with our data, previous studies have also reported a lower prevalence and incidence of UFs in women with normal serum levels of 25-hydroxyvitamin D3 compared to those with a deficiency of D3 [32,34,35]. In a case-control study by Srivastava et al. (45 women with UF cases and 45 women without UF), the mean serum level of 25-hydroxyvitamin D3 (±SD) was significantly lower in women with UFs compared to controls (15.10 ± 6.09 vs. 26.09 ± 7.90 respectively, $p < 0.001$). Furthermore, 20% of the cases and 6.7% of the controls had a 25-hydroxyvitamin D3 deficiency ($p < 0.001$) [36].

In the present study, recurrent UFs in the intervention group were smaller in size than those in controls (13.5 vs. 21.2 mm, respectively), and this difference was statistically significant. In a randomized clinical trial, Arjeh et al. studied the effect of oral vitamin D on the volume of UFs: 60 women with a vitamin D deficiency were randomly given either vitamin D (50,000 IU tablet, n = 30) or placebo (n = 30) daily for three months. In that study, vitamin D inhibited the growth of UFs [32]. Ciavattini et al. investigated 108 women with 'small burden' UFs (<4 tumors; <50 mm in diameter). The first group (n = 53) received vitamin D3 supplements daily at a dose of 2000 IU for one year, and the second group (n = 55) received no treatment. Vitamin D3 reduced the progression of UFs to extensive disease. Furthermore, the need for conventional surgical or medical therapy in the intervention group was less than controls [35]. Ciavattini et al. used 2000 IU daily, twice the dose used in our study. No definitive dose recommendation has yet been published for prolonged (one year) vitamin D supplementation [26]. In the present study, we prescribed a dose of 1000 IU to avoid possible side effects. According to *in vitro* study by Blauer et al., bioactive vitamin D inhibits myometrial cells and the growth of fibroids in the tissues of women undergoing hysterectomy [37]. The proliferation of leiomyoma cells *in vitro* and the growth of leiomyoma in animal models *in vivo* were reduced by vitamin D3 [30]. Sharan et al. found that vitamin D inhibits the growth of fibroid cells by downregulating the proliferating cell nuclear antigen, cyclin-dependent kinase 1, and B-cell lymphoma 2, and

suppressing the expression and activity of catechol-O-methyltransferase [38].

5. Strengths and limitations

The main strength of the present study was the randomized blind assessment of patients while considering several criteria to reduce the effect of confounders on the study outcomes. Although the present study provided important data, the limitations are worthy of mention. One of the limitations of the study was its small sample size. A second limitation was the short follow-up period (i.e., 1 year). With a one-year follow-up period, it is unclear whether vitamin D merely delays UF recurrence, or can prevent recurrence of UFs. Although the effect of vitamin D on the growth of UFs has been demonstrated in animal studies *in vivo*, these preclinical findings have not been examined in human trials. High-quality clinical trials with large sample sizes and a long follow-up period will be needed to confirm the findings of the present study.

6. Conclusion

In this randomized, double-blind, placebo-controlled pilot study, vitamin D reduced the recurrence and size of UFs and seems to be safe, although further well-designed studies are required, appropriately powered to demonstrate a significant difference in the size and number of recurrent UFs.

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Author contribution

GhM, MV, HM conceptualized and designed the study. GhM, MV, HM participated in data collection. GhM, HM, HS, and LA analyzed the data. GhM, IA, EG, and LA coordinated the writing of the manuscript. All of the authors critically read the initial manuscript, commented on the text, and approved the final version.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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