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Original Article

Cardiac rhabdomyomas: clinical progression, efficacy and safety of everolimus treatment

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ABSTRACT

Background. Primary cardiac tumors are extremely rare. Cardiac rhabdomyoma is the most common primary cardiac tumor. 50-80% of solitary rhabdomyomas and all multiple rhabdomyomas are associated with tuberous sclerosis complex. Due to spontaneous regression, surgery is necessary only in severe hemodynamic compromise and persistent arrhythmias. Everolimus, a mechanistic target of rapamycin (mTOR) inhibitor, can be used in the treatment of rhabdomyomas seen in tuberous sclerosis complex. We aimed to evaluate the clinical progression of rhabdomyomas followed-up in our center between the years 2014-2019 and evaluate the efficacy and safety of everolimus treatment on tumor regression.

Methods. Clinical features, prenatal diagnosis, clinical findings, tuberous sclerosis complex presence, treatment and follow-up results were evaluated retrospectively.

Results. Among 56 children with primary cardiac tumors, 47 were diagnosed as rhabdomyomas, 28/47 patients (59.6%) had prenatal diagnosis, 85.1% were diagnosed before one year of age and 42/47 patients (89.3%) were asymptomatic. Multiple rhabdomyomas were present in 51% and median diameter of tumors was 16mm (4.5 - 52 mm). In 29/47 patients (61.7%) no medical or surgical treatment were necessary while 34% of these had spontaneous regression. Surgery was necessary in 6/47 patients (12.7%). Everolimus was used in 14/47 patients (29.8%). Indications were seizures (2 patients) and cardiac dysfunction (12 patients). Regression in size of rhabdomyomas was achieved in 10/12 patients (83%). Although, in the long-term, the amount of tumor mass shrinkage was not significantly different between patients who received everolimus and untreated patients (p=0.139), the rate of mass reduction was 12.4 times higher in patients who received everolimus. Leukopenia was not detected in any of the patients, but, hyperlipidemia was noted in 3/14 patients (21.4%).

Conclusions. According to our results, everolimus accelerates tumor mass reduction, but not amount of mass regression in the long term. Everolimus may be considered for treatment of rhabdomyomas which cause hemodynamic compromise or life-threatening arrhythmias before surgical intervention.

Key words: cardiac tumor, everolimus, rhabdomyoma, tuberous sclerosis complex.

Primary cardiac tumors in children are extremely rare. Cardiac rhabdomyoma is the most common primary cardiac tumor.[1-4] Most rhabdomyomas are related with tuberous sclerosis complex (TSC), but they may also occur as isolated lesions. Patients with rhabdomyomas are mostly asymptomatic. However, depending on their location, rhabdomyomas may obstruct inflow or outflow of blood, affect conduction pathways, sinus or atrioventricular nodes and cause congestive heart failure, arrhythmia, cyanosis, respiratory distress, and murmur. Large or multiple rhabdomyomas can cause stillbirths or sudden death due to impairment in myocardial function and arrhythmias. Echocardiography has a primary role for both diagnosis and follow-up of rhabdomyomas.

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Magnetic resonance imaging can be used as a complementary tool when diagnosis is not clear or for preoperative planning, and, cardiac catheterization is rarely required. Although histological evaluation with biopsy is the gold standard in confirming the diagnosis, it is rarely required.[1]

Since spontaneous regression of rhabdomyomas have been well documented, surgical or therapeutic interventions are only recommended for cases with severe hemodynamic compromise or persistent arrhythmias.[1-9] There is no relationship between the spontaneous regression rate or size of the tumor and its number or location.[10] The survival rate of the disease is between 81-92%.[10-12]

As tuberous sclerosis complex has autosomal dominant inheritance caused by mutations in the TSC1 (Tuberous sclerosis Complex) and TSC2 genes in the mTOR pathway responsible for the regulation of cell growth, mechanistic target of rapamycin (mTOR) inhibitors, mostly everolimus, have been used in the treatment of rhabdomyomas.[13-16] Everolimus is effective for the reduction of tumor size, and, is even life-saving for complications such as arrhythmias and ventricular outflow obstruction.[17] It is also used for treatment of tuberous sclerosis associated giant cell astrocytomas or angiomyolipomas. In addition to simple gastrointestinal system side effects, side effects such as leukopenia, susceptibility to infections, stomatitis, skin rash, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, hypophosphatemia, hyperuricemia and bone marrow suppression have also been reported.[18]

We aimed to evaluate patients diagnosed with cardiac rhabdomyomas and followed-up in Hacettepe University İhsan Doğramacı Children's Hospital Pediatric Cardiology and Pediatric Oncology Departments between January 1, 2014 and June 30, 2019. We also aimed to observe the efficacy and safety of everolimus for the treatment of rhabdomyomas.

Material and Methods

Among 56 patients aged between 0-18 years who were admitted to our institution and who were found to have a cardiac mass by echocardiography, 47 patients were diagnosed as cardiac rhabdomyomas. During echocardiographic examination, intracardiac masses were classified and diagnosed as rhabdomyomas when they were highly echogenic, homogeneous, especially multiple, well-circumscribed, intramural or intracavitary nodules with a finely speckled pattern occurring anywhere within the heart. Differentiation from intracardiac thrombi, myxomas, and hemangiomas were made by the absence of circumscribed echolucent areas as a result of hemorrhage formation. Differentiation from fibromas was made by the absence of calcification and cystic degeneration in rhabdomyomas.[19]

The demographic characteristics, diagnosis, presence of intrauterine diagnosis, clinical complaints, comorbidities, clinical follow-up, examinations, treatment details and outcome of patients who were diagnosed as rhabdomyomas by echocardiography, radiological investigations or pathologic examinations were evaluated retrospectively. Data were collected from electronic records and patient files. Echocardiographic data consisted of results from both our hospital's and other referral center's data. Records of patients who received everolimus were also evaluated. Everolimus was started at a dose of 4.5 mg/m^2/week (two days of the week, twice daily) and dose adjustment was made according to serum everolimus levels. Everolimus treatment indications, treatment durations, responses to treatment and side effects were analyzed. Echocardiographic data of patients who received everolimus and who did not receive everolimus were compared to analyze everolimus efficacy.

The study was approved by the Hacettepe University Non-Interventional Clinical Research Ethics Committee (GO-19/690).

Statistical analysis

All statistical analyzes were performed using IBM SPSS Statistics for Windows Version 23.0 package program. Numerical variables were summarized as mean±standard deviation, median (minimum - maximum) values. Categorical variables were shown with numbers and percentages. The Mann-Whitney U test was used to compare the regression in mass sizes of tumors of patients who received and did not receive everolimus because it did not comply with the normal distribution. Statistical significance was accepted as $p<0.05$.

Results

The study included 22 female and 25 male patients. Out of 47 patients, 28 patients (59.6%) had prenatal diagnosis and 12 patients (25.5%) were diagnosed before one year of age. Totally, 85.1% of the patients had a diagnosis of rhabdomyoma before the age of one.

The median age of the patients with postnatal diagnosis was 0.5 years (1 day-16.1 years). Single cardiac rhabdomyomas were present in 23 patients (49%), and multiple rhabdomyomas in 24 patients (51%). Demographic characteristics, referral reasons, clinical findings, tumor locations, and associated diseases are summarized in Table I.

Twenty two patients (46.8%) did not have any clinical findings. Arrhythmias were present in 12 patients (25.5%), murmur in nine patients (19.1%), valve insufficiency in eight patients (17%) and pericardial effusion in two patients (4.3%). Three patients had respiratory distress and one patient had bruising. Of the 23 patients with a single rhabdomyoma, five patients (21.7%) had arrhythmias, two (8.7%) had valve insufficiency, two (8.7%) had both valve insufficiency and arrhythmias. Of the 24 patients with multiple rhabdomyomas, six patients (25%) had murmur, five (20.8%) had arrhythmias, and three (12.5%) had valve insufficiency.

Table I. Demographic and clinical characteristics of all patients with cardiac rhabdomyomas.

Gender, n (%)	
Male	25 (53%)
Female	22 (47%)
Prenatal diagnosis	
Yes	28 (59.6%)
No	19 (40.4%)
Age of patients with postnatal diagnosis	
Mean (years)	2.7±4.9
Median (years) (range)	0.5 (1 day-16.1 years)
Referral reasons, n (%)	
Prenatal diagnosis	28 (59.6%)
Prematurity	1 (2.1%)
Murmur	7 (14.9%)
Respiratory distress	2 (4.3%)
Bruising	1 (2.1%)
Palpitations	1 (2.1%)
Symptoms	
Asymptomatic	42 (89.3%)
Respiratory distress	3 (6.4%)
Bruising	1 (2.1%)
Palpitations	1 (2.1%)
Number of tumors, n (%)	
Single	23 (49%)
Multiple	24 (51%)
Tumor size (mm)	
Median largest diameter at diagnosis	16
Minimum diameter	4.5
Maximum diameter	52
Tumor location, n (%)	
Left ventricle	17 (36.2%)
Left and right ventricle	16 (34%)
Right ventricle	2 (4.3%)
Interventricular septum	1 (2.1%)
Additional disease, n (%)	
Tuberous sclerosis complex	33 (70.2%)
Cleft palate and lip	1 (2.1%)
No treatment, n (%)	29 (61.7%)
Follow-up results without any treatment	
Complete regression (n)	2
Partial regression (n)	14
Total regression, n (%)	16 (34%)
Everolimus, n (%)	14 (29.8%)
Treatment response, n (%)	12 (85.7%)
Surgery, n (%)	6 (12.7 %)

Median diameter of tumors at the time of diagnosis was 16 mm (minimum: 4.5 mm, maximum: 52 mm). Thirty-three patients (70.2%) with rhabdomyomas were also diagnosed as TSC. Of these patients, 20/33 patients (60.6%) had epileptic seizures and were on antiepileptic treatment. Cranial imaging was performed in 18/33 patients with tuberous sclerosis complex. 14/18 had a history of epileptic seizures. All 18 patients with cranial imaging had findings consistent with TSC. Giant cell astrocytomas were detected in three patients (9.1%) and angiomyolipomas were documented in four patients (12.1%).

Treatment

In 29/47 patients (61.7%), no medical or surgical treatment was necessary, during the follow-up, 34% of these had spontaneous regression. Everolimus treatment were necessary in fourteen patients. Patient characteristics of those given everolimus and treatment results are shown in Table II. Surgery were necessary in six patients (12.7%), four patients due to severe left ventricular outflow tract obstruction, one patient due to severe right ventricular outflow tract obstruction, one patient because of a giant mass in left ventricle, decreased left ventricular functions and pericardial effusion.

Indications for everolimus treatment were cardiac dysfunction in 12/14 patients (85.7%) (valve dysfunction in seven (58.3%), cardiological inflow or outflow obstruction in three (25%), life-threatening arrhythmias (one patient had frequent ventricular premature contractions causing syncope, one patient had ventricular tachycardia) in two patients (16.7%)) and epileptic seizures in 2/14 patients (14.3%). Antiepileptic therapy was also used in two patients whom everolimus was started for neurological complications, and seizures were under control.

Regression in size of rhabdomyomas were achieved in 10/12 patients (83%). Considering the two patients with seizures, everolimus treatment was successfully achieved in 12/14 patients (86%).

The target serum everolimus levels were between 3-8 ng/ml. The target serum levels were reached in all nine patients whose data could be reached, and dose adjustments were made according to the serum levels. Serum everolimus level data were not available in five patients. Most common side effect was hyperlipidemia, which was observed in 3/14 patients (21.4%). However, in only one patient, hyperlipidemia reached a level that required treatment cessation. Leukopenia was not detected in any of the 14 patients who received everolimus treatment.

To evaluate the efficacy of everolimus on tumor regression, we compared 14 patients who received everolimus with 33 untreated patients. However, two patients were excluded because of surgery, one patient, because of spontaneous regression during the follow-up and ten patients for insufficient echocardiographic data, finally 20 patients were included in the untreated patients group.

The median amount of tumor mass shrinkage was -5.75 mm (-42mm-+10mm) in patients who received everolimus, and -2mm (-18mm-+11.5mm) in untreated patients. There was no statistically significant difference between the groups (p=0.139). However, when the rate of tumor size reduction was evaluated, the rate of reduction was 39.3% in patients who received everolimus and 3.2% in untreated patients within the first six months of treatment. In conclusion, the rate of tumor mass reduction was 12.4 times higher in patients with everolimus treatment compared to untreated patients.

Everolimus treatment was given to a patient with a 52x36 mm giant cardiac rhabdomyoma surrounding the left ventricle who was diagnosed prenatally and without a family history of tuberous sclerosis complex (Figs 1 and 2). The average drug blood level of everolimus achieved was 5.4 ng/ml. The mass regressed to 26x26 mm after two months of everolimus treatment, and to 12x4 mm after four months of treatment so everolimus dose was decreased (Figs 3 and 4). However, at 6 months the size

Table II. Clinical characteristics of patients who had everolimus treatment.

Patient No	Age	CR	Diagnosis of TSC	Everolimus indication	Treatment duration (months)	Everolimus serum level (ng /ml) (min-max (median))	Target serum level (3-8 ng /ml)	Pre-treatment size (mm)	Post-treatment size (mm)	Regression (%)	Complications
1	1 y 5 m	S	-	RVOT obstruction	4	1-3.6 (2)	Yes	20x15	22x15	none	Hyperlipidemia
2	2 y 2 m	S	-	Giant mass	13	0.6-47 (2.6)	Yes	52x36	26x26	50	Hyperlipidemia
3	15 y 5 m	S	+	Arrhythmias	11	2-5.1 (3.2)	Yes	18x10	0	100	-
4	17 y	S	+	Seizures	21	0-4.9 (0.7)	Yes	7x7	7x6,5	none	-
5	10 y	S	+	Arrhythmias, MR	11	No data	No data	29x22	39x33	none	Hyperlipidemia
6	1 y 1 m	S	+	Giant mass	6	0.9-4.6 (1.8)	Yes	50x36	8x6	84	-
7	6 y 6 m	S	-	Arrhythmias	No data	No data	No data	23x10	7x7	69	-
8	2 y 10 m	M	+	MR	8	No data	No data	26x17	20x6	23	-
9	5 y 4 m	M	+	LVOT obstruction	9	0.4-10.1 (3.6)	Yes	12x9 (9 masses)	13x7 (2 masses)	0	-
10	5 y 8 m	M	+	LVOT obstruction	7	0.6-14.4 (4.3)	Yes	8x7	6x5	26	-
11	7 y 4 m	M	+	TR	6	No data	No data	20x15	15x9	27	-
12	3y 7 m	M	+	LVOT obstruction	6	0-14.5 (1.7)	Yes	29x20	25x11	12	-
13	2 y 11 m	M	+	Seizures	Treatment is ongoing	3.8-9.1 (7.4)	Yes	10x5	0	100	-
14	8 y 1 m	M	+	Treatment started in another center	26	No data	No data	21x19	15x8	28	-

CR: cardiac rhabdomyoma, LVOT: left ventricular outflow tract, m: months, M: multiple, MR: mitral regurgitation, RVOT: right ventricular outflow tract, S: single, TR: tricuspid regurgitation, TSC: tuberous sclerosis complex, y: years.

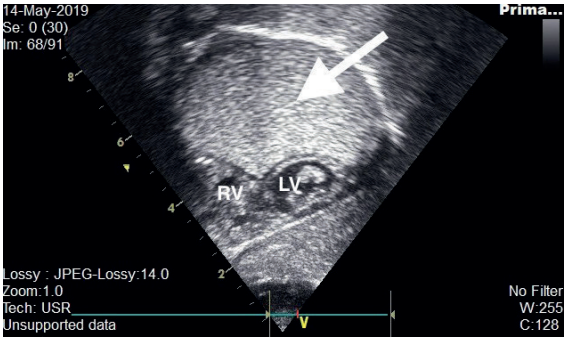

Fig. 1. Transthoracic subcostal view showing 52x36 mm giant cardiac rhabdomyoma (arrow) surrounding the left ventricle (LV) and extending to the right ventricular (RV) outflow tract and interventricular septum.

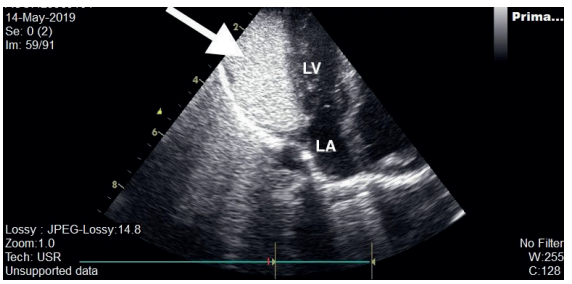

Fig. 2. Transthoracic echocardiography apical 4-chamber view showing cardiac rhabdomyoma (arrow) in the left ventricle (LV). LA: left atrium.

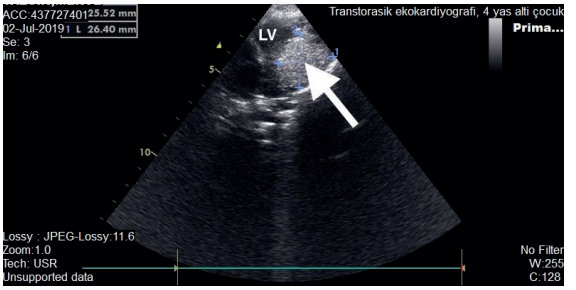

Fig. 3. Two months after everolimus treatment, transthoracic echocardiographic view. Cardiac rhabdomyoma (arrow) surrounding the left ventricle (LV) regressed from 52x36 mm to 26x26 mm.

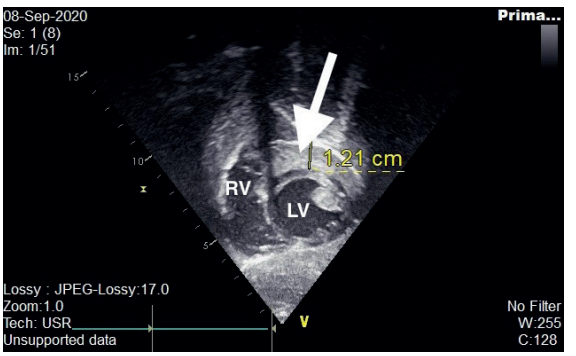

Fig. 4. Four months after everolimus treatment, transthoracic echocardiographic subcostal view. Cardiac rhabdomyoma regressed from 52x36 mm to 12x4 mm in size. LV: Left ventricle, RV: Right ventricle.

of the tumor had doubled once again. During the follow-up, the patient had hyperlipidemia (total cholesterol: 217 mg/dl, LDL: 145 mg/dl, triglyceride: 211 mg/dl), so the treatment was discontinued. Everolimus treatment was given to another patient without signs of tuberous sclerosis complex because of mass-related ventricular tachycardia. Approximately 60% regression was achieved after two months, and the patient did not require ablation or implantable cardiac defibrillator during everolimus treatment.

Discussion

Cardiac tumors are extremely rare in children and the most common primary cardiac tumor is cardiac rhabdomyoma.[2] Cardiac rhabdomyomas can present with tuberous sclerosis complex with a rate of 40-100% and they may be the first signs of the disease even from the prenatal period.[20-22] Jozwiak et al.[23] reported that 66% of patients with cardiac rhabdomyomas were younger than two years of age. In accordance with this research, in our study, 59.6% of the patients were diagnosed prenatally, 25.5% were younger than one year of age. In total, the percentage of patients diagnosed under one year of age was 85.1%.

Forty two of the 47 patients (89.3%) with rhabdomyomas were asymptomatic. This rate is very high when compared to the literature. In the pediatric cardiac tumor series which consisted of 255 articles, the rate of asymptomatic patients was 7.2%. The most common symptoms were respiratory distress

(14.2%), cyanosis (6.9%), chest pain (2.8%). The most common clinical findings were murmur (28.9%), heart failure (19.1%), and arrhythmias (14.9%).[15] However, since this series consisted of patients who had undergone surgery, it is not unusual that serious symptoms such as heart failure and arrhythmias leading to surgery were present in these patients. In another study, 24.7% of the 166 pediatric cardiac tumor patients were asymptomatic and 12% were detected prenatally. The most common clinical manifestations were murmur (32.5%), respiratory distress (7.8%), arrhythmias (6.6%) and pericardial effusion (5.4%).[24] The high rate of asymptomatic patients in our study can be explained by the high number of patients detected in the prenatal period.

In literature, succesful and rapid regression of rhabdomyomas with everolimus treatment have been reported as case reports[25-28] and as case series[14,29]. Çetin et al.[25] showed that 4 months of everolimus treatment reduced rhabdomyomas, arrhythmias and outflow tract stenosis in a 3 month-old patient with multiple cardiac rhabdomyomas causing left ventricular outflow tract obstruction, tuberous sclerosis and Wolff-Parkinson-White syndrome. Öztunç et al.[28] reported that arrhythmias were reduced after everolimus treatment in a patient with tuberous sclerosis and supraventricular tachycardia due to a cardiac rhabdomyoma. Davis et al.[30] reported that everolimus was started in a patient who was diagnosed as cardiac rhabdomyoma and without diagnosis of tuberous sclerosis for polymorphic ventricular tachycardia at the age of 10 months and at the end of the six months of treatment, ventricular tachycardia was not detected. They stated that everolimus can be considered in the treatment of not only patients with cardiac rhabdomyoma accompanying tuberous sclerosis, but also in patients without tuberous sclerosis. Also in our study, although patients 2 and 7 (Table II) were not diagnosed as tuberous sclerosis, size of rhabdomyomas were reduced with everolimus treatment. Dhulipudi et al.[14] also showed that everolimus treatment regressed cardiac rhabdomyomas 11.8 times faster compared to spontaneous regression treatment in their five patient series. However, it is noteworthy that one patient had sudden cardiac death in the fourth month of treatment. The results of Aw et al.[13] were also similar in terms of regression rate of everolimus treatment. Martínez-García et al.[17] summarized the mass and arrhythmia reducing effects of everolimus in the article in which they compiled 17 cases and case series. In the literature, there are reports that were successfully treated with a daily dose of 1.5-2 mg/m^2 of everolimus, with serum levels targeted to be between 5-15 ng/ml[27,31-33]. Chang et al.[29] gave everolimus treatment to three newborns with cardiac rhabdomyomas, starting from a dose of 0.3-0.67 mg/m^2/day, with target serum levels between 3-7 ng/ml, which is lower than reported in the literature. Rhabdomyomas were regressed after two months without any side effects. In our center, our initial treatment dose of 4.5 mg/m^2/week is similar as a total weekly dose and supports findings of Chang et al.[29] Doğan et al.[34] also showed the efficacy of everolimus treatment by keeping serum everolimus between 3.6-7.8 ng/ml.

In accordance with the literature, our study showed that there was no difference in the amount of reduction in the size of the tumors with everolimus treatment in the long term. However, the rate of mass reduction was found to be 12.4 times higher in everolimus patients compared to untreated patients.[13,14,35-37] Our results have shown everolimus should be used only to rapidly shrink rhabdomyomas that disrupt hemodynamics or cause life-threatening arrhythmias.

Due to spontaneous regression, rhabdomyomas that do not cause hemodynamic compromise or life-threatening arrhythmias can be followed-up without medical treatment or surgical intervention.[1-9] Echocardiography is essential to evaluate tumor size and cardiac function. In addition, we also suggest to perform electrocardiogram and 24-hour rhythm monitoring during the follow-up of rhabdomyoma patients, due to high rates of arrhythmias in our study (26%).

The fact that no serious complications with everolimus other than hyperlipidemia in one patient, supports the notion that everolimus treatment is also safe.

In accordance with the literature, the relationship of tuberous sclerosis complex with multiple cardiac rhabdomyomas were very high in our study.[38] Therefore, patients who do not have a family history of tuberous sclerosis complex but who have multiple cardiac rhabdomyomas in the prenatal period, should be closely followed up for signs of postnatal tuberous sclerosis complex.

As a limitation, our study was a retrospective study and it was not a randomized controlled study.

According to our study results, everolimus accelerates tumor mass reduction, but not the amount of mass regression in the long term. Everolimus may be considered for treatment of rhabdomyomas that cause hemodynamic compromise or life-threatening arrhythmias before surgical intervention.

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Ethical approval

This study does not include human and/or animal experimentation and it was conducted in compliance with the ethical principles according to the Declaration of Helsinki, and it was approved by the Hacettepe University Non-Interventional Clinical Research Ethics Committee on July 2, 2019 (Number: GO-19/690).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: SY, DA, EA; data collection: SY, EA, BA, CA, HHA, IE, TK, DA; analysis and interpretation of results: SY, EA, BA, CA, DA; draft manuscript preparation: SY, EA, BA, DA. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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