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Right ventricular diastolic function in post-surgical Tetralogy of Fallot patients: A pilot study to make a comparison between echocardiography and cardiac MRI

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ABSTRACT

Background: right ventricular (RV) systolic dysfunction is associated with poor outcomes in Tetralogy of Fallot (ToF) patients. Conversely, the influence of diastolic dysfunction in this setting is poorly known. In addition, evaluation of RV diastolic function by cardiac MRI is rarely performed.

Materials and methods: twenty-four surgically treated ToF patients were enrolled in the study (54% males; median age at study: 28 (18–50) years; median age at surgery: 1.9 (0.4–8.2) years. They were studied by echocardiography to assess RV diastolic function in terms of traditional and TDI-derived parameters. At cardiac MRI, RV diastolic function was assessed by using phase-contrast analysis of flow through the tricuspid valve in short axis view. Diastolic dysfunction was graded as impaired relaxation, pseudo-normal, or restrictive physiology.

Results: fifteen (62.5%) ToF subjects had echocardiographic evidence of diastolic dysfunction and eleven (45.8%) at cardiac MRI. Statistically significant correlation between echocardiographic and cardiac MRI parameters of diastolic dysfunction was weak ($p < 0.05$). The degree of RV diastolic dysfunction (expressed as E/E' at TDI) was associated with right atrial volume indexed for body surface area at cardiac MRI ($p < 0.0001$). Greater number of interim palliative procedures was associated with higher E/E' (RV diastolic dysfunction) at echocardiography ($p < 0.0003$).

Conclusions: diastolic dysfunction, as determined by echocardiography and cardiac MRI-derived measures, is prevalent in ToF. These measures are weakly associated with each other. Notwithstanding the limitations of this pilot study, the development of cardiac MRI parameters capable of correlating with RV relaxation is needed in ToF setting.

Introduction

Tetralogy of Fallot (ToF) is the most common cyanotic congenital heart defect (CHD) [1]. Its surgical repair is usually performed by a one-step or two-steps procedure, depending on the patient's clinical condition (especially in the past, in cyanotic ToF patients definitive surgery was preceded by an aorto-pulmonary shunt to relieve symptoms) [2]. Although this surgery is routinely performed with low morbidity and mortality, in the medium and most of all long-term follow-up ToF subjects may encounter complications such as heart failure and arrhythmias, so that their survival rate shows a downward trend as time goes by Ref. [3]. Right ventricular (RV) systolic dysfunction, which may develop as a consequence of RV progressive enlargement due to long-standing post-surgical pulmonary valve regurgitation, is known to be associated with poor outcomes in this setting [4]. Conversely, the influence of RV diastolic dysfunction is still poor known and under debate [5].

The assessment of RV and left diastolic function is routinely required for a full and detailed evaluation of the heart by transthoracic

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echocardiography [6], whilst quantification of RV diastolic function with cardiac MRI imaging is rarely performed [7].

We studied the possible association between traditional echocardiographic parameters of RV diastolic function and those cardiac MRI-based on the basis of phase-contrast evaluation of *trans*-tricuspidal flow in a group of surgically treated ToF patients.

Materials and methods

Twenty-four surgically treated ToF patients were enrolled in the study. All of them were in NYHA functional class I and II.

Criteria of exclusion were as follows: genetic or chromosomal abnormalities, NYHA functional classes III and IV, significant arrhythmias (atrial fibrillation as well as frequent premature supraventricular and ventricular complexes) pre-operative hypoplasia or absence of confluence of the pulmonary artery branches, association with atrio-ventricular septal defect or absent pulmonary valve, residual wide opening between the two ventricles, residual peak gradient in the RV outflow tract >40 mmHg by Doppler echocardiography, significant regurgitation of the atrio-ventricular valves, and presence of a prosthetic conduit between RV and the pulmonary artery.

All ToF patients had undergone transthoracic and cardiac MRI assessment. The study was approved by the University of Cagliari Institutional Ethics Committee (PG/2015/1859) and conducted in accordance with the Declaration of Helsinki. All enrolled participants gave their informed written consent. Right ventricular diastolic function assessment at echocardiography. The recruited patients had been studied by *trans*-thoracic echocardiography to assess RV diastolic function in terms of traditional and Tissue Doppler-derived parameters [namely tricuspid valve (TV) E/A, deceleration time of the E wave (DT), E/E']. Examination was conducted by the same Cardiologist according to a previously stablished protocol, that is in left lateral decubitus position using a GE-Vingmed Vivid 7 machine (GE Healthcare, Horten, Norway), with a 3.1–8 MHz probe [8]. Sinus rhythm and end-expiratory apnoea were established in all patients at time of exam. The four-chambers apical view was used to make the assessment. Sample volume had a fixed amplitude of 3 mm. For the traditional bi-dimensional assessment of RV diastolic function, pulsed Doppler sample volume was put between tricuspid leaflets tips. As to Tissue Doppler evaluation, in view of its strong angle-dependence, the ultrasound beam was aligned as much as possible parallel to wall motion, having the smallest available angle of incidence between the Doppler scan beam and longitudinal ventricular motion. No angle correction was used. An average of 6–8 beats were collected for evaluation avoiding images of pre- and post-premature beats. The images collected were recorded and stored. At least three consecutive measurements were made on recorded images and their mean was calculated [8].

Right ventricular diastolic function assessment at cardiac MRI

All cardiac MRI studies had been performed using a 1.5 T clinical Signa HDxt scanner (GE-Healtcare, Milwaukee, WI, USA). All images were obtained during breath holding at mid-expiration. After localizing scans, vertical and horizontal long-axis as well as short-axis images were obtained using an SSFP cine sequence. Contiguous short-axis images covering the entire RV were planned for SSFP cine imaging on end-diastolic SSFP images of both long-axis directions.

At cardiac MRI, RV diastolic function was assessed by using phase-contrast analysis of flow through the TV in short axis. A magnitude image was used for anatomic orientation of the imaging slice and to identify TV contours as well. Using both images, a region of interest was carefully drawn on each time frame of the data set. Within each of these regions, the peak instantaneous velocity for each time frame was obtained. A post-processing analysis of through plane phase-contrast velocity mapping images across TV through the whole cardiac cycle using a dedicated software cvi42® (Circle Cardiovascular Imaging Inc., Calgary, AB, Canada) was conducted, thus delivering a TV time flow curve (Fig. 1) [9].

Diastolic dysfunction was graded as impaired relaxation, pseudonormal, or restrictive physiology (See Table 1) [10]. Echocardiography and MRI were done the same day.

The cardiac MRI results thus obtained were subsequently compared to findings from RV echocardiography.

Statistics

The results of the ToF study population ($n = 24$) were first analyzed, and after that the findings obtained by echocardiography were compared with those from cardiac MRI by means of the non-parametric Mann Whitney *U* test, as they were not normally distributed. Variables expressed as % were compared by using the chi-squared test. The relationship between the various echocardiographic and cardiac MRI-derived diastolic parameters were assessed by Pearson's correlation coefficient and by plotting corresponding regression lines. Multivariate analysis was not applied owing to the small sample size.

Statistical significance was set at $p < 0.05$ throughout the paper. For all analysis, commercially available computer software (SPSS version 24.0, SPSS Inc., Chicago Illinois, USA) was used.

Results

Patients' main characteristics are summarized in Table 2 (male/female ratio: 13/11; median age at study: 28 (18–50) years; median age at surgery: 1.9 (0.4–8.2) years).

In the enrolled cohort, the two genders were quite equally distributed, with just a slight prevalence of males, thus substantially confirming the reported in literature substantial equal distribution of this pathology between the two sexes [11].

Fifteen (62.5%) ToF subjects had echocardiographic evidence of RV diastolic dysfunction and eleven (45.8%) at cardiac MRI. This difference was not statistically significant (p = ns. See Table 3). RV diastolic dysfunction was prevalent in those ToF subjects addressed to a two-steps surgery (Blalock-Taussig systemic-to-pulmonary shunt and/or ductal stenting preceding the complete repair) rather than straight to a complete corrective surgical repair, though this difference was not statistically significant: 9/15 (60.0%) at echocardiography vs 7/11 (63.6%) at cardiac MRI (p = ns). A weak statistically significant correlation was found between a few echocardiographic (E/A, E/E′) and cardiac MRI (E/A) parameters of RV diastolic dysfunction (both $p < 0.05$. See Figs. 2 and 3). The degree of RV diastolic dysfunction (expressed as E/E' at TDI) was associated with right atrial volume indexed for body surface area at cardiac MRI ($p < 0.0001$. See Fig. 4). Greater number of interim palliative procedures was associated with higher E/E' (RV diastolic dysfunction) at echocardiography ($p < 0.0003$) (Table 3).

Discussion

RV diastolic dysfunction is defined as raised RV filling pressures, caused by passive (RV chamber rigidity) as well as active (impaired RV relaxation) mechanical impairment of RV musculature function during diastole. Its first description by Riggs dates back to 1993 [12].

As confirmed by our findings, RV diastolic function impairment is frequently encountered in post-surgical ToF individuals and seems to be related with troubles in the early post-operative period and a more favourable course in the late post-surgical follow-up [13–17]. In this respect, RV diastolic dysfunction has been hypothesized to reduce the degree of pulmonary valve regurgitation, owing to RV stiff musculature and increased end-diastolic pressure, thus improving exercise performance in ToF patients [18]. However, its clinical significance is still mater of concerns and quite far to be fully elucidated. Other scientific evidence suggests that in ToF, measures of diastolic dysfunction are linked with the risk of future re-interventions, owing to the correlation

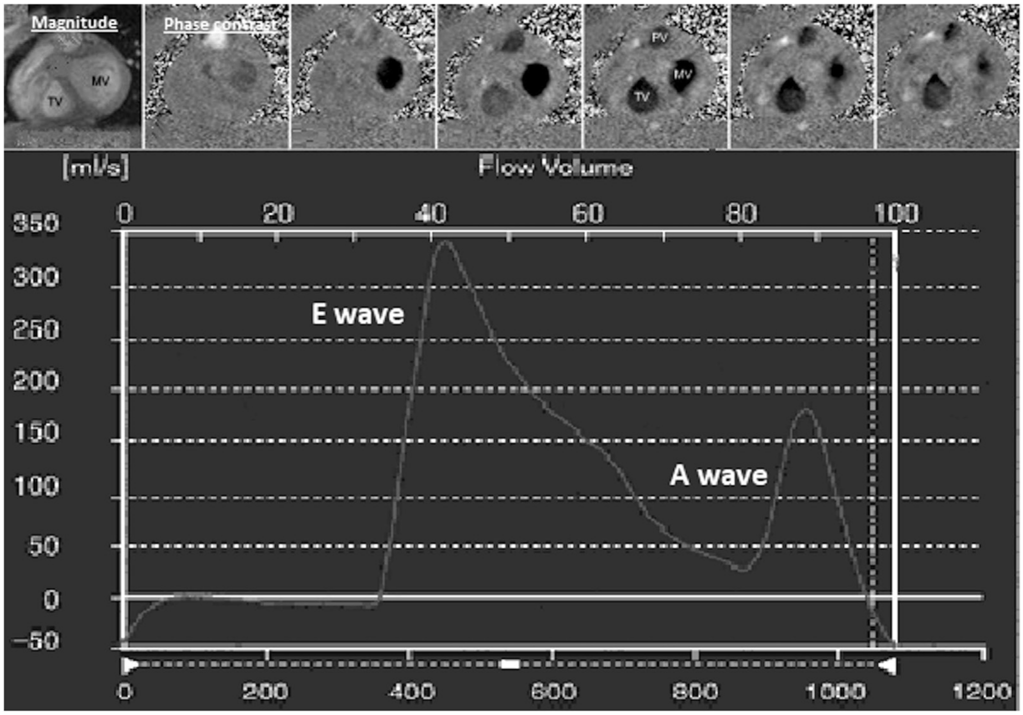

Fig. 1. (Upper panel) Magnitude and phase velocity sets of images. The latter display the through plane phase-contrast velocity mapping through the tricuspid valve. **(Lower panel).** Post processing analysis of through plane phase-contrast velocity mapping images across the tricuspid valve. A time flow curve of tricuspid valve flow (RV early [E wave] and atrial [A wave] filling) was determined.

Table 1
Right ventricular diastolic disfunction grading [10].

-Impaired relaxation	E/A<0.8; DT >200 msec
-Pseudonormal	E/A 0.8–2.1; E/E'>6
-Restrictive physiology	E/A>2.1; DT < 120 msec

Abbreviations: E/A: ratio between waves A and E; DT: deceleration time.

with greater degree of RV enlargement [19].

The vast majority of studies focused on assessing RV diastolic function in ToF were performed by echocardiography. However, the latter is quite limited in its ability to provide an accurate measure of RV systolic and diastolic function owing to this ventricle complex geometry as well as the usually available poor images because of the presence of surgical scars [13–17,20].

Conversely, cardiac MRI, though time-consuming, allows to overcome all the above stated limitations. Nowadays it is considered the mainstay in congenital heart disease patients follow-up [20].

Among the studied ToF patients, the statistically significant correlation between echocardiographic and cardiac MRI parameters of RV diastolic dysfunction was weak. Though apparently quite surprising, this may be explained by a few technical explanations, as reported in the “Limitations” section at the end of this paragraph. In the subset of ToF patients, RV diastolic function as assessed by TV phase-contrast analysis was previously found to be significantly associated with end-diastolic and end-systolic indexed for body surface area RV volumes as well as with end diastolic volume RV to left ventricle ratio [9]. A comparison with Doppler and Tissue Doppler-derived echo parameters of diastolic function was not performed [9]. However, echo parameters of diastolic function are considered the gold-standard to assess both ventricles distensibility, so that all the developed new cardiac MRI parameters of diastolic function should be compared with them [20]. Not only, but diastolic function at cardiac MRI is still poor studied compared to systolic function [7].

A correlation was detected between the degree of RV diastolic dysfunction at echo (Expressed as E/E′ at TDI) and right atrial volume indexed for body surface area at cardiac MRI. This was expected, since a

Table 2
Clinical characteristics of the population in the study.

	Gender	Age at study (years)	Follow-up() (years)	Age at corrective surgery (years) and surgical technique	First surgical step (if patient had a 2 steps surgery	Age at the moment of first surgical step (years)
1.	M	19	18.5	0.5 (IP)		
2	M	20	19.6	0.4 (IP)		
3	M	22	21.4	0.6 (TA)		
4	M	22	21.4	0.6 (IP)		
5	M	24	23.4	0.6 (TA)		
6	M	26	25.5	0.5 (TA)		
7	M	27	24.8	2.2 (TA)	PDA	0.2
8	M	28	26.1	1.9 (TA)		
9	M	29	28.1	0.9 (TA)	B-T	0.1
10	M	30	27.9	2.1 (TA)	B-T	0.1
11	M	41	37.7	3.3 (TA)	B-T	0.6
12	M	43	41.4	1.6 (TA)	B-T	0.3
13	M	50	41.8	8.2 (TA)		
14	F	18	17.6	0.4 (IP)		
15	F	20	19.6	0.4 (TA)		
16	F	20	19.6	0.4 (IP)		
17	F	20	19.5	0.5 (IP)		
18	F	21	16.9	4.1 (IP)	PDA, then B-T	0.5, then 0.7
19	F	22	21.6	0.4 (TA)		
20	F	24	22.1	1.9 (TA)		
21	F	32	28.3	3.7 (TA)	B-T	0.8
22	F	34	31.1	2.9 (TA)	B-T	0.4
23	F	39	36.0	3.0 (TA)	B-T	0.5
24	F	44	37.4	6.6 (TA)	B-T	1.2

Abbreviations: M: male; F: female; TA: transannular patch; IP: infundibular patch; PDA: ductus arteriosus stenting; B-T: Blalock-Taussig shunt.

Table 3
Comparison between cardiac MRI and echocardiography.

	Cardiac MRI	Echocardiography	Statistical significance
Prevalence of diastolic dysfunction in all the sample size (%)	62.5	45.8 *	p = ns
Prevalence of diastolic dysfunction in two-steps surgery patients (%)	60.0	63.6 *	p = ns
TV E/A	1.2(0.4–2.4)	1.2(0.6–2.3)	p = ns
TV DT (msec)	190(148–219)	186(152–216)	p = ns
TV E/E′	9.9(6.1–16.2)	–	–
RA volume (ml/m^2) [a]	53(31–74)	56(32–72)	p = ns
RV EF (%) [b]	48(37–54)	46(38–55)	p = ns
RA mean longitudinal strain [c]	–	23.8%	

Acronyms: MRI: magnetic resonance imaging; TV: tricuspid valve; DT: deceleration time; RA: right atrium; RV: right volume; EF: ejection fraction.
*$p < 0.0003$.
[a] Calculated by area-length and disk summation.
[b] Calculated by means of the ellipsoid method [38].
[c] 42.1% in healthy controls ($p < 0.0001$).

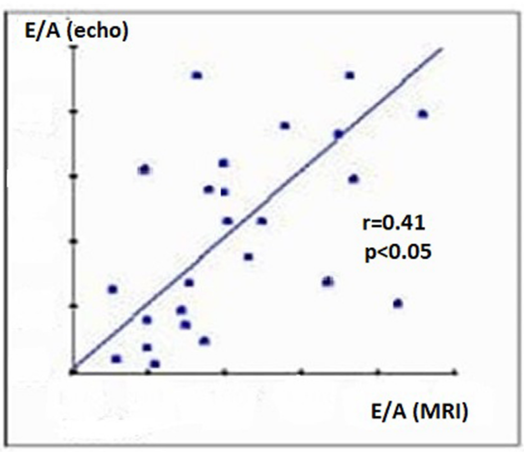

Fig. 2. Correlation between tricuspid valve E/A ratio at echocardiography and tricuspid valve E/A ratio at cardiac MRI.

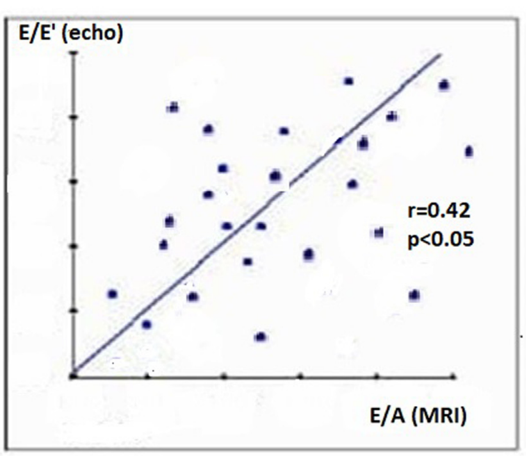

Fig. 3. Correlation between right ventricle E/E′ ratio at tissue Doppler echocardiography and tricuspid valve E/A ratio at cardiac MRI.

stiffer RV leads to an increased amount of TV regurgitation and in turn to a steady rise in right atrial pressure as well as a progressive right atrial

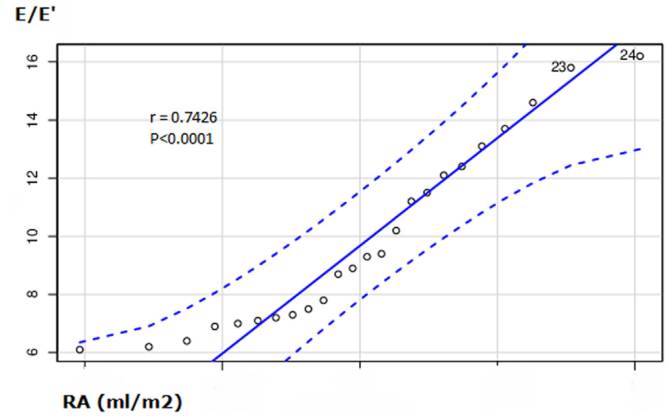

Fig. 4. Correlation between right ventricular diastolic disfunction at echocardiography (E/E′ ratio) and right atrial volume indexed for body surface area at cardiac magnetic resonance.

enlargement [21,22].

Again, a higher number of palliative interventions (Blalock-Taussig shunt between the right pulmonary artery and the right subclavian artery and/or stenting of ductus arteriosus) preceding the definitive surgical procedure was associated with higher E/E' (RV diastolic dysfunction) at echocardiography. This finding also was expected. In fact, it was already reported that greater number of interim procedures was related with higher catheter-based RV end-diastolic pressure (RVEDP), E/e′, and presence of diastolic dysfunction by echocardiography. That was confirmed at univariate as well as multivariate analysis, that is after adjusting for multiple possible confounding factors (such as gender, preterm birth, ToF anatomical subtypes, age at repair, type of repair at RVOT) [22]. Many issues can have contributed to that (increased pericardial rigidity contrasting with RV diastolic expansion, the extent of surgical scar and fibrosis at cardiac muscle, post-surgical paradoxical systolic septal motion, and ventricular dyssynchrony) [5].

Late gadolinium enhancement analysis was performed in our study, but a correlation between the amount/distribution of RV fibrosis and the occurrence/severity of diastolic function not found, unlike other studies [23]. In our opinion, it depends on the relatively small sample size and the fact that RV reduced relaxation is related not only to the onset of post-surgical scar and fibrosis, but also on the hypertrophied RV tissues.

This study was undoubtedly hampered by a few limitations, namely: 1) evaluating blood flow through TV by means of standard bi-dimensional phase-contrast velocity mapping sequences is hampered by cardiac motion, since the imaging plane is fixed throughout the cardiac cycle while TV may move up to about 25 mm toward the apex in systole [24,25]; 2) blood flow through TV was assessed in short axis with cardiac MRI, while was evaluated in four chambers with echocardiography. These two planes are orthogonal and this may had weakened the significance of correlations; 3) other alternative methods are potentially available to quantify TV regurgitant volume [for instance, the formula TV regurgitant volume = RV stroke volume (calculated by SSFP cine images) less forward flow volume in the pulmonary artery (measured on phase-contrast velocity mapping). The accuracy of this method is low in the presence of irregular heart rhythm or pulmonary valve insufficiency; the formula TV regurgitation volume = RV stroke volume less LV stroke volume, if only TV is involved; diastolic torsion rate, a method which has no echo correlate; recently proposed 4D phase-contrast cardiac MRI flow evaluation, which allows to overcome the issue related to TV annulus motion, because of retrospective valve tracking and velocity encoding in all the three orthogonal spatial dimensions simultaneously during the cardiac cycle, thus allowing a comprehensive visualisation of complex regurgitant flow patterns. Currently this technique is mainly used for research and should be tested for its clinical utility] [26–28]; 4) TV is thin (1–2 mm) and so that is particularly sensitive to partial volume effects, owing to the slice thickness of cardiac MRI images (5–8 mm). In this respect, high care is required in placing image slices perpendicular to the TV plane to minimize these effects. Slice thickness was reduced to 4–5 mm as well. Notwithstanding these adjustments, some aspects of TV anatomy may remain difficult to visualize. Again, the temporal resolution used for the acquisition of TV flow-sensitive imaging was 40 ± 10 ms. Concerning measurements reproducibility and accuracy, all MRI measurements were performed by the same trained Radiologist (5-year experience in the field), while echocardiographic measurements were done by the same trained Cardiologist (15-year experience) [29,30]; 5) as a general rule, evaluation of RV diastolic function should include multiple parameters. In this respect, impaired RV compliance can result in reversal flow in the hepatic veins with atrial contraction and/or inferior vena cava lack of collapsibility [31]; 6) relatively small sample size (only the patients undergoing echocardiography and cardiac MRI the same day and in NYHA class I and II were included in the study); 7) objective diagnosis of RV diastolic dysfunction implies doing cardiac catheterization, with detection of increased RV end-diastolic filling pressure in the presence of a normal or reduced RV end-diastolic volume.

Conclusions

Compared to RV systolic function, diastolic RV filling pattern is still poorly studied in ToF subjects [32]. Due to its high spatial and temporal resolution, cardiac MRI is considered the mainstay in evaluating post-surgical congenital heart disease patients [33]. However, RV diastolic function evaluation with this technique is still under debate, and clear recommendations still far to be released. By using the cine-phase contrast tool, cardiac MRI allows to analyse blood flow through the TV and in turn potentially RV diastolic function as well. On the other hand, the weak correlation with traditional *trans*-thoracic parameters of diastolic function seems to highlight some limitations which need to be considered, at least in the ToF setting, though already highlighted as to left ventricle [34,35]. As soon as cardiac MRI will have the ability to better characterize a range of diastolic impairments, it will likely become an important diagnostic test in the future, capable of comprehensive RV function evaluation in ToF [36,37]. In the meantime, echo still has a lot to offer.

Funding

None.

Conflicts of interest

Nothing to declare.

Authors' contribution

PPB: conceptualization, methodology, investigation, writing; MD: methodology, writing; GC: writing; ARM: review and editing; MM: review and editing; LS: supervision. All Authors have approved the submitted version of the paper.

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