Cardiology in the Young

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Evaluation of the relationship between ventricular function and serum growth differentiation factor-15 levels in patients with operated tetralogy of Fallot

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Original Article

Cite this article: Önal D, Eroğlu AG, Akyel NG, Yüksel EK, Karakaş H, Pirdal BZ, and Adaletli İ (2021) Evaluation of the relationship between ventricular function and serum growth differentiation factor-15 levels in patients with operated tetralogy of Fallot. *Cardiology in the Young* **31**: 1969–1974. doi: 10.1017/S1047951121001360

Received: 26 January 2021
Revised: 10 March 2021
Accepted: 10 March 2021
First published online: 8 April 2021

Keywords:
Cardiac MRI; growth differentiation factor-15; left ventricle; right ventricle; tetralogy of Fallot

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Abstract

Aim: Growth differentiation factor-15 is a novel biomarker of increasing importance in cardiovascular diseases. This study aimed to evaluate the relationship between ventricular measurements assessed by cardiac magnetic resonance imaging (MRI) and serum growth differentiation factor-15 levels in children with surgically corrected tetralogy of Fallot. *Materials and method:* Serum growth differentiation factor-15 levels were measured in 40 patients (mean age: 15.2 ± 2.9 years; 52.5% male; 87.5% NYHA I). End-diastolic volume index, end-systolic volume index, and ejection fractions of both ventricles and pulmonary regurgitation fraction were measured on cardiac MRI. The correlation between growth differentiation factor-15 levels and cardiac MRI parameters of the patients was investigated. Also, growth differentiation factor-15 levels of the patients were compared with healthy controls since reference values have not been determined in children. *Results:* The mean growth differentiation factor-15 level was 254.9 ± 6.3 pg/ml in the patient group. There was no correlation between growth differentiation factor-15 levels and cardiac MRI parameters in patients. Also, there was no significant difference in growth differentiation factor-15 levels between the patients and control groups. *Conclusion:* The serum levels of growth differentiation factor-15 were uncorrelated with ventricular size, function, and pulmonary regurgitation fraction assessed by cardiac MRI in children with operated tetralogy of Fallot. Moreover, growth differentiation factor-15 levels were not different in these patients from healthy children.

In patients with surgically corrected tetralogy of Fallot, cardiac symptoms occur due to complications, such as chronic pulmonary valve insufficiency, right ventricular enlargement, and dysfunction in the third decade of life even though they may remain asymptomatic for years. It has been suggested that pulmonary valve replacement in the asymptomatic period normalises right ventricular size leading to an improvement of right ventricular functions.[1] The indications for pulmonary valve replacement in asymptomatic patients are identified in the current guidelines.[1–3] Threshold values of right ventricular dimensions evaluated by cardiac magnetic resonance imaging (MRI) were specified in line with studies reporting the normalisation rates of right ventricular size following pulmonary valve replacement.[4] However, in a recent study, it has been shown that persistent right ventricular dilation after pulmonary valve replacement was not associated with adverse clinical outcomes.[5]

Investigation of the role of cardiovascular serum biomarkers at the molecular level of the cardiac re-modelling process and their prognostic significance may assist conventional diagnostic methods in cardiovascular diseases. Routine use of the N-terminal brain natriuretic peptide which is the biomarker related mostly to left ventricular functions is recommended for diagnosis and monitoring of heart failure in adults.[6] Novel biomarkers may be useful also for evaluating right ventricular functions and defining indications for pulmonary valve replacement in patients with operated tetralogy of Fallot.

Growth differentiation factor-15 is a novel biomarker which is a serum protein released from many tissues and has been associated with a variety of diseases including kidney diseases, cancer, diabetes mellitus, obesity, sepsis, lung diseases, and cardiovascular diseases. It is thought to be linked to oxidative stress, hypoxia, or inflammation.[7] An increased level of growth differentiation factor-15 in cardiovascular diseases suggests that it has a role in the cardiac re-modelling process. Referring to the studies conducted in adults, it has been shown that growth differentiation factor-15 levels independently predict all-cause mortality.[8,9] There are fewer studies on paediatric patients than adults, and these studies mostly focus on left ventricle function.[10–12]

This study aimed to evaluate the relationship between ventricular size and functions assessed by cardiac MRI and serum growth differentiation factor-15 levels in children with operated tetralogy of Fallot.

Materials and method

Selection of the participants

The study was conducted cross-sectionally between November 2019 and February 2020 at our Pediatric Cardiology Department. Forty patients with operated tetralogy of Fallot aged 9–21 years were recruited according to certain inclusion and exclusion criteria. The exclusion criteria for patients were defined as residual moderate-to-severe pulmonary stenosis or pulmonary atresia at birth, surgical repair with a conduit, history of pulmonary valve replacement, residual medium–large ventricular septal defect, additional cardiac anomalies, cardiac pacemaker, renal or hepatic impairment, diabetes mellitus, autoimmune disease, or obesity (body mass index z score >2 according to standards for Turkish children).[13] Controls with cardiovascular anomalies or any other diseases were also excluded.

Cardiac MRI was performed on all patients and serum growth differentiation factor-15 and N-terminal brain natriuretic peptide levels were measured in venous blood samples. The same biomarkers were also measured in 40 healthy controls with similar age, gender, and body measurements to the patients.

All procedures contributing to this work comply with the ethical standards of the national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by Cerrahpaşa Medical Faculty Ethics Committee (A-37 on November 5, 2019). A written informed consent was taken from all participants and their legal guardians.

Data collection

A detailed history was taken from both patients and controls. Date of birth, gender, and contact information were recorded. Patients' age at the time of the study, age at tetralogy of Fallot repair, type of surgery, and history of palliative shunt surgery were also recorded. Functional capacity was graded as I-II-III-IV by New York Heart Association (NYHA) Functional Classification.[14] Physical examination was performed and blood pressure was measured. Weight and height were measured, and body mass index (kg/m^2) and body surface area (Haycock formula) were calculated.[15] Subjects with a body mass index z score above 2 (obesity) and hypertension were not included in the study.[16] QRS duration was measured by a 12-lead electrocardiogram in both patients and controls.

Transthoracic two-dimensional echocardiography imaging was performed on the patients and controls in the Pediatric Cardiology Outpatient Clinic, using a Philips IE 33 ultrasound device (Philips Healthcare, Inc., Andover, MA, USA) with an appropriate probe. All participants were evaluated with a two-dimensional, M-mode, colour flow Doppler, PW Doppler, and CW Doppler. Findings such as any additional anomalies or presence of conduit were evaluated in the echocardiographic examinations of the patient group.

Laboratory testing

Venous serum samples were obtained from both patients and controls. Complete blood count, serum urea, creatinine, transaminases, and C-reactive protein measurements were done to meet inclusion criteria. The 5 cc blood samples were centrifuged, and serum samples were stored at −80 °C. N-terminal brain natriuretic peptide and growth differentiation factor-15 levels were determined using the sandwich – ELISA method (Elabscience®, Texas, USA for N-terminal brain natriuretic peptide; Thermo Scientific™, Massachusetts, USA for growth differentiation factor-15).

Cardiac MRI protocol

Cardiac MRI studies were performed on a 1.5 T system (Ingenia, Philips Medical Systems; Best, the Netherlands) with a 32-channel phased-array torso coil. Cardiac synchronisation was performed with vector electrocardiography.

The assessment of ventricular volumes was performed using a multi-phase, multi-slice volumetric dataset, acquired using a two-dimensional balanced steady-state free precession sequence. Slices were acquired parallel to the short axis of the ventricles. Imaging parameters were time of repetition/time of echo: 2.4 ms/1.22 ms; flip angle: 60'; field of view: 300 × 300 mm; matrix: 176 × 156 mm; slice thickness: 8 mm; 12–14 slices; and gap: 0.

Right and left ventricular volumes were calculated at the workstation using semi-automated software (Extended MR workspace version 2.5.3.1, Philips Medical Systems, Best, the Netherlands). Ventricular volumes were measured by drawing from the endocardial borders in both systole and diastole. Papillary muscles and trabeculations were excluded from the ventricular volume. End-diastolic, end-systolic, volumes and ejection fractions of the right and left ventricles were calculated. All volume measurements were adjusted for body surface area and expressed as mL/m^2.

Pulmonary artery flow was acquired by velocity-encoded phase-contrast MRI during breath-holding. Image planes were located at the midpoint of the main pulmonary artery, at the level of the aortic sinus, and perpendicular to the flow direction. Imaging parameters were; time of repetition/time of echo: 4.3 ms/2.6 ms; flip angle: 10'; velocity-encoded value: 150 ms; field of view: 300 × 300; matrix: 176 × 156; and slice thickness: 8 mm.

Pulmonary artery flow measurements were calculated using a semi-automated vessel edge direction algorithm (Extended MR workspace version 2.5.3.1, Philips Medical Systems, Best, the Netherlands). Forward flow, backward flow, net flow (calculated by forward flow–backward flow) and, regurgitation fraction were calculated. All volume measurements were adjusted for body surface area (mL/m^2).

Statistics

Statistical analyses were performed using SPSS v.21 (SPSS Inc., Chicago, IL, USA). Shapiro–Wilk, Q–Q plot, and histograms were used for assumptions of normality, and the homogeneity of variances was verified with Levene's test. Continuous variables were presented as mean ± standard deviation for normally distributed variables or median (25th–75th percentile = inter-quartile range) for non-normally distributed variables. Categorical variables were presented with frequency and percentage. Comparisons between two groups of continuous variables were performed using the student t-test for normally distributed data and the Mann–Whitney U-test for non-normally distributed data. The chi-square test was used for the comparison of categorical variables and the Pearson's test was used for correlation analysis. The p-value of <0.05 was considered statistically significant in all analyses.

https://doi.org/10.1017/S1047951121001360 Published online by Cambridge University Press

Table 1. Comparison of demographic data and QRS duration between patient and control groups

	All subjects (n = 80)	Patients (n = 40)	Control (n = 40)	p
Age (years)	15.24 ± 2.5	15.2 ± 2.9	15.3 ± 2.1	0.778*
Gender (male) n (%)	41 (51.2%)	21 (52.5%)	20 (50%)	0.823**
Weight (kg)	54.3 ± 13.2	52.9 ± 14.9	55.73 ± 11.1	0.341*
Height (cm)	161.5 ± 12	159.43 ± 13.31	163.68 ± 10.35	0.115*
BMI (kg/m^2)	20.5 ± 3.4	20.43 ± 3.82	20.68 ± 2.99	0.746*
BSA (m^2)	1.55 ± 0.24	1.52 ± 0.28	1.59 ± 0.20	0.160*
QRS duration (sec)	0.11 ± 0.03	0.13 ± 0.02	0.08 ± 0.01	<**0.001***

Continuous variables: mean ± standard deviation, categorical variables n (%)
BMI: body mass index; BSA: body surface area
Bold shows statistical significance
*Student's t-test
**Chi-squared test

Results

A total of 40 patients (15.2 ± 2.9 years of age; 52.5% male) were included. The control group consisted of 40 healthy children matched for age and sex with the patient sample. The demographic data of the patient and control groups are shown in Table 1. There was no significant difference between the patients and controls in terms of age, gender, weight, height, body mass index, and body surface area values. The blood pressures of all participants were within the normal range according to age and percentile curves.[16]

The mean age of the patients at corrective surgery was 21.2 ± 10.4 months. Infundibular resection was performed in one patient and transannular patch enlargement was performed in all other patients to relieve right ventricular outflow tract obstruction. The mean follow-up duration following corrective surgery was 13.3 ± 2.9 years. Seven patients (17.5%) underwent palliative shunt operation before corrective surgery. Five patients were classified as NYHA II and 35 patients as NYHA I (87.5%). The mean QRS duration was 0.13 ± 0.02 seconds in the patient group and 0.08 ± 0.01 seconds in the control group. Thirty-seven patients had a complete right bundle branch block and 1 patient had an incomplete right bundle branch block. The QRS duration and morphology of two patients were normal. Electrocardiography measurements of controls were within the normal range. QRS duration in patients was significantly longer compared to controls (Table 1, $p < 0.001$).

Echocardiographic examination demonstrated a small residual ventricular septal defect in 8 (20%), mild pulmonary stenosis in 5 (12.5%), very mild-to-mild aortic regurgitation in 10 (25%), mild tricuspid regurgitation in 18 (45%), mild mitral regurgitation in 2 (5%), and right aortic arch in 12 (30%) patients. Echocardiographic examinations of the control group were found to be normal.

According to the MRI findings (Table 2), the mean right ventricular end-diastolic volume index was 96.7 ± 31 mL/m^2 and mean right ventricular end-systolic volume index was 56.7 ± 21.9 mL/m^2. There was only one patient with a right ventricular end-diastolic volume index of >150 mL/m^2 and five patients with a right ventricular end-systolic volume index of >80 mL/m^2 according to pulmonary valve replacement indications.[3] The mean right ventricular ejection fraction was calculated as 42.4 ± 9.4%. The mean left ventricular end-diastolic volume index was 58.2 ± 10.9 mL/m^2 and mean left ventricular end-systolic volume index was 24.7 ± 5.6 mL/m^2. The mean left ventricular ejection fraction was calculated as 57.1 ± 7.45%. The mean pulmonary regurgitation fraction was measured 41.9 ± 18.9%. There were 4 patients with pulmonary regurgitation fraction < 20%, 17 patients with 20–40%, and 19 patients with >40%.

The mean growth differentiation factor-15 level was 254.94 ± 67.33 pg/ml in patients and 260.54 ± 61.24 pg/ml in controls. There was no significant difference between the groups according to the student t-test (p = 0.698). The mean N-terminal

Table 2. Demographic, clinical, and laboratory characteristics of the patients (n = 40)

Demographics	
Age (years)*	15.2 ± 2.9
Weight (kg)	52.9 ± 14.9
Height (cm)	159.4 ± 13.3
Gender (male)[2]	21 (52.5%)
BMI (kg/m^2)	20.4 ± 3.8
BSA (m^2)	1.52 ± 0.28
Surgery	
Age at total correction (month)*	21.2 ± 10.4
Follow-up since last surgery (years)*	13.3 ± 2.9
Type of total correction	
Transannular patch**	39 (97.5%)
Infundibular resection**	1 (2.5%)
Palliative shunt**	7 (17.5%)
Clinical status	
NYHA I**	35 (87.5%)
NYHA II**	5 (12.5%)
Systolic blood pressure (mmHg)*	107.2 ± 9.36
Diastolic blood pressure (mmHg)*	71.6 ± 7.5
QRS duration (seconds)	0.13 ± 0.02
Biochemistry	
NT-proBNP (pg/ml)***	15.52 (14.44–18.95)
GDF-15 (pg/ml)*	254.9 ± 67.3
Cardiac MRI parameters	
RVEDVi (mL/m^2)*	96.7 ± 31
RVESVi (mL/m^2)*	56.7 ± 21.9
RVEF (%)*	42.4 ± 9.4
LVEDVi (mL/m^2)*	58.2 ± 10.9
LVESVi (mL/m^2)*	24.7 ± 5.6
LVEF (%)*	57.1 ± 7.45
PRF (%)*	41.9 ± 18.9

BMI: body mass index; BSA: body surface area; GDF-15: growth differentiation factor 15; LVEDVi: left ventricle indexed end-diastolic volume; LVEF: left ventricular ejection fraction: LVESVi: left ventricle indexed end-systolic volume; MRI: magnetic resonance imaging; NT-proBNP: n-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association classification; PRF: pulmonary regurgitation fraction; RVEDVi: right ventricular end-diastolic volume index; RVEF: right ventricular ejection fraction; RVESVi: right ventricular end-systolic volume index
*Mean ± standard deviation
**n (%)
***Median (IQR)

https://doi.org/10.1017/S1047951121001360 Published online by Cambridge University Press

Table 3. Correlation analyses between GDF-15 and demographic data of patient and control groups

	Patients (n = 40)		Controls (n = 40)	
Category	r	p*	r	p*
Age	−0.033	0.840	0.130	0.426
Weight	−0.003	0.987	0.034	0.836
Height	−0.062	0.705	0.034	0.834
BMI	0.028	0.864	−0.171	0.291
BSA	−0.019	0.905	−0.216	0.181
QRS duration	−0.113	0.488	−0.001	0.993

BMI: body mass index; BSA: body surface area; GDF-15: growth differentiation factor 15
*Pearson correlation

Table 4. Correlations between GDF-15 and patients' cardiac MRI findings (n = 40)

Category	r	p*
RVEDVi (mL/m^2)	0.033	0.839
RVESVi (mL/m^2)	0.035	0.830
RVEF (%)	−0.118	0.470
LVEDVi (mL/m^2)	−0.199	0.219
LVESVi (mL/m^2)	−0.130	0.423
LVEF (%)	−0.060	0.713
PRF (%)	−0.199	0.218

GDF-15: growth differentiation factor-15; LVEDVi left ventricle indexed end-diastolic volume; LVEF left ventricular ejection fraction, LVESVi left ventricle indexed end-systolic volume; PRF pulmonary regurgitation fraction; RVEDVi right ventricular end-diastolic volume index; RVEF right ventricular ejection fraction; RVESVi right ventricular end-systolic volume index
*Pearson correlation

brain natriuretic peptide levels were 17.01 pg/ml and 18.36 pg/ml in patients and controls, respectively while the medians were 15.52 (14.44–18.95) pg/ml and 15.53 (13.92–22.35) pg/ml. Based on the Mann–Whitney U-test, no significant difference was observed between the two groups (p = 0.877).

No correlation was found in growth differentiation factor-15 levels and any of the following variables: age, weight, height, body mass index, body surface area, or QRS duration between the patient and control groups evaluated separately (Table 3). There was no correlation between growth differentiation factor-15 and MRI variables in the patient group (Table 4). The cut-off points for right ventricular ejection fraction (<47%) and left ventricular ejection fraction (<55%) were determined in accordance with current pulmonary valve replacement indications.[3] A cut-off point of 40% was specified for severe pulmonary regurgitation fraction.[1] Growth differentiation factor-15 levels of patients below and above this cut-off were compared, and no significant difference was found between the groups (Table 5).

Table 5. Comparison of GDF-15 according to cut-off points of RVEF, LVEF and PRF

	Below the cut-off		Cut-off and above		
	n	Median (25th–75th quartile)	n	Median (25th–75th quartile)	p****
RVEF*	27	246.25 (199.2–301.7)	13	258.4 (208.8–293.7)	0.686
LVEF**	12	252.36 (232.6–337.6)	28	294.3 (200.9–294.3)	0.409
PRF***	21	257.3 (202.8–306.7)	19	256 (211.2–285.6)	0.645

GDF-15: growth differentiation factor-15; LVEF left ventricular ejection fraction; PRF pulmonary regurgitation fraction; RVEF right ventricular ejection fraction
*Cut-off %47
**Cut-off %55
***Cut-off %40
****Mann–Whitney U-test, p significance value

Discussion

In patients with operated tetralogy of Fallot, re-intervention may be required due to residual pulmonary stenosis, residual ventricular septal defect, and/or severe pulmonary regurgitation which are the most common cause. It is important to identify risk factors for cardiac re-modelling and adverse events, to determine the patients before their heart failure symptoms begin, and to eliminate pulmonary regurgitation with timely pulmonary valve replacement. Pulmonary valve replacement is indicated in all symptomatic patients, but the timing of pulmonary valve replacement in asymptomatic patients is still unresolved.[1–3,5] It is assumed that understanding the cardiac re-modelling mechanism and its relationship to biomarkers can be useful for diagnosing heart failure, prognosis, and follow-up of cardiac diseases, such as operated tetralogy of Fallot. As an example, serum brain natriuretic peptide and N-terminal brain natriuretic peptide measurements are recommended for diagnosis and follow-up of the patients with symptoms of heart failure in current guidelines.[6] Moreover, studies show that these biomarkers are associated with an increased risk of left ventricular dysfunction and heart failure in asymptomatic patients with left ventricular hypertrophy.[17] However, cardiovascular biomarker studies are generally conducted in adults and focus on their association with left ventricular re-modelling rather than the right ventricle.[18,19] Also, there are contradictory results in the literature about the relationship of biomarkers with specific heart diseases, which may be due to the other conditions that might affect the level of markers, the heterogeneity of cardiovascular disease aetiology in the patient groups, the absence of MRI in the evaluation of the ventricles, the lack of reference values, or the lack of control groups.

To the best of our knowledge, this is the first study evaluating the relationship between ventricular size and function assessed by MRI and serum growth differentiation factor-15 levels in patients with operated tetralogy of Fallot. Growth differentiation factor-15 levels of the patients were not correlated with ventricular size or function and pulmonary regurgitation fraction. Furthermore, no significant correlation was found between growth differentiation factor-15 levels and demographic–clinical variables. Growth differentiation factor-15 levels in clinically well patients with operated tetralogy of Fallot were not different from healthy children. Due to the nature of the biomarkers, it is necessary to identify certain inclusion and exclusion criteria for patients and controls in biomarker studies. In our study, patients with moderate and severe residual pulmonary stenosis, moderate–large residual ventricular septal defect, or additional cardiac anomalies were excluded due to variability in cardiac re-modelling pathogenesis. Also, other conditions such as anaemia and obesity which can affect the serum levels of the markers were attentively detected and excluded. Reference values of growth differentiation factor-15 have not been determined in children and young adults yet.[18] Thus, patients and controls were matched for age, gender, and anthropometric measurements in our study.

https://doi.org/10.1017/S1047951121001360 Published online by Cambridge University Press

The cut-off values for the severity of pulmonary regurgitation have not been clarified yet using cardiac MRI, which has gained importance in recent years. In the latest guideline published by the European Society of Cardiology in 2020, pulmonary regurgitation fraction >30–40% measured by cardiac MRI was described as severe pulmonary regurgitation.[1] Therefore, the cut-off for pulmonary regurgitation fraction in the patient group was determined as 40% in our study. There was no significant difference in growth differentiation factor-15 levels between the sub-groups of patients below and above this value.

Using the recommended limit values for ejection fractions, no significant difference was shown in the comparison of serum growth differentiation factor-15 levels of patients whose right ventricular ejection fraction was below or above 47% and whose left ventricular ejection fraction was below or above 55%. This finding suggested that growth differentiation factor-15 was not associated with the systolic function of the ventricles. There was only one patient with a right ventricular end-diastolic volume index of >150 mL/m^2 and 5 patients with a right ventricular end-systolic volume index of >80 mL/m^2, which are the cut-off values recommended for pulmonary valve replacement indication in the guidelines.[3] Hence, the patients could not be divided into groups in terms of their right ventricular volume, and growth differentiation factor-15 levels could not be compared.

The results of the studies on left ventricular functions in adults cannot be assumed to be also valid in paediatric patients due to different pathophysiological and compensatory mechanisms of heart failure since heart failure in children is mostly associated with congenital heart diseases and right ventricular dysfunction. Hauser et al[10] assessed diagnostic performance and reference values of four novel biomarkers including growth differentiation factor-15 in paediatric patients with heart failure. These biomarkers were measured in 114 patients with a mean age of 5.9 years (IQR: 2.1–12.5) and 89 controls. Growth differentiation factor-15 was a poor indicator to distinguish between patients with HF and the controls. In our study, the patient group was homogeneous in terms of demographic and clinical characteristics, and the control group was composed of patients who had similar demographic characteristics as the patients. Our operated tetralogy of Fallot patients had large right ventricles and a different anatomy, but no significant difference in growth differentiation factor-15 level or N-terminal brain natriuretic peptide levels was found between the patients and controls. Raedle-Hurst et al[11] measured growth differentiation factor-15 levels in 38 patients, including children and young adults with univentricular heart and Fontan circulation. Echocardiography was performed on all participants. Growth differentiation factor-15 levels were found to be significantly higher in the group with EF < 50% and those with higher NYHA/Ross classes. The diastolic function of a single ventricle was not found to be related to any biomarkers. Patients had a wide range of ages in the study (4–36 years) and ages at surgery (2–22 years). The patient group had heterogeneous aetiology. For these reasons, serum levels of the markers might be affected. Norozi et al[12] investigated the role of growth differentiation factor-15 in terms of heart failure in patients with operated congenital heart diseases. Growth differentiation factor-15 and N-terminal brain natriuretic peptide were measured, and an exercise test was performed on 317 patients with a mean age of 26.5 ± 8.5 years, including adolescents and young adults. It was not stated if other conditions that could affect the level of biomarkers were excluded. A healthy control group was not included, and radiological imaging was not performed. Growth differentiation factor-15 level was found to have a significant correlation with NYHA classification, peak oxygen consumption, and N-terminal brain natriuretic peptide levels. Eighty-two of these patients with a mean age of 30.5 ± 8.9 years were operated for tetralogy of Fallot, and the age at surgery (7.3 ± 5.9 years) was greater, unlike our study. Reference values for operated tetralogy of Fallot patients were taken from the results of patients with operated atrial septal defect/ventricular septal defect. It was shown that in NYHA I patients, N-terminal brain natriuretic peptide level and peak oxygen consumption were higher in the operated tetralogy of Fallot group compared to the reference group, but growth differentiation factor-15 levels did not differ from the reference group. In our study, the number of patients with NYHA II was inadequate, and thus comparison could not be made between NYHA I and NYHA II. Growth differentiation factor-15 levels were evaluated in a homogeneous group with predominantly right ventricle with altered function. It was considered that growth differentiation factor-15 might not have a role to evaluate ventricular size and function.

Our study was based on cardiac MRI, which is the gold standard imaging for evaluating the ventricular size and function. However, it had the limitation of a small sample size. To clarify the prognostic importance of novel biomarkers, prospective large-scale studies evaluating the heart with more objective imaging methods, such as cardiac MRI are needed.

In conclusion, the levels of the novel biomarker growth differentiation factor-15, which has been shown to increase in cardiovascular and various other diseases, were uncorrelated with ventricular size, function, and pulmonary regurgitation fraction assessed by cardiac MRI in children with operated tetralogy of Fallot. Moreover, growth differentiation factor-15 levels were not different in these patients from healthy children.

Acknowledgements. We kindly thank the patients, the controls, and their families who participated in the study.

Financial support. This work was supported by the Scientific Research Project Coordination Unit of İstanbul University-Cerrahpaşa (Project number: TTU-2020-34506) and the Turkish Pediatric Association.

Conflict of interest. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by Cerrahpaşa Medical Faculty Ethics Committee (A-37 on November 5, 2019). A written informed consent was taken from all participants and their legal guardians.

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https://doi.org/10.1017/S1047951121001360 Published online by Cambridge University Press