Early-Onset Myocardial and Vascular Toxicity in Childhood Acute Lymphoblastic Leukemia Survivors: The Predictive Value of the Right Heart

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Research Article

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Abstract

Purpose.

Childhood acute lymphoblastic leukemia (ALL) survivors who underwent chemotherapy with anthracyclines have an increased cardiovascular risk. Few are data about right ventricle function (RV) in these patients. The aim of the study was to evaluate left and right cardiac chambers and vascular endothelial function in ALL survivors.

Methods.

We enrolled 54 ALL survivors and 37 healthy controls. All patients underwent auxological evaluation, blood pressure, biochemical parameters of endothelial dysfunction, flow-mediated dilatation (FMD) of the brachial artery, mean common carotid intima-media thickness (c-IMT), antero-posterior diameter of the infra-renal abdominal aorta (APAO), and echocardiographic assessment.

Results.

ALL subjects had significantly lower FMD ($p = 0.0041$), higher left ($p = 0.0057$) and right ($p = 0.0021$) TEI index as compared to controls. Tricuspid annular plane excursion (TAPSE) was 16.9 ± 1.2 mm *vs* 24.5 ± 3.7 mm, $p < 0.0001$. Cumulative anthracycline doses were related to TAPSE ($r = 0.77$, $p < 0.001$). The ROC curve analysis revealed that left and right TEI index, TAPSE, FMD showed significant association to ALL condition. TAPSE > 18 mm was the best discriminant rule to spot ALL patients (AUC: 0.966, $p < 0.0001$, sensibility: 100%, specificity: 89.2%).

Conclusion.

ALL survivors treated with anthracyclines demonstrated systo/diastolic alterations of the RV and reduced endothelial function compared with healthy controls. Although multimodality diagnostic is available, echocardiography plays pivotal role in everyday clinical practice. The early recognition of subclinical cardiac and vascular impairment is of utmost importance for the cardio-oncologist to implement strategies preventing overt cardiovascular disease.

Introduction

Pharmacological approaches to childhood acute lymphoblastic leukemia (ALL) have improved a lot in recent decades, so that a fatal disease has become one with 5-year survival rates over 90% [1]. Therefore, the majority of ALL children are expected to become long-term survivors, although unfortunately, many of them are still likely to experience adverse late effects related to chemotherapies [2–5]. High incidence in cardiotoxicity is well documented in long term childhood ALL survivors who underwent anthracycline

treatment, especially doxorubicin and daunorubicin [6, 7]. Anthracyclines promote myocardial injury by inducing myocyte morphology and function alterations, myocardial sarcoplasmic reticulum damage, and mitochondria vacuolization which can negatively impact left ventricular (LV) function and compliance [8, 9]. Depending on cumulative anthracycline doses, up to 65% of childhood ALL survivors can experience subclinical abnormalities of the LV in adulthood [10].

Few data are available about the influence of chemotherapies on right ventricle (RV) function in long-term childhood ALL survivors [11–13]. Furthermore, although in the wide scenario of vascular endothelial damage of chemotherapy [3], some data pointed out the impact of anthracyclines on vascular function, without conclusive results [14–16].

The aim of our study was to investigate the cardiovascular function in childhood ALL survivors treated with antracyclines, focusing on the right heart functional parameters predictive of subclinical damage. The early detection of chemotherapy-induced alterations both on the cardiac chambers and on the vascular walls is crucial for a better and early stratification of patients' overall cardiovascular risk, to effectively predict cardiovascular events and manage adjunctive cardiovascular risk factors during follow up.

Materials And Methods

Patients

This was a longitudinal, cohort study. Fifty-four childhood ALL survivors (35 females), mean age: 9.7 ± 4.2 (range 4–19) years, were recruited at the Paediatric Haematology and Oncology Clinic, University Hospital of Bari, Italy. Patients received treatment according to the ongoing international ALL protocols adopted by the AIEOP (Italian Association of Paediatric Haematology and Oncology). Six patients received ALL treatment according to high-risk protocols, 28 intermediate risk and 18 standard risk. Nine patients were treated with cranial irradiation for central nervous system prophylaxis. Chemotherapy was held since at least 3 months (range 4–100 months, average 28 months).

Inclusion criteria were: (a) age ranging between 4–20 years; (b) ALL in complete remission; (c) end of antineoplastic therapy since at least three months. Exclusion criteria were: (a) evidence of ALL; (b) cardiovascular diseases and/or endocrine and/or metabolic disorders; (c) genetic syndromes.

As control group we enrolled 37 healthy subjects matched by age and sex who underwent biochemical evaluation, cardiological and vascular ultrasound (US) screening. The study protocol was approved by the local Ethic Committee. Written informed consent was signed by all parents or patients above 18 years old. The study was in agreement with Helsinki Declaration on Human Experimentation.

Methods

All patients underwent complete physical examination (including anthropometric parameters), biochemical, right and left cardiac and vascular US evaluations.

Auxological parameters

Evaluation of anthropometric variables (height, weight, and waist circumference) was performed with the patients in underwear. Body weight was determined to the nearest 0.1 kg and height was measured with a Harpenden stadiometer to the nearest 0.1 cm. Body mass index (BMI) was calculated and expressed as kg/m^2. Arterial blood pressure was measured according to the international guidelines on the Screening and Management of High Blood Pressure in Children and Adolescents [17]. Puberty was classified according to Tanner's staging system [18].

Biochemical and haemostatic markers

Fasting glycemia, insulin, total cholesterol (TC), high (HDL-C) and low (LDL-C) density lipoprotein cholesterol, triglycerides (TG), were measured after overnight fasting in all subjects. Insulin resistance was assessed by HOMA index (HOMAIR) [19].

Commercial ELISA tests were used for total adiponectin and multimeric high-molecular weight (HMW) subfraction (ELISA 47-ADPH-9755; ALPCO Diagnostics, Salem, Vermont), and Endothelin-1 levels (R&D System Europe, Lille, France).

Cardiovascular US measurement

Cardiovascular US studies included measurement of mean common carotid intima-media thickness (mean-IMT), flow mediated dilatation (FMD) of the brachial artery, and antero-posterior abdominal aorta diameter (APAO), while M-Mode, B-Mode Echocardiography and Tissue Doppler Imaging (TDI) were performed in order to investigate cardiac morphology and function [20].

Evaluation of mean-IMT

Ultrasonographic echo-color Doppler studies of left and right common carotid arteries were performed bilaterally by the same physician with a Philips Sonos 5500 using a 7.5 MHz high resolution probe. The patients were placed in supine position, with the neck extended and rotated contra-laterally by 45°: common carotid arteries were examined on the sagittal axis in lateral view. Mean-IMT was defined as the low-level echo gray band that does not project into the arterial lumen and was measured during end-diastole according to the method described by Pignoli et al. [21] The measurements were bilaterally performed 1 cm proximally to the carotid bulb, three times each, and then mean-IMT was calculated. Agreement between measurement was very high, 0.98 according to the intra-class correlation coefficient (ICC; good if ≥0.80) [22].

Evaluation of Flow-Mediated Dilation (FMD)

FMD of the brachial artery was non-invasively assessed using a high-resolution ultrasound probe in a quiet, air-conditioned environment (22–24°C). The subjects were fasted for at least 8–12 hours. A

dedicated software, certified by the CNR of Pisa (MVE II), of analyzed the images. Measurements were made by the same observer to reduce biases. The subjects were studied in the supine position. A sphygmomanometer cuff was inserted close to the brachial artery. After 1 minute of basal image acquisition, the cuff was inflated till 200–220 mmHg in order to promote an ischemic stimulus. After 5 minutes, we deflated the cuff: the increase in shear stress results in production of nitric oxide (NO) which provides the stimulus for vasodilation. After 15 seconds from the end of ischemia, the flow rate was measured and then the degree of hyperemia. The FMD was calculated as the ratio between the changes in diameters of the brachial artery (maximum expansion after deflation baseline/baseline diameter) divided by its basal value and it was expressed as percentage [23]. The measure of the FMD showed good reproducibility in our study, with a calculated ICC of about 0.95.

Antero-posterior diameter of infrarenal abdominal aorta (APAO)

APAO was performed by a single operator using a single high-resolution vascular ultrasound Philips 5500 equipped with a 3 MHz electronic probe. The electronic probe was placed one centimeter left of the umbilicus. Then the best image in long-axis projection of the abdominal aorta was obtained. The APAO was defined as the maximal external cross-sectional diameter measurement of the infrarenal abdominal aorta. It was calculated as the distance between the near and the far walls of the abdominal aorta [24, 25]. APAO showed a good reproducibility in our study as we found an ICC of about 0.92.

Echocardiography and TDI

All patients underwent echocardiography of both left and right chambers, in agreement with international guidelines [26]. Pulsed-wave TDI was used in order to evaluate the velocity of the ventricle walls and the related parameters of systolic and diastolic function of both LV and RV [23]. The cardiac structures examined were: mitral valve annulus, basal and mid part of the LV lateral wall, interventricular septum, basal part of the RV lateral wall, and the lateral tricuspid annulus [27]. We calculated mitral and tricuspid E/A ratio and E/E' ratio. Systolic and diastolic time parameters related to both RV and LV were measured throughout the entire cardiac cycle [28, 29]. Left (l-IVCT) and right (r-IVCT) isovolumetric contraction time, left (l-ET) and right (r-ET) ejection time, left (l-IVRT) and right (r-IVRT) isovolumetric relaxation time were measured to obtain the LV and RV TEI index [(IVRT + IVCT)/ET]. The calculated ICC for all of the echocardiographic measurements was 0.87.

Statistical Analysis

We applied t-test to compare the mean values of variables between cases and controls, with the Welch modification to account for heteroscedasticity.

Linear regression models were exploited to assess the association between dose and cardiovascular outcomes in the cases. Each regression model included the other variables as confounders and the lasso penalty was applied to the discard nonsignificant ones [30].

Multivariate regression analysis was used to determine the effect of cumulative anthracycline doses and vascular and cardiac parameters.

Receiver-operating characteristic (ROC) curve analysis was performed to assess the power of the cardiac variables in discriminating between ALL patients and controls: for each ROC curve, the area under the curve (AUC), the optimal cut-off value and corresponding Youden Index were obtained.

The limit of statistical significance was set at 0.05.

Results

Baseline and cardiovascular characteristics of the study population were listed in Table 1. No significant differences were found between ALL children and controls according to age. SBP and DBP were not different between the two groups. Indeed, ALL patients showed higher BMI and waist circumference than controls. Biochemical measurements also exhibited higher fasting glucose levels in ALL patients than controls, although no differences were found according to insulin and HOMA-IR measurements. Furthermore, total cholesterol, LDL cholesterol, and triglycerides were statistically different between patients and controls. In addition, the ALL patients showed a statistically significant increase in adiponectin and HMW adiponectin than controls, while no difference emerged in the endothelin-1 levels.

Table 2 shows vascular and cardiac findings in ALL patients and controls. Brachial artery FMD measurements were significantly lower in ALL patients, while no differences were found according to morphological alterations in vascular walls as the values of mean IMT and APAO were similar between the two groups.

According to cardiac parameters, patients and controls did not show significant difference in left ventricle ejection fraction (LVEF). Nevertheless, both left and right TEI index measurements were higher in ALL patients than controls (0.42 ± 0.07 *vs* 0.36 ± 0.11, p=0.0057; 0.43 ± 0.10 *vs* 0.34±0.14, p=0.0021, respectively). Tricuspid annular plane excursion (TAPSE) measurements were lower in ALL patients than controls (16.9 ± 1.2 mm *vs* 24.5 ± 3.7 mm, $p < 0.0001$), both in the univariate and multivariate analysis. Figure 1 portrays the boxplots comparing the distributions of the cardiovascular and vascular variables having significantly different mean values between ALL patients and controls.

We tried to identify the best cut-off values among clinical, anthropometric, laboratory, and cardiac/vascular parameters which were able to discriminate ALL patients from controls. The ROC curve analysis (Table 3) revealed that left TEI index, right TEI index, TAPSE, FMD, fasting glucose levels, adiponectin and BMI showed significant association to ALL condition. Among them, TAPSE was the variable with the best discriminant power, AUC=0.966, best cut-off value= 18 mm leading to sensitivity=100% and sensibility=89.2%.

As regard to cumulative doses of anthracyclines, they were 210 mg/mq in 1/54 patient, 240 mg/mq in 48/54 patients (assigned to standard and intermediate risk protocols), 310 mg/mq in 1/54 patient and 350 mg/mq in 4/54, allocated in the high risk protocol. In the regression analysis, the cumulative anthracycline dose (mg/m^2) resulted related to TAPSE: the higher the cumulative dose, the worst the systolic function of right ventricle, as assessed by the inverse relationship between the two variables ($r = 0.77$, $p < 0.001$).

Discussion

This study demonstrates the subclinical impairment of cardiac left and in particular right function, and vascular function in childhood ALL survivors treated with anthracycline-based regimens.

The assessment of RV function recently gained increasing interest within cardio-oncology due to its role in predicting the occurrence of heart failure [31-34]. In our sample of ALL childhood survivors, subclinical alterations of the RV function were outlined by the higher values of right TEI index and lower TAPSE measurement. Interestingly, to higher cumulative doses of anthacyclines corresponded significantly lower values of TAPSE. Moreover TAPSE values <18 mm succeeded in distinguish between patients and controls with high sensitivity and specificity (100% and 89.2%, AUC: 0.966, $p < 0.0001$). To our knowledge such intriguing result has not been reported before. Christiansen et al. [11] found reduced values in TAPSE in adult survivors of childhood malignant lymphoma or ALL who had been exposed to anthracyclines, mediastinal radiotherapy, or both. Particularly, a global reduction in RV function, as outlined by alterations also in fractional area change, peak systolic tricuspid annular velocity, and free wall strain, was observed. In line with our results, Christiansen et al. found no variations in term of right diastolic function between ALL patients and controls [11]. Cardiotoxicity has been associated mainly to anthracycline doses >300 mg/mq [29]. However, signs of cardiotoxicity have been reported also with lower anthracycline doses of 100 mg/mq [35]. In the present study anthracycline doses varied from 210 mg/mq to 350 mg/mq, therefore some cardiotoxicity might be expected in our sample. Bayram et al. [35] observed reduced right ventricle myocardial velocities, as assessed by TDI, in childhood leukemia survivors treated with low-dose of anthracyclines, thus deriving the impairment in systolic and diastolic function of the cardiac chamber, but do not provide any data about right TEI index. Interestingly, Kocabaş et al. [36] outlined the progressive increase in right TEI index with the increase in cumulative anthracycline doses. Although our study did not demonstrate the correlation between right TEI index increase and cumulative dose, the identification of progressive decrease in TAPSE with the increase in cumulative anthracycline doses confirmed the impairment in right ventricle function in ALL survivors. Indeed, patients treated with anthracyclines were reported to show impairment in right ventricular systolic and diastolic functional reserves when they underwent stress echocardiography; thus, they had subtle alterations in right cardiac chamber which can be exacerbate from stress [37,38]. All of these findings should be taken into account as the RV function seems to be a stronger predictor of developing or worsening heart failure than LV function [39].

Previous studies focused on the remodeling of left cardiac chambers during chemotherapy [8-10,29].

A worsening of LV function was observed in 7% of ALL patients after a mean period of 6 years after chemotherapy [40]. Conversely, in our study, we did not observe statistically significant differences in terms of LVEF between ALL patients and controls. However, ALL patients showed higher values in left TEI index than controls, which can be considered an early sign of systo-diastolic alteration in left cardiac chambers. Particularly, left TEI index values >0.38 may distinguish ALL survivors from healthy controls. This finding is in agreement with previous literature data [35,41].

We did not demonstrate alterations in vascular morphology in ALL survivors as compared to controls. Mean IMT and APAO were similar between the two groups. ALL survivors showed a statistically significant decrease in endothelial function as expressed by FMD. Derangement in endothelial function after anthracycline treatment has been previously reported in cancer survivors [3,42-47]. Jenei et al. [42] outlined the occurrence of both endothelial dysfunction and increased aortic stiffness in long term survivors of childhood cancer, both related to cumulative anthracycline dose (in mg/m^2). Long et al. [47] confirmed the reduction in FMD values and subclinical left ventricle diastolic dysfunction during exercise stress in patients treated with anthracyclines. In our study we did not find any correlation of vascular parameters with different cumulative doses of anthracyclines.

Furthermore, when planning the follow up studies for such a growing population of childhood ALL survivors one more consideration should be given: although multimodality diagnostic and imaging (see magnetic resonance, nuclear imaging) represent essential tools to study preclinical heart injury, echocardiography is a simple imaging tool in everyday practice to monitor clinical cardiotoxicity, in order to recognize the preclinical changes.

Finally, as regard to the metabolic markers of endothelial dysfunction, namely HMW-AD, endothelin-1 and insulin resistance [48], in our study population we confirmed the reported data on impaired metabolic profile in young survivors of ALL [3], however we did not find any correlations with cardiovascular parameters and total doses of anthracyclines.

Conclusions

Childhood ALL survivors treated with anthracyclines showed contemporary early echocardiographic signs of RV and endothelial dysfunctions. Detection of early cardiac and vascular impairment should be mandatory in order to prevent additional risk factors and progression of the cardiovascular toxicity and, thus improving the long term quality of life of the patients.

Declarations

Conflict of interest

None declared.

DISCLOSURES

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COMPETING INTEREST

The authors have no relevant financial or non-financial interests to disclose.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. **Paola Muggeo** has drawn the design of the work, contributed to the interpretation of data, wrote the manuscript and revised it until its final version; **Pietro Scicchitano** made the acquisition of cardiovascular data, analyzed the data and gave contribution to the drafting of the manuscript and revised it; **Vito Michele Rosario Muggeo** analyzed the data and critically revised the article; **Chiara Novielli** contributed mainly in the acquisition of data and drafting the article; **Paola Giordano** took part to the conception and the design of the study and revised the article; **Marco Matteo Ciccone** made the acquisition and interpretation of cardiovascular data, he eneterely revised the article; **Maria Felicia Faienza** gave great contribution to the interpretation of data, very critically and carefully revised the paper; **Nicola Santoro** participated to the conception and design of the study and revised the article. All authors read and approved the final *manuscript.*

ETHICS APPROVAL

The study was approved by the local institutional research ethics committee

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Tables

Table 1. Anthropometric, clinical, and laboratory characteristics of the study population and controls.

Characteristic	ALL patients (n = 54)	Controls (n = 37)	P value
Age (yrs)	9.9±4.2	10.3±2.8	0.52
BMI (Kg/m^2)	21.1±4.8	17.5±1.9	**<0.0001**
Waist circumference (cm)	71.5±15.3	55.1±7.9	**<0.0001***
SBP (mmHg)	105.6±10.3	104.8±5.7	0.63*
DBP (mmHg)	66.0±7.6	63.8±5.7	0.11
Fasting glucose level (mg/dl)	82.3±6.4	77.4±6.2	**<0.0001***
Insulin (uIU/mL)	12.5±8.6	13.0±2.6	0.70
HOMA IR	2.6±2.0	2.5±0.6	0.79
Total C (mg/dl)	150.7±23.7	126.4±13.0	**<0.0001**
LDL-C (mg/dl)	86.4±18.0	59.8±14.1	**<0.0001**
HDL-C (mg/dl)	50.6±9.9	58.9±8.2	**<0.0001***
Triglycerides (mg/dl)	68.3±30.6	48.2±15.3	**<0.0001**
Endothelin-1 (pg/ml)	2.1±0.6	2.0±0.5	0.69
Adiponectin (µg/mL)	7.8±3.0	9.0±2.0	**0.0288**
HMW Adiponectin (µg /ml)	4.4±2.4	5.8±1.8	**0.0059**

Data are expressed as mean±standard deviation. *= statistically significant association confirmed at multivariate analysis, i.e. after adjusting for other variables

Abbreviations: ALL: acute lymphoblastic leukemia; **BMI:** Body Mass Index; **DBP:** Diastolic Blood Pressure; **HDL-C:** high density lipoprotein cholesterol; **HMW:** Human High Molecular Weight; **HOMA IR:** Homeostatic Model Assessment for Insulin Resistance; **LDL-C**: low density lipoprotein cholesterol; **SBP:** Systolic Blood Pressure; **Total C:** total cholesterol

Table 2. Echocardiographic and vascular characteristics of the study population and controls.

Characteristic	ALL patients (n = 54)	Controls (n = 37)	P value
FMD (%)	8.7±3.5	11.6±5.0	**0.0041**
Mean IMT (mm)	0.46±0.07	0.45±0.06	0.22
APAO (mm)	10.1±2.0	10.2±1.9	0.71
LVEF(%)	59.7±8.6	61.7±6.3	0.22
Left TEI index	0.42±0.07	0.36±0.11	**0.0057**
Right TEI index	0.43±0.10	0.34±0.14	**0.0021**
Left E/A ratio	2.2±0.7	2.0±0.5	0.15
Right E/A ratio	1.9±0.6	1.9±0.6	0.97
TAPSE (mm)	16.9±1.2	24.5±3.7	**<0.0001***

Data are expressed as mean±standard deviation. *= statistically significant association confirmed at multivariate analysis, i.e. after adjusting for other variables

Abbreviations: ALL: acute lymphoblastic leukemia; **APAO:** antero-posterior diameter of the infrarenal abdominal aorta; **FMD:** flow-mediated vasodilatation of the brachial artery; **LVEF:** left ventricle ejection fraction; **mean-IMT:** mean carotid intima-media thickness; **TAPSE:** tricuspid annular plane excursion.

Table3. Receiver operating curve (ROC) to identify the most reliable parameter related to survival in childhood acute lymphoblastic leukemia (ALL).

Parameter	ALL survivors (n=54)	Controls (n=37)	Cut-off	Sensibility	Specificity	AUC	p
Left TEI index	0.42±0.07	0.36±0.11	>0.38	74.1	51.3	0.656	0.0084
Right TEI index	0.43±0.10	0.34±0.14	>0.29	94.4	37.8	0.667	0.0082
TAPSE (mm)	16.9±1.2	24.5±3.7	≤18	100	89.2	0.966	<0.0001
FMD (%)	8.68±3.52	11.6±5.01	≤11	85.2	51.4	0.680	0.0033
Fasting glucose levels (mg/dl)	82.3±6.4	77.4±6.2	>80	59.3	81.1	0.744	<0.0001
Adiponectin (µg/mL)	7.76±2.98	9.01±1.98	≤6.18	35.2	100	0.630	0.0360
Body mass index (Kg/m^2)	21.1±4.8	17.5±1.9	>20.4	51.8	94.6	0.752	<0.0001

Abbreviations: ALL: acute lymphoblastic leukemia; **AUC:** area under the curve; **FMD:** flow-mediated vasodilatation of the brachial artery; **ROC:** receiver operating curve; **TAPSE:** tricuspid annular plane excursion.

Figures

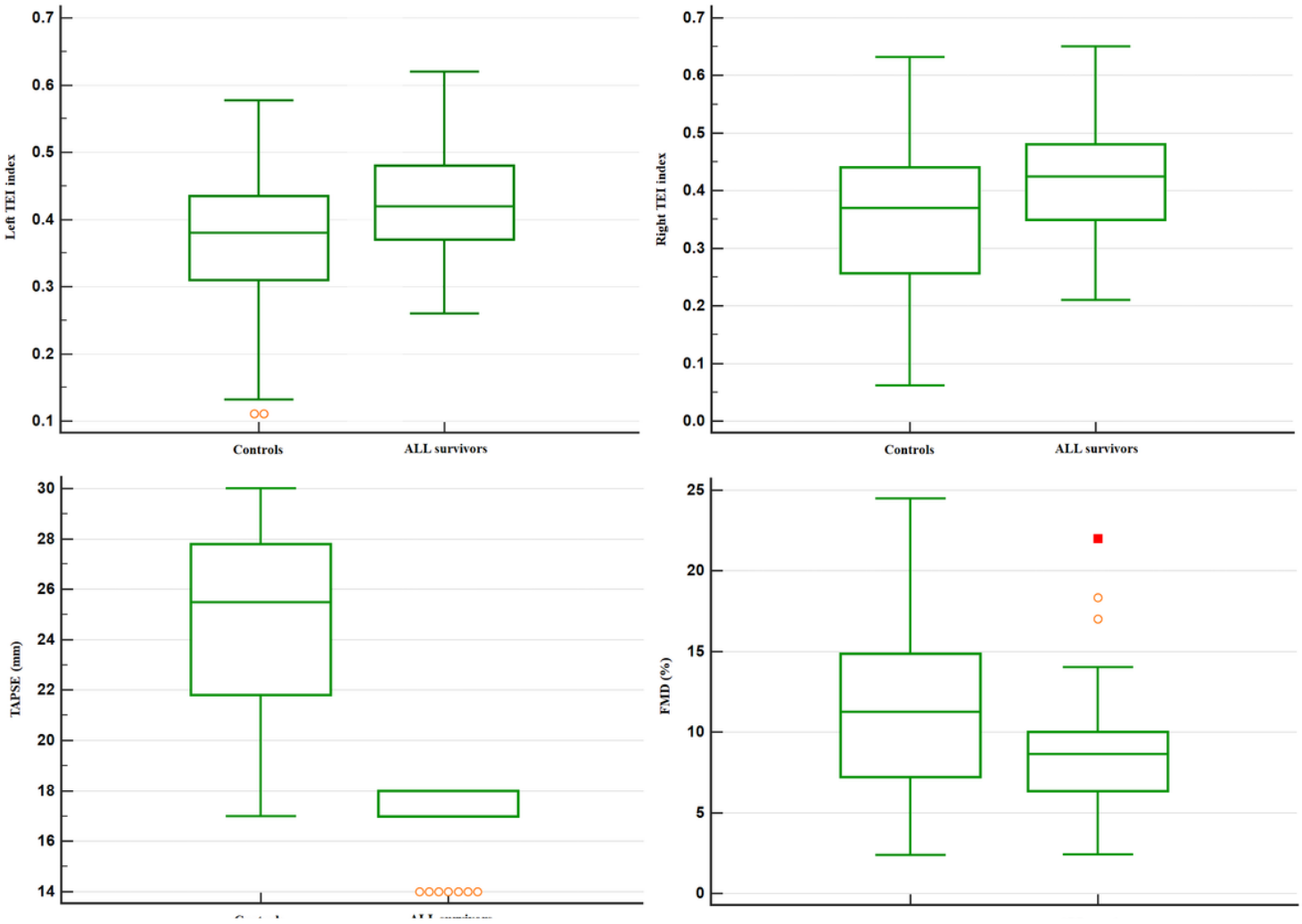

Figure 1

Box plots of left and right TEI index, tricuspid annular plane excursion (TAPSE), and flow-mediated vasodilatation of the brachial artery (FMD) in healthy controls and childhood cancer survivors.