

Comparison of Left Atrial Strain Parameters After Doxorubicin Therapy in Pediatric Patients With Leukemia and Healthy Children: A Cross-Sectional Case–Control Study

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Abstract

Objective:

To compare left atrial strain parameters during reservoir, conduit, and contraction phases in pediatric patients with leukemia treated with doxorubicin and age- and sex-matched healthy controls, and to evaluate their potential role in detecting subclinical cardiotoxicity.

Methods:

This single-center, cross-sectional case–control study included 22 pediatric patients with acute lymphoblastic leukemia who received a cumulative doxorubicin dose of 240 mg/m² and 25 healthy controls. All participants underwent comprehensive echocardiographic evaluation, including two-dimensional speckle-tracking analysis. Left ventricular global longitudinal strain (GLS) and left atrial strain parameters were assessed. Intergroup comparisons and correlation analyses were performed using appropriate statistical methods.

Results:

The mean follow-up duration after completion of chemotherapy was 4.6 ± 2.6 years. Left atrial reservoir, conduit, and contraction strain values were numerically lower in the leukemia group but did not differ significantly from controls. Mean reservoir strain was $39.4 \pm 7.8\%$ in patients and $48.9 \pm 6.5\%$ in controls ($p = 0.353$). Conduit strain showed a trend toward significance ($25.1 \pm 6.3\%$ vs. $32.4 \pm 7.1\%$, $p = 0.078$). Contraction strain and GLS were comparable between groups. Left ventricular wall thickness and end-diastolic diameter were significantly lower in patients, while ejection fraction remained preserved. No significant correlations were observed between strain parameters and follow-up duration.

Conclusion:

At mid-term follow-up after moderate-dose doxorubicin therapy, left atrial strain parameters and GLS remained largely preserved in pediatric leukemia survivors. These findings suggest the absence of overt subclinical myocardial dysfunction at this dose level, emphasizing the importance of long-term strain-based surveillance in this population.

INTRODUCTION

Leukemia is one of the most common malignancies of childhood, and survival rates particularly in acute lymphoblastic leukemia (ALL) have improved markedly with modern chemotherapy protocols [1]. The incorporation of anthracyclines, especially doxorubicin, into treatment regimens has played a major role in increasing cure rates, resulting in a steadily growing population of childhood cancer survivors [2, 3]. However, improved survival has also drawn increasing attention to treatment-related late cardiovascular complications, which may significantly affect long-term clinical outcomes [1, 3].

Doxorubicin is a cumulative and dose dependent agent with well-established cardiotoxic effects mediated through multiple molecular and cellular mechanisms, including oxidative stress, mitochondrial dysfunction, and cardiomyocyte apoptosis [3–5]. Anthracycline related cardiotoxicity encompasses a broad clinical spectrum, ranging from acute myocardial injury during therapy to late onset cardiomyopathy developing years after completion of treatment [5]. Importantly, myocardial involvement may remain clinically silent for prolonged periods, emphasizing the need for sensitive methods capable of detecting subclinical cardiac dysfunction.

Conventional echocardiographic parameters, particularly left ventricular ejection fraction, have long been used for cardiac surveillance; however, their sensitivity in detecting early myocardial injury is limited. Consequently, myocardial deformation imaging using two-dimensional speckle tracking echocardiography has emerged as a valuable tool for identifying subclinical cardiac involvement in children treated with anthracyclines [6].

In recent years, the left atrium has been increasingly recognized not merely as a passive filling chamber but as an integral component of cardiac performance, reflecting left ventricular filling dynamics through its reservoir, conduit, and contractile functions. Alterations in left atrial function may occur early in the course of myocardial involvement and may precede overt systolic dysfunction. Although interest in left atrial strain analysis has grown, data regarding its role in detecting anthracycline-related subclinical cardiotoxicity in pediatric leukemia survivors remain limited. [7].

MATERIALS AND METHODS

This study was designed as a single-center, cross-sectional case–control investigation conducted at a tertiary university hospital. The study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the local Clinical Research Ethics Committee (Approval No: 2025–6510, Date: November 11, 2025). Written informed consent was obtained from the parents or legal guardians of all participants prior to enrollment. The case group consisted of pediatric patients aged 5–17 years who were followed with a diagnosis of acute lymphoblastic leukemia (ALL) and had received doxorubicin therapy according to the treatment protocol. All patients were in the maintenance phase of therapy. Chemotherapy regimens, cumulative doxorubicin doses, and follow-up durations were retrospectively reviewed from electronic medical records. Exclusion criteria included congenital heart disease, valvular heart disease, known cardiomyopathy, a history of arrhythmia, or inadequate image quality for strain analysis.

The control group comprised 25 healthy children with an age- and sex distribution similar to that of the case group, who had been referred to the outpatient clinic for evaluation of a heart murmur or chest pain and were found to have completely normal echocardiographic findings, physical examinations, and electrocardiograms, with no known systemic disease. Participants with insufficient image quality were also excluded from the control group.

All participants underwent two-dimensional, M-mode, color, and Doppler echocardiographic examinations during the same session using a Vivid T9 ultrasound system (GE Healthcare, Horten, Norway). All measurements were performed by a single investigator experienced in pediatric cardiology, with the patient in the supine position, in accordance with the guidelines of the American Society of Echocardiography (ASE). Left ventricular ejection fraction was calculated using the modified biplane Simpson method. Left ventricular internal dimensions, wall thicknesses, and diastolic function parameters were recorded according to standard protocols. Each parameter was assessed as the average of three consecutive cardiac cycles.

Myocardial deformation analysis was performed using two-dimensional speckle-tracking echocardiography. For left ventricular strain assessment, grayscale images acquired from apical two-, three-, and four-chamber views were analyzed, with frame rates maintained between 50 and 90 frames per second. Endocardial borders were manually traced, automatically generated speckle-tracking contours were visually inspected, and manual adjustments were applied when necessary. Left ventricular global longitudinal strain (GLS) was calculated as the average of peak systolic longitudinal strain values obtained from the three apical views.

Left atrial strain analysis was performed using the apical four-chamber view. The left atrial endocardial border was manually delineated, excluding the pulmonary veins and left atrial appendage, and automated tracking was verified. Strain analysis was referenced to the onset of the QRS complex. Left atrial strain values corresponding to the reservoir, conduit, and contraction phases were obtained, and mean values from three consecutive cardiac cycles were calculated for each parameter.

In this manner, myocardial deformation parameters reflecting subclinical functional alterations of both the left ventricle and left atrium were comprehensively evaluated. Representative examples of left atrial strain analysis obtained from the apical two and four-chamber view, illustrating region-of-interest delineation and reservoir, conduit, and contraction phases, are shown in Fig. 1A and 1B.

Statistical Analysis

Statistical analysis was performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was assessed using the Shapiro–Wilk test. Normally distributed variables were expressed as mean $\pm$ standard deviation, whereas non-normally distributed variables were presented as median (interquartile range). Intergroup comparisons were conducted using the independent samples t-test for normally distributed variables and the Mann–Whitney U test for non-normally distributed variables. Categorical variables were compared using the chi-square test. In the patient group, relationships between left atrial strain parameters and cumulative doxorubicin dose, follow-up duration, left ventricular GLS, and ejection fraction were evaluated using Spearman correlation analysis. A p value < 0.05 was considered statistically significant.

RESULTS

A total of 47 children were included in the study, comprising 22 pediatric patients with leukemia and 25 age- and sex-matched healthy controls. Baseline demographic and clinical characteristics of the study population are summarized in Table 1. The mean age did not differ between groups, whereas body weight was significantly lower in the leukemia group. All patients received a cumulative doxorubicin dose of 240 mg/m² according to the treatment protocol, except for two patients who were treated with higher cumulative doses of 420 mg/m² and 480 mg/m² due to classification into a high-risk treatment group. The mean follow-up duration after completion of chemotherapy was 4.6 ± 2.6 years.

Left atrial and left ventricular myocardial deformation parameters are presented in Table 2 and illustrated in Fig. 2. Left atrial reservoir strain, left atrial contraction strain, and left ventricular global longitudinal strain were comparable between the leukemia and control groups. Left atrial conduit strain was numerically lower in the leukemia group compared with healthy controls (25.1 ± 6.3% vs. 32.4 ± 7.1%), although this difference did not reach statistical significance.

Conventional two-dimensional echocardiographic measurements are detailed in Table 3. Left ventricular wall thickness and left ventricular end-diastolic diameter were significantly lower in the leukemia group compared with controls, whereas left ventricular ejection fraction remained preserved and did not differ between groups. This pattern indicates the presence of structural cardiac differences in the absence of overt systolic dysfunction.

To better illustrate the dissociation between structural and functional cardiac findings, a schematic summary of the composite structural–functional cardiac profile is presented in Fig. 3. While ventricular dimensions were reduced in leukemia survivors, myocardial deformation parameters reflecting systolic and atrial function remained largely preserved.

Correlation analyses between time since completion of therapy and myocardial deformation parameters are shown in Table 4. No meaningful correlations were observed between follow-up duration and left atrial strain components or GLS, suggesting the absence of a detectable time-dependent deterioration in myocardial deformation within the studied follow-up period.

DISCUSSION

In the present study, left atrial strain components (reservoir, conduit, and contraction phases) and left ventricular global longitudinal strain (GLS) were evaluated in pediatric patients with leukemia who had received a cumulative doxorubicin dose of 240 mg/m² and were compared with age- and sex-matched healthy controls. Despite a mean follow-up duration of approximately 48 months, left atrial strain parameters and GLS were largely comparable between the two groups. In contrast, conventional two-dimensional echocardiography revealed significantly lower left ventricular wall thickness and end-diastolic diameter in the leukemia group, while left ventricular ejection fraction remained preserved.

The left atrium has increasingly been recognized as an integral component of cardiac performance, reflecting left ventricular filling dynamics through its reservoir, conduit, and contractile functions. Left

atrial strain assessed by speckle-tracking echocardiography has been proposed as a sensitive, noninvasive marker of early diastolic dysfunction and elevated left ventricular filling pressures [8–11]. In this context, the absence of significant differences in left atrial reservoir and contraction strain parameters in our cohort suggests that overt diastolic dysfunction may not be present during mid-term follow-up after exposure to a cumulative doxorubicin dose of 240 mg/m². However, the borderline reduction observed in conduit strain may indicate subtle early alterations in diastolic function, as this phase is considered particularly sensitive to changes in ventricular relaxation. This finding may reflect an early subclinical effect that could not be confirmed statistically due to the limited sample size.

Anthracycline-related cardiotoxicity is mediated through multiple molecular and cellular mechanisms, including oxidative stress, mitochondrial dysfunction, and cardiomyocyte apoptosis, which may lead to myocardial injury before the development of overt systolic dysfunction [8, 12–14]. Previous studies have demonstrated that GLS may decline before reductions in left ventricular ejection fraction and therefore serve as an early marker of subclinical systolic dysfunction in children treated with anthracyclines [15, 16]. In contrast, the preservation of GLS in our study suggests that subclinical systolic impairment may not have developed within the evaluated cumulative dose range and follow-up period. Nevertheless, this finding should be interpreted cautiously, as late-onset anthracycline-related cardiotoxicity has been reported to occur several years after completion of therapy [17].

In addition to functional parameters, structural echocardiographic measurements revealed significantly lower left ventricular wall thickness and end-diastolic diameter in the leukemia group compared with healthy controls. Similar structural alterations have been reported in childhood cancer survivors exposed to anthracyclines and have been attributed to early myocardial remodeling associated with cardiotoxicity [16, 17]. Importantly, these changes may occur in the absence of measurable systolic dysfunction. At the same time, growth impairment and reduced somatic development frequently observed during and after leukemia treatment may also contribute to smaller cardiac dimensions [17]. Therefore, the observed structural differences in our cohort are likely multifactorial, reflecting both potential anthracycline-related myocardial effects and differences in physical growth.

Consistent with this interpretation, body weight was significantly lower in the leukemia group compared with healthy controls. Undernutrition and weight loss are common during the treatment course of childhood leukemia and have been shown to negatively affect growth and development [19]. Reduced body weight and altered body composition may influence cardiac size and geometry, representing important confounding factors in the interpretation of echocardiographic measurements. Accordingly, anthropometric parameters should be carefully considered when evaluating cardiac structure in pediatric oncology survivors.

Correlation analyses demonstrated no significant relationship between time since completion of therapy and left atrial strain parameters or GLS. Anthracycline-induced cardiotoxicity is known to follow a progressive course, with clinical manifestations potentially emerging many years after treatment completion [17]. The absence of a time-dependent association in our study may therefore reflect the

relatively limited follow-up duration and does not exclude the possibility of late-onset myocardial involvement. Longer-term prospective studies incorporating serial strain assessments are needed to better characterize temporal changes in myocardial deformation.

Only two patients in the leukemia group received cumulative doxorubicin doses exceeding 240 mg/m², and these patients exhibited lower left atrial strain values compared with those who received standard doses, although statistical significance could not be demonstrated. Given the well-established dose-dependent nature of anthracycline-related cardiotoxicity [8, 12, 17], this observation is consistent with existing literature and should be regarded as hypothesis-generating. Confirmation of this trend will require larger cohorts including patients exposed to a wider range of cumulative anthracycline doses.

LIMITATIONS

Several limitations of this study should be acknowledged. First, the single-center design and relatively small sample size may limit the generalizability of the findings. Second, baseline (pre-treatment) strain measurements were not available, precluding the assessment of within-patient changes over time. Third, because all patients received similar cumulative doses of doxorubicin, a dose–response analysis could not be performed. In addition, potential confounding factors such as exposure to radiotherapy and other cardiotoxic agents were not evaluated in detail.

CONCLUSION

In conclusion, the finding that left atrial strain parameters and left ventricular GLS were comparable to those of healthy controls in children who received a cumulative doxorubicin dose of 240 mg/m² with a mean follow-up of 48 months suggests the absence of overt subclinical systolic or diastolic dysfunction at this dose level. Nevertheless, because the risk of late-onset anthracycline-related cardiotoxicity cannot be entirely excluded, continued regular echocardiographic follow-up preferably incorporating strain-based imaging remains essential into adulthood. Furthermore, the presence of lower body weight and smaller left ventricular dimensions highlights the impact of cancer therapy on growth and development and underscores the need for a multidisciplinary follow-up approach in this population.

Declarations

FINANCIAL SUPPORT

No specific financial support or funding was received for this study.

Conflict of Interest Statement

The authors declare no conflict of interest.

Funding Statement

No specific funding was received for this study.

Ethics Approval

This study was approved by the Local Clinical Research Ethics Committee of Ege University Faculty of Medicine. Written informed consent was obtained from the parents of all participants.

Author Contributions

ŞŞÖ, HK, BKB: Study design, data collection, manuscript writing

ZÜ, NK, DYK, ED: Data analysis, interpretation

EL,MY, BBA, HK: Patient recruitment, data acquisition

All authors: Critical revision and final approval

(All authors approved the final manuscript.)

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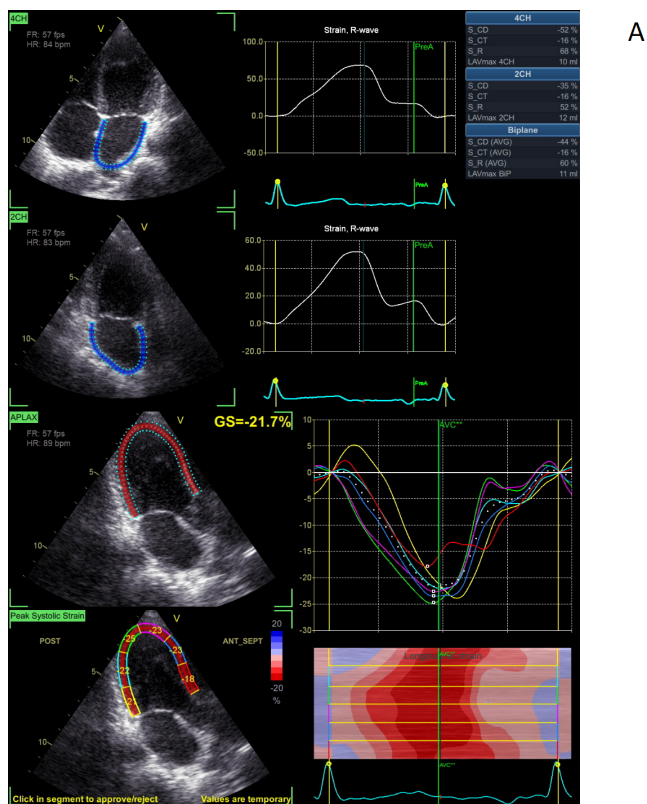
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Tables

Tables are available in the Supplementary Files section.

Figures



B Leukemia patient - LA strain (4CH), LV GLS (APLAX) and bull's-eye

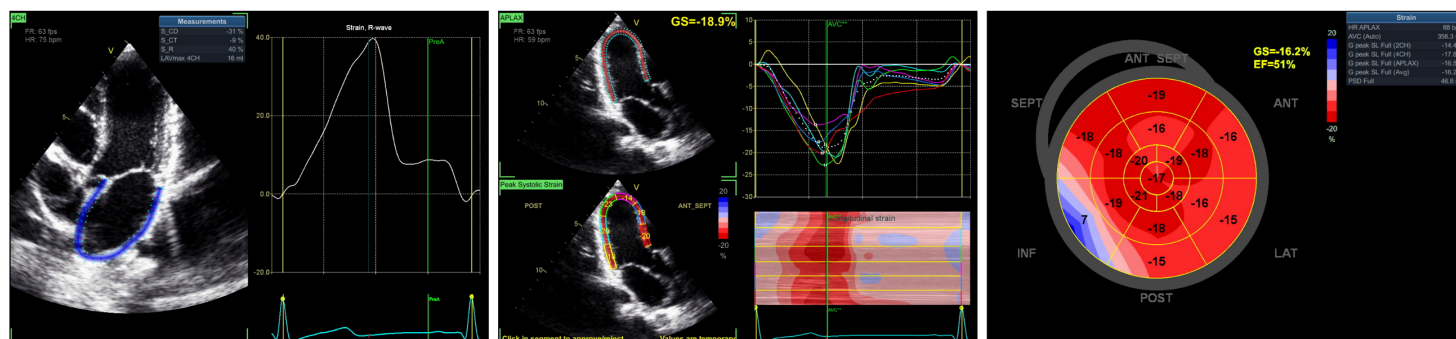


Figure 1

Representative examples of two-dimensional speckle-tracking echocardiography.

(A) Healthy control demonstrating left left ventricular and aplanx view and left atrial strain analysis from the apical two and four-chamber view, with clearly identifiable reservoir, conduit, and contraction phases referenced to the onset of the QRS complex.

(B) Pediatric patient with leukemia following high-dose doxorubicin therapy, illustrating left ventricular and left atrial strain analysis obtained using the same acquisition and analysis protocol.

Images are provided to demonstrate the methodology of myocardial deformation assessment and phase identification and are not intended for quantitative comparison.

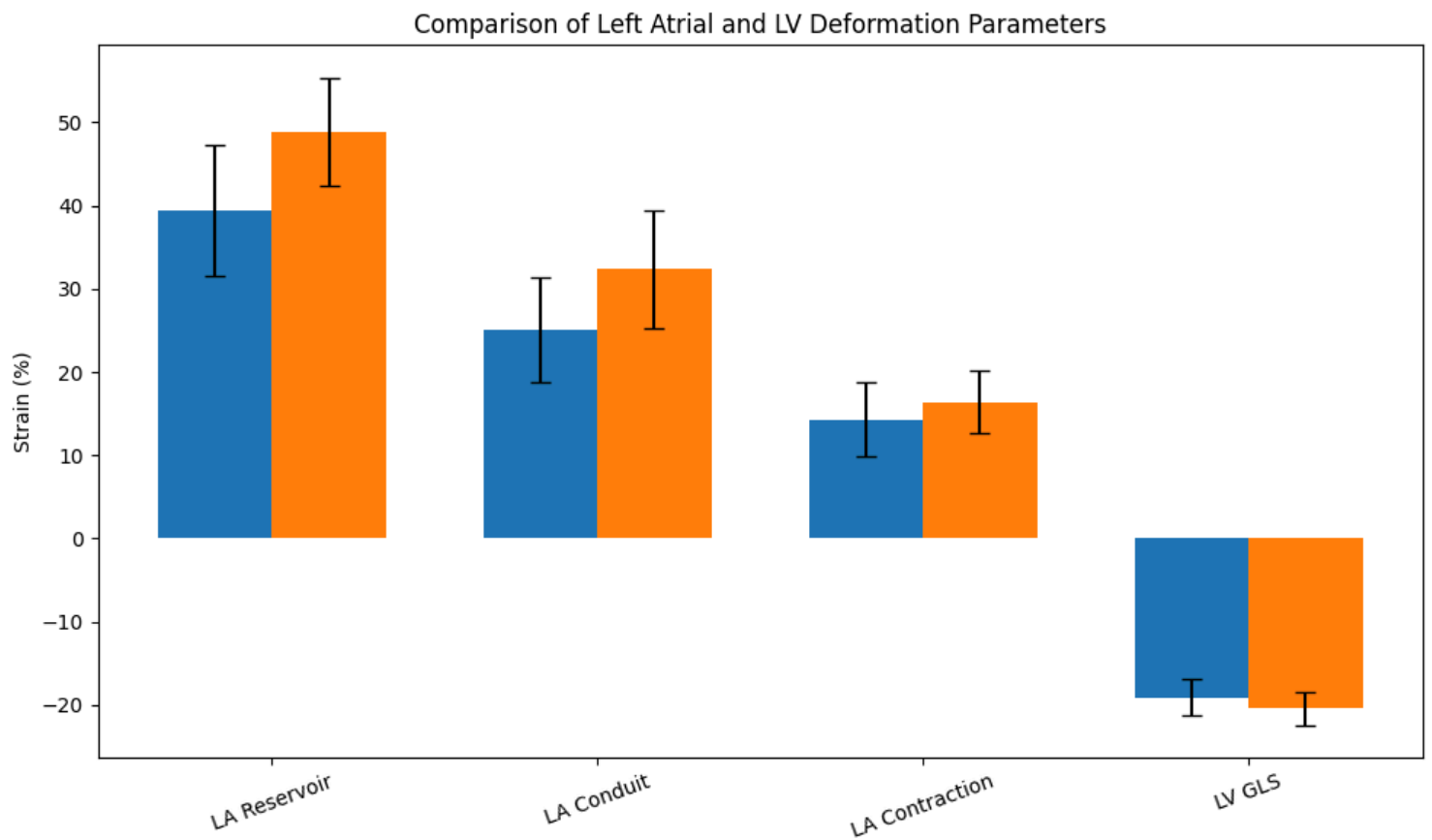


Figure 2

Comparison of left atrial strain components and left ventricular global longitudinal strain between pediatric leukemia survivors and healthy controls.

Bars represent mean values with standard deviation. Left atrial conduit strain showed a numerical reduction in the leukemia group without reaching statistical significance.

Structural and Functional Cardiac Profile After Doxorubicin Therapy in Pediatric Leukemia Survivors

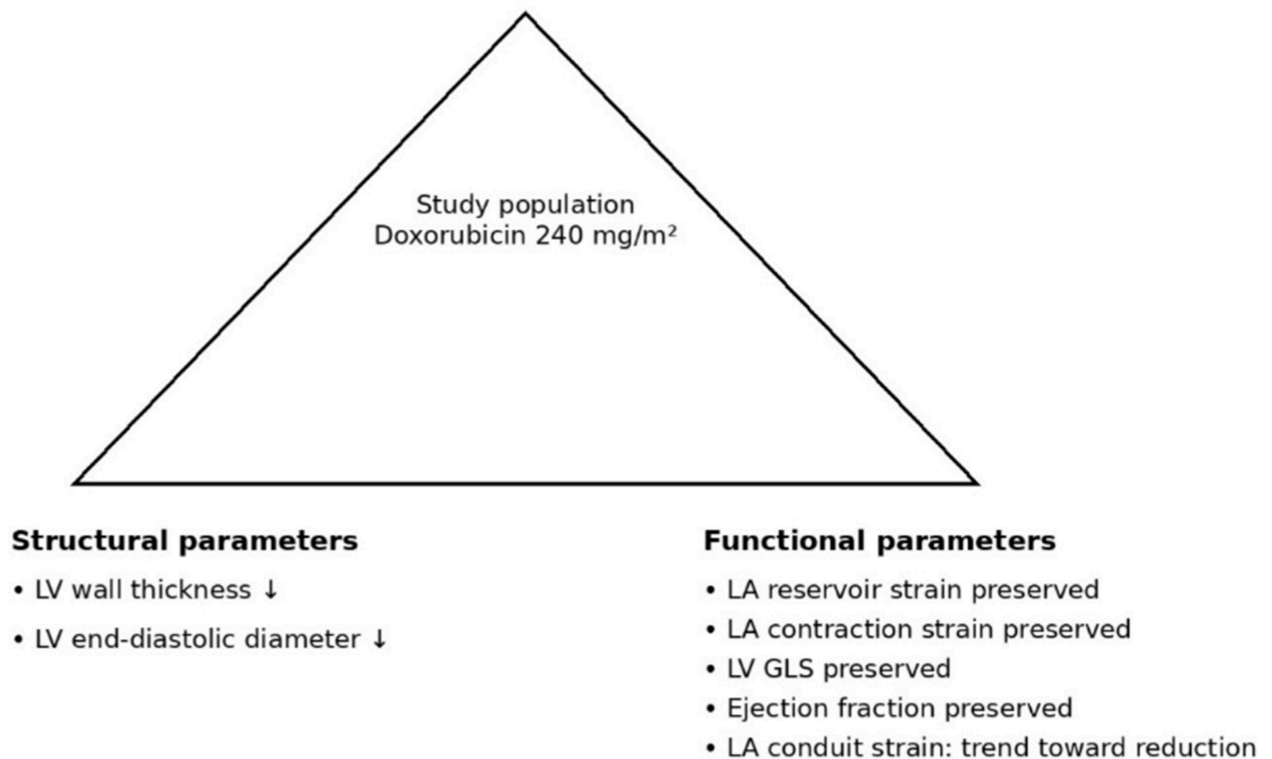


Figure 3

Structural and functional cardiac profile after doxorubicin therapy in pediatric leukemia survivors.

This schematic figure summarizes the dissociation between structural and functional cardiac findings in pediatric leukemia survivors treated with a cumulative doxorubicin dose of 240 mg/m². While left ventricular wall thickness and end-diastolic diameter were reduced, left atrial strain components and left ventricular global longitudinal strain remained largely preserved. A numerical reduction in left atrial conduit strain was observed without reaching statistical significance.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [TABLES.docx](#)