Permanent longitudinal strain damage of cardiotoxic drugs in childhood cancer: What is the safe level?

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ABSTRACT

Objective : **Anthracycline administration in children is associated with cardiac dysfunction. Speckle-tracking echocardiography (STE) can detect subclinical cardiac damage that may go undetected by conventional two-dimensional (2D) echocardiography. This study aims to investigate medium-term anthracycline cardiotoxicity using STE and determine a safer administrable level of anthracyclines (ACs).**

Methods : **This observational case–control study enrolled 37 healthy controls and 78 pediatric cancer survivors who received chemotherapy. The patients were divided into two groups: cardiotoxic received (CR) and cardiotoxic free (CF). Data on segmental longitudinal strain (LS), global LS (GLS), and 2D echocardiographic parameters were collected after a drug-free period of at least one year.**

Results : **A total of 115 children with a mean age of 108 ± 55 months, of whom 66% were males, were included in the study. Both the groups of cancer survivors exhibited significantly reduced GLS compared to healthy controls (CR vs. controls, $P = 0.001$; CF vs. controls, $P = 0.013$), but no significant difference in left ventricular ejection fraction (LVEF) was observed ($P = 0.75$). Overall, cancer survivors treated with ACs demonstrated a significant reduction in strain in 10 left ventricular segments, particularly in the basal segments ($P < 0.05$). Among CR patients, those with impaired GLS ($n = 43$, GLS worse than −21.9) had significantly higher mean age and cumulative anthracycline dose compared to CR patients with normal GLS (age, $P = 0.024$; anthracycline dosage, $P = 0.036$). Using an anthracycline cutoff of 223 mg/m² resulted in a higher detection rate (49% vs. 25%) and fewer missed cases (51% vs. 74%) compared to the 360 mg/m² anthracycline cutoff.**

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Conclusion : **Childhood cancer survivors demonstrate significantly reduced GLS while preserving a normal LVEF, which does not differ significantly from reference values of healthy children. The reduction in strain appears to be associated with higher anthracycline doses and older age. Lowering the anthracycline threshold to 223 mg/m^2 may improve the predictability of a decline in cardiac function using strain imaging at medium-term follow-up.**

Keywords : Anthracycline, cardiotoxicity, chemotherapy, global longitudinal strain abnormalities, speckle-tracking echocardiography

INTRODUCTION

Cancer therapy-related cardiac dysfunction (CTRCD), arising from the concurrent administration of anthracyclines (ACs), was initially identified in the 1960s.[1] Survivors of childhood cancer face an increased risk, eightfold higher, of experiencing severe cardiovascular side effects that can persist throughout their lives.[2] Recently published international guidelines advocate for a risk-based screening of pediatric cancer patients before commencing treatment with high-dose ACs.[3-5]

The conventional approach of assessing left ventricular ejection fraction (LVEF) alone is insufficient for the screening of CTRCD. In contrast, two-dimensional global longitudinal strain (2D-GLS) demonstrates greater sensitivity in the early detection of left ventricle (LV) dysfunction, with a reduction in 2D-GLS preceding a decline in LVEF.[6-9] Monitoring LV dysfunction following anticancer treatments forms the foundation of surveillance techniques, enabling the early identification of cardiotoxicity signs to modify patients' treatment plans and mitigate the risks of further cardiac complications.[10]

The extent of damage caused by cardiotoxic drugs remains imprecisely understood, particularly in the context of children, and has received limited research attention. Furthermore, the longitudinal screening of childhood cancer survivors to compare their baseline echocardiographic data with subsequent prospective changes is challenging due to the scarcity of resources. Many cardio-oncology centers lack access to comprehensive information regarding the appropriate threshold values for their specific population and may struggle to adhere to international guidelines if patients have not undergone baseline echocardiography, which is crucial for recognizing cardiotoxicity. Consequently, we conducted a case–control study to determine and compare LV function characteristics between pediatric cancer survivors who received chemotherapy and healthy children. In addition, we sought to reexamine the safe threshold of cardiotoxic anthracycline dosage in light of the cardiac strain damage detected through speckle-tracking echocardiography (STE).

METHODS

Study population

This observational case–control study recruited a total of 115 children, including 78 pediatric cancer survivors and 37 healthy controls via systematic random sampling between 2018 and 2019. The study received approval from the institute's Ethics Committee. The inclusion criteria consisted of children aged 5–18 years who were cancer survivors (leukemia, lymphoma, Wilms tumor, and small cell tumor) and had completed chemotherapy at least 1 year before the start of the study. In addition, participants needed to have a negative history of congenital heart diseases, cardiac surgery, or invasive cardiac intervention. Exclusion criteria encompassed age over 18 years, a history of heart failure (LVEF <40%), valvular heart disease or valve replacements, implanted heart devices, completion of chemotherapy less than a year ago, poor echocardiographic views, a history of systemic diseases involving the heart (e.g., metabolic diseases), and congenital or acquired cardiac disorders. Children who had discontinued chemotherapy due to a cardiac complication were also excluded from the study.

Patient groups

The 78 patients were divided into two groups based on the cardiotoxicity of the chemotherapeutic agents they had received. The first group included 68 patients who had received cardiotoxic treatments (CR), while the second group consisted of 10 patients who had not received cardiotoxic treatments (cardiotoxic free [CF]). Informed consent was obtained from all participants, and comparisons were made between the patient groups and a sex- and age-matched healthy control group. The healthy control group had no history of cancer or significant medical conditions.

Echocardiographic procedure

A semi-automated STE was performed using the Vivid S6 GE ultrasound machine. Initially, participants underwent screening using conventional 2D and M-mode transthoracic echocardiography to assess LV systolic function, as well as tissue Doppler and mitral inflow Doppler to evaluate diastolic function.

Image acquisition for STE was conducted in standard parasternal and apical windows. Based on standard apical four-chamber, LV two-chamber, and long-axis images, segmental longitudinal strain (LS) and GLS were measured. The term "strain" refers to myocardial deformation represented as a negative percentage change in length, and it was reported in this study using the standard 18-segment model.[11,12] Frame rate between 45 and 75 was selected based on the heart rate of patients and was used to ensure optimal 2D images for strain analysis. Two expert board-certified pediatric cardiologists performed all echocardiographic measurements using the same devices. The cardiologists were blinded to the study group categories. Instead of conducting two separate analyses by two cardiologists and comparing the results for variability, we implemented a rigorous quality control process to ensure accurate results. This involved double-checking the quality of the images and selecting points for STE analysis before the calculation began. Both cardiologists reviewed the chosen points and confirmed the acceptable quality of the 2D images and the selected points for automated functional imaging (AFI) calculation. Any images that did not reach a consensus between the two cardiologists were excluded from the analysis. As there was significant variation in normal GLS, the 95th percentile GLS of the healthy controls was calculated, and strain values more negative than –21.9 (95th percentile) were considered the lower limit of normal GLS. The upper limit of normal global strain in healthy children was determined to be –25.5%. The terms "impaired" (worse than the 95th percentile of the control group) and "normal" (better than the 95th percentile of the control group) were used to avoid ambiguity in interpreting GLS values.

Statistical analysis

All statistical analyses were performed using SPSS v13.0 (IBM Corp, NY, USA) and $P < 0.05$ was considered statistically significant. The strain data from seven segments showed a nonnormal distribution according to the one-sample Kolmogorov–Smirnov test, while the remaining LV segments and GLS exhibited a normal distribution. Mean data for normally distributed variables were analyzed using the ANOVA test and independent *t*-test. Skewed data were analyzed using two nonparametric tests, including the independent-sample median test and the Mann–Whitney *U* test. Categorical data were compared using Chi-square test and Fisher's exact test. The normal GLS cutoff was determined based on the 95th percentile of the healthy controls using weighted average analysis.

RESULTS

A total of 115 subjects participated in the study, with 68 assigned to the CR group, 10 to the CF group, and 37 to the healthy control group. Table 1 summarizes the demographic information and baseline clinical data of the participants. The mean age of the CR, CF, and control groups was 128.7 ± 36.4 months, 83.5 ± 29.9 months, and 104.5 ± 54.0 months, respectively ($P = 0.052$ when comparing CR vs. healthy controls). The mean duration since the completion of chemotherapy in the CR group was 27.9 ± 13.2 months. There were no significant differences in age and sex among the groups, indicating a sufficient match between the CR patients and controls in terms of age and sex. The assessment of systolic function showed that all patients had normal LVEF with a mean of 70.2 ± 15.3 (range: 55%–84%). No cases of reverse E/A ratio or abnormal tissue Doppler indices were observed. In addition, no cases of pulmonary hypertension were found based on tricuspid and pulmonary valve regurgitation gradients [Table 1].

Table 1: Baseline demographic data and clinical features of the study participants

Variables	Mean or count (SD)			*P*
	CR group (*n*=68)	CF group (*n*=10)	Healthy controls (*n*=37)	
Age (months), mean±SD	128.7±36.4	83.5±29.9	104.5±54.0	0.052[¥], 0.002*
Sex				
Male	47	4	24	0.196
Female	21	6	13	
Diagnosis				
Leukemia	40	6	NA	
Lymphoma	11	1	NA	
Wilms	7	1	NA	
SC	10	2	NA	
Cumulative dose of AC	198.88±126.8	NA	NA	
LVEF % (mean±SD)	70.25±5.3	70.4±5.4	72.05±3.2	0.753
Drug-free time (months), mean±SD	27.91±13.2	26.2±22.7	NA	
Pro-BNP level (pg/mL)	67.45±57.7	NA	NA	
GLS	–21.39±2.99	–22.03±1.64	–24.04±1.34	0.001[¥], 0.013[$]

*CR versus CF, [¥]CR versus control, [$]CF versus control. CR: Cardiotoxic-receiving patients, CF: Cardiotoxic-free patients, SC: Small cell tumor, LVEF: left ventricular ejection fraction, GLS: Global longitudinal strain, SD: Standard deviation, NA: Not available, AC: Anthracycline, Pro-BNP: Pro–B-type Natriuretic Peptide

Table 2: Comparison of the mean longitudinal strain of segments with normally distributed longitudinal strain across the study population (ANOVA test)

Segments	Mean LS for normally distributed segments			*P*
	CR (*n*=68)	CF (*n*=10)	Healthy controls (*n*=37)	
Basal anterolateral	−20.57±6.36	−22.20±6.35	−24.05±3.15	0.010*
Basal inferolateral	−19.59±5.85	−21.20±7.08	−23.68±2.49	0.001*
Basal inferior	−19.43±5.30	−16.50±5.93	−23.38±1.73	<0.001* (0.015$)
Middle anteroseptal	−21.25±2.86	−21.90±3.75	−23.27±2.02	0.002*
Middle anterior	−22.32±5.25	−24.00±5.79	−24.95±3.16	0.026*
Middle anterolateral	−21.18±6.46	−22.20±5.80	−24.16±2.75	0.032*
Apical anterior	−22.82±6.99	−25.00±6.68	−24.62±3.07	0.255
Apical anterolateral	−22.37±7.37	−24.80±7.23	−24.24±2.57	0.238
Apical inferolateral	−22.54±7.41	−22.60±6.89	−24.92±2.90	0.173
Apical inferior	−22.34±7.04	−25.30±5.10	−24.97±4.14	0.069
Apical inferoseptal	−24.26±5.56	−25.70±5.39	−24.76±3.32	0.660
GLS	−21.39±2.99	−22.03±1.64	−24.04±1.34	0.001* (0.013$)

*Significant *P*<0.05 between CR survivors and normal healthy control group, $Significant *P*<0.05 between CF survivors and normal healthy control groups. LS: Longitudinal strain, CR: Cardiotoxic received, CF: Cardiotoxic free, GLS: Global LS

The analysis of global and regional longitudinal strains

Table 2 presents the mean LS values of the cardiac segments with a normal distribution (11 segments) across the study population. Both the groups of cancer survivors showed significantly decreased levels of mean GLS. Among them, the cancer survivors who had received anthracycline-based cardiotoxic regimens in their chemotherapy exhibited the most significant decrease in GLS, which was statistically significant ($P = 0.001$). When assessing regional LV longitudinal function, more than half of the segments (six segments) showed a significant decline in wall motion in patients treated with ACs compared to the CF group and healthy controls ($P < 0.05$). The inferior basal segment demonstrated the greatest reduction in LS, with LS values of −19.43 ± 5.30 and −16.50 ± 5.93 in the CR and CF groups, respectively. Most patients had preserved apical segmental strains.

Figure 1 illustrates box plots comparing the median strain reported from LV segments with *nonnormal* LS distribution. Among these seven segments, a significant reduction in cardiac deformation was observed in both the groups of cancer survivors. The basal anterior, basal anteroseptal, and basal inferoseptal segments showed the highest degree of strain decrease compared to healthy controls ($P < 0.001$). In addition, the strain difference in the inferior middle segment was also statistically significant ($P = 0.02$).

Overall, in addition to GLS, cancer survivors treated with ACs exhibited a significant reduction in strain function across 10 LV regions compared to the control group, with the basal segments being the most affected area [Table 2 and Figure 1].

Factors affecting global longitudinal strain in patients treated with anthracyclines

In this study, normal GLS values were more negative than −21.9 (e.g. −22, −23, etc.). A subject with GLS worse than −21.92 fell above the normal upper limit. Using a GLS cutoff of −21.9, 43 CR patients demonstrated impaired GLS. According to Table 3, CR patients with impaired GLS had a significantly higher mean age compared to CR patients with normal GLS (136.3 ± 36 months vs. 115.7 ± 33 months; $P = 0.024$). In addition, children with impaired GLS reported a significantly higher cumulative dose of anthracycline ($P = 0.036$). However, there were no significant differences in mean pro-BNP: pro–B-type natriuretic peptide (pro-BNP) levels and drug-free time between the impaired and normal GLS subgroups [Table 3].

Moreover, the analysis of GLS across four major initial cancer diagnoses revealed no significant difference ($P = 0.87$) [Supplementary Table 1], indicating that the type of cancer does not significantly affect GLS values.

Safe anthracycline dosage

The analysis in Table 4 examined patients based on two cutoff values for ACs: the conventional cutoff of 360 mg/m^2 and the mean anthracycline dose of 223 mg/m^2 in the impaired GLS CR group. The cutoff value of 223 mg/m^2 was determined based on the mean anthracycline dose administered to patients in the impaired GLS CR group. The cumulative anthracycline cutoff at 360 mg/m^2 did not yield a significant differentiation between the impaired and normal groups ($P = 0.068$). It was observed that in approximately 74% of impaired GLS cases, the anthracycline dosage was below 360 mg/m^2. However, when the anthracycline threshold was lowered to 223 mg/m^2, there was a greater inclusion of impaired GLS patients and improved identification of patients at risk ($P = 0.016$). In summary, the anthracycline cutoff at 223 mg/m^2 demonstrated a higher detection rate (49% vs. 25%) and fewer missing cases (51% vs. 74%) compared to the 360 mg/m^2 anthracycline cutoff for patients at risk of cardiotoxicity.

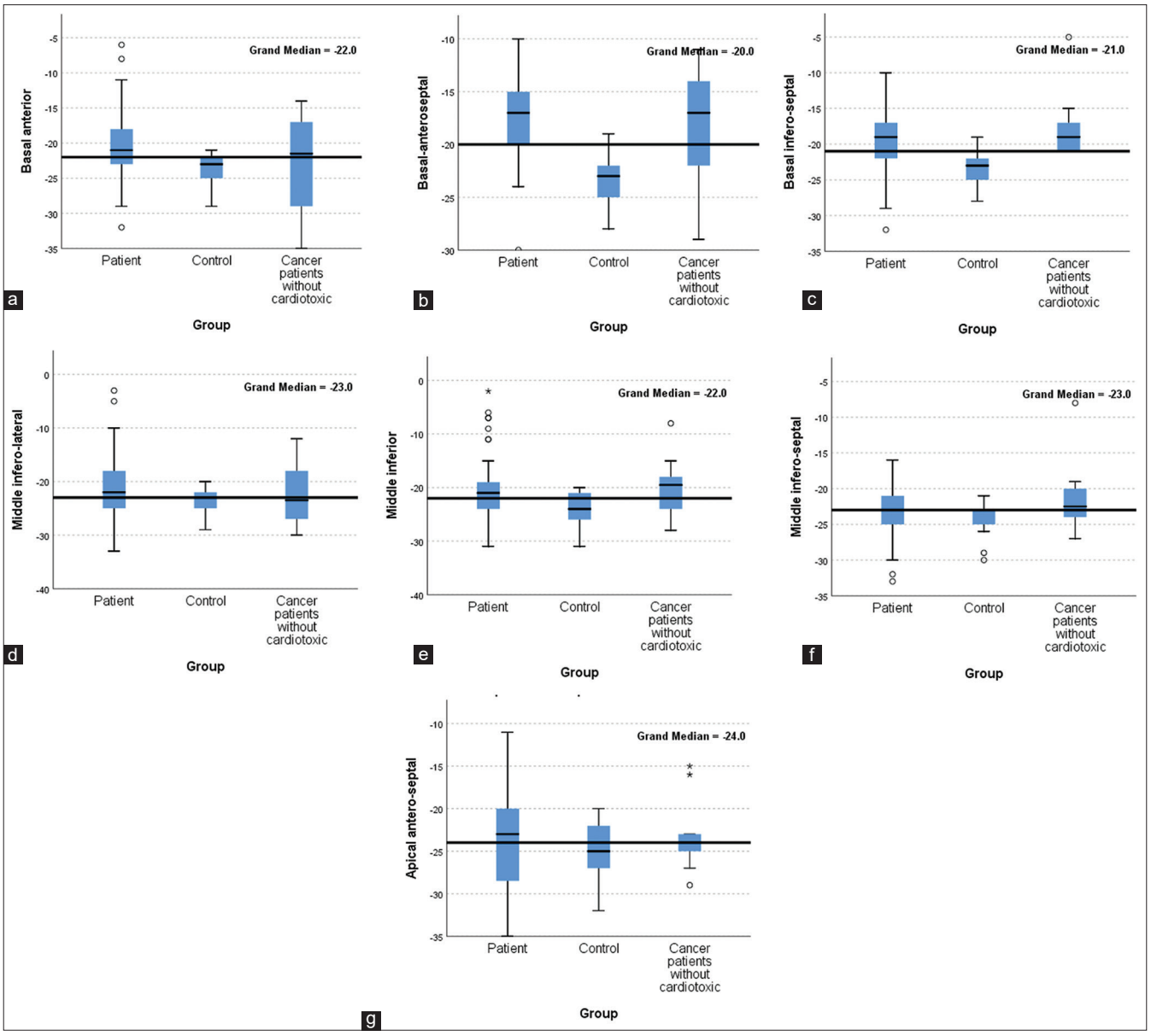

Figure 1: Comparison of the median longitudinal strain (LS) obtained from segments with nonnormal LS distribution between patients who received cardiotoxic treatments, cardiotoxic-free patients, and the control group using the independent-samples median test. Each box displays the median for each segment, as well as the grand median of all segments. (a) Basal anterior segment; *P* = 0.001, (b) Basal anteroseptal segment; *P* < 0.001, (c) Basal inferoseptal segment; *P* < 0.001, (d) Middle inferolateral segment; *P* = 0.210, (e) Middle inferior segment; *P* = 0.029, (f) Middle inferoseptal segment; *P* = 0.078, (g) Apical anteroseptal segment; *P* = 0.647

DISCUSSION

Current cardio-oncology guidelines require the assessment of various echocardiographic parameters to screen for CTRCD. While LVEF has traditionally been used to define CTRCD, GLS has gained importance due to its higher sensitivity in detecting LV cardiac dysfunction.[9,13] However, recent expert consensus in the setting of preserved LVEF with abnormal GLS showed low agreement on cardiology referral and did not recommend medical intervention for childhood cancer survivors.[4]

This study aimed to explore the medium-term sequelae of cardiotoxic drugs on childhood cancer survivors compared to healthy children and cancer survivors treated with noncardiotoxic cancer therapies. It is important to note that this study did not conduct a longitudinal evaluation of CTRCD criteria parameters. Instead, we compared cancer survivors who had completed chemotherapy at least 1 year ago with healthy controls using 2D echocardiographic and STE data to investigate the role of STE and its significance.

Based on six databases, the normal range of LVEF falls between 53% and 73%.[1] In this study, all patients'

routine 2D echocardiographic parameters and pro-BNP levels were within the normal range, and no abnormal ejection fraction was detected during follow-up. This finding is not surprising, as LVEF and biochemical studies focusing on acute conditions often detect cardiac dysfunction only after significant damage has occurred.[5,14] Similarly, Singh *et al*.[15] found no significant difference in patients' LVEF before and after cancer therapy. Despite having preserved LVEF, the cancer survivors in our study exhibited significantly reduced contractile ability in 10 out of 18 segments of their LV walls, particularly among those treated with ACs. Studies in adults have also observed a significant reduction in segmental LS across all segments.[15] This finding highlights the impact of cardiotoxic drugs and supports the notion that subclinical cardiac dysfunction may persist as abnormal LS even 1 year after chemotherapy. It also underscores the limitation of 2D echocardiography in detecting residual damage caused by cardiotoxic chemotherapy regimens. Cardiomyocytes have limited regenerative properties; thus, the damage inflicted by chemotherapeutic agents is mostly irreversible.[16] Moreover, our results demonstrate that cancer treatment has a negative cardiac effect even in patients who have not received cardiotoxic drugs. Among the regions affected, the basal segments were the most involved and exhibited the greatest degree of strain reduction. One might raise the question as to whether this occurrence can be attributed to a potential measurement error. However, the authors have observed that the basal segment generally provides better image quality and yields more accurate results, whereas the apex is a weak point in STE. Consequently, our findings underscore the need for further investigation to definitively establish a link between the susceptibility of the basal segments of the heart and cardiotoxicity. Notably, the pattern of segmental involvement does not correspond to an obvious coronary territory. It appears that damage to different segments, particularly the basal segments, caused by cardiotoxic drugs is not limited to or correlated with coronary territories. Instead, multiple mechanisms such as mitochondrial damage, fibrosis formation, necrosis, or apoptosis of myocardial cells are likely involved.[17] The susceptibility of cardiomyocytes to the adverse effects of ACs is multifaceted and not dependent on a single theory. However, we recommend further studies to evaluate the susceptibility of basal segments. LS, being device dependent, lacks a universal standard of normality, particularly for the pediatric age group. The British guideline for echocardiographic assessment of adult cancer patients receiving anthracycline defines possible subclinical cardiotoxicity as a decline in LVEF of <10 absolute percentage points to a value <50% or a relative reduction in LV-GLS of >15% from baseline.[18] In this study, we established a self-calculated cutoff value of −21.9% based on the 95th percentile of GLS data in normal healthy controls to distinguish individuals with abnormal GLS. Recent studies have also reported −19.3 ± 3.4% to −21.22 ± 1.86% as the reference centiles for LV-GLS in healthy children.[19,20] The variability of strain values may explain the difficulty in making assumptions by comparing patients to a single reference value, highlighting the need for serial values to detect clinically significant changes.

Table 3: The frequency of global longitudinal strain impairment across different variables in cardiotoxic-received survivors

GLS category (cutoff=−21.90)	Number of patients (68 CR patients) (%)	Mean±SD	*P*
Age (month)			
Impaired	43 (63)	136.3±36.1	0.024*
Normal	25 (36)	115.7±33.9	
Total dose of anthracycline (mg/m^2)			
Impaired	43 (63)	223.6±125.6	0.036*
Normal	25 (36)	156.2±125.4	
Pro-BNP level			
Impaired	37 (54)	65.1±60	0.687
Normal	19 (27)	71±52.8	
Drug-free time (month)			
Impaired	43 (63)	28.6±13	0.541
Normal	25 (36)	26.6±13	

*Significant *P* value by *t*-test. 95th percentile of the control group (mean±2SD) is the GLS of−21.9 and more positive GLS labeled as impaired GLS. SD: Standard deviation, CR: Cardiotoxic-received, GLS: Global longitudinal strain, Pro-BNP: Pro–B-type natriuretic peptide

Table 4: Comparison of high-dose versus low-dose anthracycline frequency across patient groups with impaired or normal global longitudinal strain

	GLS category		Total patients (*n*=68), *n* (%)	*P*
	Impaired GLS (worse than−21.9), *n* (%)	Normal GLS, *n* (%)		
Anthracycline dosage (cutoff: 360 mg/m^2)				
<360 mg/m^2	32 (58.2)	23 (41.8)	55 (100)	0.068
≥360 mg/m^2 (high dose)	11 (84.6)	2 (15.4)	13 (100)	
Anthracycline dosage (cutoff: 223 mg/m^2)*				
<223 mg/m^2	22 (52.4)	20 (47.6)	42 (100)	0.016**
≥223 mg/m^2 (high dose)	21 (80.8)	5 (19.2)	26 (100)	
Total	43 (100)	25 (100)	68	

*The cutoff was obtained based on the mean anthracycline dose in patients with impaired GLS, **Significant *P* value by Fisher's exact test. 95th percentile of the control group is the GLS−21.9, and a more positive GLS was labeled impaired GLS. Two cutoff points were analyzed: The traditional cutoff of ≥360 mg/m^2 and the newly calculated cutoff of ≥223 mg/m^2. GLS: Global longitudinal strain

The LS results of our patients treated with ACs demonstrated that not only did their mean GLS (−21.3 ± 2.9%) fall below the cutoff point, but also 63.2% of these patients (43 out of 68) had abnormal GLS. In a study on childhood cancer survivors in the pediatric age group, Wolf *et al.*[21] reported a mean GLS of −18.7% for cancer survivors, which was significantly worse than the GLS of healthy children. Comparatively, the mean GLS of their patients was worse than our GLS results. In addition, we found a significantly decreased GLS in cancer survivors treated without cardiotoxic drugs compared to the controls (P = 0.013). The GLS reduction in cardiotoxic-free survivors may suggest that anthracycline is not the sole factor affecting this parameter and that childhood cancer itself may cause a reduction in strain. However, the cardiotoxic drug-free group included only 10 patients, which is too small to draw reliable interpretations. Although initially not included in the study, the CF group exhibited observable cardiac effects even with noncardiotoxic drugs based on STE data. While the interpretation of these results should be approached with caution, mentioning their data sheds light on the potential mid-to-long-term cardiotoxic effects of any chemotherapy regimen, including those labeled as noncardiotoxic. Further studies with larger cohorts and more effective methods are warranted to validate and expand upon the effects of noncardiotoxic chemotherapy on cardiac function in children. Furthermore, our additional analysis measuring GLS across different initial cancer diagnoses showed that different cancer types were not associated with significant differences in GLS [Supplementary Table 1]. The best approach to monitoring is to compare the longitudinal base in one patient and track the change in GLS over time for the same patient. However, due to the nature of this study, we could not determine the relative change of sequential GLS if it exceeded the known 15% change from the baseline level.[18] To date, no conclusive strain-to-baseline ratio has been suggested for pediatric patients, and even the existing adult cutoff may change in the future.

Further analysis based on the −21.9% cutoff point revealed that older age and a higher dose of anthracycline increased the likelihood of impaired GLS [Tables 3 and 4]. This may result from a more aggressive chemotherapy regimen in older children. Several existing studies have also concluded that age is a major determinant of peak systolic strain values.[19,20,22] Acheampong *et al.*[20] reported that age accounts for approximately 8% of the variation in GLS. Therefore, age-specific reference values are necessary for interpreting 2D-STE parameters.[22] Marcus *et al.*[22] averaged the LS values of six segments (three septal and three lateral wall segments) and determined the lower and upper limits of global longitudinal peak systolic strain for different age categories. They reported the 5th and 95th percentiles of GLS for a normal healthy population aged between 10 and 14 years as −19.2% and −24.4%, respectively.[22] As expected, the cumulative dose of anthracycline was higher in the impaired GLS group than in patients with normal GLS (223.6 ± 125.6 vs. 156.2 ± 125.4; P = 0.036). The 2016 European Society of Cardiology guideline established a cutoff value of 360 mg/m^2 for the cumulative dose of doxorubicin (anthracycline).[5] However, when we analyzed patients based on a cumulative dose of 360 mg/m^2, a significant portion of impaired GLS cases seemingly received a "low" cumulative dose of anthracycline (74%) [Table 4]. A plausible but notable argument is that a cutoff of 360 mg/m^2 for anthracycline cardiotoxicity is much higher than the safe threshold, and as a result, many patients with abnormal GLS could be overlooked. Finding a balance between minimizing cardiotoxicity and maintaining treatment efficacy is crucial. In our study, we proposed a lower anthracycline cutoff at 223 mg/m^2 based on the mean cumulative anthracycline dosage in patients with worse-than-lower-normal GLS values. To address this concern, we suggest an intermediate approach that involves closer monitoring of GLS and early introduction of cardioprotective strategies such as angiotensin-converting enzyme inhibitors or antioxidant drugs in patients who have crossed a cumulative anthracycline dose threshold of 220 mg/m^2 and exhibit evidence of worsening GLS on echocardiography. By resetting the anthracycline threshold to 223 mg/m^2, a significant portion of patients with impaired GLS were categorized as having a new "high dose" of anthracycline (≥223 mg/m^2), and the difference between the high- and low-dose groups was also significant in terms of identifying patients at risk (P = 0.016). This decreasing trend in the anthracycline threshold has been noted in the most updated versions of recent guidelines, which recommend cardiac surveillance every 3 months in patients with a cumulative dose of 250 mg/m^2.[18] Consistent with this study, the American Society of Clinical Oncology in 2017 recommended stratifying high- and low-risk patients using doxorubicin with a cutoff of 250 mg/m^2.[5] The similarity of the results of this pediatric study with the updated guidelines is interesting and underscores the necessity of investigating the definition of safe anthracycline levels in children. Hence, further studies on children are strongly recommended to determine a safer and more effective anthracycline dose and minimize residual cardiotoxicity.

A longitudinal study design is crucial for assessing changes in GLS and recognizing cardiotoxicity, as it allows each patient to act as their own control. However, this study is limited by the lack of baseline echocardiography conducted before cancer therapy. Without baseline data, we had to compare cross-sectional

data among independent populations, which introduces potential confounding factors and limits the ability to draw definitive conclusions. Another limitation is that the study includes a small sample size of the CF group. The limited number of patients in this group raises concerns about statistical power and potential bias. As a result, the findings related to the CF group warrant caution in interpreting the results and should be considered adjunctive data. It is important to acknowledge the limitations of 2D-STE itself. This imaging technique is dependent on image quality, can be affected by distortions due to planar movement, and may have poor tracking of distal-level structures. In addition, STE performance can be compromised when the frame rate is either too high or too low.[23] These limitations should be taken into consideration when interpreting the results of this study. The clinical implications of abnormal STE findings in various pediatric diseases are still not well understood, and therefore, the determination of their clinical impact is beyond the scope of the present study. Further research is needed to elucidate the significance of abnormal STE findings in specific pediatric conditions.

CONCLUSION

Regional and GLSs, as assessed by 2D-STE, prove to be more sensitive parameters compared to other indices of 2D echocardiography. Our findings indicate that higher doses of anthracycline and older age are associated with a higher risk of reduced GLS in the midterm follow-up. Among the different myocardial segments, the basal segments appear to be more susceptible to damage. It is worth noting that the current cutoff of anthracycline cumulative doses ≥360 mg/m^2 may lead to a significant number of cases with decreased GLS being missed, and this threshold demonstrates poor sensitivity in predicting cardiac damage. Based on our findings, lowering the threshold for the introduction of cardioprotective strategies and close monitoring of the heart by STE when anthracycline dosage crossed 223 mg/m^2 may identify more at-risk cases and decrease cardiac sequelae of the cardiotoxic regimen. However, it is important to emphasize that we do not recommend changing the current anthracycline dosage recommended in different guidelines based solely on the findings of this study. The limitations in our study design necessitate further investigation to determine a safer administrable level of anthracycline.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Global longitudinal strain across the different initial diagnoses

Diagnosis	*n*	Mean±SD	*P*
Leukemia	42	−21.5±3.1	0.871
Lymphoma	11	−21.2±1.9	
Wilms	7	−21.5±3.8	
SC	12	−20.7±2.5	
Total	72	−21.3±2.9	

SD: Standard deviation, SC: Small cell tumor