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Pediatric Malignancies: Is the Pre-chemotherapy Left Ventricular Function Normal?

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Abstract

Purpose: We compared the left ventricular (LV) systolic function in children with cancer before initiation of chemotherapy with matched controls using speckle tracking echocardiography.

Methods and Results: In this retrospective study, we analyzed the echocardiograms of 89 cancer patients before the initiation of chemotherapy and 82 age (8.4±5.2 vs. 8.9±3.9 years, p=0.4) and gender matched (64% vs. 67%, males, p= 0.4) healthy controls. Peak systolic LV longitudinal strain (LS) was significantly lower in cancer patients in apical two (-19.8±3.0 vs. -23.5±4.0, p<0.001), three (-19.4±3.2 vs. -23.4±4.0, p<0.001) and four-chamber views (-19.7±3.4 vs. -22.5±3.0, p<0.001) compared to controls, as was global longitudinal strain (GLS) (-19.8±2.7 vs.-23.4±3.2, p<0.001). The pre-chemotherapy group also had a higher E/e' ratio compared to controls at the septal (9.3±3.9 vs. 7.9±1.7, p=0.005) and lateral annulus (7.9±3.3 vs. 5.9±1.4, p<0.001) of the mitral valve. The LV ejection fraction was lower in cancer patients compared to controls (63.5±4.9 vs. 66.8±4.1, p < 0.001), although still within normal limits. There were no differences in LV myocardial performance index (0.30±0.05 vs. 0.30±0.09, p-0.65) and shortening fraction (35.8±5.2 vs. 36.1±6.1, p-0.75) between the two groups. Sub-group analysis showed no difference in LV GLS between patients with solid tumors (n=56) and blood cancers (n=33) (GLS -19.2± 2.9 vs. 19.5±2.4, p value>0.05).

Conclusion: Our data demonstrating abnormalities in LV GLS in pediatric cancer patients even prior to initiation of chemotherapy are novel and perplexing. Further longitudinal follow-up is required to assess the implications of this abnormal LV function in these patients.

Keywords

Malignancy, Pediatric echocardiography, Strain

Introduction

The outcomes of childhood cancer have improved over the last three decades with a significant decrease in mortality from 6.5 to 2 per 100,000 patients (1). However, cardiovascular complications continue to be the major causes of morbidity and late mortality in pediatric cancer survivors (2). The etiology of cardiotoxicity in cancer survivors is multifactorial, with anthracycline exposure, other chemotherapeutic agents, radiation therapy, and comorbidities such as hypertension, diabetes mellitus and coronary artery disease being major risk factors (3) (4). Left ventricle (LV) dysfunction, ranging from asymptomatic dysfunction to symptomatic heart failure, can occur during chemotherapy or many years after the completion of chemotherapy. Echocardiography is the most commonly used non-invasive tool to assess LV function. LV ejection fraction (EF) and shortening fraction (SF) are currently used measures of assessment of systolic function in cancer patients before, during and many years after completion of chemotherapy (5). Both these conventional echocardiographic parameters are limited in that they are dependent upon LV preload and afterload.

Speckle tracking echocardiography (STE) is a relatively newer technique which quantifies global and regional myocardial function by measuring the myocardial deformation in different phases of the cardiac cycle. Studies have shown that STE can detect abnormalities in LV function before changes in conventional echo parameters in various populations including cancer survivors exposed to cardiotoxic chemotherapy (6, 7). STE is reproducible and has been shown to be independent of the preload, patient age, angle of interrogation and ventricular geometry (8).

A few studies in adult patients with cancer have reported the presence of LV dysfunction prior to initiation of chemotherapy. This finding is associated with a higher incidence of symptomatic heart failure and mortality following chemotherapy (6, 9, 10). Assuncao et al compared 76 adult patients with acute leukemia and 76 patients without cancer matched for age, gender, hypertension and the presence of diabetes. Leukemia patients had a lower global longitudinal strain and higher LV mass and volumes compared to matched patients without cancer, even before receiving chemotherapy (11). Adult patients, however, have other risk factors for cardiovascular disease including diabetes mellitus, systemic hypertension, and coronary artery disease, which are very rare in children. The prevalence of LV systolic

dysfunction in children with malignancies before the initiation of chemotherapy and its implications remain unknown. The primary aim of this study was to evaluate LV systolic function by STE in children with malignancies before starting chemotherapy, in comparison to matched controls. Our secondary aims were: (i) to compare LV systolic function (EF and FS) and diastolic function (E/A ratio and Tissue Doppler-derived E/e' ratio) in cancer patients before starting chemotherapy with healthy controls (ii) to compare global function by myocardial performance index (MPI) in cancer patients before starting chemotherapy and healthy controls and (iii) to compare various echocardiographic parameters between groups of patients with solid and hematological malignancies.

Methods:

This was a single center, observational study conducted at the Children's Hospital of Michigan. Children (≤18 years of age) diagnosed with a malignancy who had an echocardiogram performed before the initiation of chemotherapy between January 2014 and October 2016 were included as the "pre-chemotherapy group." Patients with (i) congenital heart defects (except patent foramen ovale), (ii) dilated cardiomyopathy (iii) hemodynamically significant pericardial effusion, (iv) metabolic disorders, and (v) patients who had poor quality images were excluded from the study. We also excluded patients in whom more than 2 segments were not traced properly (n= 4). Healthy normal children who presented to the cardiology clinic for evaluation of musculoskeletal chest pain, innocent murmurs and vasovagal syncope and had normal electrocardiograms and echocardiograms served as controls. The study was approved by the Wayne State University School of Medicine and Detroit Medical Center Institutional Review Board. Chart review was performed and clinical data including, age, gender, and diagnosis of malignancies were recorded. Malignancies were subdivided into (i) solid tumors which included Wilm's tumor, lymphomas, osteosarcomas, and rhabdomyosarcoma and (ii) hematological malignancies such as acute lymphoblastic leukemia and acute myeloid leukemia. Laboratory parameters including complete blood count with differential (including hemoglobin, hematocrit, platelets, and mean corpuscular volume), lactate dehydrogenase (LDH), serum uric acid and serum ferritin were collected and compared between patients with solid and hematological malignancies.

Echocardiographic Data

LV systolic function and LV mass:

The LV ejection fraction (EF) was calculated using the modified Simpson's method (biplane method of disc) from apical 4-chamber (Ch) and 2-Ch views as recommended by the American Society of Echocardiography and European Association of Echocardiography and the formula LVEF= (End diastolic volume-End Systolic volume)/End diastolic volume. (12) The SF was calculated using LV (internal, septal and posterior wall) diameters in end-diastole and end-systole on conventional M mode echocardiography and the standard formula (LV end diastolic dimension – LV end systolic dimension) / LV end diastolic dimension. (13) LV mass was calculated from the M mode measurements using the Devereux formula and was indexed to the subject's height $(cm)^{2.7}$ LV mass$=0.8\{1.04[([LVEDd + IVSd + PWd]^3 − LVEDd^3)]\} + 0.6$ where LVEDd, IVSd and PWd represent LV, interventricular septal and posterior wall thickness in diastole respectively. (14)

LV diastolic function:

For assessment of diastolic function, the ratio of the velocity of early diastolic filling (E) to the velocity of diastolic filling due to atrial contraction (A) was measured from the spectral Doppler of LV inflow (E/A) (Fig. 1A). Tissue Doppler derived velocities of the septal and the lateral annulus of the mitral valve due to early diastolic filling (e'), diastolic filling due to atrial contraction (a') and velocity due to ventricular systole (s') were analyzed as well(Fig. 1C) (13).

LV global function:

Global LV function was assessed using MPI, calculated as the ratio of the sum of the time spent in isovolumetric contraction (ICT) and relaxation phase (IRT) divided by the ejection time(ET) as shown in Fig. 1B (15).

Speckle Tracking Echocardiography:

The echocardiograms were performed using iE 33 (Phillips, Andover, MA) and stored in compressed Digital Imaging and Communication in Medical (DICOM) format for offline analysis. Two-dimensional peak systolic longitudinal strain (LS) was measured using vendor-independent software (2D Cardiac Performance Analysis, Tom Tec Imaging Systems,

Unterschlessheim, Germany). The images were analyzed using the single best loop from the apical 2-Ch, 3-Ch and 4-Ch views. The LV endocardial border was traced semi-automatically in systole. The images were played and tracings were manually adjusted when appropriate. The software measured the LS from 2-Ch, 3-Ch and 4-Ch views and calculated the global peak systolic longitudinal strain (GLS) as an average of these three values (Fig. 2). These analyses were performed by a single reader who was blinded to clinical details (GK).

Statistical Analysis

Continuous variables were expressed as mean (SD), median (IQR) and categorical variables were expressed as number (%). The two groups with and without malignancy were compared using Student t-test, Chi-square test and Mann Whitney-U test as appropriate. Subgroup analyses included a comparison of biochemical markers and echocardiographic parameters in the groups with solid and hematologic malignancies using non-parametric Mann-Whitney U test. Linear regression analysis was performed to identify risk factors associated with abnormal GLS, adjusting for age and gender. The intra-class correlation coefficient (ICC) was calculated to assess the inter-observer variability in a random sample of 20 patients. Statistical analyses were performed using SPSS version 21 (SPSS, Chicago, IL, USA) and significance was defined by p-value <0.05.

Results:

Our cohort consisted of a total of 171 patients, of whom 89 (52%) were cancer patients who had an echocardiogram performed before initiation of chemotherapy, and 82 (48%) were healthy controls. The two groups were comparable in age (mean (SD) 8.4±5.2 vs. 8.9±3.9 years, p=0.4), weight (34.1±24.3 vs. 36.8±19.3 Kg, p=0.43) and gender distribution (64% vs. 67% males, p=0.40) as shown in Table I. Among the 89 patients in the pre-chemotherapy group, 56 (62.9%) had solid tumors and 33 (37.1%) had hematological tumors; the different sub-types of tumors are summarized in Table II.

Pre-chemotherapy group vs. healthy controls
Conventional echocardiography:

The pediatric cancer patients had a lower LV EF compared to the matched healthy controls (63.5±4.9 vs. 66.8±4.1, p < 0.001), although still within normal limits. The SF (35.8±5.2 vs. 36.1±6.1, p=0.75), LV mass indexed to $Ht^{2.7}$ (36.9±19.2 vs. 32.5±9.1, p=0.06) and MPI, a marker of global LV function (0.30±0.05 vs. 0.30±0.09, p=0.65) were not significantly different between groups. The pre-chemotherapy group of patients had a smaller LV internal diameter in diastole (3.9 ± 0.8 vs. 4.15 ± 0.7, p=0.02), higher E/e' ratio at the septal (9.3±3.9 vs. 7.9±1.7, p=0.005) and lateral annulus (7.9±3.3 vs. 5.9±1.4, p<0.001) of the mitral valve and lower E/A ratio (1.6±0.48 vs. 2.3±0.72, p<0.001), compared to healthy controls (Table III).

Speckle tracking echocardiography: The LS was significantly lower in the pre-chemotherapy group compared to healthy controls in the 2-Ch (-19.8±3.0 vs. -23.5±4.0, p<0.001), 3-Ch (-19.4±3.2 vs. -23.4±4.0, p<0.001) and 4-Ch views (-19.7±3.4 vs. -22.5±3.0, p<0.001) as shown in Table III and Fig. 3. Also, GLS was significantly lower in the pre-chemotherapy group compared to the healthy controls (-19.8±2.9 vs.-23.4±3.2, p<0.001). A total of 26 (29%) cancer patients had a GLS lower than the 5th percentile (-18.75) of healthy controls. On regression analysis, we found that a diagnosis of cancer was independently associated with abnormalities in GLS, after adjusting for age and gender (Table IV).

Inter-observer Variability:

The Intra-class Correlation Coefficient (ICC) for LS was 0.94 (95% confidence interval 0.86-0.98, f value 17.16, p <0.001) indicating minimal inter-observer variability.

Solid vs. Hematological Malignancies

There were no differences in age, weight, height, heart rate and blood pressure between patients with solid (n=56) and hematological malignancies (n=33) (Table V). Patients with hematological tumors had a higher white count, were more anemic, and had significantly higher LDH (p=0.003), uric acid (p<0.001) and ferritin (p<0.001) compared to those with solid tumors (Table VI).

Conventional echocardiography: Spectral and tissue Doppler derived measurements of diastolic function such as E/A ratio, E/e' ratio at the septal and the lateral annulus of the mitral valve, and LV systolic function measured by EF and SF were not significantly different among patients

with solid and hematological tumors. Even though MPI was statistically different between the two subgroups, it was in the normal range for both groups (Table V).

Speckle tracking echocardiography

LV LS measured from 2-Ch, 3-Ch and 4-Ch views and GLS were not different between these groups (Table V).

Discussion:

The present study demonstrates that children with cancers have abnormal LV systolic function, reflected by decrease in peak systolic longitudinal strain (LS) in different planes (2-Ch, 3-Ch and 4-Ch apical views) as well as a decrease in global longitudinal strain (GLS) prior to exposure to chemotherapy when compared to matched healthy controls. The diagnosis of cancer was independently associated with abnormalities in GLS, after adjusting for the patient's age and gender. Interestingly all the patients had normal conventional parameters such as SF and MPI. Our findings are similar to recently published results in adults (median age: 56 years) by Assuncao et al of lower GLS (-19.3±2.7 vs. 20.9± 1.9, p<0.001) but similar LV EF (62± 6 vs. 62± 5, p=0.34) in the group with acute leukemia compared to matched patients without cancer (11).

In adults with cancers, a baseline abnormal strain prior to initiating chemotherapy has been shown to be associated with adverse cardiovascular risk following chemotherapy (9, 16). Ali et al followed 450 adult leukemia patients for a median duration of 159 days (range 13-2891 days) after the start of chemotherapy and found that 28 (6 %) patients had cardiac events (defined as death or symptomatic heart failure with a decrease in EF (58 ±10 vs. 62±7, p=0.005)). Patients with cardiac events had significantly lower pre-chemotherapy GLS (-15±2.8% vs. -19.7±2.7, p<0.001). Interestingly, absolute GLS <-17.5% was associated with a six-fold increase in cardiac events (9). Among 2,234 adult patients with breast and hematological cancers, 158 (7%) had LVEF of 50-59% before initiation of chemotherapy (16). Over a median duration of 659 days, 12 (7.6%) patients in this group developed major adverse cardiac events (heart failure or death) at a median duration of 173 days. Baseline GLS was significantly lower (-16±2.5 vs. -17.7±2.6, p=0.015) compared to patients without events and independently predicted a major adverse cardiovascular event defined as New York Heart Association class III, IV

congestive heart failure or cardiac death (p=0.0065) (16). In a prospective study of 86 adults with various malignancies receiving anthracyclines (median age 48, range 30-63.5 years), 6 patients developed a decrease in LV EF by more than 10% to below 53% one year after completing chemotherapy. GLS measured before initiation of chemotherapy was significantly lower (-19.1 vs. -21.2, p=0.042) in the group that developed anthracycline-induced cardiotoxicity compared to the group that did not (17). Abnormal LV systolic function, defined by LVEF less than 55%, was noted in 12 of 88 (13%) patients with breast cancer and leukemia even before the initiation of chemotherapy. These patients had higher mortality and comprised 40% (4 out of 10 total deaths) of the mortality after chemotherapy compared to patients with normal LV function before chemotherapy (18).

Changes in the LV GLS from baseline have been noted in early phases of chemotherapy and also have been shown to be associated with subsequent LV dysfunction during follow up. Asymptomatic patients (n=19) who received anthracycline (mean dose, 296 ± 103 mg/m^2) therapy showed a significant decrease in LV GLS at 4 (change 8.7% $\pm$0.2%, p=0.033) and 8 months (change 9.2 $\pm$ 0.3%, p=0.015) from their baseline value (-19.9$\pm$2.1) and compared to age and gender matched controls (20.5 $\pm$ 1.5%, p=0.011). LV EF decreased significantly at 8 months (4.3$\pm$ 0.1%, p=0.044) and correlated with the segmental changes in the mid and apical LV longitudinal peak systolic strain (7). Among 43 breast cancer patients, 8 developed cardiotoxicity at 6 months following the start of chemotherapy, defined as more than 5% decrease in LV EF to <55% in symptomatic heart failure or more than 10% decrease in asymptomatic patients. A decrease in longitudinal (-20.5$\pm$2.2 to -19.3$\pm$2.4, p=0.01) and radial (55$\pm$12 to 52$\pm$12, p=0.02) strain, from baseline to 3 months independently predicted cardiotoxicity at 6 months (6).

STE is becoming increasingly popular in the assessment of subclinical LV dysfunction. Abnormalities in strain are reported to occur even before changes in conventional echo parameters. A meta-analysis of one retrospective and 15 prospective studies involving 5,721 patients with heart failure, myocardial infarction, valvular heart diseases, has shown that decrease in global longitudinal strain is independently associated with mortality and has superior prognostic value to LV EF (19). STE is accurate and validated as a measure of myocardial strain (8, 20). The American Society of echocardiography and European Association of Cardiovascular

imaging recommend serial measurements of global longitudinal strain, ideally beginning from prior to initiation of chemotherapy. The global longitudinal strain is an ideal deformation parameter in the early detection of subclinical LV dysfunction, defined as > 15% decrease from the baseline value (21).

In the current study, we found evidence of a difference in diastolic function parameters (E/e' and E/A ratio) in cancer patients and controls. Also, the E/e' ratio was higher in cancer patients at the septal (9.3±3.9 vs. 7.2±1.6) and the lateral annulus (7.9±3.3 vs. 5.8±1.9) of the mitral valve, compared to previously published values in 55 healthy children between 6 and 9 years.(22) Corresponding mean E/A ratios were 1.6±0.48 in our cancer cohort, 2.3±0.72 in the controls, and 1.99 ± 0.51 in the published normative study. However, the clinical significance of these differences in values is uncertain and whether they indicate subtle diastolic dysfunction cannot be established.

Diastolic dysfunction in adult cancer patients exposed to chemotherapy has been reported previously (23). A pediatric study reported normal diastolic function, as assessed by E/A ratio of 2.1± 4.3, septal E/E' ratio of 7.2± 2 and lateral E/E' ratio of 5.5±1.2, in 63 cancer patients aged 13.7±4.5 years, 5 years from completion of anthracycline chemotherapy with a median cumulative dose of 165 (range 45 to 520) mg/m^2 (24) . In contrast, an increase in MPI with increasing doses of anthracycline exposure from 200 to 300 mg/m^2 dose has been demonstrated (15). However, data on diastolic function or global myocardial performance in pediatric cancer patients before initiating chemotherapy is lacking. In our study, MPI was similar in cancer patients and healthy controls.

Effect of Hematological cancer vs. Solid Cancers

In our study, there were no significant differences in GLS in patients with leukemia and solid tumors. This is in contrast to the reported higher abnormalities in adults with leukemia, compared to solid tumors. In a subgroup analysis, 28 women with leukemia showed significantly lower GLS (-19.4±3 % vs. -21.2±2.2%), compared to 28 women with breast cancer and (-21.5±2.1%) non-cancer patients, with no differences in LV volumes and mass (11). Ali et al reported a higher incidence of symptomatic heart failure and cardiac death in adults with acute

leukemia (10 of 80, 13%) compared to lymphoma (18 of 370, 5%) following anthracycline treatment.

Plausible etiology for pre-chemotherapy LV dysfunction:

Several factors may explain the abnormalities in LV function before the initiation of chemotherapy. Inflammatory mediators have been postulated to play a role in LV remodeling. In animal models, changes in the expression of TNF and total matrix metalloproteinase inhibitor activities have been associated with LV dilation or remodeling (25). Alternatively, infiltration of the myocardium by circulating cancer cells could cause cardiac dysfunction. In an autopsy study of 420 hearts with leukemia, leukemic infiltrates and hemorrhage were observed in 69%. LV was the second most common location of leukemic infiltrates (36%) after pericardium (39%) (26).

In this novel study of LV function in pediatric cancer patients before initiation of chemotherapy, abnormal LV systolic deformation, as evidenced by changes in strain parameters, was detected even though conventional echocardiographic systolic parameters were mostly within the normal range. We also demonstrated alteration in diastolic function as measured by the E/e' ratio in this group. The pre-chemotherapy global longitudinal strain may serve as an important risk stratification tool in identifying cancer patients who are at risk for subsequent chemotherapy-related cardiovascular toxicity. These patients may need closer monitoring and may benefit from prompt intervention or prophylactic treatment.

Limitations:

The present study is limited by its retrospective nature and single center data. Even though this is retrospective data, we had sufficient quality echocardiographic images to measure the longitudinal strain in different planes from apical 2-Ch, 3-Ch and 4-Ch images as well as global longitudinal strain. In our center, all cancer patients undergo echocardiographic evaluation before starting anthracycline-based chemotherapy. However, cancer patients not receiving anthracycline chemotherapy may have been missed. Data on markers of inflammation (cytokines, C reactive protein and erythrocyte sedimentation rate), cardiac biomarkers (N-terminal pro-Brain Natriuretic peptide, cardiac troponins and creatine kinase) were not available in cancer patients before initiation of chemotherapy. Our study was designed to evaluate the

presence of abnormal GLS in the pre-chemotherapy setting; therefore longitudinal follow up to assess the prognostic implications of our findings was not performed.

Conclusion:

Our study concludes that abnormal LV systolic global longitudinal strain is present in a significant number of children with cancer prior to exposure to chemotherapeutic agents. A larger multicenter longitudinal follow-up study is needed to validate our results and assess the utility of pre-chemotherapy strain in identifying those at risk of post chemotherapy-cardiotoxicity. Further investigation into the etiology and prevention of abnormal GLS even before exposure to chemotherapy in cancer patients is needed.

Compliance with Ethical Standards:

Conflict of interest: The authors declare that they have no conflict of interest.

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors. The study was approved by the Wayne State University School of Medicine and Detroit Medical Center Institutional Review Board.

Informed consent: Not applicable. Waiver of consent obtained through Wayne State University School of Medicine and Detroit Medical Center Institutional Review Board.

Author contributions

Akam-Venkata**:** Study design, obtaining IRB approval, data collection, statistical interpretation, drafting the manuscript, revision and submission of the manuscript

Kadiu: Strain analysis of all the patients and controls, blinded to the clinical information

Galas: Concept/design, critical revision of the article

Aggarwal: Concept/design, statistics, critical revision of the article, approval of the article

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Table I: Demographic data in pre-chemotherapy group and healthy controls

Mean (SD), n%	Pre-chemotherapy group (n=89)	Healthy controls (n=82)	p valve
Age (years)	8.4 (5.2)	8.9 (3.9)	0.4
Gender (male)	57 (64%)	55 (67%)	0.4
Weight (kg)	34.1 (24.3)	36.8 (19.3)	0.43
Height (cms)	125 (33)	134.3 (27.1)	0.046*
Systolic BP (mmHg)	108 (15)	107 (13)	0.8
Diastolic BP (mmHg)	64 (12)	61 (8)	0.08

*p<0.05**Table II: Distribution of different types of solid and hematological tumors**

Type of Malignancy	n (%)
Solid tumors (n=56, 62.9%)	

Neuroblastoma	9 (10.1%)
Osteosarcoma	8 (9.0%)
Hodgkin's lymphoma	8 (9.0%)
Wilm's tumor	7 (7.9%)
T- cell Lymphoblastic Lymphoma	6 (6.7%)
Rhabdomyosarcoma	4 (4.5%)
Ewing sarcoma	3 (3.4%)
Burkitt lymphoma	3 (3.4%)
Embryonal Sarcoma	2 (2.2%)
Hepatoblastoma	2 (2.2%)
Ependymoma	1 (1.1%)
Small round cell tumor	1 (1.1%)
Hepatocellular carcinoma	1 (1.1%)
Basal Cell Carcinoma	1 (1.1%)
Hematological tumors (n=33, 37.1%)	
B precursor- Acute Lymphoblastic leukemia	22 (24.7%)
T precursor- Acute Lymphoblastic leukemia	4 (4.5%)
Acute myeloblastic leukemia	6 (6.7%)
Acute biphenotypic (lymphoid + myeloid) leukemia	1 (1.1%)

Table III: Echocardiographic parameters in pre-chemotherapy group and healthy controls

Mean (SD)	Pre-chemotherapy group (n=89)	Controls (n=82)	p value
LV 2-Ch LS	-19.8 (3.0)	-23.5 (4.0)	<0.001*
LV 3-Ch LS	-19.4 (3.2)	-23.4 (4.0)	<0.001*
LV 4-Ch LS	-19.7 (3.4)	-22.5 (3.0)	<0.001*
LV GLS	-19.8 (2.7)	-23.4 (3.2)	<0.001*
LV EF %	63.5 (4.9)	66.8 (4.1)	< 0.001*
LV FS %	35.8 (5.2)	37.7 (11.2)	0.15

LVIDD (cm)	3.9 (0.8)	4.15 (0.7)	0.02*
LV mass indexed to Ht$^{2.7}$	36.9 (19.2)	32.5 (9.1)	0.06
E/A ratio	1.6 (0.48)	2.3 (0.72)	0.001*
E/e' septal	9.3 (3.9)	7.9 (1.7)	0.005*
E/e' lateral	7.9 (3.3)	5.9 (1.4)	<0.001*
MPI	0.30 (0.05)	0.30 (0.09)	0.65

*p<0.05

LV-left ventricle, Ch-chamber, LS- peak systolic longitudinal strain, GLS-average peak systolic longitudinal strain, EF- ejection fraction, FS- fractional shortening, LVIDD- left ventricular internal diameter in diastole, E- Velocity of early diastolic filling of the left ventricle, A- Velocity of diastolic filling of the left ventricle due to atrial contraction, e'- Tissue Doppler-derived velocity of the septal and the lateral annulus of the mitral valve due to early diastolic filling, MPI- Myocardial performance index.

Table IV: Regression analysis showing association between diagnosis of cancer and global longitudinal strain

Independent Variable	β coefficient	95% confidence interval	p value
Global longitudinal strain	0.42	1.86, 3.98	<0.001
Age	0.12	-0.02, 0.21	0.11
Gender	0.03	-0.91, 1.32	0.73

Table V: Comparison of echocardiographic parameters in Solid and hematological tumors

Mean (SD)	Solid tumors (n=56)	Hematological tumors (n=33)	p value
Age (year)	8.8 (5.3)	7.7 (5.3)	0.36
Height (cm)	127 (32.5)	121.7 (34.1)	0.47
Weight (kg)	33.8 (21.8)	34.5 (29.3)	0.91
LV 2-Ch LS	-18.6 (3.2)	-19.7 (3)	0.3
LV 3-Ch LS	-19.2 (4)	-19.1 (2.9)	0.9
LV 4-Ch LS	-19.2 (3.6)	-18.7 (4)	0.6

LV GLS	-19.2 (2.9)	-19.5 (2.4)	0.7
MPI	0.31 (0.05)	0.28 (0.05)	0.04*
E/A ratio	1.69 (0.5)	1.63 (0.4)	0.5
E/e' Septal	9.6 (4.7)	8.9 (1.8)	0.4
E/e' lateral	7.9 (3.9)	7.7 (1.7)	0.7
Ejection Fraction	63.6 (5.1)	63.2 (4.5)	0.75
Shortening Fraction	36.5 (5)	34.8 (4.5)	0.1

*p<0.05

LV-left ventricle, Ch-chamber, LS- peak systolic longitudinal strain, GLS-average peak systolic longitudinal strain, E- Velocity of early diastolic filling of the left ventricle, A- Velocity of diastolic filling of the left ventricle due to atrial contraction, e'- Tissue Doppler-derived velocity of the septal and the lateral annulus of the mitral valve due to early diastolic filling, MPI-Myocardial performance index.

Table VI: Biochemical and Hematological parameters in Solid and Hematological tumors

Mean (SD)	Solid tumors (n=56)	Hematological tumors (n=33)	p value
Hemoglobin (g/dL)	11.4 (3.6)	8.4 (3.3)	<0.001*
WBC (x10^3 cells/mm^3)	10.2 (9.4)	57.2 (82.8)	<0.001*
Platelets (x10^3 cells/mm^3)	304 (138)	89 (110)	<0.001*
Retic count (%)	1.8 (1.2)	0.98 (0.7)	<0.001*
Ferritin (ng/mL)	51.5 (31)	401(309)	<0.001*
LDH (units/L)	548 (482)	1344 (1670)	0.002*
Uric acid (mg/dL)	3.7 (1.4)	5.9 (3)	<0.001*

*p<0.05

LDH: Lactate dehydrogenase, WBC- White blood cell count, Retic- Reticulocyte, ng-nanogram, mL-milliliter, L-liter.
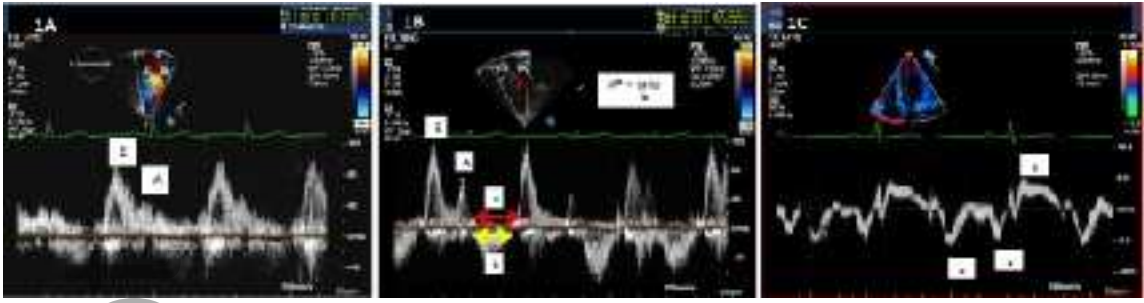

Figure Legends:

Fig.1 Spectral (1A and 1B) and Tissue Doppler (1C) Imaging of the mitral valve

Fig.2 Longitudinal strain with bull's eye plot measured from 4-chamber view
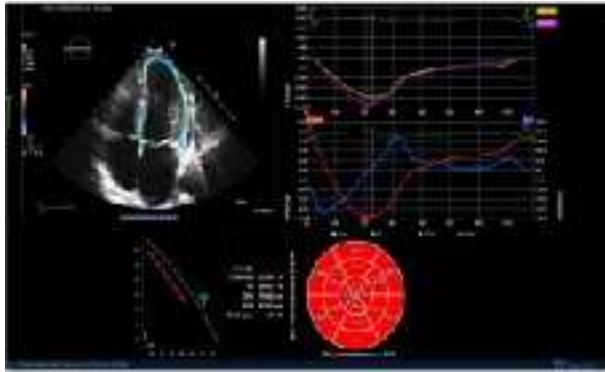
Fig.3 Box and Whisker plot comparing global longitudinal strain (3a), longitudinal strain in 2-chamber (3b), 3-chamber (3c) and 4-chamber views (3d) between healthy controls and cancer patients
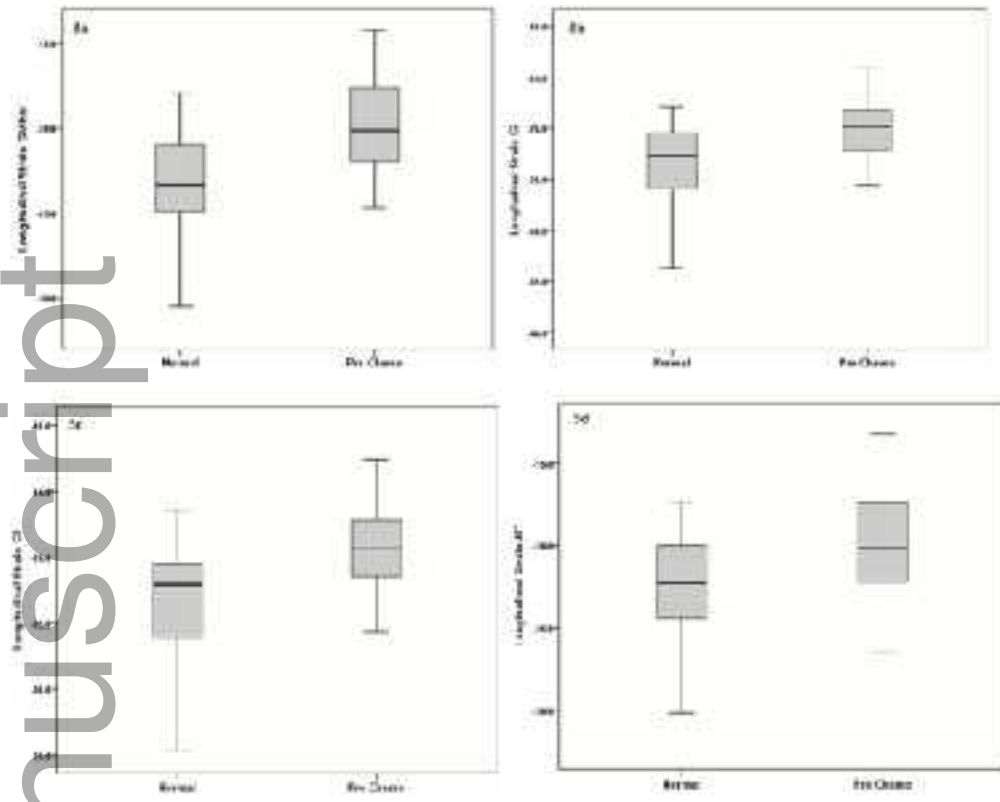
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