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Value of Left Ventricular Global Longitudinal Strain Assessed by Two-Dimensional Strain Imaging in Early Detection of Anthracycline Mediated Cardiotoxicity

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Abstract:

The goal of this study is to investigate whether alterations of myocardial global longitudinal strain and high-sensitive cardiac troponin could be detected early in patients receiving anthracycline chemotherapy & if it could predict future cardiac dysfunction. **Methods:** Thirty patients with cancer treated with Adriamycin were studied. Blood collection for measurement of high sensitive troponin and echocardiography were performed at baseline, three months & six months of chemotherapy. Global longitudinal strain (GLS), were calculated using speckle tracking echocardiography. Left ventricular ejection fraction was measured by M-mode echocardiography. **Results:** LVEF although reduced after treatment, remained within the normal range (65±3.6% at base line vs. 63±2.7% at three months vs. 62±2.6% at six months of treatment, p = 0.002).LVIDd & LVIDs was highest after 6 months of chemotherapy. GLS was significantly reduced after treatment (-20.56±1.9% vs. -18.2±2.2% at three months vs -17.1±2.1 at six months of treatment, p<0.001). Subclinical LV dysfunction (>15% reduction in GLS compared to before therapy) occurred in 43%. Serum hs-cTnI levels increased significantly after 3 months of treatment with anthracycline (0.0088± 0.012, vs. 0.345 ± 0.5 after three months of treatment, p = 0.001).There was positive correlation between EF & GLS while a negative correlation was found between hscTnI & GLS. Hs-cTnI assays was significantly increased in patients with Drop in GLS as compared with patients with no Drop in GLS after 3 months follow-up. No statistically significant difference between drop in GLS or hs-cTnI levels and cumulative dose of anthracyclines. No clinical parameters were associated with the drop in GLS or elevation of hs-cTnI levels. **Conclusion:** Measurement of LV GLS by 2D STE during & after anthracycline therapy combined with hs-cTnI

assay may allow an early identification of cardiac damage and therefore provide a way to minimize cardiac related mortality and morbidity while undergoing chemotherapy and afterwards.

Keywords: Anthracycline, cardiotoxicity, global longitudinal strain.

1. Introduction:

Chemotherapy-induced cardiotoxicity remains a significant and unresolved issue when treating cancer patients. Because Cardiotoxic effect is partially dose-dependent, oncologists have begun to decrease the cumulative dose in most protocols; however, this does not prevent cardiac damage, because histologically, myocardial changes can be detected even after exposure to low doses [1].

Cardiotoxicity is defined as a ≥5% reduction in symptomatic patients, or a ≥10% reduction in asymptomatic patients, in the left ventricular ejection fraction (EF)from baseline to a value of <55% [2].

It is now known that anthracyclines are more cardiotoxic than had been understood initially, and this holds true even at sub-maximal cumulative dosages, the cumulative dose of anthracycline is the most important risk factor for the development of cardiotoxicity. The estimated heart failure incidences were 5%, 16%, and 26% for cumulative doses of 400, 500, and 550 mg/m2 doxorubicin, respectively [3].

The most effective treatment for chemotherapy-induced cardiotoxicity is likely prevention. Therefore, efforts in the realm of cardioprotection focuses now on the early detection of left ventricular (LV) impairment, either by noninvasive imaging modalities such as echocardiography or with circulating biomarkers [4].

LV EF is a traditional echocardiographic parameter largely used to monitor myocardial function. However, it was recently suggested that evaluation of LV function based on this single parameter was not sufficient to detect subtle myocardial injury, especially in the case of asymptomatic patients where the history of potential heart damage can be hypothesized [5,6].

The integration of EF with deformation parameters represents a more accurate method for assessing heart function, especially in those cases associated with a low (less than 5%) reduction of EF [7].

Strain represents a dynamic parameter for evaluating the deformation reserve from applied force, like stress, and to detect the elastic properties of the cardiac muscle[8].

In echocardiography, strain analysis is able to provide incremental information for the early clinical detection of myocardial damage in many potential myocardial failures such as asymptomatic cardiotoxicity [9].

In particular, Speckle Tracking (ST) is a non-invasive technique recently proposed as a fundamental method to assess left ventricle (LV) function. Among the many strain-based parameters, Global Longitudinal Strain (GLS) has been demonstrated to be the most direct, validated and reproducible for the correct assessment of the LV function [7]. A reduction in GLS >15% from baseline may suggest risk of cardiotoxicity [10].

Circulating biomarkers, such as troponin and brain-type natriuretic peptide (BNP) are widely studied for use in the monitoring of cardiotoxicity. Troponin is the most widely studied biomarker for the detection of cardiotoxicity; it is recommended that troponin levels are evaluated at baseline and during and after chemotherapy [11].

The early elevation of troponin (i.e., within 72 hours after each cycle) and sustained elevation (i.e., 1 month after treatment) suggest the highest cardiotoxicity event rate [12].

Aim of the work:

The aim of this work is to find out whether early changes in left ventricular function in patients receiving anthracycline chemotherapy can be detected by 2D global longitudinal strain.

2. Patient & Method:

Study design & patient population

This observational cross section study included 30 patient with newly diagnosed cancer for which they received Adriamycin for average period between (3-6) months. All the patients were enrolled from Beni-Suef University Hospital in the period from September 2017 to June 2018. All subjects gave informed consent before study enrollment. The current protocol received local ethics committee approval.

Inclusion Criteria:

In order to be included in our study, patients should have:

- Cancer & scheduled to receive treatment including Anthracyclines
- Normal sinus rhythm
- Excellent echocardiographic image
- Normal left ventricular systolic function.
- Absence of regional wall motion abnormalities

Exclusion Criteria:

- Patients with baseline LVEF<50%
- Patients with abnormal baseline global longitudinal strain
- Patients who had prior treatment with Cardiotoxic drugs.
- Patient with history or plane for radiation therapy.
- Patient with moderate or severe valvular heart disease.

- Patient with coronary vascular disease (Chronic coronary Syndrome or Acute coronary Syndrome).
- Patients with moderate or severe renal or liver failure.
- Patients with prosthetic valves or pacemaker.
- Patients with atrial fibrillation or frequent premature beats.

Method

Following obtaining the written informed consent, all patients were studied before chemotherapy and at 3 and 6 months of treatment, using:

- Recording of demographic data.
- 12-lead electrocardiogram.
- 2D Transthoracic Echocardiography.
- High sensitivity cardiac troponin I assays.

Echocardiographic Acquisition:

Transthoracic echocardiography were performed in the left lateral decubitus position using an ultrasound machine (EPIQ 7, Philips Medical Systems, and Andover, MA). The same ultrasound machine was used to acquire all echocardiograms in each patient.

Left ventricular internal diameter at diastole (LVIDd) and left ventricular internal diameter at systole (LVIDs) were measured in the parasternal long-axis view or parasternal short axis view using M-Mode& Left ventricular ejection fraction (LVEF) were calculated.

The acquisition of images for measurement of LV GLS were performed in the three standard apical 2D views (apical 4-chamber, A4C, apical 2-chamber, A2C, and apical 3-chamber, A3C) & it were ECG gated & involved three beats.

QLAB version 8.1 (Philips Medical System) was used for strain analyses. The automatic tracking analysis was performed in the apical four-chamber, two chamber &apical three chamber views for longitudinal strain.

The LV endocardial border was traced in all apical 2D views. The adequacy of tracking were verified manually and readjusted to achieve optimal tracking.

Peak longitudinal strain (LS) measurements were obtained from the basal, mid-segments of the anterior, inferior, anteroseptal, anterolateral, inferoseptal, and inferolateral walls, apical segments of the anterior, inferior, septal, and lateral walls, and the apex; in total 17 segments.

High sensitivity cardiac troponin I assays:

Blood was collected into EDTA tubes, centrifuged, and the plasma was removed and stored at −80°C.

The cTnI concentrations were measured with highly sensitive cTnI reagents on Beckman Coulter Access immunoassay system, with a lower detection limit of (0.003ng/mL) able to detect any small elevation in cardiac troponin.

Technologists recording the cTnI results were blind to the clinical and echocardiographic data of participants.

Statistical Analysis:

The collected data were coded then entered and analyzed using the SPSS version 25 (Statistical package for social science) for windows 10.

The following tests were used:

- Descriptive analysis of the results
- Cross tabulation and Chi Square test.
- Student t- test.
- Friedman test and Wilcoxon signed rank test with Bonferroni adjustment method.
- The Correlation coefficient (r).
- P: significance value

  P value > 0.05 Not significant

  P value ≤ 0.05 Significant

3. Results:

Our study included thirty patient with different types of solid tumor treated with varying doses of Adriamycin for certain period. We followed the patient for six months from starting treatment with chemotherapy.

I. Baseline demographic features

A total of 30 patients, 25 females & 5 males, ranging in age from 21 to 75 years with mean age (46.31± 13.8) were included in the statistical analysis **(Table 1)**

Table (1) Baseline demographic features; (N=30):

Age; years	
Mean ±SD	46.31 ±13.8
Minimum	21
Maximum	75
Range	54
Sex; N (%)	
Female	25 (83.4)
Male	5 (16.6)

II. Baseline clinical characteristic:

The mean body mass index was (26.55 ±3.2). Three patients had a history of hypertension and two patient had a history of diabetes, which were well controlled on medical therapy. Four patients had a history of smoking or were current smokers **(Table 2).**

Table (2): Baseline clinical characteristic (N=30):

BMI; kg/m^2		
Mean ±SD	26.55 ±3.2	
Minimum	20	
Maximum	34	
Range	14	
DM; N (%)		
No	28 (93.4)	
Yes	2 (6.6)	
HTN; N (%)		
No	27 (90)	
Yes	3 (10)	
Smoking; N (%)		
No	26 (86.6)	
Yes	4 (13.4)	

III. Baseline oncology diagnosis:

Eighteen patients had breast cancer; eleven patients had lymphoma & one patient with lower limb sarcoma **(Table 3)**

Table (3): Distribution of the Studied Cases by Oncology Diagnosis; (N=30):

Diagnosis	N	%
Br. Cancer	18	60
H. Lymph.	5	16.6
NHL	6	20
LL Sarcoma	1	3.4

The Cumulative dose of Adriamycin:

The mean cumulative dose of Adriamycin was (456.89 ± 89.8) mg/m^2 **(Table 4)**.

Table (4): C. Dose

	Descriptive Statistics	
Mean ±SD	456.89 ±89.8	
Minimum	240	
Maximum	630	
Range	390	

Effect of chemotherapy on conventional echocardiographic parameters

As demonstrated in **Table (5)**; **Left Ventricular Internal Diameter at diastole** was greatest after 6 months of chemotherapy but without a statistically significant difference as compared with dimensions before chemotherapy and after 3 months.

Left Ventricular Internal Diameter at systole was greatest after 6 months of chemotherapy with overall significant difference (p-value= 0.002). By applying statistical analysis to identify which pairs of means were statistically different; End Systolic Dimension before chemotherapy was significantly smaller as compared with dimension after 3 months of therapy (p-value= 0.026) and as compared with dimension after 6 months of therapy (p-value= 0.001).

Ejection Fraction was greatest at baseline assessment before chemotherapy with overall significant difference (p-value= 0.002). By applying statistical analysis to identify which pairs of means were statistically different; Ejection Fraction before chemotherapy was significantly higher as compared with Ejection Fraction after 3 months of therapy (p-value= 0.011) and as compared with Ejection Fraction after 6 months of therapy (p-value= 0.001). **Whilst there was a statistically significant reduction in LVEF after anthracycline therapy, no patients developed cardiotoxicity (i.e. reduction in LVEF >10% to <55%)**

Table (5): follow up of Studied Cases by 2D Transthoracic Echocardiography; (N= 30):

	2D Transthoracic Echocardiography			**p-value**
	Before Chemotherapy	**After 3 Months**	**After 6 Months**	
LVIDd (Left Ventricular Internal Diameter at diastole)				
Mean ±SD	4.39 ±0.4	4.50 ±0.4	4.54 ±0.4	0.296
Minimum	3.80	3.70	3.70	
Maximum	4.90	5.20	5.10	
Range	1.10	1.50	1.40	
LVIDs (Left Ventricular Internal Diameter at systole)				
Mean ±SD	2.84 ±0.2	2.98 ±0.3	3.07 ±0.2	**0.002***

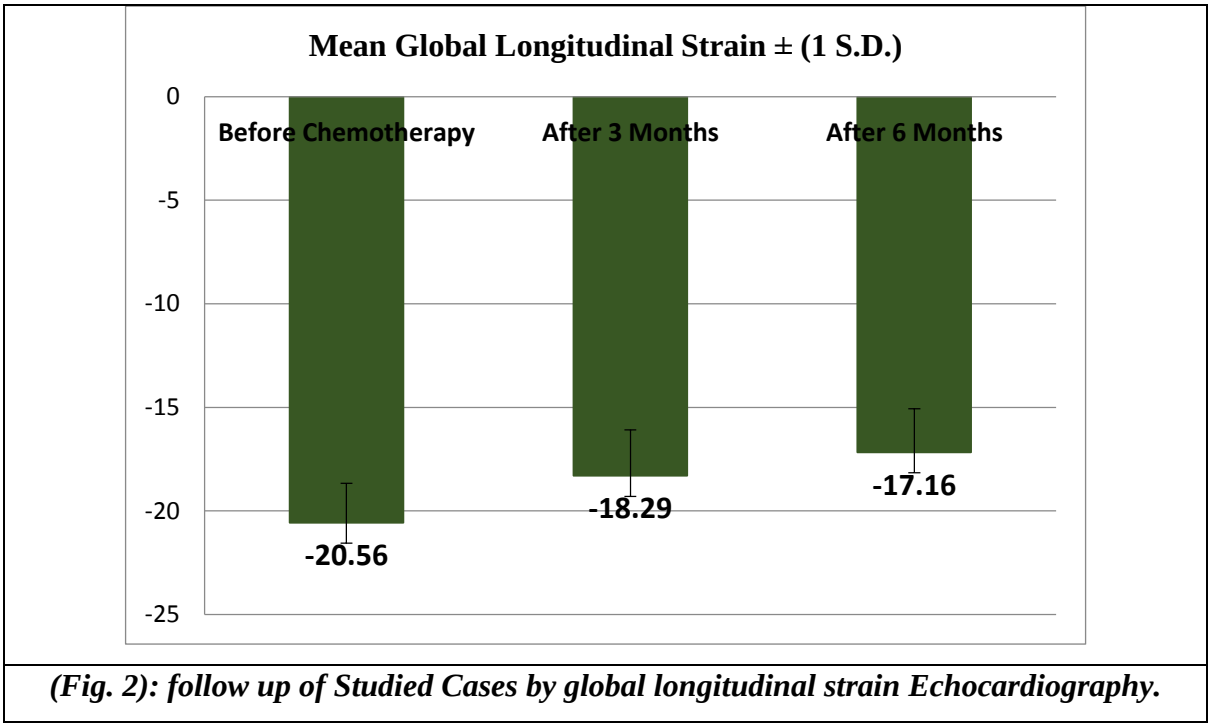
Minimum	2.30	2.50	2.45	
Maximum	3.10	3.70	3.50	
Range	0.80	1.20	1.05	
EF (Ejection Fraction)				
Mean ±SD	65.08 ±3.6	63.03 ±2.7	62.33 ±2.6	**0.002***
Minimum	58.60	57.10	58.80	
Maximum	73.30	67.80	69.80	
Range	14.70	10.70	11.00	

***p-value** ≤0.05 was considered significant by Friedman test*

Wilcoxon signed rank test with Bonferroni adjustment method.

Two-dimensional speckle tracking echocardiography

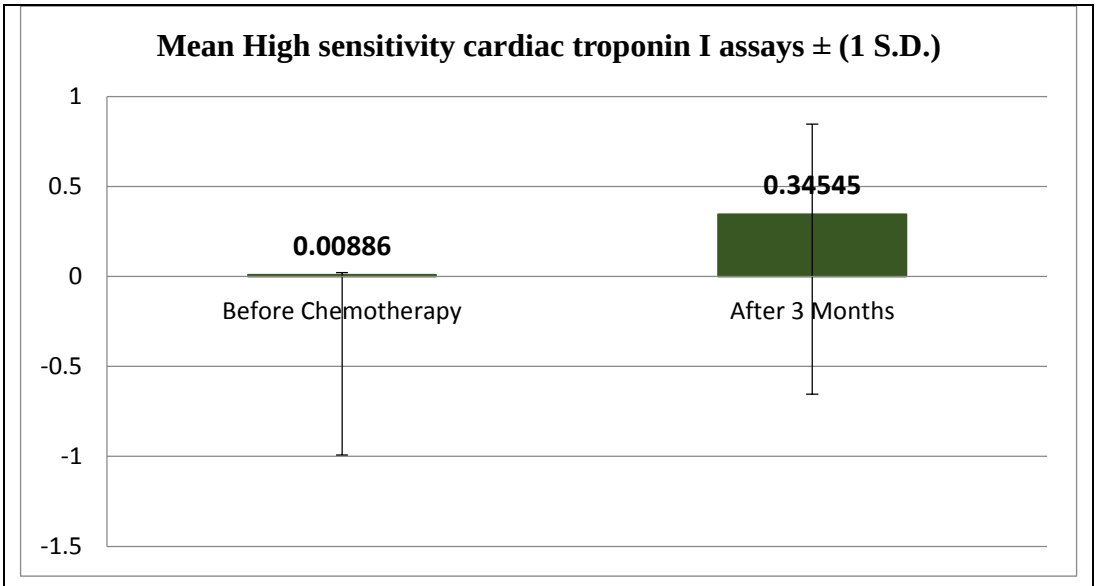
The Global Longitudinal Strain was significantly reduced at three & six months of chemotherapy from (-20.56 ± 1.9%) at the beginning to (-18.29 ± 2.2%) at three months to (-17.1 ± 2.1%) at six months. **(Figure 2)**.



(Fig. 2): follow up of Studied Cases by global longitudinal strain Echocardiography.

High sensitivity cardiac troponin measurements

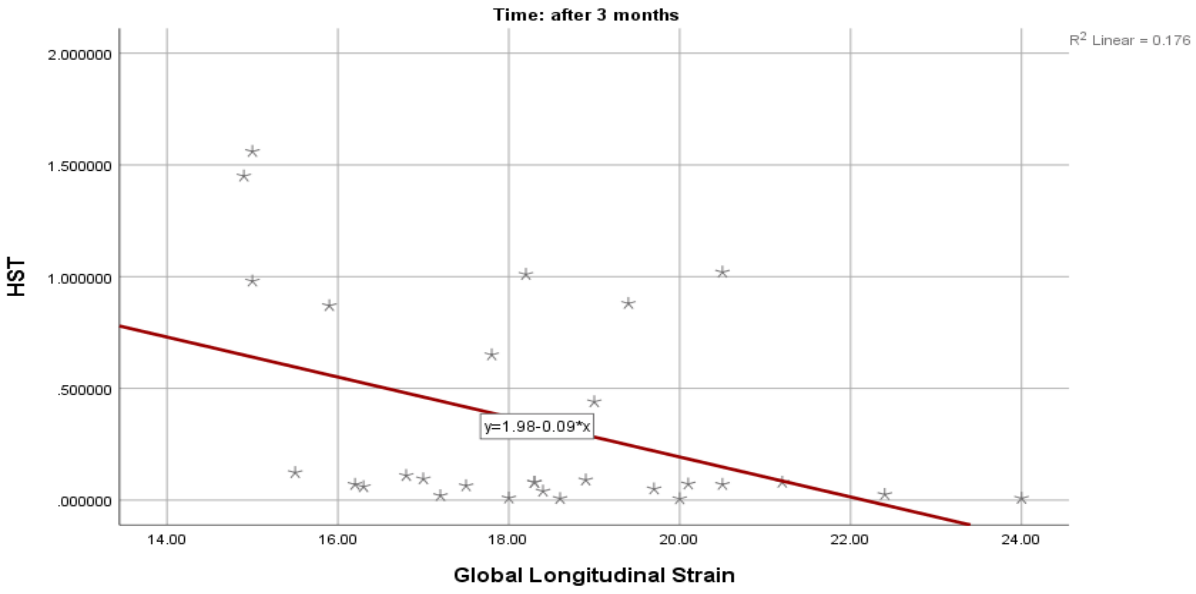
High sensitivity cardiac troponin I assays was significantly increased three months after chemotherapy as compared with baseline assessment before chemotherapy. **(Fig. (3)).**



(Fig. 3): High sensitivity cardiac troponin I assays

Correlation between GLS and High sensitivity cardiac troponin I

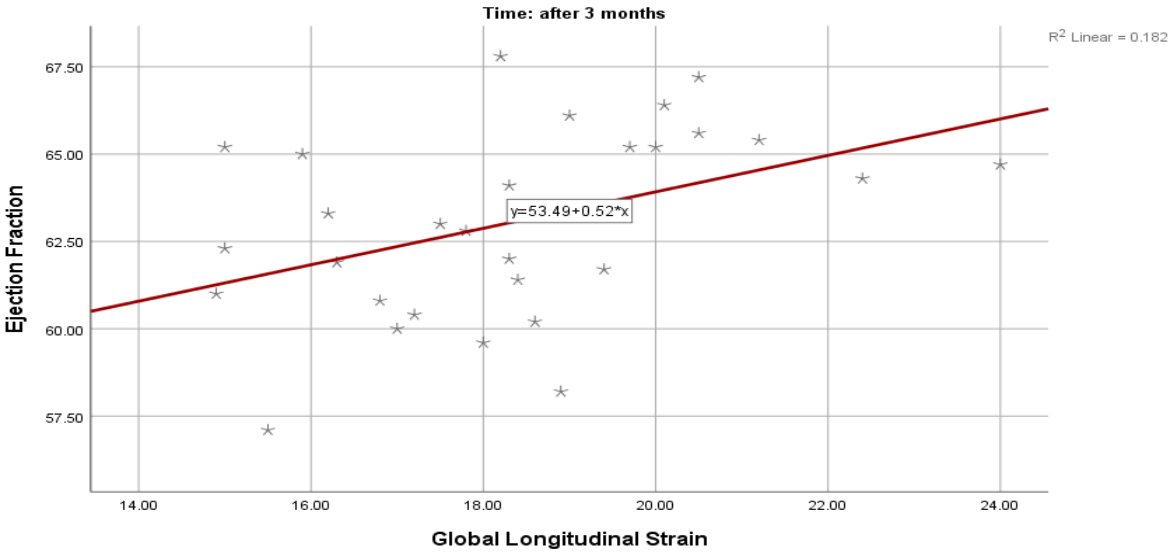
Our results showed that there was negative correlation between Global Longitudinal Strain and HST after 3 months (GLS decrease as HST increase after three months of treatment) (Figure 4).



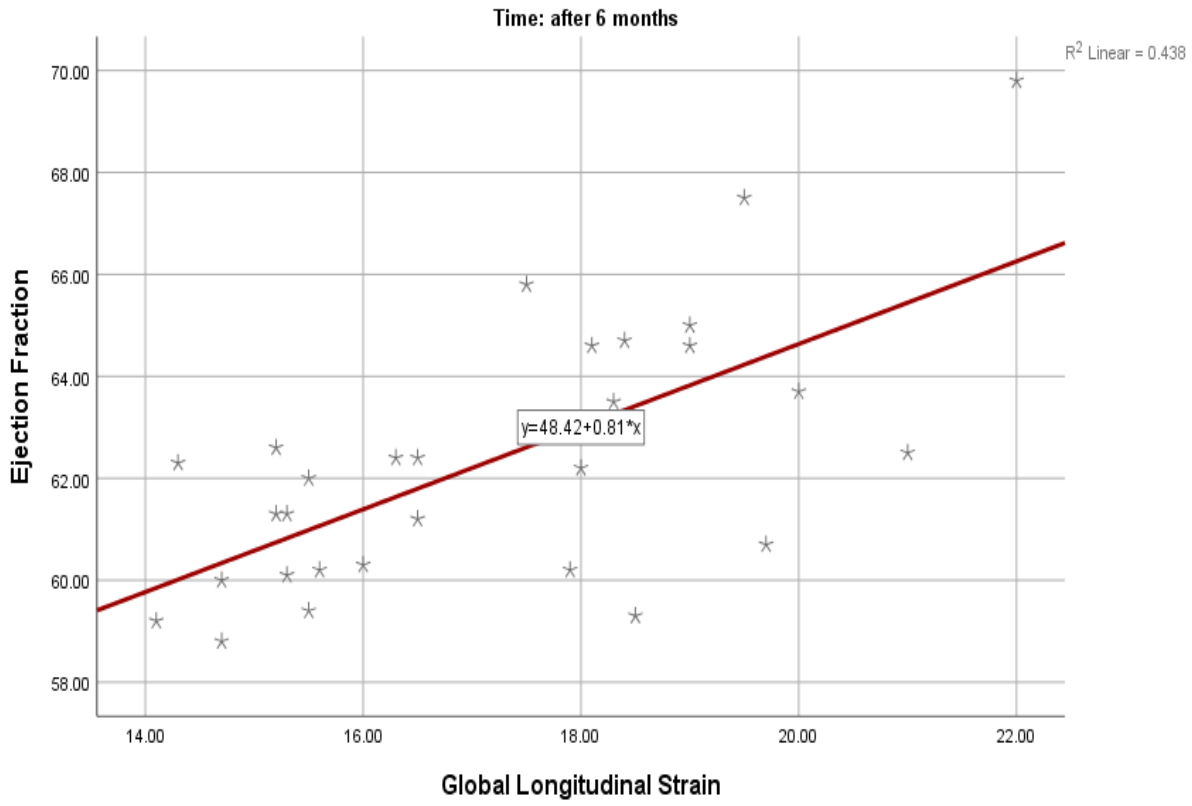
(Fig. 4) There was negative moderate correlation between Global Longitudinal Strain and HST after 3 months; (r= 0.419, p-value= 0.024)

Correlation between Global Longitudinal Strain and EF

There was positive correlation between global longitudinal strain and ejection fraction at three & six months of treatment with adriamycin (both showed significant decrease over the period of follow up).



(Fig. 5) There was positive moderate correlation between Global Longitudinal Strain and EF after 3 months; (r= 0.427, p-value= 0.021)



(Fig. 6) There was positive strong correlation between Global Longitudinal Strain and EF after 6 months; (r= 0.761, p-value< 0.001)

Sub clinical left ventricular dysfunction:

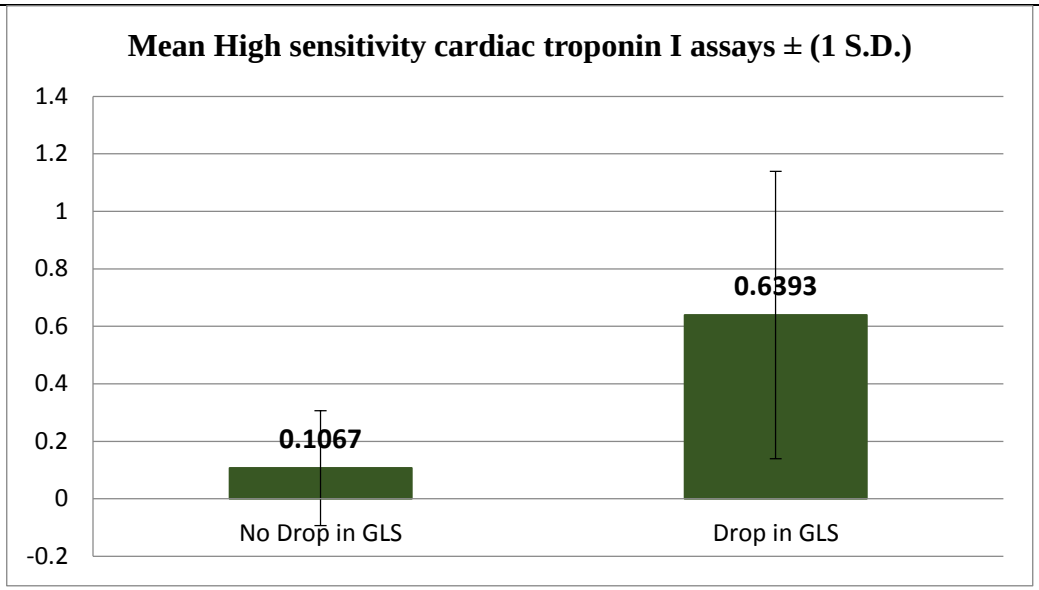
Subclinical LV dysfunction, defined as >15% reduction in global longitudinal strain, occurred in 13 patients at 6 months follow up without clinical symptoms of heart failure or reduction in LVEF >10% to <55%.

Table (5): Number of patients who developed drop in GLS > 15 %

Patients developed drop in GLS N (%)		
Drop< 15%	17 (56.6)	
Drop > 15%	13 (43.3)	

Relation between Drop in GLS More than 15% and HST

High sensitivity cardiac troponin I assays was significantly increased in patients with Drop in GLS as compared with patients with no Drop in GLS after 3 months follow-up.



(Fig. 7): Relation between Drop in GLS More than 15% and High sensitivity cardiac troponin I assays after 3 months

Relation between Drop in GLS more than 15% and Other Studied Variables:

Subclinical LV dysfunction (drop in GLS > 15%) was not associated with age, sex, any cardiovascular risk factors (smoking, hypertension, diabetes, BMI), type of cancer, Adriamycin dose.

Table (6): Relation between Drop in GLS more than 15% and Other Studied Variables:

	Drop in GLS		
	No Drop in GLS N= 17	**Drop in GLS N= 13**	p-value*
DM; N (%)			
No	15 (88.2)	13 (100.0)	0.492
Yes	2 (11.8)	0 (0.00)	

HTN; N (%)			
No	16 (94.1)	11 (84.6)	0.397
Yes	1 (5.9)	2 (15.4)	
Smoking; N (%)			
No	15 (88.2)	11 (84.6)	0.591
Yes	2 (11.8)	2 (15.4)	
Sex; N (%)			
Female	15 (88.2)	10 (76.9)	0.628
Male	2 (11.8)	3 (23.1)	
Diagnosis; N (%)			
Br. Cancer	10 (58.8)	8 (61.5)	0.824
H. Lymph.	3 (17.6)	2 (15.4)	
NHL	3 (17.6)	3 (23.1)	
LL Sarcoma	1 (5.9)	0 (0.00)	
Cumulative Dose			
Mean ±SD	453.75 ±94.9	460.78 ±86.9	0.386
Minimum	320	240	
Maximum	630	560	
Range	310	320	
Patients' age			
Mean ±SD	44.47 ±15.3	49.38 ±11.2	0.339
Minimum	21	35	
Maximum	75	68	
Range	54	33	
BMI			
Mean ±SD	26.24 ±2.7	27.24 ±3.7	0.521
Minimum	20	21	
Maximum	31	34	
Range	11	13	

*p-value was considered significant at ≤0.05 by Chi Square-test.

*p-value was considered significant at ≤0.05 by independent sample t-test.

No statistically significant difference

4. Discussion:

Chemotherapy-induced cardiotoxicity remains a significant and unresolved issue when treating cancer patients. Because Cardiotoxic effect is partially dose-dependent, oncologists have begun to decrease the cumulative dose in most protocols; however, this does not prevent cardiac damage, because histologically, myocardial changes can be detected even after exposure to low doses [15].

Current approaches to surveillance are often inadequate to detect myocardial disease, which can delay medical therapy and lead to symptomatic heart failure. Despite its feasibility, the left ventricular ejection fraction (LVEF) is not sensitive enough to reveal subclinical or regional myocardial dysfunction [16].

Strain imaging could provide earlier detection of myocardial dysfunction and offer an additional noninvasive measure to follow these patients longitudinally. Several parameters that explore myocardial deformation, such as LV global longitudinal systolic strain (GLS), global radial strain (GRS), strain rate, LV twist (LVtw) or torsion, and LV untwisting rate could be useful as non-invasive approaches for the early detection of subclinical chemotherapy-induced cardiac toxicity, as recently reported [17].

There are many reasons accounting for the increased sensitivity of longitudinal strains compared with the LVEF in the detection of early cardiotoxicity. Chemotherapy-induced cardiotoxicity has a regional pattern, which has been supported by the findings of Ho et al. In general, longitudinal LV mechanics, which are predominantly governed by the subendocardial region of the myocardium, are the most vulnerable component of LV mechanics and therefore most sensitive to diseases affecting the myocardium. Perel et al. observed a regional and diffuse pattern of subendocardial enhancement using cardiac magnetic resonance imaging in two patients with anthracycline-induced cardiomyopathy. It was conceivable that abnormal GLS could be compensated by the relatively unaffected mid-myocardial and epicardial mechanical function, maintaining normal overall LV function, at least in the early stage [21].

Anthracyclines remain the most widely prescribed anticancer agents for several hematologic malignancies (non-Hodgkin's/ Hodgkin's lymphoma, acute/chronic myeloblastic

leukaemia, acute lymphoblastic leukaemia, multiple myeloma) and solid tumors (breast cancer, osteosarcoma, etc.) [41].

It is now known that anthracyclines are more Cardiotoxic than have been initially understood [18]. This toxicity is cumulative and dose dependent, with an incidence of clinically detected heart failure in 1.6% to 2.1% of patients, within the first year after treatment [19].

Monitoring for early signs of cardiotoxicity during a patient's treatment with chemotherapy can be done by using strain measurements [20]. Two-dimensional–speckle tracking echocardiography (2D-STE) is a promising technique that can evaluate cardiac mechanics in the 3 domains of contractility [21].

Cardiac troponin T and I (hs-TnI and hs-TnT) are biomarkers of myocardial damage. Over the last few years, a new generation of troponin assays has become available, which is referred to as high-sensitive assays, able to detect very low concentrations of troponin [22].

There are several reasons why some trials fail to demonstrate an association between conventional troponin and LV dysfunction. One explanation is the use of different biomarker assays, specifically the lower sensitivity conventional troponin assays. Troponin elevation in chemotherapy-induced cardiotoxicity is often mild and may not be detectable on conventional assays [23].

However, the newer high-sensitive troponin assays can detect troponin at very low concentrations. With increased sensitivity comes reduced specificity and unfortunately not every raised reading using high-sensitive troponin assays in cancer patients reflects Chemotherapy-induced cardiotoxicity.

Concomitant medical conditions such as acute kidney injury, sepsis, pulmonary embolism, and tachyarrhythmias are common in cancer patients and can increase troponin levels. In addition, there is the issue of biological variance in healthy individuals. Hence, physicians need to interpret positive troponin results with care and in the appropriate clinical context [22]

The use of high-sensitive troponin assays has since been integrated into several studies. Elevated high sensitive cTnI concentrations and a strong association with peak systolic longitudinal myocardial strain have been recognized among patients treated with anthracycline-containing regimens, who later developed cardiotoxicity [14].

Sawaya et al.,(2011) and his colleagues found that elevated high-sensitive troponin levels, together with echocardiographic markers of myocardial deformation, predicted the occurrence of cardiotoxicity among oncology patients receiving anthracycline [39], while Ky et al.,(2014) demonstrated that an early rise in high-sensitivity TnI from baseline to 3 months was

associated with an increased cardiotoxicity risk among similar patients [40].

The aim of this work was to find out whether early changes in the left ventricular function in patients receiving anthracyclines chemotherapy can be detected by 2D global longitudinal strain.

Regarding the baseline demographic characteristics:

In our study, the age of patients ranged from 21 to 75 years, with mean age was 46.31 ± 13.8 years. This was in concordance to **Gripp et al., (2018)**; (who evaluated the incidence of cardiotoxicity among patients treated for breast cancer, the independent factors associated with this event and the ability of the strain to identify it early) showed that the mean age of the population studied was 49.7 ± 12.2 years [24]. It also agreed with **Boyd et al., (2017)** (who evaluated changes in LV systolic and diastolic function in breast cancer patients early after anthracycline chemotherapy.) and **Arciniegas Calle et al., (2018);** (who studied early changes in left ventricular (LV) and right ventricular (RV) mechanics associated with combined anthracycline-trastuzumab treatment for breast cancer), both showed that the mean age was 52 ± 9. [21, 25]

Regarding the general medical characteristics

We reported that BMI ranged from 20 to 34 kg/m2, with mean BMI value was 26.55 ±3.2 kg/m2. This was in consistent with **Gripp et al., (2018);** who found that mean BMI was 26.1 kg/m2 [24]. Furthermore, this agreed with **Boyed et al., (2017);** who documented that average BMI was 27.5 ± 6.9 [25].

We showed that non-diabetic patients in our study (93.4%), which was higher than percentage of diabetic patients (6.6%).This agreed with **Gripp et al., (2018)** and **Boyd et al., (2017)**; who showed that diabetic patients represented only 4.1% and 6% respectively [24, 25]. In addition, **Arciniegas Calle et al., (2018)**; reported that only 5% were diabetic [21].

We documented that non-smokers (86.6%) occupied higher percentage in our cases compared to smokers (13.4%). This was in consistent to **Boyd et al., (2017)** and **Arciniegas Calle et al., (2018);** who reported that smokers represented only 26% and 20% of their patients respectively [21, 25].

Our work showed that the dose of anthracyclines ranged from 240 to 630mg/m2, with mean value of dose was 456.89 ± 89.8mg/m2. This was lower than the dose used in **Gripp et al., (2018);** who recorded mean dose of 600mg/m2 (534-760), while it was higher than the mean dose reported by **Patel et al., (2018);** 308.6 ± 152.0 mg/m2 and by **Arciniegas Calle et al., (2018)**; 252 ± 45 mg/m2. [21, 24, 26]

Regarding 2D echocardiography:

In our study we followed-up the studied cases by conventional 2D transthoracic echocardiography measuring the left ventricular internal diameter at diastole (LVIDd), left ventricular internal

diameter at systole (LVIDs) and left ventricular ejection fraction.

Our result showed that left ventricular internal diameter at diastole (LVIDd) & left ventricular internal diameter at systole (LVIDs) was highest after 6 months of chemotherapy with overall significant difference (p-value= 0.002). Left ventricular Ejection Fraction was highest at baseline assessment before chemotherapy than after three & six months of treatment with anthracycline with overall significant difference (p-value= 0.002). However no patient developed echocardiographic criteria of cardiotoxicity (≥5% reduction in symptomatic patients, or a ≥10% reduction in asymptomatic patients, in the left ventricular ejection fraction (EF) from baseline to a value of <55%)

This was agreed with **Boyd et al., (2017);** who showed that EF significantly decreased following treatment but no patients developed cardiotoxicity [25]. Also, this was in consistent with **Santoro et al., (2017);** (who compared standard echo, 2D, and 3D speckle tracking echocardiography (STE) for detection of subclinical anthracycline cardiotoxicity in breast cancer patients.) and showed that 2D ejection fraction (EF) was not significantly changed after treatment period of four months (p=0.111) [32].

On the other hand, this was inconsistent with **Gripp et al., (2018)** who showed that 10 % of patient developed cardiotoxicity during the follow up period of twelve months [24] & with **Arciniegas Calle et al., (2018)** who showed that 20 % of patient developed cardiotoxicity in one year follow up period [21].

This difference may be attributed to difference in clinical characterization of the patients, number of studied patients, type and dose of anthracycline & longer follow up period.

We followed-up the studied cases by global longitudinal strain (GLS) echocardiography and we showed that before chemotherapy GLS was significantly higher than after three months, and the latter was higher than after six months (p < 0.001).

This was in consistent with **Boyd et al., (2017);** who showed that pre-treatment GLS was higher than post-treatment GLS, with significant difference between them (p<0.001) [25]. This was also in accordance to **Santoro et al., (2017);** who showed that pre-treatment GLS was significantly higher than post-treatment GLS (p<0.001) [32] Moreover, **Gripp et al., (2018) & Arciniegas Calle et al., (2018)**; showed the same result, with significant p value <0.01 [24-21].

Our study showed that 13 of studied patients (43%) developed subclinical left ventricular dysfunction in form of drop in GLS > 15% at six months of treatment with preservation of left ventricular ejection fraction.

This was in concordance with **Boyd et al., (2017)** who showed that Subclinical LV dysfunction, defined as >11% reduction in GLS, occurred in 29 patients (22%) [25]. Also **Hu et al,**

(2018) (who evaluated GLS for early detection subclinical anthracyclines' cardiotoxicity in children with solid tumor.) showed that 26% of patients who received low-to-moderate dosage of anthracyclines developed evidence of subclinical cardiac injury with drop in GLS > 15% that was noted within 6 months after therapy with anthracyclines [37]. Moreover, **Santoro et al., (2017),** showed a reduction of GLS between post-anthracycline exam and baseline > 15% in 17% of the patients [32].

In relation to that, **Gripp et al., (2018)** showed that a 14% reduction in GLS (or absolute value of -16.6) was able to early identify patients who may develop anthracyclic and / or trastuzumab-associated cardiotoxicity [24]. Also **Arciniegas Calle et al., (2018);** showed that left ventricular longitudinal strain & LV circumferential strain were reduced significantly in patients with cardiotoxicity ($P < .05$) [21].

This emphasis the important role of GLS in early assessment of LV function & the need for longer term multicenter studies to determine the extent of early changes in GLS that best predicts future cardiotoxicity, in patients receiving anthracycline.

Published literature regarding the LV suggests that not all reduction in LV GLS is related to Cardiotoxic effects of chemotherapy. Instead, cancer-induced cardiac stress via inflammatory effects and autonomic dysfunction may play a role acutely to cause LV GLS reduction [33].

Regarding high sensitive troponin assay

Our work showed that high sensitivity cardiac troponin I was significantly increased three months after chemotherapy as compared with baseline assessment before chemotherapy.

This was in accordance to **Jones et al., (2017)** (who assessed serial high-sensitive cardiac troponin-I concentrations in patients receiving anthracycline-containing and non-anthracycline-containing regimens) and found a significant increase in high-sensitive cardiac troponin-I in the anthracycline group following five cycles of treatment [38].

This was also in accordance to **Blaes et al., (2015)**; (who investigated the utility of high-sensitivity cardiac troponin T (hscTnT), N-terminal pro-B-type natriuretic peptide, cardiac troponin T and I, and creatine kinase (CK)-MB in cancer patients receiving anthracycline-based chemotherapy), he showed that following treatment with doxorubicin, high sensitivity cardiac troponin T increased significantly (P value 0.001). [34]

In addition, this agreed with **Advani et al., (2017);** (who studied high-sensitivity troponin T and NT-proBNP Kinetics in Breast Cancer patients) and showed that high sensitivity cardiac troponin has increased significantly after Anthracyclines chemotherapy. [35]

Our results showed that there was a negative correlation between Global Longitudinal Strain

and hscTnI after 3 months of treatment, which means that with the drop in GLS there was elevation in hscTnI.

Also high sensitivity cardiac troponin I was significantly increased in patients with Drop in GLS > 15 % as compared with patients with no Drop in GLS after 3 months follow-up.

This agreed with **Wang W et al., (2017)** (who investigated the clinical value of 2D-STE combined with hs-cTnT in early detection of the cardiotoxicity induced by chemotherapy drug) and showed that the reduction of GLS was positively associated with the enhancement of hs-cTnT after chemotherapy (r=0.60, P<0.01) [39].

This also in consistent with Yu Kang et al., (2013) (who investigated whether alterations of myocardial strain and high-sensitive cardiac troponin T (cTnT) could predict future cardiac dysfunction in patients after epirubicin exposure) and reported that elevation in cTnT from baseline to the third cycle of chemotherapy was associated with decrease in GLS and combination of both can predicted later cardiotoxicity [14].

Our study showed non-significant correlation between hs-cTnI levels and cumulative anthracyclines dose. This was in accordance to **Jones et al., (2017);** who showed that there was no direct correlation between hs-cTnI levels and cumulative anthracyclines dose (r < -0.22) [38].

Relation between GLS & different variables:

Our study showed that there was no statistically significant relation between drop in GLS and cumulative dose of anthracyclines. This was agreed with **Boyd et al., (2017)** who showed that Subclinical LV dysfunction was not associated with type of anthracycline therapy or dose [25]. **Gripp et al., (2018)** also showed that no association was observed between cardiotoxicity & Cumulative dose of anthracyclines [24].

This was against **Hu et al., (2018);** who showed that the mean LV GLS decreased significantly (P = 0.04), in subgroup with anthracyclines' cumulative dosage ≥300 mg/m2, compared with subgroup with anthracyclines' cumulative dosage <300 mg/m2 [37].

The lack of correlation in our study between drop in GLS & cumulative dose of anthracycline may be due limited number of studied patient that can mask significant association.

The incidence of myocardial damage after anthracyclines chemotherapy may be enhanced by smoking, preexisting cardiovascular disease, coexisting damage or individual patient genetic predisposition [31].

Development of sub clinical LV dysfunction in the current study was not associated with any cardiovascular risk factors, specifically, age, obesity, diabetes, hypertension and smoking. This was in consistent with **Gripp et al., (2018) & Boyd et al., (2017)** who showed that development of LV dysfunction was not associated with any cardiovascular risk factors or

clinical parameters[24, 25]. This was also agreed with **Arciniegas Calle et al., (2018)** who showed that There was no difference in cardiotoxicity for patients with more than or less than 3 CV risk factors [21]. This may be explained by the low prevalence of risk factors in the studied patients.

Our findings together with the previous studies provide great evidence for the benefit of evaluating a LV global longitudinal strain as an additional index for evaluating myocardial function during and after anthracyclines treatment. It provides a great tool for the early detection of abnormal myocardial function and could lead to earlier intervention and clinical treatment.

Study Limitation

The study was limited by the following factors;

1. This single-center study included limited number of patients (n = 30) because of cost constraints.
2. Due to cost constraints, other cardiac biomarkers could not be obtained in this study.
3. The study was limited by the short duration of patient follow-up, and therefore the longer term impact of early reduction in GLS is uncertain; longer term follow up is ongoing to determine the significance of these early observations.
4. Another imaging modality may have provided additional information about LV systolic function; the use of MRI was beyond the scope of the current study. 3D echocardiography, contrast imaging and stress testing were not performed in the current study.
5. Image acquisition and measurements were performed using equipment from a single vendor (Philips); therefore, values are not comparable with non-Philips machines [222].

5. Conclusion:

From our study we concluded that, measurement of left ventricular global longitudinal strain by two dimensional speckle tracking echocardiography during & after anthracycline therapy combined with high sensitive cardiac troponin assay may allow an early identification of cardiac damage and therefore provide a way to minimize cardiac related morbidity and mortality while undergoing chemotherapy and afterwards.

Recommendations

Depending on the result of our study and previous studies, we recommend to include global longitudinal strain measurement by two-dimensional speckle tracking echocardiography whenever available in routine follow up of patients receiving anthracycline treatment during and after the course of chemotherapy

Recommendations for future studies:

- Large number of patients needed to be studied.
- Longer follow up period is recommended to detect the long term consequences of reduction in global longitudinal strain and risk of developing cardiotoxicity in those patients.

- Assessment of left ventricular function by other imaging modality as cardiac MRI and 3D echocardiography and correlating their result with global longitudinal strain.

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