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ORIGINAL ARTICLE

Assessment of Cardiotoxicity in Survivors of Acute Lymphoblastic Leukemia by Tissue Doppler Imaging

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ABSTRACT

Background: Cardiotoxicity development in survivors of acute lymphoblastic leukemia is one of the most serious chronic complications of cancer therapy. This study aimed to assess the frequency of doxorubicin cardiotoxicity in survivors of childhood acute lymphoblastic leukemia. **Methods**: We utilized a cross-section case-control study design and included 50 ALL survivors attending a pediatric oncology clinic for follow-up after finishing chemotherapy and 50 age- and sex-matched controls. All participants were subjected to a full general examination. The cardiac status was assessed by Echocardiography and Tissue Doppler Technique. **Results:** Tissue doppler parameters S" (myocardial systolic velocity) m/sec, E" (early phase of diastole negative velocity) and A" m/sec (late phase of diastole negative velocity), A (peak early mitral inflow velocity), and E (peak late mitral inflow velocity) wave DT(deceleration time), GCS(global circumferential strain) &GLS(global longitudinal strain) were statistically lower among ALL survivor than controls, but MPI(myocardial performance index) was statistically higher among ALL survivor than controls. **Conclusions:** Our results demonstrated that all echocardiographic and Tissue Doppler parameters are lower among ALL survivors than controls, except that MPI(myocardial performance index), LVED (left ventricular end-diastolic dimension), and LVES(left ventricular end-systolic dimension) is higher among ALL survivors than controls indicating cardiac dysfunction among ALL survivors.

Keywords: Doxorubicin**,** ALL survivors, cardiotoxicity.

INTRODUCTION

Acute lymphoblastic leukemia (ALL) has the highest prevalence among other types of cancer in children **[1].** Doxorubicin is a chemotherapeutic agent widely used to treat many types of childhood malignancies, achieving the increased 5-year survival rates for childhood cancer to more than 80% nowadays. Unfortunately, a major obstacle of anthracyclines is the risk of cardiotoxicity, manifested as asymptomatic cardiac dysfunction in up to 57% and cardiomyopathy with subsequent clinical heart failure in up to 16% of patients. Subclinical cardiac abnormalities are persistent and progressive after receiving Doxorubicin therapy and can lead to significant clinical symptoms. Doxorubicin-induced congestive heart failure (CHF) is often resistant to therapy and has a high mortality rate of up to 72**% [2].** Many studies recorded that cardiotoxicity developed in all survivors previously treated with doxorubicin chemotherapy during their disease **[3].** Sadly, the most serious chronic complication of doxorubicin is cardiotoxicity. Mortality related to cardiac causes is 10-fold

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higher among childhood cancer survivors as compared with age-matched control subjects **[4]**

Several risk factors predisposing to doxorubicin cardiotoxicity development as Down syndrome in girls, younger age, higher dose and cumulative dose **[5]**

Another risk factor that causes doxorubicin cardiotoxicity is specifically the formation of doxorubicin-iron complexes which is turned into semiquinone free radical which react with oxygen causing lipid peroxidation and damaging DNA **[6]**

In other meaning, elevated iron tissue concentration increases the risk of doxorubicin cardiotoxicity development indicating that it is important if an iron-chelating agent as dexrazoxane precedes doxorubicin chemotherapy treatment as this will lessen iron tissue concentration consequently free radical formation **[7]**

METHODS

Sample size: The sample size of the current cross-section case-control study was calculated based on assuming that the total number of acute lymphoblastic leukemia survivors attending pediatric oncology clinic for follow up is 50 ALL survivors per 6 months (according to the 2017 attendance rate), all survivors were included and 50children as a control group.

Study Design and subject recruitment: We designed a cross-section case-control study that included 50 ALL survivors attending pediatric oncology outpatient clinic for follow up after finishing chemotherapy and 50 control subjects from outpatient clinics for other reasons at Children Hospital, Zagazig University between the 1st of July 2017 and 15th of April 2018. ALL survivors including 26 males and 24 females and 50 sex and age-matched children as a control group.

All survivors were included and 50 children as control group were selected by systemic random technique, recruiting every 4th subject. ALL survivors attend a pediatric oncology clinic for follow-up after finishing chemotherapy. All participants and their parents were informed of the study design and written informed consent was collected from all parents of participants or their relatives.

The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Approval for performing the study was obtained from the Institutional Review Board (IRB) of Zagazig University.

Inclusion criteria: ALL survivors treated with doxorubicin and finished their chemotherapy protocol CCG for at least one year to be included in our study to assess their cardiac function.

Exclusion criteria: We excluded patients with the following criteria: patients with a history of hepatic, renal impairment, congenital heart disease, Diabetes millions. or patients with other cancer or still on chemotherapy.

Echocardiography and Tissue Doppler imaging: Echocardiographic exams were performed with all subjects positioned in supine decubitus and left lateral decubitus with sedation if required using oral chloral hydrate.

Echocardiographic exams were performed by the same operator using a Vivid 7 (GE Vingmed Ultrasound, Horten, Norway) machine equipped with a multi-frequency matrix M3S and a 7s transducers and Esaote Class C machine with simultaneous ECG recording at the Echocardiography Laboratory of Children's Hospital, Zagazig University.

Initially, routine diagnostic imaging was performed, including color flow mapping, pulsed, and continuous wave Doppler. Color Doppler myocardial imaging was performed with the standard subcostal, apical four-chamber, short axis, and long-axis parasternal and suprasternal views.

Sector size and depth were chosen to achieve a frame rate of 130 ± 20. Gain settings, filters, and pulse repetition frequency were adjusted to optimize color saturation, and continuous 1-channel electrocardiography monitoring was used throughout the study.

Three consecutive cardiac cycles were recorded during normal quiet respiration. Data were stored. The studies were video-recorded for subsequent analysis.

All the images were acquired in cine loops of three cardiac cycles recorded at a frame rate of 60–111 frames per second, saved in the digital format, and analyzed by offline

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software (XStrain™ software for MyLabTM50 XVision, Esaote SPA, Genoa, Italy).

For quantification of the circumferential and radial strains and strain rates, six segments (anteroseptal, anterior, lateral, posterior, inferior, and septal; **(Figure1)** of the endocardium were semiautomatically selected by aided heart segmentation (AHS, MyLabTM50 XVision) for analysis. For quantification of the LV longitudinal strain and strain rate, six segments (basal septal, mid septal, apical septal, apical lateral, mid-lateral, and basal lateral**; (Figure 2)** of the endocardium were semiautomatically selected by the AHS tool for analysis. Global circumferential/ longitudinal peak systolic strain (CSG/ LSG), systolic strain rate (CSR/ LSRg), were calculated by obtaining the average strain or strain rate of all the six segments in the circumferential, radial, and longitudinal directions, respectively. Images not providing adequate visualization of one or more segments of the endocardium were excluded.

Laboratory investigations: 3 cm^3 venous blood samples were obtained for each subject. Complete Blood Count (CBC), random blood glucose level, liver function tests, kidney function tests,), lipid profile (total cholesterol, triglycerides, HDL, and LDL), serum ferritin were performed for all participants.

Statistical Analysis:

The collected data were computerized and statistically analyzed using the SPSS program (Statistical Package for Social Science) version 16.0 (SPSSInc., 2007). For the statistical calculations, data coding was done.

RESULTS

This cross-section case-control study included 50 ALL survivors with a mean age (±SD) of 12.15years (±2.9), and 50 control subjects with a mean age (±SD) of 12.1 years (±2.8) without a statistically significant difference between ALL patients and healthy control regarding age and sex. **(Table1)**

Echocardiography assessed that conventional left ventricular systolic function between ALL survivors and control, showed that fractional shortening was statistically lower among ALL survivor patients than control, ($p<0.05$) (**Table2)**.

Echocardiographic dimensions LVES left ventricular end-systolic dimension &LVED left end-diastolic dimension parameters were statistically higher among ALL survivor patients than in control, but PW thickness was statistically lower in ALL survivors than healthy controls ($p<0.05$). (**Table2)**

Tissue Doppler velocities S" m/sec, E" and A m/sec" were statistically lower among ALL survivors than in the control group and there was no statistically significant difference between both groups as regard E/E". (**Table2)**.

Pulsed Wave Tissue Doppler conventional left ventricular diastolic function A and E were statistically significantly lower among ALL survivors than in the healthy control group, also E wave deceleration time was statistically lower among ALL survivors than in the control group. (**Table2)**.

Global Left Ventricular longitudinal and circumferential strain among the studied groups were statistically significantly lower among ALL survivors than in the control group. (**Table2)**. **The myocardial performance index** was statistically higher among ALL survivors than in the healthy control group. (**Table2)**

Cardiotoxicity was found in 10% of the studied ALL survivors. (**Table3)**

Relation between the cumulative dose of doxorubicin and cardiotoxicity among the studied ALL survivors showed that 6.8% of ALL survivors who received less than 300 mg /m^2 of doxorubicin had cardiotoxicity versus 33.3% of patients who received more than 300 mg /m^2 doxorubicin, with a statistically significant difference. (**Table4)**.

Table (1): Demographic data of the studied survivors of ALL children and the control group.

Demographic data	ALL (N=50) No. %	Control (N=50) No. %	MWT/χ^2	P-value
Age (years)				
Mean ± SD	**12.156 ± 2.92**	**12.1 ± 2.8**	**1223.5**	**0.854**

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Demographic data	ALL (N=50) No.	%	Control (N=50) No.	%	MWT/χ^2	P-value
Median (Range)	12 (7-18)		12 (6-17)			(NS)
Sex						
Male	26	52.0	30	60.0	0.649	#0.546
Female	24	48.0	20	40.0		(NS)

MWT: Mann Whitney U test. # $\chi^{2:}$ Chi-square test. P < 0.05: is significant. NS: Not significant.

Table2: Echocardiographic dimensions among the studied groups.

Echocardiographic dimensions among the studied groups.				
Parameters		ALL(N=50)	Healthy control(N=50)	P-value
Echocardiographic dimensions				
LIVES (mm)	Mean ± SD Median (Range)	35.00 ±2.94 35 (29-39)	25.88 ±4.82 26 (17-37)	0.000* (HS)
LOVED (mm)	Mean ± SD Median (Range)	46.2 ± 1.79 42 (10-46)	40.14 ± 4.66 40 (32-51)	0.000* (HS)
PW (mm)	Mean ± SD Median (Range)	7.1 5 ± 1.16 7 (5-11)	11.6±2.6 9(7-18)	0.000* (HS)
Conventional left ventricular systolic function among the studied groups.				
EF %	Mean ± SD Median (Range)	69.2 ± 9.12 68(51-80)	75.3±6.34 75.5(65-86)	0.001* (HS)
FS%	Mean ± SD Median (Range)	41.18 ± 7.13 45(24-48)	44.7±6.7 43.5(35-55)	0.024* (S)
Tissue Doppler mitral annular velocities among the studied groups.				
S" m/sec	Mean ± SD Median (Range)	0.07 ± 0.01 0.07 (0.05-0.09)	0.08±0.012 0.08(0.07 -0.1)	`0.001 (HS)
E m/sec"	Mean ± SD Median (Range)	0.15 ± 0.021 0.15(0.11-0.18)	0.19±0.019 0.19(0.17-0.23)	0.000* (HS)
A"m/sec	Mean ± SD Median (Range)	0.095 ± 0.024 0.088(0.06-0.16)	0.14±0.04 0.15(0.08-0.20)	0.000* (HS)
E/E"	Mean ± SD Median (Range)	5.74 ± 0.89 5.6(4.6-8)	6.24±2.24 5.7(3.4-10)	0.887 (NS)
Pulsed wave Doppler conventional left ventricular diastolic function and E wave deceleration time among the studied groups.				
A m/sec	Mean ± SD Median (Range)	0.90± 0.14 0.94 (0.63-1.04)	1.13±0.40 0.92(0.80-1.9)	0.000* (HS)
Em/sec	Mean ± SD Median (Range)	0.50 ± 0.07 0.52(0.30-0.59)	0.62±0.011 0.65(0.4-0.80)	0.000* (HS)
E/A	Mean ± SD Median (Range)	1.78 ± 0.39 1.8(1.3-2.8)	1.63±0.29 1.66(1.2-2.1)	0.087 (NS)
DT (ms)	Mean ± SD Median (Range)	132.28 ± 30.99 133(88-189)	171.2±36.76 191(101-210)	0.000* (HS)
Global Left Ventricular longitudinal and circumferential strain among the studied groups				
Global long strain (GIS)	Mean ± SD Median (Range)	-15.4 ± 3.6 16.9 (-19 to -6.15)	-23.26±1.66 23.4(19.7-25.7)	0.000* (HS)
Long strain rate (LSR)	Mean ± SD Median (Range)	4.11 ± 15.44 1.01(-79 to -0.69)	1.84±0.23 1.77(1.5-2.24)	0.000* (HS)
Global circ strain (GCS)	Mean ± SD Median (Range)	-12.52 ± 2.99 11.2(-16 to -0.61)	-20.69±3.0 20.9(16.6-24.3)	0.000* (HS)
Circ strain rate (CSR)	Mean ± SD Median (Range)	0.856 ± 0.43 0.80(-1.2-0.80)	2.08±0.19 2.09(1.8-2.32)	0.000* (HS)
Myocardial performance index (MPI) among the studied groups				
MPI	Mean ± SD Median (Range)	0.71 ± 0.09 0.69 (0.57-0.86)	0.33±0.05 0.34(0.25-0.4)	0.000* (HS)

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Table (3): The prevalence of cardiotoxicity among ALL survivors group.

Cardiotoxicity	ALL cases(N=50)	
	No.	%
No	45	90.0
Yes	5	10.0

Table (4): Relation between the cumulative dose of doxorubicin and cardiotoxicity among the studied ALL survivors.

cardiotoxicity	Dose of doxorubicin				χ2	P-value
	<300 mg (N=44)		≥ 300 mg (N=6)			
	No.	%	No.	%		
No	41	93.2	4	66.7	4.12	0.042* (S)
Yes	3	6.8	2	33.3		

χ2: Chi-square test. *P < 0.05 is significant.

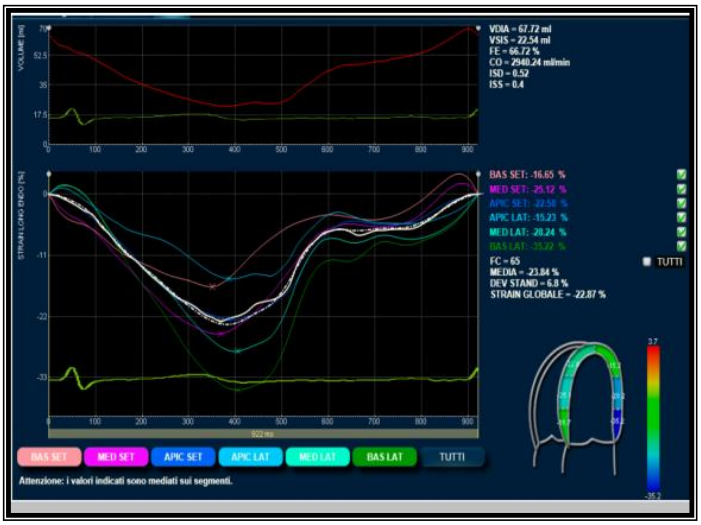

Figure (1): Peak systolic longitudinal strain

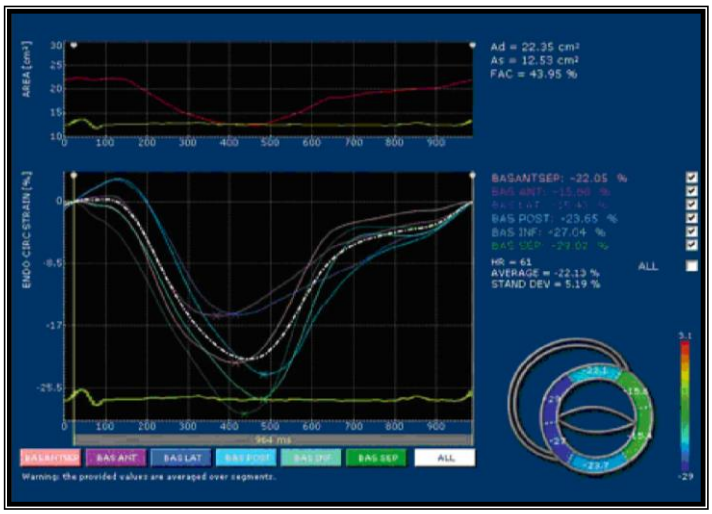

Figure (2): Peak systolic circumferential strain.

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DISCUSSION

Administration of intensive chemotherapy, better methods of risk assessments, and supportive care led to an increase in survival rate in children with ALL. More than 85% of all children with ALL can be successfully treated **[8]**. Successful treatment increases survival but it also increases the risk of side effects for those patients.**[9]**

Late effects are mostly Doxorubicin-associated with cardiovascular abnormalities **[10]** Doxorubicin among antibiotics is the most potent chemotherapeutic agent since its usage 50 years ago. Agents in this pharmacological group of antineoplastic drugs include doxorubicin, daunorubicin, epirubicin, and idarubicin. They are the most important agent for many chemotherapy protocols in the treatment of different cancer as **[11],** Lymphoma **[12],** leukemia **[13]**

We aimed to evaluate the cardiac status among ALL survivors to detect survivors who developed early cardiotoxicity to improve event-free survival(EFS). In the current study, the parameters of Tissue Doppler about anthracycline- cumulative dose were investigated in 50 ALL survivors of acute leukemia and 50 control.

Our study revealed that 6.8% of ALL patients who received less than 300 mg/m doxorubicin had cardiotoxicity in contrast 33.3% of patients who received more than 300 mg /m doxorubicin, with a statistically significant difference.

This was in agreement with a previous study by (**Sherief et al., 2012**) whose study showed that there was an increase in left ventricular dimensions is related to an increasing cumulative dose of anthracycline which was a common abnormal echocardiographic finding in anthracycline-induced cardiotoxicity.

The conventional left ventricular systolic function between ALL survivors and healthy control were Ejection fraction mean ± SD was 69.2 ± 9.12 & 75.3±6.34, Fractional shortening mean ± SD is 41.18 ± 7.13 & 44.7± 6.7 for ALL survivors &controls respectively all were statistically lower among ALL survivor patients than healthy control, ($p<0.05$).

In agreeing with Sherief et al **[14]** LVED(left ventricular end-diastolic dimension) and LVES(left end-systolic dimension) were significantly increased with increased cumulative anthracycline dosage.

Reduced left ventricular systolic function, expressed by a decrease in EF and FS. Our study showed that Tissue Doppler of lateral mitral annular velocities S m/ sec Mean ± SD was 0.07 ± 0.01&0.08±0.012, E" Mean ± SD was 0.15 ± 0.021& 0.19±0.019 and A" Mean ± SD was 0.095 ± 0.024 & 0.14±0.04 **for ALL survivors & controls respectively**, all were statistically lower among ALL survivor patients than healthy control and there was no significant difference between both groups as regard E/E" Mean ± SD was 5.74 ± 0.89&6.24±2.24 (P-value =0.887).

Pulsed wave doppler conventional left ventricular diastolic function, Mitral A Mean ± SD was 0.90± 0.14&1.13±0.40 and Mitral E Mean ± SD is0.50 ± 0.07&0.62±0.011 wave velocities blood flow over mitral valve were statistically lower among ALL survivor patients than healthy control, also deceleration time Mean ± SD132.28 ± 30.99&171.2±36.76 **for ALL survivors &controls respectively**, all were statistically lower among ALL survivor than healthy control with high significance.

These tissue Doppler image results were in line with Kapusta L et al **[15]** whose study showed Quantitative TDI parameters: peak late diastolic myocardial velocities, as well as transmyocardial systolic and diastolic velocity differences, were significantly lower in late survivors than in the healthy pediatric population ($p < 0.01$).

Myocardial performance index Mean ± SD was 0.71 ± 0.09 & 0.33 ± 0.05 **for ALL survivors &controls respectively**, so MPI was statistically higher among ALL survivors than controls.

Our results were in line with Karakurt C **[16],** Myocardial performance index was also higher in the survivor's group than in the control group ($p<0.01$).

Our study showed that longitudinal and circumferential strain was statistically lower among ALL survivor patients than in healthy control. **Global long strain (GIS)** Mean ± SD was 15.4 ± 3.6&23.26±1.66, Long strain rate

(LSR) Mean ± SD was-4.11 ± 15.44&-1.84±0.23 Global circ strain (GCS) Mean ± SD was 12.52 ± 2.99&20.69±3.0, Circ strain rate (CSR) Mean ± SD was-0.856 ± 0.43&-2.08±0.19 for ALL survivors &controls respectively.

These results were in line with Mavinkurve-Groothuis **[17]** whose study showed that global myocardial strain, strain rate, and time to peak systolic strain in asymptomatic survivors of childhood cancer were significantly lower compared with healthy controls (p values <0.0001) and were significantly related to several systolic and diastolic left ventricular parameters.

Conclusions: Our results demonstrated that all echocardiographic and Tissue Doppler parameters are lower among ALL survivors than controls, except that MPI is higher among ALL survivors than controls indicating cardiac dysfunction among ALL survivors.

Recommendations: It,s better to start using the Tissue Doppler technique in cardiac function assessment in early detection of doxorubicin cardiotoxicity among ALL childhood survivors.

No conflict of interest.

No financial disclosure

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