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Left ventricular function in pediatric all survivors using speckle-tracking echocardiography and its relation to N-terminal brain natriuretic peptide

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The aim of the present research is to investigate cardiac abnormalities using plasma N-terminal pro brain natriuretic peptide (NT-proBNP) and speckle-tracking echocardiography in asymptomatic pediatric acute lymphoblastic leukemia (ALL) survivors who received cardiotoxic drugs during their treatment. The Institutional Review Board (IRB) of the Menoufia Faculty of Medicine approved the study. Research work was performed in accordance with the Declaration of Helsinki. 40 pediatric ALL survivors and 25 healthy children were enrolled. Complete blood cell count, renal function tests and liver function tests, iron & lipid profile, fasting blood sugar and plasma NT-proBNP level in addition to conventional and speckle-tracking Echocardiography were done. NT-proBNP was highly more significant in survivors than controls. Cardiac parameters as LV global longitudinal systolic peak strain (GLPS) of the three apical views, the GLPS of apical four chamber view (GLPS-A4C), the GLPS of apical two chamber view (GLPS-A2C), the GLPS of apical long axis view (GLPS-LAX), and the "NT-proBNP levels were significantly higher in survivors when compared to controls". NT-proBNP and 2-D speckle tracking echo show promise in detecting cardiac dysfunction in childhood cancer survivors beyond what is detected by conventional echocardiography. So, it should be added to the follow-up studies of CCS.

Key words: *N-terminal pro brain natriuretic peptide, 2-D speckle tracking echocardiography, acute lymphoblastic leukemia, survivors*

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Long-term complications of chemotherapy are varied and common. The cardiovascular-related complications are of particular concern. Survivors are eight times more likely to die from cardiac causes and 15 times more likely to experience congestive heart failure (CHF) than the general population. Their increasingly higher risk of cardiac death is associated with exposure to cardiotoxic treatments [1]. Anthracyclines are widely used antineoplastic agents for the treatment childhood malignancies. Almost 60% of children with cancer receive anthracyclines as a part of their treatment [2]. Doxorubicin is one of the most effective available anthracycline chemotherapeutic agents that have been widely used in the treatment of pediatric malignancies. Its efficacy is often limited by its associated cardiotoxicity, which leads to cardiomyopathy that may evolve into heart failure. Cardiotoxicity can arise acutely, during or shortly after treatment. cardiotoxicity can also occur late with some individuals showing initial clinical signs of toxicity years post therapy. Regardless of dose in the form of cardiac arrhythmias, pericarditis, potentially fatal CHF and acute pulmonary edema can occur during doxorubicin therapy [2]. Cardiotoxic treatments are also associated with subclinical changes in left ventricular (LV) structure and function that commonly

include decreased LV wall thickness and increased LV systolic wall stress (afterload), which can progress to clinically relevant disease. Subclinical cardiac abnormalities are persistent and progressive after anthracycline therapy and can lead to significant clinical symptoms but in many cases, cardiac abnormalities normalize post therapy [3]. Natriuretic peptides are produced within the heart and released into the circulation in response to increased wall tension, reflecting increased volume or pressure overload. Under pathologic stimuli, the prohormone brain natriuretic peptide (BNP) is synthesized, cleaved to BNP, releasing N-terminal fragment of the BNP (NT-proBNP) [4]. The 2-dimensional strain echocardiography is an echocardiographic modality based on measurement of myocardial deformation using speckle-tracking. Myocardial strain and strain rate imaging have been demonstrated to have potential value for the quantification of global and regional systolic and diastolic myocardial function. It seems that regional dysfunction can be detected earlier than global dysfunction [5]. Early and accurate diagnosis of ventricular dysfunction in asymptomatic cardiac patients may permit a prompt onset of therapy of subclinical cardiotoxicity before the development of life-threatening complications [6].

MATERIALS AND METHODS

This study was performed on 40 pediatric patients (24 males and 16 females) with mean age (11.15 ± 3.94) years who finished their chemotherapy treatment in the Hematology and Oncology Unit, Pediatric Department, Menoufia University Hospitals during their follow-up visits. All the patients were treated by chemotherapy according to the approved protocol of the unit (total XV (with no radiotherapy or stem cell transplantation). The study was conducted from October 2018 to March 2020. Also, the study included 25 healthy children with matched age and sex as controls. Written informed consent was obtained from each patient's legal guardians as well as permission from the faculty ethical committee. The following broad inclusion and exclusion criteria were used: Inclusion criteria: Pediatric Childhood Cancer survivors (CCS) who received anthracycline in the form of Doxorubicin as part of their treatment protocol at least 6 months after finishing chemotherapy. Excluded subjects: those with any cardiac disease either, congenital or acquired, any associated systemic disease that can affect the cardiac function e.g., hypertension, and/or medication that can affect cardiac function, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, or beta-blockers. All the groups studied were subjected to: detailed history taking & examination (general and local), laboratory investigations including routine complete blood cell count, renal function tests and liver function tests, iron & lipid profile, fasting blood sugar and plasma NT-proBNP level. Venous blood samples were obtained from an indwelling catheter after 30 minutes of rest in supine position. The blood samples were withdrawn into chilled tubes containing EDTA. The whole blood was centrifuged; plasma was decanted, immediately frozen, and stored at -27°C until assayed (within 6 months after sampling). Plasma concentration of NT-proBNP was measured by electrochemiluminescence immunoassay. The normal NT-proBNP levels were very high after birth, then decreased drastically in the first days. The peptide levels continued to decline gradually with age, showing a significant decrease between the ages of 1 month and 18 years. [7]. Imaging: conventional & speckle echocardiography was performed by the same cardiologist who was blinded to the clinical details. For all patients, standard measurements were LV posterior wall thickness at diastole (LVPW), interventricular septum thickness at diastole (IVS), LV dimensions at end-systole (LVES), and LV dimensions at end-diastole (LVED). Shortening fraction (FS) and ejection fraction (EF) of the LV were calculated from M-mode measurements of LV dimensions at the level of mitral valve

leaflets in parasternal long-axis view. Diastolic functions of the left ventricle were measured (peak early (E) and late (A) diastolic wave velocities of the mitral valve as well as E/A ratio). All measurements were compared with the normal values of LVPW, IVS, LVES, and LVED which were taken from the standard tables according to ages and BSA [8]. An EF of less than 55% and FS of less than 29% were considered abnormal [9]. Speckle-tracking echocardiography: for measurement of LV longitudinal strain, two-dimensional loop views from four-chamber, three-chamber and two-chamber views were obtained. All recordings included at least three cardiac cycles stored for off-line analysis. Stored images were opened by the machine software, which automatically brought up the end-systolic frame of the cardiac cycle. In the end-systolic frame, endocardial border was traced manually, beginning at one end of the mitral annulus and ending at the other end. The software after that generated a region-of-interest (ROI) that included the entire myocardial thickness. The ROI was adjusted to achieve a satisfactory image by the cardiologist.

The software after that tracked the myocardial speckles frame by frame and generated moving images displaying the tracking. Careful visual inspection of the moving image was done to determine the adequacy of the tracking. If the tracking wasn't accurate, readjustment of the ROI or selection of a new ROI was done. The software at last divided the LV myocardium into six segments and generated segmental and global longitudinal strain. As the myocardium usually shortens in longitudinal direction during systole, the longitudinal strain was displayed below the baseline. The apical long-axis image (i.e. three-chamber view) was analyzed. In this view, the movement of aortic leaflets helped in timing the aortic valve closure, which was essential for the software to perform the deformation analysis. The same process was repeated with the apical four chambers and two-chamber images. The strain values for all the segments were recorded and averaged to obtain the global longitudinal strain. The ultrasound system also provided Bull's eye display of the regional and global longitudinal strain [10]. The results were collected, tabulated and statistically analyzed by SPSS (Statistical Package for Social Science) version 22.0 on IBM compatible computer. Two types of statistics were used: descriptive statistics: e.g. percentage (%), mean and standard deviation (SD). Analytic statistics: e.g. Chi-squared test (χ^2), Student t-test, Mann-Whitney test (U) (non-parametric test), Pearson's correlation and Spearman's correlation are tests used to measure the association between two variables. Correlation coefficient test (r) results may be positive (+) or negative (–) correlation. A p -value of < 0.05 was considered statistically signifi-

cant. A p -value of < 0.0001 was considered statistically highly significant [11].

RESULTS

The results of this study are shown in *tables 1–3*. *Table 1* showing the age and gender of studied groups. With regards to relation of conventional Echocardiographic parameters and NT-proBNP, EF and FS (which represents the LV systolic function) were significantly lower in the survivors' group than in the control group, though still within the normal values. NT-proBNP was significantly higher in the survivors group than in control group while there was no significant difference in LVEDD and LVESD (*table 1*). In this study, there was significant positive correlation with each of the following (duration of chemotherapy, cumulative dose of Doxorubicin, triglycerides (TG) and low-density lipoproteins (LDL)) while there was no significant correlation between NT-proBNP and each of the following (age at diagnosis, height, weight, body mass index (BMI), hemoglobin (Hb), creatinine, lipid profile, serum ferritin, glucose, LVESD, LVEDD, FS, EF, E, A and E/A ratio) (*table 2*). Results showed that analysis of the LV global longitudinal systolic peak strain (GLPS) of the three apical views, the GLPS of apical four chamber view (GLPS-A4C), the GLPS of apical two chamber view (GLPS-A2C), the GLPS of apical long axis view (GLPS-LAX), and the average GLPS (GLPS-Avg) were significantly lower in the survivors group than in the control group (*figure 1*). In addition, there was no significant correlation between (GLPS-Avg) and each of the following: age at study, age at diagnosis, duration of chemotherapy, cumulative dose of Doxorubicin, height, weight, BMI, Hb, serum ferritin, creatinine, glucose, lipid profile, LVEDD, LVESD, EF%, FS% & E/A ratio (*figure 2*).

DISCUSSION

Anthracycline-induced cardiotoxicity is suggested to be through production of oxygen free radicals, highly reactive hydroxyl radicals and peroxynitrite which induce apoptosis and cardiac myocytes damage as the heart is particularly poorly protected against oxidative stress Chatterjee et al. [12]. Natriuretic peptides are released by the myocardium in response to volume and pressure overload Horacek et al. [13]. Speckle tracking Echocardiography (STE) is based on the analysis of discrete areas of the myocardial wall, referred to as "speckles"; any modification of each speckle can be tracked, frame by frame, in any direction of the imaging plane, and parameters of velocity, strain, and strain rate can be evaluated Mor-Avi et al. [14]. There is a growing interest in the use of biomarkers & STE for detection of anthracycline-induced cardiotoxicity.

In the present study, EF, and FS (which represents the LV FS) were significantly lower in the survivors group than in the control group though still within the normal values. No significant difference in LVEDD and LVESD was detected (*table 1*). Results are in consistency with study of Cheung et al. [15]. They found that of the 36 patients, 28 (78%) had a LVEF $\geq 50\%$. Also, EF values were significantly lower in the patient group (54.2 ± 5.8 vs $58.6 \pm 5.7\%$, $p = 0.01$). Also, Ylänen et al. [16]. showed that the survivors group had lower

Table 1

Comparison between the studied groups regarding conventional Echocardiographic parameters and NT-proBNP

Data	Studied group (n = 65)		Test of significance	p-value
	survivors (n = 40)	control (n = 25)		
LVEDD: Mean \pm SD Range	38.8 \pm 3.85 31–48	39.2 \pm 5.5 30–49	T 0.305	0.706 NS
LVESD: Mean \pm SD Range	26.1 \pm 2.91 19–30	25.2 \pm 4.91 18–34	T 0.854	0.396 NS
EF, %: Mean \pm SD Range	64.5 \pm 4.22 56–73	67.7 \pm 2.48 63–72	T 3.37	0.001 S
FS, %: Mean \pm SD Range	32.4 \pm 4.22 28–41	34.2 \pm 1.28 32–36	T 2.06	0.043 S
NT-proBNP: Mean \pm SD Range	449.6 \pm 104.7 182–597	96.3 \pm 15.3 75–133	T 16.7	≤ 0.001 HS

Notes. T – Student's T test; LVEDD – LV end diastolic diameter; LVESD – LV end systolic diameter; EF – ejection fraction; FS – fractional shortening; HS – highly significant.

Table 2

Correlation of NT-proBNP with age at diagnosis, duration of chemotherapy, cumulative dose of Adriamycin, height, weight, BMI, Hb, serum ferritin, Creatinine, glucose, lipid profile and some Echo values among survivors

Parameter	NT-proBNP	
	r	p-value
Age at diagnosis years	0.256	0.112 (NS)
Duration of chemotherapy months	0.356	0.024 (S)
Cumulative dose of Adriamycin, mg/m ²	0.36	0.02 (S)
Height	0.03	0.81 (NS)
Weight	0.02*	0.90 (NS)
BMI	0.136	0.279 (NS)
Hb	01	0.22 (NS)
Serum ferritin	0.04*	0.80 (NS)
Creatinine	0.121	0.45 (NS)
Glucose	–0.06	0.69 (NS)
Cholesterol	0.08	0.61 (NS)
TG	0.262*	0.03 (S)
HDL	0.02*	0.90 (NS)
LDL	0.269	0.03 (S)
LVEDD	–0.003	0.98 (NS)
LVESD	0.136	0.279 (NS)
EF	–0.151	0.353 (NS)
FS	–1.00	0.427 (NS)
A	0.03	0.81 (NS)
E	–0.032	0.802 (NS)
E/A	–0.06	0.70 (NS)

Notes. r – correlation coefficient, Pearson correlation; * – spearman correlation.

Figure 1
LV GLPS by STE among studied groups

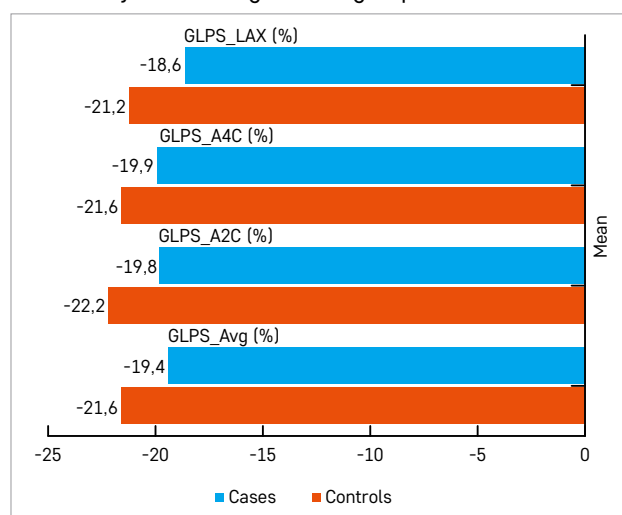
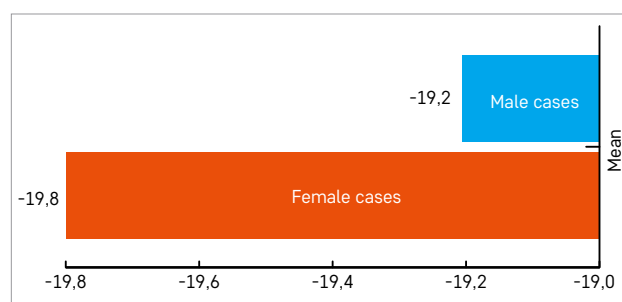


Figure 2
LV GLPS-Avg regarding gender in survivors group (%)



EF and FS compared to the control group ($p < 0.001$). NT-proBNP was significantly higher in the survivors group than control group (table 1). Data is consistent with the following: Zidan et al. [17] who performed across-sectional study on 58 asymptomatic survivors of childhood cancer. Twenty-four child showed abnormally high levels of NT-proBNP. They explained that natriuretic peptides were released by the myocardium in response to volume and pressure overload. Similarly, Armenian et al. [18], performed across-sectional study in which anthracycline-exposed CCS that show HR (high risk) survivors had significantly higher serum NT-proBNP levels (71 pg/dL) when compared with LR (low risk) survivors (37 pg/dL) and controls (26 pg/dL). There was significant positive correlation with each of the following (duration of chemotherapy, cumulative dose of Doxorubicin, TG and LDL) while there was no significant correlation between NT-proBNP and each of the following: (age at diagnosis, height, weight, BMI, Hb, creatinine, lipid profile, serum ferritin, glucose, LVESD, LVEDD, FS, EF, E, A and E/A ratio) (table 2). Results are consistent with the following studies: Zidan et al. [17] the previously mentioned study that showed that there was no significant relation between abnormal NT-proBNP levels and the gender of patients. However abnormal NT-proBNP levels were significantly

related to duration of follow-up. While, against our study, abnormal NT-proBNP levels were significantly related to age at diagnosis and cumulative anthracycline dosage ($p < 0.001$). Abnormal NT-proBNP levels were associated with younger age of patients, longer duration of follow-up, and higher cumulative anthracycline dose. Also, Mavinkurve-Groothuis et al. [19] who performed study on 122 asymptomatic CCS underwent a detailed echocardiography showed that sixteen had abnormal NT-proBNP levels compared to sex and age-appropriate norms. There was no significant relation between abnormal NT-proBNP levels and age at diagnosis, gender, follow-up duration, age at follow-up, BSA. However, abnormal NT-proBNP levels did significantly relate to cumulative anthracycline dosage as a continuous variable ($p < 0.003$). Mladosevicova et al. [20] showed that although no patient had echocardiographic abnormalities, significant differences were found in values of LV ejection fraction (LV EF). Deceleration time (DT) between survivors exposed and not exposed to anthracyclines NT-proBNP values positively correlated with ANT dose ($p = 0.0028$) but failed to correlate with LVEF ($p = 0.4245$) and DT ($p = 0.4269$).

In addition, Zidan et al. [17] in the previously mentioned study, reported that 15% had abnormal echocardiography. Abnormal LV systolic function (EF and FS) and diastolic function (E velocity and E/A ratio) were not significantly related to abnormal NT-proBNP levels. In the present study, regarding the data of Speckle Tracking Echocardiography (STE) (used to analyze the LV GLPS of the three apical views), it was found that the GLPS of apical four chamber view (GLPS-A4C), the GLPS of apical two chamber view (GLPS-A2C), the GLPS of apical long axis view (GLPS-LAX), and the average GLPS (GLPS-Avg) were significantly lower in the survivors group than the control group ($p < 0.001$) (table 3). This agrees with the Yu et al. [21]. They performed a cross-sectional study that included 134 adult CCS (mean age: 31.4 ± 8.8 years; 55% male). They have been previously treated with anthracyclines (mean cumulative dose: 320 ± 124 mg/m²), with ($n = 52$) or without ($n = 82$) mediastinal radiotherapy. They found that the mean FS,

Table 3
STE findings of LV in studied groups

Parameters	Cases (n = 40)	Controls (n = 25)	t-Test	p-value
GLPS-LAX, %: Mean \pm SD Range	-18.6 \pm 2.7 (-22.9) – (-8.1)	-21.2 \pm 0.73 (-23.0) – (-19.9)	5.83	< 0.001 HS
GLPS-A4C, %: Mean \pm SD Range	-19.9 \pm 2.0 (-23.1) – (-14.6)	-21.6 \pm 0.79 (-22.6) – (-19.8)	4.63	< 0.001 HS
GLPS-A2C, %: Mean \pm SD Range	-19.8 \pm 2.6 (-26.3) – (-13.0)	-22.2 \pm 0.90 (-23.9) – (-20.4)	5.34	< 0.001 HS
GLPS-Avg, %: Mean \pm SD Range	-19.4 \pm 1.9 (-23.3) – (-12.1)	-21.6 \pm 0.54 (-22.8) – (-20.7)	7.00	< 0.001 HS

LVEF, and GLPS were 33.3%, 61.1% and 18.0%, respectively. Also, the prevalence of LV systolic dysfunction (defined as FS < 27%, LVEF < 55% or GLPS ≤ 16%) was 5.2%, 6.0%, and 23.1%, respectively. Abnormal GLPS was observed in 24 (18%) patients despite a normal LVEF.

Also, in 2015, Pignatelli et al. [22] performed a prospective, cross-sectional study to compare myocardial strain indices derived by STE with LVEF to detect Anthracycline-induced LV systolic dysfunction. The study included 25 CCS (8 males & 17 females) with a mean age (9.8 ± 5.8) years. The median cumulative dose of anthracycline was $\geq 150 \pm 124.4$ mg/m². The GLPS was considered abnormal when found \geq SD from the mean of normal values obtained in a healthy cohort from another study (Marcus et al. [23]). They found that 15 (60 %) survivors showed abnormal GLPS. In addition, GLPS was lower than the normal reference values in all survivors but significantly lower across two age ranges (older survivors). The values in survivors aged from 10 to 14 (5 survivors) and those from 15 to 19 (8 survivors) compared to the normal reference values ($p < 0.0001$).

Armstrong et al. [24] found that only 5.8% of the survivors had a LVEF < 50%. However, systolic dysfunction detected by global longitudinal (31.8%) and global circumferential (23.1%) strain were more prevalent than an abnormal LVEF. Among survivors with preserved LVEF ($\geq 50\%$), comprehensive echocardiography identified significant systolic dysfunction (28.0%, global longitudinal strain).

Al-Biltagi et al. [2] showed that average GLPS of the LV was significantly lower in leukemic children than in the control group ($p < 0.01$). Also, the average GLPS of the LV showed significant reduction in the patient group before and after the doxorubicin treatment ($p = 0.04$). Our result demonstrated that there was no significant correlation between GLPS-Avg and each of the following: age at study, age at diagnosis, gender, duration of chemotherapy, cumulative dose of Adriamycin, height, weight, BMI, Hb, serum ferritin, creatinine, glucose, lipid profile, LVEDD, LVESD, EF%, FS% & E/A ratio (table 2). As regards the correlation of GLPS-Avg with the cumulative dose of anthracyclines, results of this paper were in accordance with the results reported by Yu et al. [21]. They found that there was no significant association between echocardiographic parameters of LV systolic or diastolic func-

tion (by 2D echocardiography or 2DSTE) and cumulative anthracycline dose. In 2015, Mavinkurve-Groothuis et al. [25] studied the role of global myocardial strain and strain rate in monitoring subclinical heart failure in a large group of asymptomatic long-term CCS. They found that there was no significant relation between GLPS and gender, age at diagnosis, age at follow-up and cumulative anthracycline dosage. These results were in accordance with the results obtained in our study. In the same study, they found that a lower GLPS was significantly related to a lower FS, EF. These results contrasted with our results.

In contrast with our results, Mavinkurve-Groothuis et al. [26] found that the cumulative anthracycline dose correlated negatively with global longitudinal strain ($p = 0.004$). Cheung et al. [15] performed a study that included 45 survivors. They found that the cumulative anthracycline dose correlated significantly with global longitudinal strain ($p = 0.027$). In 2015, Armstrong et al. [24] found that GLPS was associated with anthracycline dose > 300 mg/m². Also, survivors with metabolic syndrome were almost twice as likely to have an abnormal global longitudinal strain. Each of the individual components of the metabolic syndrome (abdominal obesity, triglycerides ≥ 150 mg/dl, low high-density lipoproteins (HDL) (< 40 mg/dl) and fasting Glucose ≥ 100 mg/dl) was associated with an increased risk of abnormal global longitudinal strain.

CONCLUSION

NT-proBNP and 2-D speckle tracking echo show promise in detecting cardiac dysfunction in childhood cancer survivors beyond what is detected by conventional echocardiography. This may be worth following longitudinally survivors of childhood cancer, to determine whether these could be early detectors of clinically relevant cardiac dysfunctions in such survivors.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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