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Original Article

Troponin-I and left ventricular function in pediatric high-risk acute lymphoblastic leukemia after daunorubicin treatment

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Abstract

Background Daunorubicin is a chemotherapy drug for leukemia treatment, but it can cause cardiotoxicity. When heart damage occurs, myocardial sarcomeres release troponin-I, which could potentially be useful as a cardiotoxicity biomarker.

Objective To assess for possible correlations between troponin-I and echocardiographic parameters of left ventricular function after administration of daunorubicin in children with high-risk acute lymphoblastic leukemia (ALL).

Methods This cross-sectional study on 37 children with high-risk ALL was performed from July 2017 to December 2018, in Padang, West Sumatera. The left ventricular systolic function parameters measured were ejection fraction (EF) and fractional shortening (FS); the left ventricular diastolic function parameter was E/A ratio. Troponin-I measurements and echocardiography were performed after daunorubicin treatment at the end of induction phase chemotherapy. Pearson's correlation test was used to analyze for a correlation between troponin-I and echocardiographic parameters.

Results Subjects had a mean age of 6.27 (SD 4.43) years, and males comprised 56.8%. Subjects' mean troponin-I concentration was 5.49 (SD 0.86) ng/mL, and mean EF, FS, and E/A values were 65 (SD 5) %, 36 (SD 4) %, and 1.52 (SD 0.56), respectively. Troponin-I was not significantly correlated with EF (r=0.062; P=0.715) or FS (r=0.309; P=0.172). However, there was a weak, significant negative correlation between troponin-I and E/A ratio (r=-0.383; P=0.019)

Conclusion Troponin-I level has no significant correlations with the echocardiographic parameters of left ventricular systolic function. However, there is a weak significant negative correlation between troponin-I level and the left ventricular diastolic parameter of E/A ratio. **[Paediatr Indones. 2021;61:107-14 ; DOI: 10.14238/pi61.2.2021.107-14**].

Keywords: *troponin-I; daunorubicin; children; echocardiography; left ventricular function*

Cancer treatment is rapidly advancing, but the various therapeutic modalities may have long-term side effects.[1] Cardiotoxicity is one of the serious chronic complications of chemotherapy.[2] Anthracycline, while superior as a chemotherapy, can lead to irreversible cardiomyocyte death.[3,4] Daunorubicin, in the anthracycline family, has been widely used in leukemia treatment protocols.[5] The incidence of acute cardiotoxicity induced by anthracycline ranges from 3 to 21%.[6] Detection of cardiomyocyte damage due to anthracycline should be done before irreversible left ventricular dysfunction occurs. The clinical approach to monitoring toxic effects includes heart performance assessment prior to, during, and after drug therapy.[6] Diastolic dysfunction is an early sign of cardiomyopathy due to anthracycline.[7] Changes in diastolic function initiate changes in systolic function. Left ventricular echocardiographic parameters include ejection fraction (EF) to assess systolic function and E/A ratio to assess diastolic function.[8] Guidelines from

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the *Cardiology Committee of the Children's Cancer Study Group* recommend controlling cardiotoxicity by assessing fractional shortening (FS).[9]

Cardio-specific biomarker measurements can be a valid diagnostic tool for early identification, assessment, and monitoring of cardiotoxicity. Such measurements would prevent interobserver variability in echocardiographic interpretation.[10] Troponin-I and troponin-T are sensitive and specific biomarkers for myofibril damage.[11] Troponin-I is more specific than troponin-T.[12] Since troponin can be detected early in the first cycle of anthracycline administration, it has been used to detect early cardiotoxicity, before changes in EF occur, especially in children.[13] Increased serum troponin released from cardiac myocyte sarcomeres is related to the degree of heart damage. Such increases at the beginning of and during therapy are predictive future severe ventricular dysfunction.[14]

The aim of this study was to assess for possible correlations between troponin-I and echocardiographic parameters of left ventricular function after administration of daunorubicin in children with high-risk acute lymphoblastic leukemia (ALL).

Methods

This cross-sectional, analytic study was done from July 2017 to December 2018 at the Department of Child Health, Andalas University/Dr. M Djamil Hospital, Padang, West Sumatera. Subjects were included by consecutive sampling. Of 60 pediatric patients diagnosed with high-risk ALL, 37 patients fulfilled the inclusion criteria of high-risk ALL, less than 18 years of age, undergoing chemotherapy induction cycle on the sixth week, and normal echocardiographic examinations. Participants' parents provided written informed consent. Exclusion criteria were not completing the induction phase chemotherapy protocol, having a diagnosis of cardiac abnormalities before therapy (heart failure, myocarditis, arrhythmias, myocardial ischemia, myocardial infarction, pericardial effusion), or receiving radiation.

Subjects underwent troponin-I examination from venous blood specimens within 8 hours to 10 days after the last daunorubicin administration in the sixth week of the induction phase. Troponin-I was measured using a mini *VIDAS, Biomerieux 69280*, per manufacturer's instructions. At that time, subjects underwent echocardiographic evaluation (*Echocardiogram Philip HD 11 XE M-Mode*, transducer pediatric 5 Mh1z) of left ventricular systolic and diastolic parameters by a pediatric cardiologist blinded to the troponin-I blood level.

High-risk acute lymphoblastic leukemia was defined as a blood cell malignancy originating from the bone marrow was characterized by white blood cell proliferation, with manifestations of abnormal cells in the peripheral blood and one or more risks found: age <1 year or> 10 years, hyperleukocytosis (leukocyte values >50,000/mm^3), mediastinal mass >2/3 of the diameter of the thoracic cavity, > 5 μm of leukemia cells in cerebrospinal liquor (cerebrospinal-meningeal leukemia), T-cell leukemia or mixed leukemia (bilineage leukemia) and >1000 blast/m^3 cells on peripheral blood examination after one week of starting therapy in the usual risk ALL group.[15] Troponin-I was a part of the contractile protein of the heart that inhibits ATPase activity of actomyosin.[16] Left ventricular ejection fraction (LVEF) was a change in the volume of the left ventricle from the end of the diastolic phase to the end of the systolic phase.[17] Normal EF values were considered to be 56-78%.[18] Fractional shortening (FS) was the percentage change in the dimensions of the left ventricular cavity during systolic contraction and was a parameter often used to express systolic function.[19] Normal values were considered to be 28-38%.[17] The E wave was an echocardiogram wave on a pulsed wave Doppler that represents the initial passive fast filling phase of the left ventricular diastole (mitral inflow).[20] Normal values were considered to be 0.91 ± 0.11 m/sec.[21] The A wave was an echocardiographic wave on a pulsed wave Doppler representing the active late diastolic ventricular (mitral inflow) late filling phase.[20] Normal values were considered to be 0.49 ± 0.08 m/sec).[21] The E/A ratio was the ratio between E and A waves, a parameter of the speed of transmitral flow in early and late diastole. It reflected the difference in pressure gradient between the left atrium and the left ventricle and showed the severity of diastolic dysfunction. Normal values were considered to be 1.5-2.3.[22] Assesment of diastolic dysfunction base on recommendations for echocardiographic assessment of left ventricular diastolic function.[23]

Data were grouped into numerical and categorical variables. Numerical variables were displayed as mean (standard deviation) or median (minimum-maximum), while categorical variables were displayed as frequencies and percentages. Kolmogorov-Smirnov normality test for troponin-I results, EF, FS, and E/A ratio. Normally distributed numerical data were analyzed by Pearson's correlation test. Statistical analyses were performed with *SPSS version 20.0* software. This study was approved by the Medical Ethics Committee of Universitas Andalas/ Dr. M Djamil Hospital, Padang.

Results

Subjects' characteristics are shown in **Table 1**. Their mean age was 6.27 (SD 4.43) years and most subjects were male. In addition, most subjects had ALL type L1. **Table 2** shows that subjects' mean troponin-I level was increased compared to normal values. The normal limits were considered to be 0-0.03ng/mL.[9]

Pearson's correlation test revealed no significant correlation between troponin-I level and EF after administration of daunorubicin, with r=0.062 and P> 0.05 (**Figure 1**). In addition, Pearson's correlation test revealed no significant correlation between troponin-I level and FS after administration of daunorubicin, with r=0.172 and P>0.05 (**Figure 2**). However, Pearson's correlation test revealed a significant negative correlation between troponin-I levels and E/A ratio after the administration of daunorubicin. This variable had weak correlation, with r=-0.383 and P=0.019, indicating that increased troponin-I level was associated with decreased E/A ratio.

Table 1. Subjects' characteristics

Characteristics	(N = 37)
Mean age (SD), years	6.27 (4.43)
Sex, n	
Male	21
Female	16
Classification, n	
Morphology (French-American-British/FAB)	
ALL L1	20
ALL L2	13
Immunology classification	
T-cell leukemia	4
Mixed leukemia	0
Mean troponin-I (SD), ng/mL	5.49 (0.86)
Mean EF (SD), %	65 (5)
Mean FS (SD), %	36 (4)
Mean E/A ratio (SD)	1.52 (0.56)

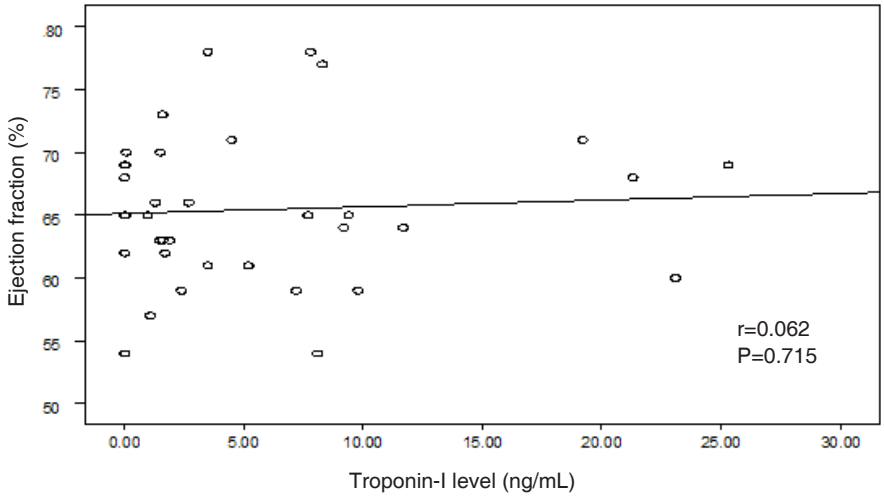

Figure 1. Analysis of troponin-I levels and EF post-daunorubicin administration

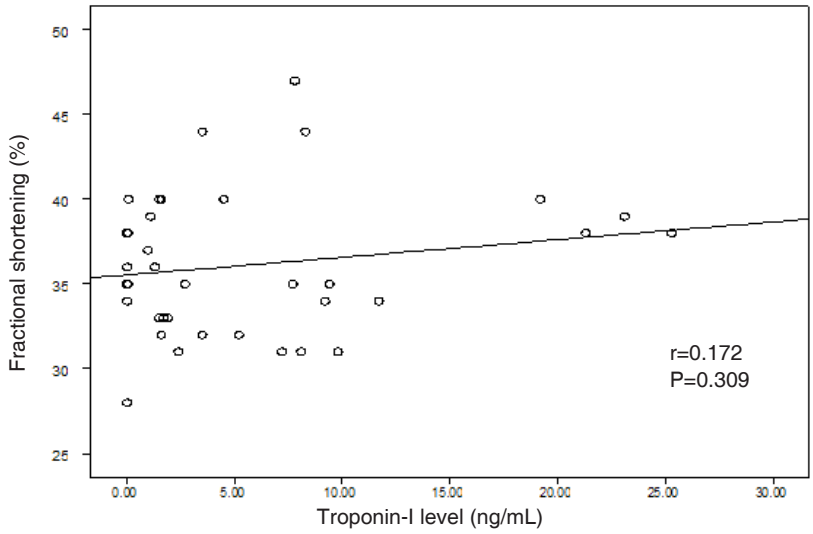

Figure 2. Analysis of troponin-I levels and FS post-daunorubicin administration

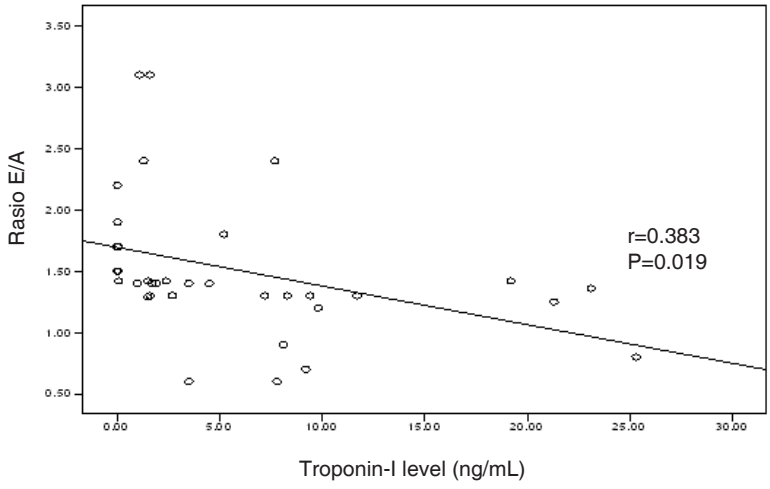

Figure 3. Analysis of troponin-I levels and E/A ratio post-daunorubicin administration

Discussion

Our subjects' mean age was 6.27 (SD 4.43) years, in agreement with other studies.[24,25] A study also found that the highest proportion of ALL was in children 1 to 9 years of age (49.5%).[26] Our subjects were predominantly male (21/37) and had type L1 ALL (20/37), similar to prior reports.[24,26,27]

Subjects' mean troponin-I level was 5.49 (SD 0.86) ng/mL, with a range of 0.01-25.30 ng/mL. Increased troponin-I is indicative of increased risk of cardiotoxicity.[14] The percentage of patients with elevated troponin-I in our study was higher than in a systematic review which reported elevated troponin levels in 30-34% of patients, or in about 1/3 of patients with cardiotoxic chemotherapy.[28] Troponin can be used to predict clinically significant left ventricular dysfunction over a minimum of the previous three months, as well as the degree and severity of future left ventricular dysfunction. Patients with persistently increased troponin values within one month after the last chemotherapy had an 85% probability of cardiac abnormalities.[28] The mechanism of increasing troponin-I levels may be related to myocardial injury.[29] Myocardial apoptosis occurs due to anthracycline (daunorubicin) infiltration in myocytes, causing

mitochondrial damage.[30] Troponin-I is a contractile protein released into circulation after myocardial damage.[31] Anthracycline-induced cardiotoxicity was found in 50% of patients who experienced an increase in troponin-I and in only 1.5% of patients with normal troponin-I levels.[29]

A previous study found that the average EF decreased by 3.3% and FS decreased by 2.5%, with a greater cumulative anthracycline dose at 300 mg/m^2.[32] In our study, there were no significant correlations between troponin-I levels and EF or FS, after daunorubicin treatment of high-risk ALL patients, with cumulative dose at 160 mg/m^2 ($P>0.05$).

While Rahman's study concluded that there was no statistically significant impairment of left ventricular systolic function in subjects after daunorubicin treatment, this condition may have been caused by a relatively low dose of daunorubicin and short follow-up.[33] A study reported that EF had low sensitivity to assess small changes in left ventricular function.[34] In contrast, other study reported a correlation between increased troponin-I and decreased EF in patients within one month after anthracycline therapy. They concluded that an increase in troponin-I could detect very small myocardial injuries that might lead to cardiac dysfunction.[35] In addition, another study found systolic dysfunction at long-term follow-up after daunorubicin administration,[36] possibly due to potential growth disorders and reduced heart muscle mass. Likewise, a study also reported a strong association between an increase in troponin values above normal and left ventricular EF ($r=-0.87$; $P<0.0001$). Their subjects also received other classes of drugs that strengthened cardiotoxic effects, such as ifosfamide or etoposide, and echocardiographic monitoring was carried out until seven months after troponin-I examination.[37] Two of our patients experienced a decrease in EF, but it did not reach 10%.

A study found impaired left ventricular systolic function in the form of a reduction in FS < 30%, even at a daunorubicin dose of < 100 mg/m^2.[7] There was no decrease in FS in our subjects. The FS is the most commonly used examination for detecting subclinical anthracycline cardiotoxicity.[9] Following the guidelines of the *Cardiology Committee of the Children's Cancer Study Group*, anthracycline cardiotoxicity is considered significant if there is a decrease in FS of < 10 percentile or < 29%.[38]

We assessed left ventricular diastolic function by E/A ratio, which reflects the difference in pressure gradient between the left atrium and left ventricle, shows the severity of diastolic dysfunction and pressure of left atrial and ventricular filling.[20] The diastolic function disturbance pattern can be in the form of a decrease in relaxation and restrictive pattern. The relaxation pattern includes the nadir of the E reduction, the peak of the A increase, and the E/A ratio decrease. The restrictive pattern includes the peak of E elevation, the nadir of A reduction, and the E/A ratio increase. The pattern of decreased relaxation is found on hypertrophic or dilated cardiomyopathy, left ventricular hypertrophy, ischemic heart disease, decreased preload as in dehydration, increased afterload as in excessive infusion and vasoconstriction. Restrictive patterns are found in restrictive cardiomyopathy and heart failure.[18]

Diastolic dysfunction is classified into grade 1 (E/A <0.8), grade 2 (E/A between 0.8 to 1.5), and grade 3 (E/A ≥ 2.0). Diastolic dysfunction grade I represents impaired myocardial relaxation with normal left ventricle filling pressures. Grade II represents impaired myocardial relaxation with mild to moderate elevation of LV filling pressures. Grade III with severe diastolic dysfunction and restrictive left ventricle filling occurs.[39] An E/A ratio <1 occurs in slow ventricular relaxation, but normal filling pressure. The left ventricular filling phase is not completed until the end of the diastolic phase and increases left atrial volume during atrial contraction, causing a larger A wave to offset the smaller E wave. An increase in the E/A ratio of > 2 is found in a reversible restrictive pattern, with reduced left ventricular flexibility, increased filling pressure, and slowed relaxation. The E wave velocity peaks with very fast deceleration indicating an increase in left ventricular stiffness.[40]

An early sign of cardiomyopathy due to anthracycline is a disorder in diastolic function.1 Left ventricular diastolic dysfunction without systolic dysfunction in adults and children after long-term anthracycline therapy is evidenced by radionuclide multi-gated acquisition (MUGA) method and Doppler echocardiography.[7] Handojo et al. found a decrease in diastolic function in more than half of patients who received anthracycline.[32] Decreased diastolic function precedes decreased systolic function,[41] while a study reported that diastolic function abnormalities were associated with increased anthracycline doses due to

impaired left ventricular relaxation and decreased mitral E peak velocity.[42]

In our study 21.6% of patients had diastolic dysfunction, three with grade 1 and five with grade 3. The normal mean E/A ratio was likely due to the short duration of patient follow-up. A previous study found increased E/A ratio in 8.7% of pediatric patients with ALL in the induction phase and cardiomyopathy in 5% in the consolidation phase.[25] Rahman's study also found diastolic dysfunction in children with ALL after a cumulative dose of 120 mg/m^2, while systolic function was not impaired.[33] Pearson's correlation test in our study revealed a significant, negative correlation between troponin-I levels and E/A ratio after the administration of daunorubicin.

A limitation of our study was that patients with anemia, infection, and history of hyperhydration could not be excluded from the study, because they were in the induction phase of chemotherapy, and many had anemia during the study period. Further more, our subjects could not be classified entirely by FAB or immunologically.

Further study is needed on diagnostic test design about troponin-I as a biomarker of cardiotoxicity in children receiving anthracycline chemotherapy, as well as a study with a cohort design for long-term monitoring of cardiotoxicity in children after receiving anthracycline chemotherapy.

Conflict of Interest

None declared.

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