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Clinical, Echocardiographic and Laboratory Cardiac Monitoring in Breast Cancer Patients Undergoing Chemotherapy with Anthracycline Agents: A Pilot Study on Cardioprotective Algorithms at Mohammad Hoesin General Hospital, Palembang

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Abstract

Background: Improved cancer therapy and early disease detection increase the survival rate, but also increase the risk of The risk of Cancer-Therapy Related Cardiac Dysfunction (CTRCD), which ranges between 2 and 48% for patients with breast cancer treated by anthracyclines. There was limited data about the prevalence of CTRCD in South Sumatra. Studying demographic factors and potential laboratory cardiac markers in a specific population will give others additional important information.

Methods: In 2024, from March until November, 30 breast cancer patients, aged 51.50 (41-69) years, were included in this analysis. All patients were receiving anthracycline chemotherapy at Mohammad Hoesin General Hospital. Demographic, laboratory, and echocardiographic data were collected at baseline and after 3 cycles of treatment.

Results: From 30 patients, cardiovascular risk factors were detected: hypertension 30%, diabetes 10%, dyslipidemia 13.3%, body mass index 23.32 (13.30- 31.18), and almost all patients were not smokers (96.7%). Baseline to serial echocardiography showed that anthracycline did not affect the decrease of left ventricular ejection fraction (LVEF) ($p=0.212$), but correlated with the decrease of left ventricle global longitudinal strain (GLS) ($p<0.05$). There were 16 patients with >15% global longitudinal strain (GLS) reduction, without significant clinical heart failure signs and symptoms, known as mild asymptomatic CTRCD. Laboratory examination showed anthracycline agent was not correlated with Troponin T ($p=0.093$), N-terminal pro B-type Natriuretic Peptide BNP ($p=0.150$), Serum Iron ($p=0.775$), Total Iron Binding Capacity (TIBC) ($p=0.692$), and Transferrin Saturation ($p=0.748$). Ferritin level was affected by anthracycline agents ($p = 0.026$).

Conclusion: Higher prevalence of CTRCD in the South Sumatra population was found. There was a low incidence of cardiovascular risk factors in this population, indicating a stronger isolated effect of the chemotherapy agent for cardiac dysfunction progression. GLS by echocardiography measurement remains a good marker for cardiotoxicity related to anthracycline agents. Ferritin level is a potential parameter in guiding the stages and strategies in cancer treatment.

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Keywords: *anthracycline, cardiac dysfunction, global longitudinal strain, ferritin.*

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Introduction

Breast cancer has the highest prevalence among women. The improvement of cancer therapy has increased the survival rate. Anthracycline is a common chemotherapy agent for patients with breast cancer. Increased survival has allowed to observe cardiotoxic effects of anthracycline. Early detection of myocardial dysfunction in patients treated by anthracyclines may improve cardiologic prognosis through chemotherapy dose adjust and ensure cardioprotective agents during chemotherapy.[1,2] Patients with cardiovascular risk factors increased the risk for cancer progression and cardiotoxicity since there were similar risk factors for both cardiovascular disease and cancer. Overweight and obesity are known to be risk factors for cardiotoxicity.[3] Detection of cardiotoxicity by echocardiography and biomarkers was important in early diagnosis of cancer-therapy related cardiac dysfunction (CTRCD).[4]

Echocardiography measurement includes cardiac mechanics by myocardial strain and ejection fraction. Speckle tracking echocardiography, also known as strain imaging, analyzes deformation by motion changes in a myocardial wall without relying on the endocardial border. This novel echocardiographic technique allows early detection of myocardial dysfunction, before global reduction of cardiac function.[5] The left ventricular ejection fraction (LVEF) is classically used to measure cardiac contractility and guide cardioprotective strategy during chemotherapy.[6,7] Unfortunately, LVEF was not sensitive enough in detecting minimal impairment of myocardium, until the cardiac dysfunction becomes moderate to severe.[8] Some echocardiography techniques are also potentially used to increase the accuracy of cardiotoxicity detection, such as stress echocardiography,[4] D, and contrast echocardiography.[9] Laboratory biomarkers, such as troponin measurement at completion of chemotherapy, are useful in predicting subsequent cardiotoxicity.[10,11] The earlier recognition of cardiotoxicity will help guide treatment to avoid cardiac disease progression. Future biomarkers and imaging techniques for CTRCD detection could enable pre-identify the risk of cardiotoxicity, so that a multidimensional approach can reduce cardiac disease progression while achieving the cancer treatment goal.

Methods

Study Design

This study is observational and correlational analytic with cross-sectional design. The measurement was applied to 30 breast cancer patients treated by anthracycline chemotherapy. Demographic data was collected, such as age, gender, cardiovascular risk factors, hypertension, dyslipidemia, diabetes, body mass index, and smoking status. Echocardiography and laboratory measurements were performed twice, at baseline data before chemotherapy and after the third cycle of chemotherapy.

Echocardiography

Standard trans-thoracal echocardiography for left ventricular ejection fraction value was performed, besides the main parameter, speckle tracking echocardiography or strain imaging. This study used an echocardiography machine, GE Vivid-E95. All patients were examined with conventional 2-dimensional, M-Mode, color Doppler ultrasonography and speckle tracking echocardiography. Left ventricular ejection fraction (LVEF) was performed using a method by Simpson. Echocardiography measurement was conducted by a cardiologist.

Cancer-Therapy Related Cardiac Dysfunction (CTRCD)

CTRCD based on clinical presentation and symptoms was included very severe to mild symptomatic CTRCD and severe to mild asymptomatic CTRCD. Asymptomatic mild CTRCD was defined if there was LVEF > 50% and a new relative decline of left ventricular global longitudinal score (GLS) by >15% from baseline measurement (before chemotherapy), and/or a new rise in cardiac biomarker.

Laboratory measurements

Recent studies have suggested that measurement of cardiac serum biomarkers, Troponin I or T, and N-terminal pro B-type natriuretic peptide (NT pro BNP) helps in stratifying the risk of cardiotoxicity of patients scheduled for chemotherapy. Other potential cardiac markers were important to measure since the rule

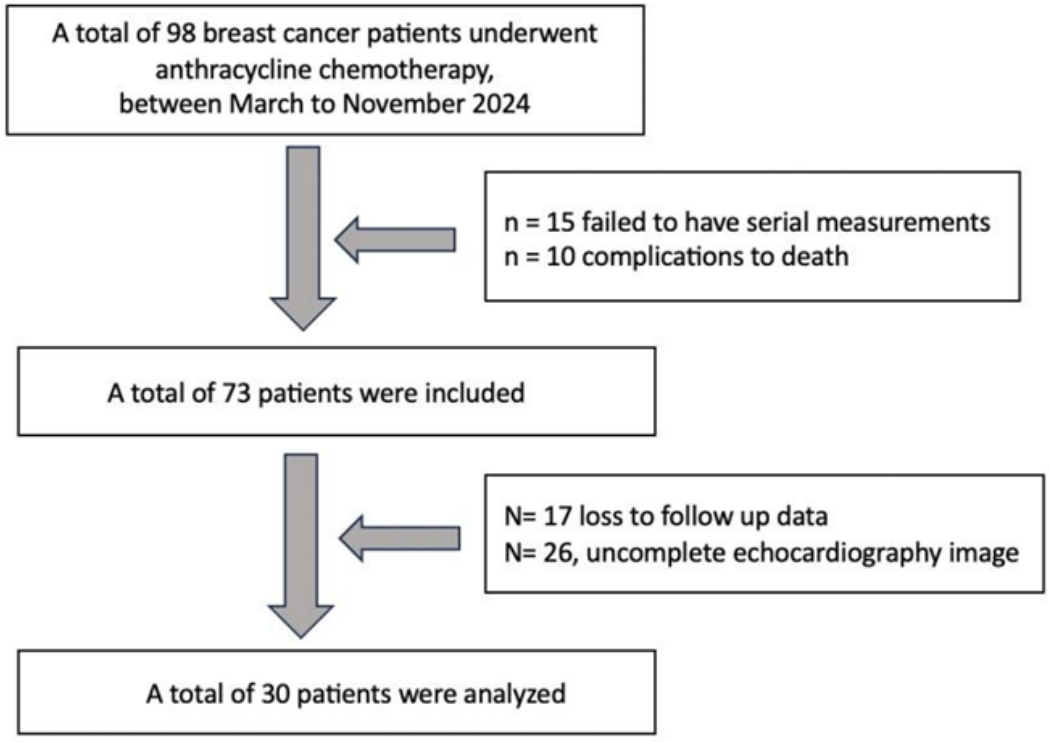

Figure 1. Study Population.

of heart failure consists of neurohormonal-metabolism pathways, such as serum iron, Total Iron-Binding Capacity (TIBC), ferritin, and transferrin saturation (TSAT).

Statistical Analysis

Statistical analysis was performed using SPSS software (SPSS, Chicago, IL). Data were expressed as mean ± SD for normal data and median (range) for abnormal data, with the Kolmogorov-Smirnov test. Bivariate analysis was used to obtain the correlation of the data in different variables.

Results

Study Population

A total of 30 patients were analyzed, from 98 patients included at the beginning of the study, who discontinued the study due to fatal incidence because of cancer and chemotherapy treatment, worsening general fitness, and failed to obtain optimal serial measurements.

Table 1 explains the baseline characteristics, echocardiographic, and laboratory parameters of the patient. The data was obtained before chemotherapy. Cardiotoxicity risk stratification was scored based on criteria from the Cardio-Oncology Study Group of the Heart Failure Association (HFA) of the ESC in collaboration with the International Cardio-oncology Society (HFA-ICOS). All patients were in low cardiotoxicity risk stratification.

Patients in this study was analyzed before and during anthracycline chemotherapy. The data before and during chemotherapy are expressed in Table 2.

The changes of laboratory parameters during chemotherapy in this study were significant in ferritin level with p value < 0.05 (p= 0.026), giving the probability that anthracycline chemotherapy correlated with ferritin level.

In this study, the LVEF of all patients were > 50%, and 16 patients (53.3%) with >15% decline of GLS, indicated asymptomatic mild CTRCD. Echocardiography parameters in 30 patients, before and during chemotherapy, showed LVEF baseline 61.33 ±

Table 1. Baseline characteristics.

	N = 30 Mean/Median ± SD
Age, years	52.70 ± 7.8
Body Mass Index,	23.52 ± 4.85
LVEF, %	61.33 ± 4.908
GLS, %	-15.94 ± 3.705
Troponin T, ng/L	24 ± 6.281
NT pro BNP, pg/ml	184,46 ± 207,095
Serum Iron, g/dL	55.2 ± 25.389
TIBC, g/dL	346.83 ± 30.748
Ferritin, ng/ml	347.15 ± 260.507
Transferrin saturation (%)	15.70 ± 4.949

4.908 reduced to 59.70 ± 6.727, with p value 0.212 (p>0.05) explained the weak correlation of LVEF and anthracycline chemotherapy. Mean baseline GLS was -15.940 ± 3.705 %. Mean decline of GLS was 22.559 ± 19.722 %, with p = 0.00, explained the correlation of GLS score with anthracycline chemotherapy (p<0.05). The patients with CTRCD have a mean age of 51.06 ± 8.136 years old and a body mass index 23.40 ± 5.69, with an incidence of hypertension 31.2%, type 2 diabetes mellitus 12.3%, dyslipidemia 12.3%, and 3.3% were smokers. Laboratory data of 16 patients with CTRCD were expressed in Table 3.

Ferritin level was significantly increased (p<0.05) from baseline to serial measurement, both in all 30 patients and 16 patients with CTRCD.

More echocardiography parameters were analyzed in 27 patients of this study, since 3 patients were identified to have incomplete data for analysis. Echocardiography parameters were expressed in Table 4.

Echocardiography data in Table 5 showed no significant correlation of those parameters before and during anthracycline chemotherapy in this study (p>0.05). In 27 patients, CTRCD was identified in the same patients of the total 30 samples. Mean decline of GLS was 22.559 ± 19.722 %, with p = 0.00.

Discussion

In this study, we found a high incidence of asymptomatic mild CTRCD (53,3%) and a higher incidence of cardiovascular risk factors in patients with CTRCD compared with a general population of patients with breast cancer treated with anthracycline chemotherapy. Age and preexisting left ventricular dysfunction have been identified most consistently as being associated with the development of clinical heart failure or a worsening of left ventricular function with chemotherapy. The cumulative dose of anthracycline or its formulation and additional chemotherapeutic agents such as anti-HER2, besides existing cardiovascular risk factors, have been known to be associated with the risk of cardiotoxicity.[13]

Laboratory findings

Ferritin level in this study was consistent to be significant associated with anthracycline chemotherapy. International guidelines on heart failure define iron deficiency as serum ferritin

<100 ng/mL or, when ferritin is 100-299 ng/mL, a transferrin saturation (TSAT) <20%. 14,15,16 However, a definition based basically on ferritin has several limitations. Most ferritin resides in cells where it binds to iron to prevent free radical production. Any cell damage, including activation of inflammatory pathways, may cause ferritin to be released; an increase in serum ferritin may occur even in the presence of iron deficiency.[17] Bone marrow biopsy as a gold-standard diagnosis demonstrates iron deficiency even when ferritin is higher.[18] Observational studies suggest that serum iron concentration and TSAT were strongly associated

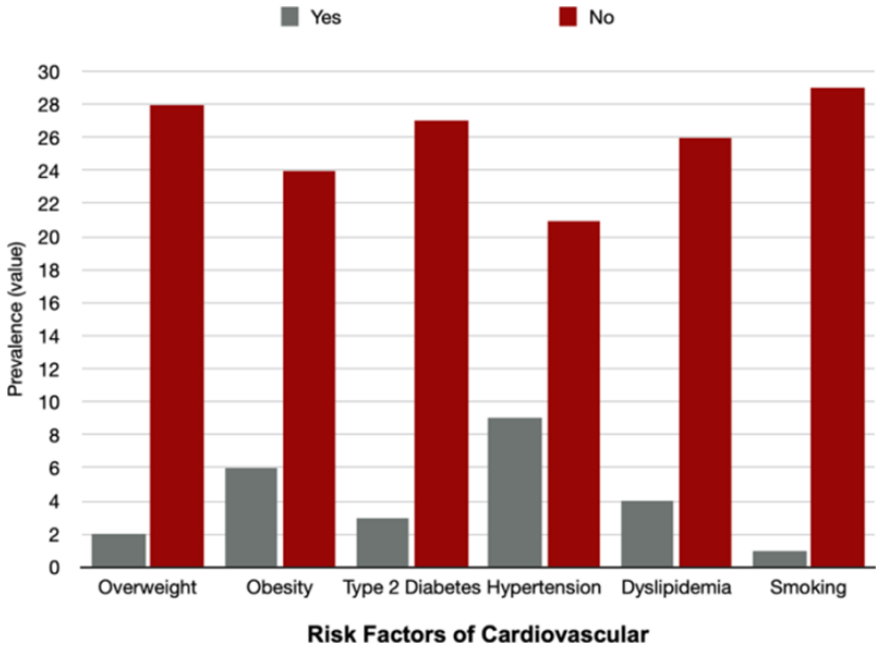

Figure 2. Incidence of cardiovascular/ cancer risk factors Patients in this study was analyzed before and during anthracycline chemotherapy.

with prognosis than serum ferritin; therefore might be a better guide to which patients benefit from parenteral iron supplementation.[18,19,20,21,22] Inflammation was an important process in the pathogenesis of cancer. The serum ferritin is elevated in inflammatory conditions and cancers. This is related to increased synthesis in macrophages, hepcidin promotes the entry of iron into the macrophages. Ferritin and ferritin/ Hb are helpful in the differential diagnosis of the stages of breast cancer. [23] Other biochemical parameters favorable for helping diagnose and stage breast cancer were hepcidin, hs-CRP, besides ferritin/Hb ratio. Increasing ferritin in breast cancer patients help identified the progressive stages of the cancer, including breast cancer patients with early cardiac dysfunction, identified as CTRCD.

Echocardiography parameters

Early cardiac dysfunction in this study was identified through speckle tracking echocardiography, producing a left ventricular global longitudinal strain (GLS) score. The 15% decline or more of GLS has strongly related to anthracycline chemotherapy in patients with breast cancer. Other parameters, including ejection fraction, RV distance, RV strain, TAPSE, RA area, and LAVI were not significantly associated with anthracycline chemotherapy. As those parameters already recommended by the international guideline of cardio-oncology, the routine measurement was still important to identified cardiac toxicity expressed with structural or functional changes in response to different chemotherapy agents.[12]

Implementation of cardiac monitoring, a guideline disparity

In Indonesia, generally cardiac monitoring related to chemotherapy was found as part of routine cardiac service in a cardiovascular clinic. The oncologist referred the patients to a cardiologist to be assessed and examined with echocardiography to stratify the cardiotoxicity risk, establish the cardiotoxicity diagnosis, and gave recommendations considering the result of the analysis. ESC ACC guideline of cardio-oncology listed the complete data of structural heart condition, chemotherapy agents, prior chemotherapy history, cardiovascular risk factors, and comorbid to establish cardiotoxicity risk stratification. In routine cardiology service, the data of chemotherapy agents was difficult to obtained, because of inadequate information in digital

Table 2. Echocardiographic parameters ratio between two groups.

	Mean/median ± SD (N=30)		p value
	Baseline	After 3 cycles	
Troponin T (ng/L)	24.00 ± 6.281	26.6 ± 6.055	0.093
NT pro-BNP (pg/ml)	184.46 ± 207.095	100.18 ± 111.259	0.150
Serum Iron (µg/dL)	55.20 ± 25.389	53.19 ± 11.228	0.775
TIBC (µg/dL)	346.83 ± 30.748	341.90 ± 18.613	0.692
Ferritin (ng/ml)	347.15 ± 260.507	462.06 ± 272.845	0.026
Transferrin saturation (%)	15.70 ± 4.949	15.53 ± 2.688	0.748

Table 3. Laboratory data of patients with CTRCD.

	Mean/median ± SD (N=16)		p value
	Baseline	After 3 cycles	
Troponin T (ng/L)	23.75 ± 6.213	26.94 ± 5.531	0.066
NT pro-BNP (pg/ml)	102.27 ± 158.919	110.69 ± 139.953	0.600
Serum Iron (µg/dL)	51.87 ± 9.378	52.93 ± 11.781	0.764
TIBC (µg/dL)	342.69 ± 22.057	338.94 ± 23.124	0.638
Ferritin (ng/ml)	260.27 ± 174.883	419.09 ± 298.142	0.021
Transferrin saturation (%)	15.13 ± 2.306	15.50 ± 2.805	0.684

Table 4. Echocardiography parameters.

	Mean/median ± SD (N=27)		p value
	Baseline	After 3 cycles	
RV distance (mm)	28.444 ± 4.585	28.593 ± 3.619	0.179
RA area (mm^2)	11.204 ± 2.985	11.137 ± 2.970	0.619
RV strain (%)	-17.57 ± 4.002	-18.71 ± 5.114	0.648
TAPSE (mm)	22.481 ± 3.167	23.481 ± 2.208	0.177
LAVI (ml/m^2)	26.76 ± 10.321	23.53 ± 7.617	0.158
LVEF (%)	61.11 ± 5.026	60.00 ± 6.397	0.389

RV, right ventricle; RA, right atrium; TAPSE, tricuspid annular plane systolic excursion; LAVI, left atrial volume index; LVEF, left ventricle ejection fraction

form sent by oncologists (medical record problem), and the flow of patients to the echocardiography unit was earlier than decision making for chemotherapy agents (patient's flow problem). The other condition was the dynamic response of chemotherapy, more over cancer progression, resulting in adjusted dose of chemotherapy agents and addition number of chemotherapy agents. On the other hand, the period of cardiac monitoring in the ESC ACC guideline was limited to only some chemotherapy agents. Furthermore complete digital system and well-organized patients' flow will support the better implementation of the ESC ACC guideline of cardio-oncology that rooted in cardiologist-oncologist collaboration.

Study Limitations

The patients' flow in several departments made the data was not well documented and became a limitation for the complete analysis. A structured collaborative working group in cancer treatment would minimize the data loss. This study also needs more samples to accurately analyze the incidence and factors contributing to cardiotoxicity in the South Sumatra population. A prospective long-period study will give useful data to reduce the incidence and progression of cardiac toxicity in a high-survival era of cancer treatment.

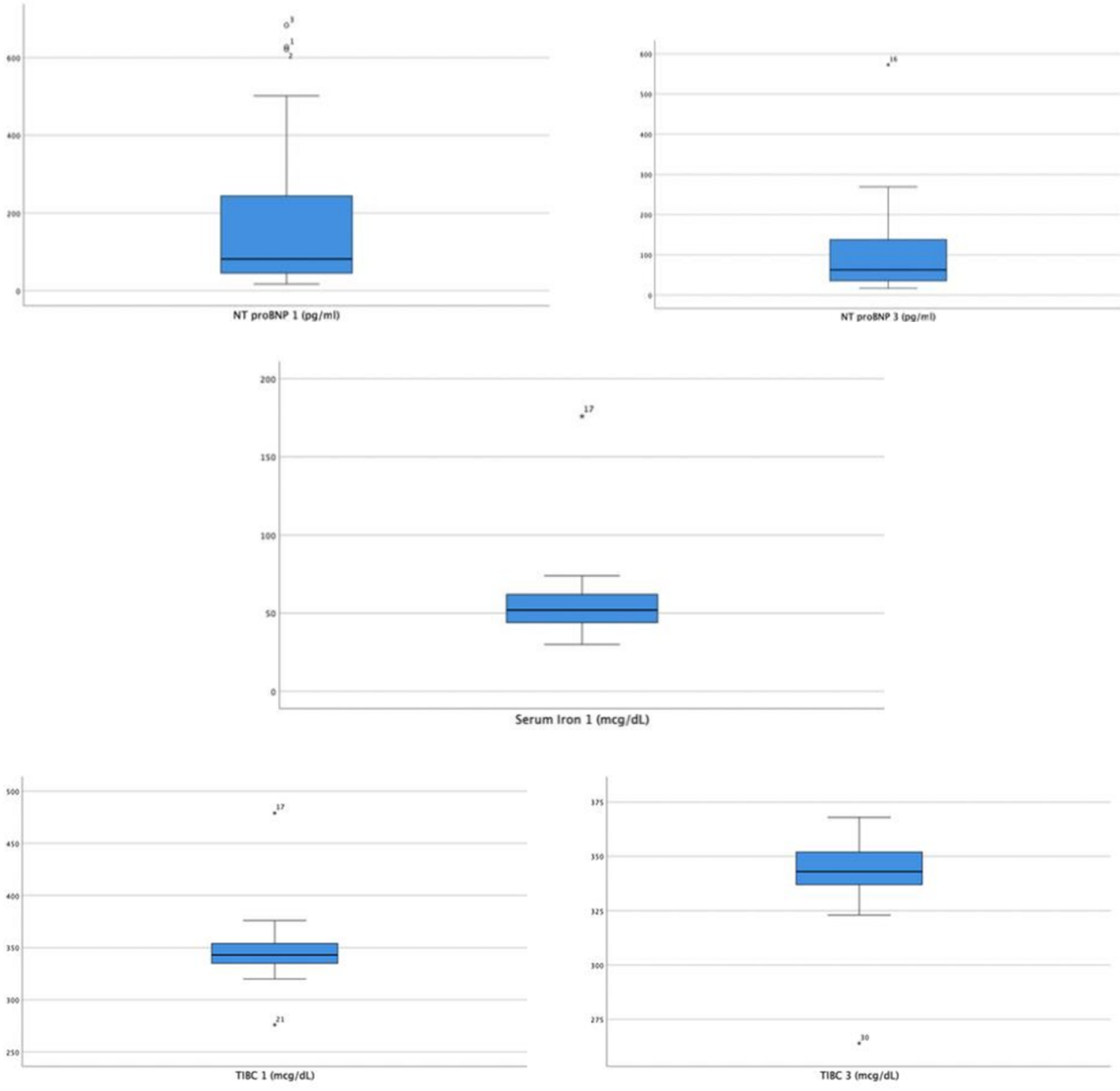

Figure 3. Outliers in laboratory data.

Conclusion

Speckle tracking echocardiography with left ventricular GLS score remains the main measurement to identify early cardiac dysfunction in patients with breast cancer who have undergone anthracycline chemotherapy, include in the South Sumatra population. A high incidence of cardiac toxicity was found, with a documented low incidence of cardiovascular risk factors. Laboratory parameters also play an important role in guiding stages and strategies in the treatment of cancer, together with optimal utilities of imaging modalities, including echocardiography. A future study was needed to identify specific potential factors that contribute to the incidence and progressivity of cardiotoxicity.

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List of Abbreviations

CRTCD	Cancer-therapy related cardiac dysfunction
HFA	Heart failure association
GLS	Global longitudinal strain
ICOS	International cardio-oncology society
LAVI	Left atrial volume index
LVEF	Left ventricular ejection fraction
NT pro-BNP	N-terminal pro B-type natriuretic peptide
RA	Right Atrial
RV	Right ventricle
TAPSE	Tricuspid annular pane systolic excursion
TIBC	Total iron-binding capacity
TSAT	Transferrin saturation

References

1. Nicolazzi MA et al. Anthracycline and trastuzumab-induced cardiotoxicity in breast cancer. *Eur Rev Med Pharmacol Sci*. 2018; 22(7):2175–2185 .
2. Lotrionte M et al. Review and meta-analysis of incidence and clinical predictors of anthracycline cardiotoxicity. *Am J Car- diol*. 2013; 112(12):1980–1984
3. Guenancia C et al. Obesity as a risk factor for anthracyclines and trastuzumab cardiotoxicity in breast cancer: a systematic review and meta-analysis. *J Clin Oncol*. 2016; 34(26):3157–3165.
4. Sawaya H, Sebag IA, Plana JC, Januzzi JL, Ky B, Tan TC, et al. Assessment of echocardiography and biomarkers for the extended prediction of cardiotoxicity in patients treated with anthracyclines, taxanes, and trastuzumab. *Circ Cardiovasc Imaging*. 2012; 5(5):596–603.
5. Thavendiranathan P, Poulin F, Lim KD, Plana JC, Woo A, Marwick TH. Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: a systematic review. *J Am Coll Cardiol*. 2014; 63:2751–68.
6. Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American society of echocardiography and the European association of cardiovascular imaging. *J Am Soc Echocardiogr*. 2014; 27(9):911–39.
7. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, et al. 2016 ESC position paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC committee for practice guidelines: the task force for cancer treatments and cardiovascular toxicity of the European society of cardiology (ESC). *Eur J Heart Fail*. 2017; 19(1):9–42.
8. Thavendiranathan P, Poulin F, Lim KD, Plana JC, Woo A, Marwick TH. Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: a systematic review. *J Am Coll Cardiol*. 2014; 63:2751–68.
9. Sijia Wang, Yi Wang, Shuang Wang The role of stress echocardiography in identifying cardiotoxicity: an in-depth exploration. *Front Cardiovasc Med*. 2024; 26;11;1236966.
10. Mavinkurve-Groothuis AM, Marcus KA, Pourier M, Loonen J, Feuth T, Hoogerbrugge PM, et al. Myocardial 2D strain echocardiography and cardiac biomarkers in children during and shortly after anthracycline therapy for acute lymphoblastic leukaemia (ALL): a prospective study. *Eur Heart J Cardiovasc Imaging*. 2013; 14(6):562–9.
11. Cicilia I, Leonita A, Nugroho J, Desak GAS. Correlation between changes of NT –proBNP and HS-Troponin I levels with cardiotoxicity in breast cancer after three cycles of CAF chemotherapy. Indonesian Journal of Clinical Pathology and *Medical laboratory*. 2019; 26(1):71-75
12. Lyon A.R., Lopez-Fernandez T., Couch L.S., et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology

(ESTRO) and the International Cardio-Oncology Society (IC-OS) *Eur Heart J Cardiovasc Imaging*. 2022; 23:e333–e465.
13. Tamar S Polonsky, Jeanne M DeCara. Risk factors for chemotherapy-related cardiac toxicity. *Curr Opin Cardiol*. 2019; 34(3):283-288.
14. Masini, G, Graham, F, Pellicori, P. et al. Criteria for Iron Deficiency in Patients With Heart Failure. *JACC*. 2022 Feb, 79 (4) 341–351.
15. McDonagh T.A., Metra M., Adamo M., et al. "2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC". *Eur Heart J* 2021;42:36: 3599-3726.
16. YC W., Mariell J., Biykem B., et al. "2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure". *J Am Coll Cardiol* 2017;70:6: 776-803.
17. Lopez A., Cacoub P., Macdougall I.C., Peyrin-Biroulet L. "Iron deficiency anaemia". *The Lancet* 2016;387:907-916.
18. Grote Beverborg N., Klip IjT., Meijers W.C., et al. "Definition of iron deficiency based on the gold standard of bone marrow iron staining in heart failure patients". *Circ Heart Fail* 2018;11:2: e004519.
19. Okonko D.O., Mandal A.K.J., Missouris C.G., Poole-Wilson P.A. "Disordered iron homeostasis in chronic heart failure: Prevalence, predictors, and relation to anemia, exercise capacity, and survival". *J Am Coll Cardiol* 2011;58:12: 1241-1251.
20. Moliner P., Jankowska E.A., van Veldhuisen D.J., et al. "Clinical correlates and prognostic impact of impaired iron storage versus impaired iron transport in an international cohort of 1821 patients with chronic heart failure". *Int J Cardiol* 2017;243:360-366.
21. Cleland J.G.F., Zhang J., Pellicori P., et al. "Prevalence and outcomes of anemia and hematinic deficiencies in patients with chronic heart failure". *JAMA Cardiol* 2016;1:5: 539-547.
22. Graham F.J., Masini G., Pellicori P., et al. "Natural history and prognostic significance of iron deficiency and anaemia in ambulatory patients with chronic heart failure". *Eur J Heart Fail Published online* May 28, 2021. https://doi.org/10.1002/ejhf.2251.
23. Anila G, Zachariah B, Biswajit D. Utility of ferritin and inflammatory biomarkers in the diagnosis of different stages of breast cancer. *Saudi Med J*. 2021 Aug;42(8):825-831.