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Original Article

Right Ventricle Free Wall Longitudinal Strain in Cancer Patients Following Chemotherapy

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ABSTRACT

Introduction: *The survival rate of cancer patients was high due to chemotherapy, but it can cause cardiotoxicity and increase morbidity and mortality. Most studies on cancer therapy-related cardiac dysfunction (CTRCD) focus more on the left ventricle. This study assesses chemotherapy's effect on the right ventricle, namely the right ventricle free wall longitudinal strain (RVFWLS).* ***Methods:*** *This study is a prospective cohort conducted from January to December 2022 on thirty-four cancer patients undergoing chemotherapy at Dr. Wahidin Sudirohusodo Hospital Makassar. The RVFWLS was assessed before and after chemotherapy using* echocardiographic*.* ***Result:*** The RVFWLS before chemotherapy was significantly lower (-23.33±3.53) compared to post-chemotherapy (-18.41±5.95) (p<0.001). The positive value of RVFWLS was noted after the chemotherapy procedure (4.92±4.88). ***Conclusion:*** *The effect of chemotherapy is a decrease in the RVFWLS value after the first cycle of chemotherapy. It should be considered for echocardiographic evaluation, especially the RVFWLS value for every cycle of chemotherapy.*

1. INTRODUCTION

With around 10 million deaths yearly, cancer is the second leading cause of mortality worldwide. In South Sulawesi, around 10.3% of cancer patients receive chemotherapy treatment. Based on Riset Kesehatan Dasar data in 2018, around one million Indonesians suffer from various types of cancer. About 24% of cancer patients in Indonesia receive chemotherapy treatment to manage their cancer. Meanwhile, the total number of cancer patients in South Sulawesi Province reached up to thirty-three thousand people, or around 1.6% of the entire population of South Sulawesi.[1,2] Advances in cancer treatment can improve patient survival and increase morbidity and mortality due to treatment side effects. Cardiovascular disease is one of the most common side effects and is feared to cause morbidity and premature death in cancer patients. This can occur due to the cardiotoxic effects of chemotherapy or the rapid development of cardiovascular disease if the patient already has previous cardiovascular risk factors.[3,4]

The persistence of cardiotoxic effects, even without symptoms, negatively affects prognosis and limits therapeutic opportunities. Clinical manifestations of chemotherapy-induced cardiotoxicity range widely from ischemia, arrhythmias, hypertension, left ventricular dysfunction, and heart failure. Heart failure caused by the effects of chemotherapy tends to have a worse prognosis than ischemic or idiopathic cardiomyopathy, so there is a need for better understanding and management procedures in this regard. The incidence of cardiotoxicity from the CARDIOTOX registry in 2020 was 37.5%. This registry monitors for 24 months post-chemotherapy. Early detection in the study was by performing an echocardiographic examination of left ventricular function and biomarkers to detect cardiotoxicity.[5]

Histologically, cardiotoxicity more often affects the sub-endocardial portion of the heart wall. The right ventricle is smaller and contains fewer myocytes than the left ventricle, making it theoretically more sensitive to the toxic effects of chemotherapy, but data are lacking.[6] The right ventricle's anatomical shape and contraction pattern are difficult to establish on plain echocardiography. A new echocardiography technique, namely speckle tracking echocardiography or speckle tracking echocardiography, provides a new picture of the right ventricle function assessment. Several studies have found that changes in strain can predict changes in RV systolic function which can consistently predict the occurrence of heart failure. Right ventricle free wall longitudinal strain (RVFWLS) examination was found to be superior to other parameters in the early detection of the development of cancer therapy-related cardiac dysfunction (CTRCD) in cancer patients.[7,8]

The majority of research on the effect of chemotherapy on heart function is more focused on the left ventricle, so we raised the effect of chemotherapy on the right ventricle, namely RVFWLS. Currently, no available data describes the RVFWLS value of cancer patients undergoing chemotherapy in the Makassar area, especially at Dr. Wahidin Sudiro Husodo General Hospital. It is also unknown whether there is a difference in the RVFWLS value of cancer patients before and during chemotherapy.

Based on the description above, it is necessary to conduct a study to determine changes in the value of RVFWLS in cancer patients undergoing chemotherapy.

2. METHODS

2.1 Study design

This type of research is a prospective cohort study during January-December 2022. The protocol of this study has been approved by the Ethics Committee of Biomedical Research on Humans, Faculty of Medicine, Hasanuddin University and Dr. Wahidin Sudirohusodo Hospital, Makassar, with registration number 223/UN4.6.4.5.31/PP36/2022 (Approval date: May 17th, 2022).

2.2 Subject

The subject of this study was cancer patients undergoing chemotherapy and referred to the cardiology department of Dr. Wahidin Sudirohusodo Hospital, aged more than 18 years old and completed chemotherapy for 1 cycle. The other inclusion criterion was that the echocardiographic result could analyze the RVFWLS.

2.3 RVFWLS measurement

RVFWLS was measured using a GE Vivid E95 echocardiography device *(GE Healthcare, USA)* and image processing using EchoPAC software version 203 *(GE Healthcare, USA)*. This two-dimensional speckle-tracking echocardiography procedure was performed before chemotherapy and repeated after one cycle of chemotherapy. RVLS is measured in the RV-focused apical four-chamber view, which provides better visualization of the whole right ventricle and avoids foreshortening of the RV apex. The frame rate is between 60 and 80 frames per second. High-quality images are essential for RV strain analysis. After endocardial border delineation, the software automatically segments the right ventricle into six segments (basal, middle, and apical segments of both the RV free wall and the interventricular septum), and tracks the movement of speckles in the myocardium throughout the cardiac cycle on two-dimensional echocardiographic images. Finally, RV longitudinal strain curves of the free wall and septum are automatically generated by the software. Two cardiologists performed validation of echocardiographic with an intraclass correlation coefficient of intra-observer reproducibility (ICC=0,91) whereas inter-observer agreement was 90%.

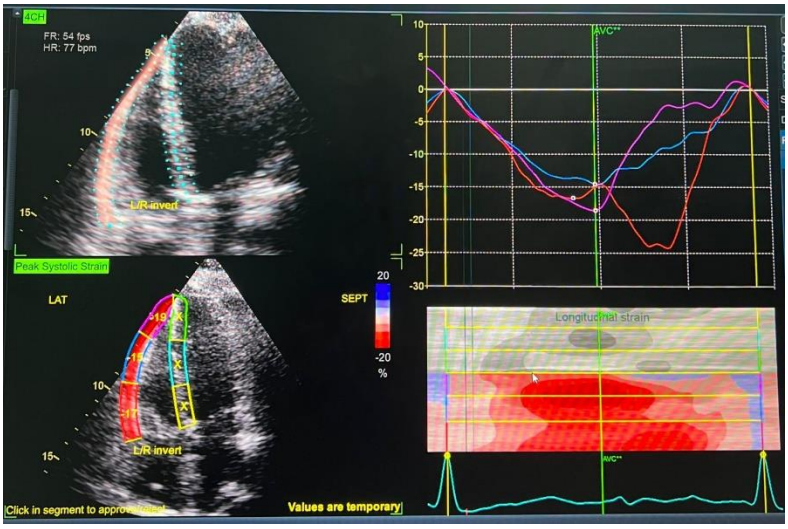

Figure 1. Result of RVFWLS

2.4 Data analysis

Data were processed using Statistical Package for Social Science (SPSS) software version 28 *(IBM, Chicago, USA).* The value of RVFWLS before and after chemotherapy was presented as mean±standard deviation (X±SD). A paired T-test was performed to assess the difference in the mean value of RVFWLS with $p<0.05$ considered a significant difference.

3. RESULTS

3.1 Subject number

During the observation time, 351 patients were recruited 248 patient was excluded because the echocardiographic result was poorly visualized. During the follow-up, 69 samples were lost to follow-up for various reasons. This resulted in 34 samples that could be analyzed for this study **(Figure 2).**

3.2 Subject characteristic

The subject distribution was dominated by females (94.1%). The malignancy type was dominated by breast cancer (85.3%) and non-breast cancer (14.7%).

Most of the subjects received anthracycline, alkylating agent, anti-microtubule-based chemotherapy regimen (n=15; 44%), followed by anthracycline, anti-microtubule (n=7; 20%), then anthracycline and alkylating agent (n=3; 9%), trastuzumab, alkylating agent (n=2; 6%) **(Table 1)**.

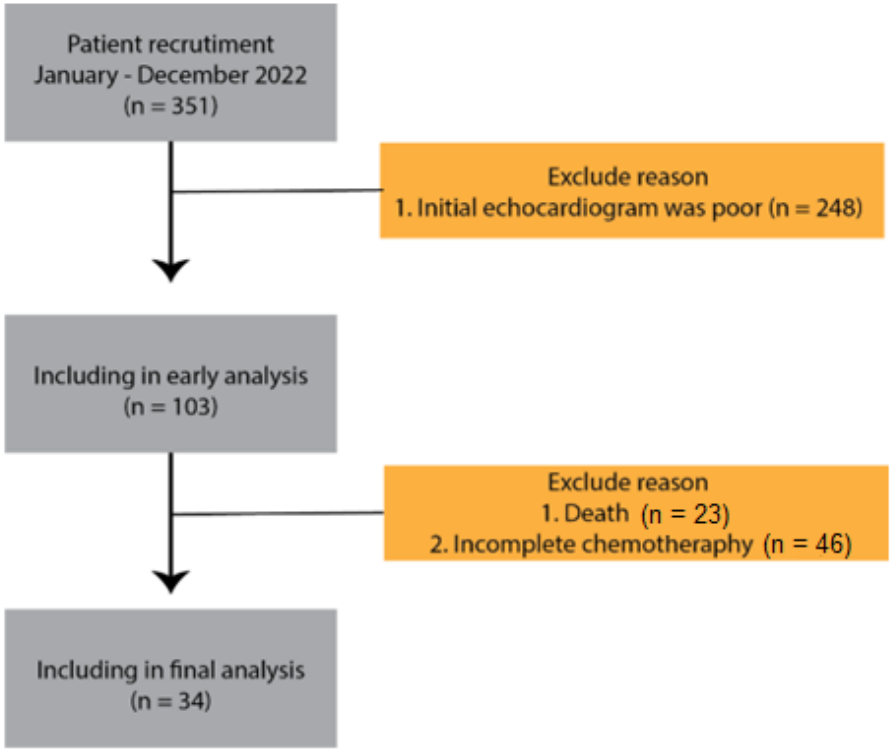

Figure 2. Participants flow diagram.

Table 1. Subject characteristics and distribution of chemotherapy agent used.

Variable	Number (%)
Age (years)	**48.44±10,56**
Body mass index	**22.44±3.65**
Sex	
Male	2 (5.9)
Female	32 (94.1)
Malignancy type	
Breast	29 (85.3)
Non-breast	5 (1.7)
Chemotherapy Agent	
anthracyclines, alkylating agents, anti-microtubule	15 (44)
anthracyclines, alkylating agents, other agents	1 (3)
anthracyclines, alkylating agents	3 (9)
anthracyclines, anti-microtubule, anti-metabolite	1 (3)
anthracyclines, anti-microtubule, anti-metabolite	1 (3)
anthracyclines, anti-microtubule	7 (20)
anthracyclines, anti-microtubule, trastuzumab	1 (3)
alkylating agent, anti-microtubule	1 (3)
alkylating agent, anti-microtubule, anti-metabolite	1 (3)
alkylating agent, trastuzumab	2 (6)
anti-metabolite, other agents	1 (3)

3.3 RVFWLS value

The RVFWLS in the cancer patient before chemotherapy was significantly lower (-23.33±3.53) compared to post-chemotherapy (-18.41±5.95) (p<0.001). The positive value of RVFWLS was noted after the chemotherapy procedure (4.92±4.88) **(Figure 3)**.

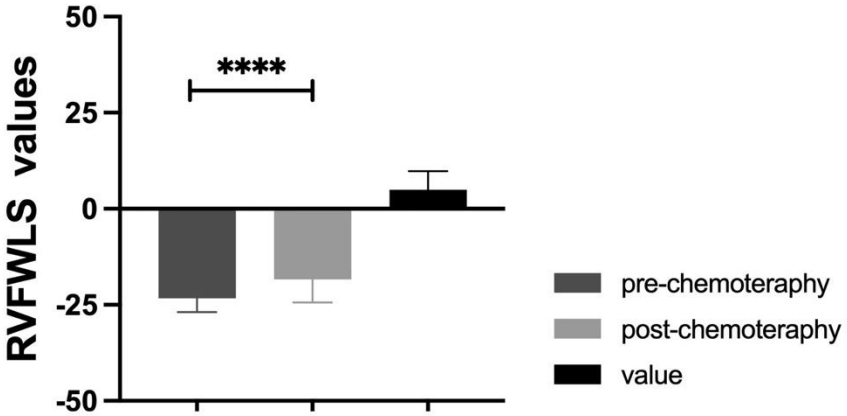

Figure 3. The RVFWLS value before and after chemotherapy in 34 subjects of cancer patients. The differences in RVFWLS value were significantly lower compared to post-chemotherapy (p<0.001)

The sub-analyses of two anthracycline chemotherapy (doxorubicin and epirubicin) showed a positive value of RVFWLS. The doxorubicin showed a positive value of RVFWLS (2.63±2.44; p<0.05). The epirubicin showed a positive value of RVFWLS value (4.40±4.84; p<0.01) **(Figure 4)**.

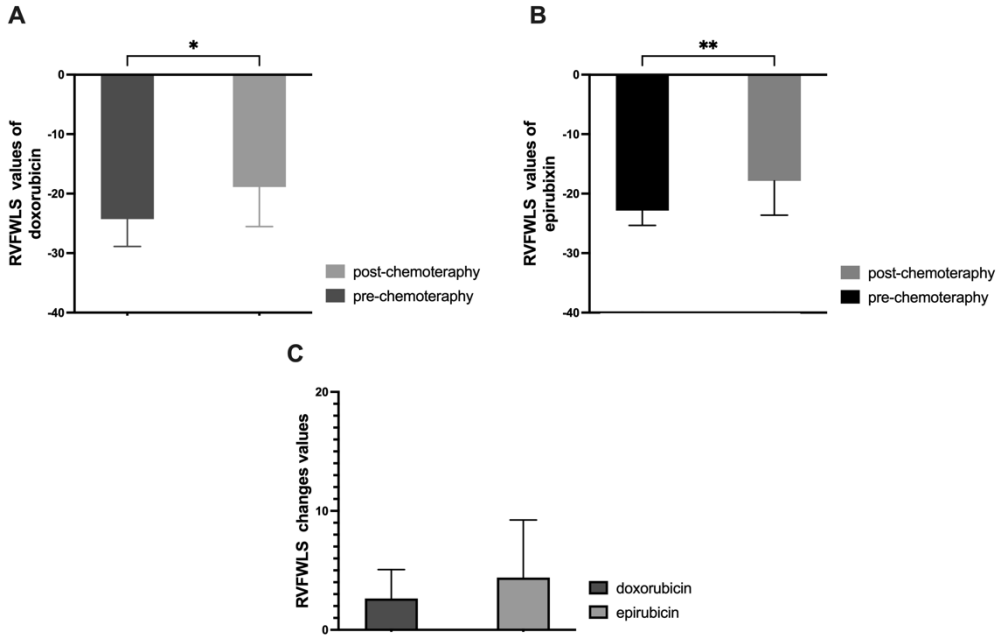

Figure 4. The RVFWLS value before and after chemotherapy using different anthracycline chemotherapy in cancer patients. (A) Doxorubicin; (B) Epirubixin; (C) Anthracycline chemotherapies showed RVFWLS changes values were positive. *p<0.05 and **p<0.0`

4. DISCUSSIONS

Most of the samples in this study were female (94.1%). Most study samples were patients diagnosed with breast cancer (85.3%). In Indonesia, breast cancer is most commonly reported compared to other types of cancer.[1,2]

This study is the first study that aims to assess right ventricular systolic function through advanced echocardiographic parameters of RVFWLS in patients with cancer or malignancies undergoing chemotherapy in Makassar. This study found a change in right ventricular systolic function in the form of a decrease in RVFWLS value before and after chemotherapy.

Right ventricular dysfunction is not considered in diagnosing CTRCD, and its incidence and prognostic value have not been well studied. In addition, ASE recommends assessing RV function during cancer treatment. RV function was associated with changes in oxygen, hemodynamics, and capacity function. In histological studies, cardiotoxic damage is more prominent in the subendocardial portion of the heart wall. The right ventricle has a thinner wall that is more sensitive to the effects of chemotherapy, although data are lacking to support this hypothesis.[6] In our study, there was a decrease in RVFWLS from before chemotherapy (-23.33 ± 3.53) to after chemotherapy (-18.41 ± 5.95) with a p-value <0.001. This is the same as the research conducted by Cherata et al, where they found a decrease in RVFWLS within 6 months.[9]

In this study, most patients received chemotherapy regimens containing anthracyclines. Anthracyclines are first-line chemotherapy regimens and have been used in breast cancer therapy for more than 30 years. Anthracyclines are known to be effective against malignancies other than breast cancer and are widely used worldwide. The risk of cardiotoxicity also accompanies this. The risk of anthracycline cardiotoxicity increases as the dose increases. Based on ASO, doses of doxorubicin ≥ 250 mg/m2, and epirubicin ≥ 600 mg/m2 increase the risk of cardiotoxicity. So that many efforts are made to reduce the level of cardiotoxicity, one of which is using early detection using echocardiography.[10,11,12]

We performed a subanalysis on two anthracycline chemotherapy regimens: doxorubicin and epirubicin. Our study found a decrease in RVFWLS from -24.28 ± 4.60 (pre-chemotherapy) to -18.89 ± 6.64 (post-chemotherapy) with a p-value =0.002. In a study conducted by Planek et al on 35 patients with lymphoma who were given doxorubicin regimens, subclinical RV dysfunction was found, where the patient's LVEF value was still good. RV dysfunction is a prognostic marker and predictor of mortality in cardiomyopathy and heart failure patients.[13]

In a study by Chang et al, 35 patients were given epirubicin therapy. Then echocardiographic assessment was carried out before chemotherapy, after the first cycle, and after the third cycle. RVFWLS examination is sensitive in predicting the occurrence of shortness of breath in breast cancer patients given epirubicin therapy. This is similar to our subanalysis, where we found a change in RVFWLS values from -22.84 ± 2.50 (pre-chemo) to -17.86 ± 5.75 (post-chemo) in patients given epirubicin regimen (p = 0.002).[7]

Frequently used anthracycline regimens are epirubicin and doxorubicin. The occurrence of cardiotoxicity is increased in anthracyclines related to cumulative dose. The dose of doxorubicin ≥ 250 mg/m2 and epirubicin ≥ 600 mg/m2 increases the risk of cardiotoxicity. At cumulative doses, epirubicin was less cardiotoxic than doxorubicin.

Whereas epirubicin appears to have a better side effect profile than doxorubicin.[14] In our subanalysis, the change in RVFWLS in the doxorubicin regimen was 5.39 ± 5.49 and epirubicin was 4.98 ± 4.59 with a p-value of 0.76. Where the value of change in RVFWLS is greater in the doxorubicin regimen.

A study by Xu et al on 95 breast cancer patients given epirubicin showed dysfunction of RV function. They concluded that longitudinal strain analysis can subclinically assess RV dysfunction when conventional RV function is still good. RVFWLS examination is superior to other parameters in detecting CTRCD early in breast cancer patients.[8]

5. CONCLUSION

In malignancy patients undergoing chemotherapy, there is a decrease in the RVFWLS value after the first cycle of chemotherapy. It should be considered for echocardiographic evaluation, especially the RVFWLS value for every cycle of chemotherapy. Further analysis is needed by correlating other echocardiographic parameters and RVWLS in malignancy patients undergoing chemotherapy.

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Conflict of Interest Statement:

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.