ЗАГАЛЬНІ ПИТАННЯ ЛІКУВАННЯ ПАЦІЄНТІВ ІЗ СЕРЦЕВО-СУДИННОЮ ПАТОЛОГІЄЮ

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Ejection Fraction Decline and Cardiotoxicity Following Anthracycline Chemotherapy: A Risk-Focused Study from an Indonesian Tertiary Care Center

Abstract

Background. Anthracycline chemotherapy is a cornerstone of cancer treatment but poses a risk of cardiotoxicity, often presenting as cancer therapy–related cardiac dysfunction (CTRCD). Monitoring left ventricular ejection fraction (LVEF) is essential to detect early cardiac impairment and support safer treatment strategies.

Aim. To assess LVEF changes after six cycles of anthracycline therapy and identify predictive factors associated with CTRCD.

Materials and methods. This observational pre–post study included 74 patients treated with anthracyclines at Dr. Wahidin Sudirohusodo Hospital, Makassar, from 2024 to 2025. LVEF was measured via echocardiographic surveillance before and after treatment. Cardiotoxicity was defined as a ≥ 10 % decrease in LVEF to ≤ 50 %. Statistical tools included Wilcoxon signed-rank test, Chi-square, ROC curve analysis, and logistic regression.

Results. The mean LVEF significantly declined from 63.08 % to 56.76 % (p = 0.001). CTRCD occurred in 20.3 % of patients. Risk factors independently associated with cardiotoxicity included age \geq 51 years (OR 2.80; p = 0.016) and cumulative anthracycline dose \geq 457.5 mg/m² (OR 3.25; p = 0.004). When both factors were present, the risk increased nearly sixfold (OR 5.75; p = 0.001).

Conclusions. CTRCD was observed in one-fifth of patients following anthracycline therapy, with age and dose being significant contributors. These findings support the integration of risk-based echocardiographic surveillance into oncology care to ensure early detection and mitigate long-term cardiac complications.

Keywords: Anthracycline, Cardiotoxicity, Cancer Therapy–Related Cardiac Dysfunction, Echocardiographic Surveillance, Cumulative Dose, Ejection Fraction

Introduction

Cancer remains one of the primary causes of global morbidity and mortality, with approximately 19.3 million new cases and 10 million deaths reported annually, according to the Global Cancer Observatory (GLOBOCAN) 2024. In Indonesia, the incidence of cancer continues

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to rise, imposing a growing burden on the healthcare system. Multiple treatment strategies are available for cancer patients, including surgery, radiotherapy, immunotherapy, and chemotherapy. Chemotherapy, a cornerstone in cancer treatment, acts by disrupting the proliferation and division of malignant cells. Despite its therapeutic effectiveness, it is frequently associated with a wide range of adverse effects, including hematologic toxicities—such as neutropenia, anemia, and thrombocytopenia, as well as non-hematologic

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complications. These non-hematologic effects may involve various organ systems, with cardiotoxicity being one of the most serious, due to its potential to impair cardiac function significantly [1-3].

a commonly used Anthracyclines, class of chemotherapeutic agents, are highly effective in the treatment of breast cancer, lymphoma, and leukemia. Nevertheless, their use carries a recognized risk of cardiotoxicity, potentially leading to structural and functional cardiac damage, such as reduced left ventricular ejection fraction (LVEF), arrhythmias, and even congestive heart failure. Cardiotoxic effects can present in acute, subacute, or chronic forms, with irreversible myocardial injury especially likely when cumulative doses exceed the recommended threshold of 450 mg/m^2 . The underlying mechanism involves the overproduction of free radicals, resulting in oxidative stress that damages cardiomyocytes and impairs mitochondrial activity. Additional risk factors—such as advanced age, preexisting cardiovascular conditions, cumulative dosage, and comorbidities including hypertension and diabetesfurther exacerbate cardiotoxic outcomes [4-7].

Given these risks, early detection and consistent monitoring of cardiac function are essential for patients undergoing anthracycline therapy. Echocardiography is widely utilized as a non-invasive tool to assess LVEF, serving as a critical parameter for evaluating cardiac performance during treatment. Importantly, research conducted by De Angelis et al. has shown that LVEF reductions may persist for up to five years following chemotherapy in breast cancer patients, highlighting the long-term nature of anthracycline-induced cardiotoxicity and its implications for patient quality of life [8-10].

Aim. This study aimed to evaluate changes in LVEF among cancer patients who had completed a minimum of six cycles of anthracycline-based chemotherapy and to identify clinical and treatment-related factors associated with cardiotoxicity. The study aimed to provide a better understanding of the long-term cardiac effects of anthracycline exposure, support the development of evidence-based monitoring strategies, and contribute to the early detection and management of cancer therapyrelated cardiac dysfunction.

Materials and methods. A pre- and post-test study was conducted at Dr. Wahidin Sudirohusodo Hospital, a tertiary referral center in Makassar, Indonesia. Ethical approval was obtained from the Ethics Committee of the Faculty of Medicine, Hasanuddin University (Approval No.: 88/UN4.6.4.5.31/PP36/2025). The study included all patients recorded in the hospital's medical records from 2024 to 2025 who received at least six cycles anthracycline chemotherapy. Inclusion criteria of encompassed patients aged ≥18 years with normal renal and hepatic function, a baseline LVEF >55 %, consent to participate, and completion of echocardiographic assessments before and after the chemotherapy regimen. Patients with a history of valvular heart disease, coronary artery disease, or cardiovascular events during chemotherapy that precluded continuation of therapy were excluded.

Cardiotoxicity Definition. Cardiotoxicity in this study was defined based on current cardio-oncology guidelines from the European Society of Cardiology (ESC 2022), the International Cardio-Oncology Society (IC-OS 2022), and the European Association of Cardiovascular Imaging (EACVI 2016). Cancer therapy-related cardiac dysfunction (CTRCD) was considered present when there was a reduction in LVEF of ≥ 10 % points from baseline to an absolute value of ≤ 50 %, in the absence of clinical signs or symptoms of heart failure [18-20].

Data Analysis. Data analysis was performed using SPSS version 25 (IBM Corp., Armonk, NY). Descriptive statistics and frequency distributions were utilized to summarize the data. The Chi-square test assessed associations between variables. Paired t-tests and Wilcoxon signed-rank tests evaluated significant changes in LVEF pre- and post-chemotherapy. Receiver Operating Characteristic (ROC) curve analysis determined the optimal cumulative anthracycline dose cut-off associated with a ≥ 10 % reduction in LVEF from baseline to an absolute value of ≤ 50 %. A p-value <0.05 was considered statistically significant.

Results. A total of 74 patients met the inclusion criteria and were enrolled in the final analysis. Among them, 39 were male (52.7 %) and 35 were female (47.3 %), with ages ranging from 18 to 72 years. The majority (67.5 %) were under 51 years of age, while 32.5 % were 51 years or older. Most patients (78.4%) had no known comorbidities. Hypertension was recorded in 9.5 % of cases, diabetes mellitus type 2 in 6.8 %, and both conditions concurrently in 5.4 %. Regarding cancer type, lymphoma was the most prevalent malignancy (55.4%), followed by osteosarcoma (25.7 %), breast cancer (14.9 %), and leukemia (4.1 %). Anthracycline dosing varied according to cancer type: 52.7 % of patients received a cumulative dose between 401-500 mg/m², primarily for breast cancer and non-Hodgkin lymphoma; 41.7 % received 201-400 mg/m², typically for osteosarcoma, Hodgkin lymphoma, and leukemia; and 5.4 % received less than 200 mg/m², exclusively in osteosarcoma cases. Based on current ESC and IC-OS definitions, 15 patients (20.3 %) were identified as having CTRCD, defined as a decline in LVEF of ≥ 10 percentage points to an absolute value of ≤ 50 % (table 1).

Baseline and post-treatment LVEF measurements indicated a statistically significant decline. The average pre-chemotherapy LVEF was 63.08 % (SD±3.81), which decreased to 56.76 % (SD±6.49) after six cycles of anthracycline-based chemotherapy. This corresponds to a mean reduction of 6.36 percentage points, or approximately 10.02 %. The difference was statistically significant (p = 0.001, Wilcoxon signed-rank test) (table 2).

Further analysis showed no significant association between LVEF decline and either sex (p = 0.406) or comorbidities (p = 0.264). However, age was a statistically significant factor. Among patients aged 51 years or older, 37.5 % experienced a decrease in LVEF of ≥ 10 %,

Table 1

Characteristics of Study Participants

Variables	n	%
Sex		
Male	39	52.7
Female	35	47.3
Age Group		
<51 years	50	67.5
≥51 years	24	32.5
Comorbidities		
None	58	78.4
Hypertension	7	9.5
Diabetes Mellitus Type 2	5	6.8
Hypertension and Diabetes Mellitus Type 2	4	5.4
Types of Malignancy		
Breast Cancer (Doxorubicin)	11	14.9
Lymphoma (Doxorubicin)	41	55.4
Leukemia (Daunorubicin)	3	4.1
Osteosarcoma (Doxorubicin)	19	25.7
Cumulative Anthracycline Dose		
< 200 mg (Osteosarcoma)	4	5.4
201-400 mg (Osteosarcoma, Hodgkin Lymphoma, Leukemia)	31	41,7
401-500 mg (Breast Cancer, Non- Hodgkin Lymphoma)	39	52.7
Cardiotoxicity		
Cardiotoxic (≥10 % reduction in LVEF from baseline to ≤50 %)	15	20.27
Non-cardiotoxic	61	79,73

Source: personal data, 2025

compared to only 12 % in those under 51 years of age (p = 0.006) (table 3).

A dose-dependent relationship was observed between cumulative anthracycline exposure and the incidence of LVEF decline. None of the patients who received less than 200 mg/m^2 experienced cardiotoxicity. In contrast, 9.7 % of those receiving $201-400 \text{ mg/m}^2$ and 30.8 % of those receiving more than 400 mg/m² developed a reduction in LVEF of ≥ 10 % to ≤ 50 %. The difference among these groups was statistically significant (p = 0.007) (Table 4).

Receiver operating characteristic (ROC) curve analysis identified a cumulative anthracycline dose of 457.5

Table 2

LVEF Before and After Anthracycline Chemotherapy

 mg/m^2 as the optimal threshold for predicting a ≥ 10 % reduction in LVEF to ≤50 %. This cutoff demonstrated an area under the curve (AUC) of 0.831, with a sensitivity of 73.3 % and specificity of 72.9 %, indicating strong discriminatory power (figure 1).

Bivariate logistic regression analysis demonstrated that both age and cumulative anthracycline dose were independently associated with a significant reduction in LVEF. Patients aged 51 years or older had 2.8 times higher odds of developing cardiotoxicity compared to younger patients (OR 2.80; 95 % CI: 1.20-6.51; p = 0.016). Similarly, those who received a cumulative anthracycline dose of \geq 457.5 mg/m² were at a significantly greater risk (OR 3.25; 95 % CI: 1.45–7.30; p = 0.004). When both risk factors were present, the likelihood of LVEF decline increased synergistically, with an odds ratio of 5.75 (95 % CI: 2.10–15.7; p = 0.001), indicating a compounded effect (table 5).

Discussion. This study demonstrated a statistically significant reduction in LVEF following anthracycline chemotherapy, with an average decline of 6.36 percentage points, or 10.02 % from baseline (p = 0.001). This reflects direct myocardial toxicity, particularly after six cycles of treatment. The findings are consistent with previous research by Cardinale et al. [12] and Curigliano et al. [11], which identified increased cardiotoxicity risk at cumulative doses exceeding 250- 450 mg/m^2 .

Age also emerged as a significant factor. Patients aged 51 years or older experienced greater reductions in LVEF, likely related to age-associated cardiovascular changes such as decreased vascular compliance and elevated oxidative stress. These results align with earlier studies noting a heightened susceptibility to cardiotoxicity in older populations. No significant associations were observed between LVEF decline and gender or comorbidities (hypertension or diabetes), though hypertension remains a known compounding factor in heart failure progression, as discussed by Sawaya et al. [13].

The dose-dependent relationship between anthracycline exposure and cardiotoxicity was reaffirmed: 30.8 % of patients receiving >400 mg/m² experienced a significant decline in LVEF, while none in the <200 mg/m² group did. This mirrors data from Swain et al. [14] and Cardinale et al. [12], who identified cumulative thresholds of 450–550 mg/m² as critical markers of risk. The use of higher cumulative anthracycline doses in this cohort primarily reflects established treatment protocols for breast

Parameter Mean Std. deviation Median Minimum-Maximum n p value Pre-Chemo 74 63.08 3.81 63.00 57.00-69.00 Post-Chemo 74 56.76 6.49 59.00 40.00-68.00 0.001* Reduction 0 6.36 4.00 17.00-1.00 -

*Wilcoxon signed-rank test

Table 3

78

Association Between Confounding Variables and Decrease in LVEF

		LVEF Change			
Variabel	-	Normal	Decreased ≥10% from baseline to EF <55 %	<i>p</i> value	
Comorbidities	None	46	12	0.264	
	Hypertension	7	0		
	DM Type II	4	1		
	Hypertension and DM Type II	2	2		
Sex	Male	32	7	0.406	
	Female	27	8		
Age Group	< 51 years	44	6	- 0.006*	
	≥ 51 years	15	9		

*Chi-square test

Table 4

Association Between Cumulative Anthracycline Dose and LVEF Reduction

Cumulative Dose (mg)	Normal LVEF (n)	≥10 % Decrease from Baseline to EF ≤50 % (n)	Total (n)	p value
< 200 mg	4	0	4	
201-400 mg	28	3	31	0.007*
>400 mg	27	12	39	0.007*
Total	59	15	74	-

Note: Chi-square test



Figure 1. ROC Curve of Cumulative Anthracycline Dose in Predicting LVEF Reduction

cancer and non-Hodgkin lymphoma, which often require intensified regimens beyond 400 mg/m². These patterns are consistent with accepted oncologic practice and provide context for the observed cardiotoxicity rates.

Applying the updated CTRCD definition [18–20], 20.3 % of patients met criteria for cardiotoxicity. This highlights the urgency of early detection and individualized cardiac surveillance for patients receiving anthracyclines. The importance of proactive monitoring is further supported by Seidman et al. [6] and Cardinale et al. [12], who advocate for early imaging to prevent progression to overt heart failure.

ROC analysis validated 457.5 mg/m² as the optimal threshold for predicting LVEF decline, consistent with regional studies. In Korea, Kang et al. [15] identified a 455 mg threshold; in Singapore, Chen et al. [16] reported a 460 mg cut-off in breast cancer patients with an AUC of 80 %. These parallels suggest a consistent cardiotoxicity threshold across Asian populations. Supporting this, a local study by Wahdiyat et al. [17] showed that cardiac impairment may occur even before high cumulative doses are reached, particularly within the first three cycles. Collectively, these findings emphasize the need for routine echocardiographic monitoring throughout treatment, especially as patients near or exceed a cumulative dose of 450 mg/m².

In our analysis, both cumulative dose and age were independently associated with cardiotoxicity. Patients over 51 years of age and those exposed to \geq 457.5 mg/m² had a significantly higher likelihood of experiencing LVEF

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Table 5

Bivariate Logistic Regression Analysis of Age and Cumulative Dose on LVEF Reduction ≥10 %

		LVEF Change				
Variable		Normal LVEF	Decreased ≥10% from baseline to EF ≤50 %	OR	95 % CI	<i>p</i> value
Cumulative Dose	<457,5 mg	43	4	3.25	1.45 – 7.30	0.004 *
	≥457,5 mg	16	11			
Age Group	< 51 years	44	6	- 2.80	1.20 - 6.51	0.016 *
	≥ 51 years	15	9			

*Bivariate logistic regression test

decline. When both risk factors were present, the odds of cardiotoxicity increased nearly sixfold. This reinforces earlier findings by Swain et al. [14] and Cardinale et al. [12], who demonstrated the combined impact of age-related vulnerability and dose intensity.

These observations support a shift toward individualized cardiac monitoring. According to the 2022 ESC guidelines on cardio-oncology [18], baseline risk assessment should be conducted before initiating anthracycline therapy. Risk factors include older age, pre-existing cardiovascular disease, and high anticipated cumulative dose. Although this study did not employ prospective risk stratification, all patients underwent echocardiographic assessment before and after treatment. Current recommendations advise that high-risk individuals undergo more frequent imaging—typically every two to three chemotherapy cycles. Our findings underscore the need to integrate risk-based echocardiographic surveillance into oncology protocols to facilitate early detection of subclinical cardiac injury and improve long-term outcomes.

Strengths and Limitations. This study employed a pre- and post-intervention design to evaluate the impact of six cycles of anthracycline chemotherapy on LVEF. The comprehensive use of statistical tools, including ROC curve analysis and logistic regression, allowed for the identification of critical risk factors such as cumulative dose \geq 457.5 mg/m² and patient age over 51 years. Conducted at Dr. Wahidin Sudirohusodo Hospital—a national referral and tertiary care center—the findings of this study are applicable to comparable clinical settings across Indonesia, particularly those managing high-risk oncology populations. A key limitation of the research lies in the absence of long-term follow-up beyond the sixth chemotherapy cycle. Given that anthracycline-induced cardiotoxicity may progress or emerge after a latency period, future studies with extended observation windows are essential. Nevertheless, the results contribute significantly to clinical practice by identifying high-risk patients and highlighting the necessity of routine LVEF monitoring to mitigate long-term cardiac complications.

Conclusions. This study demonstrated a significant decline in left ventricular ejection fraction after six cycles of anthracycline-based chemotherapy, particularly among patients aged 51 years and older and those exposed to cumulative doses \geq 457.5 mg/m². These findings highlight the critical importance of routine echocardiographic monitoring—both before treatment initiation and throughout chemotherapy—to enable early detection of subclinical cardiotoxicity. Integrating risk-based cardiac surveillance protocols into oncology care is essential to prevent irreversible cardiac dysfunction and improve long-term outcomes for cancer patients.

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80 Загальні питання лікування пацієнтів із серцево-судинною патологією

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Зниження фракції викиду та кардіотоксичність після хіміотерапії антрациклінами: дослідження, орієнтоване на ризик, проведене в індонезійському центрі третинної медичної допомоги

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Хіміотерапія антрациклінами є наріжним каменем лікування онкологічних захворювань, але створює ризик кардіотоксичності, часто проявляючись у вигляді серцевої дисфункції, пов'язаної з лікуванням онкологічних захворювань. Моніторинг фракції викиду лівого шлуночка (ФВЛШ) є важливим для раннього виявлення серцевої недостатності та підтримки безпечніших стратегій лікування.

Мета. Оцінити зміни ФВЛШ після шести циклів терапії антрациклінами та визначити прогностичні фактори серцевої дисфункції, пов'язаної з лікуванням онкологічних захворювань.

Матеріали та методи. Це спостережне дослідження до та після лікування включало 74 пацієнтів, які отримували антрацикліни в лікарні доктора Вахідіна Судірохусодо, Макассар, з 2024 по 2025 рік. ФВЛШ вимірювалася за допомогою ехокардіографії до початку лікування та після його завершення. Кардіотоксичність визначали як зниження ФВЛШ на ≥10% до ≤50%. Статистичні інструменти включали критерій знакових рангів Вілкоксона, χ^2 -критерій, аналіз ROC-кривих та логістичну регресію.

Результати. Було виявлено значне зниження середнього значення ФВЛШ з 63,08% до 56,76% (р = 0,001). У 20,3% пацієнтів спостерігалася кумулятивна кардіотоксичність. Фактори ризику, незалежно пов'язані з кардіотоксичністю, включали вік ≥51 рік (відношення шансів (ВШ) 2,80; р = 0,016) та кумулятивну дозу антрацикліну ≥457,5 мг/м² (ВШ 3,25; р = 0,004). За наявності обох факторів ризик збільшувався майже в шість разів (ВШ 5,75; р = 0,001).

Висновки. Кумулятивна кардіотоксичність спостерігалася у п'ятої частини пацієнтів після терапії антрациклінової терапії, причому вік та доза були значними факторами, що сприяли розвитку цього явища.

Ці дані підтверджують необхідність інтеграції ехокардіографічного спостереження в онкологічну допомогу для забезпечення раннього виявлення та лікування ускладнень з боку серцево-судинної системи.

Ключові слова: антрациклін, кардіотоксичність, серцева дисфункція, пов'язана з терапією раку, ехокардіографічний нагляд, кумулятивна доза, фракція викиду.

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