

Plasma Galectin-3 as a Predictor of Cardiac Dysfunction in Patients Undergoing Doxorubicin Chemotherapy: A Prospective Cohort Study

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ABSTRACT

Background: Doxorubicin is widely used in chemotherapy in oncology. However, it is associated with dose-dependent cardiotoxicity. Thus, early detection of cardiac dysfunction is crucial to preventing heart failure. This study aimed to evaluate plasma Galectin-3 levels, a biomarker of fibrosis and inflammation, as a predictive biomarker of cardiac dysfunction in cancer patients receiving doxorubicin chemotherapy. **Methods:** This observational prospective cohort study was conducted from June 2024 to February 2025 at the Integrated Cardiac Service of Cipto Mangunkusumo National General Hospital (RSCM) and Dharmais Cancer Hospital in Jakarta. Fifty-five patients completed plasma Galectin-3 and echocardiographic assessments at three time points: pre-chemotherapy, post-chemotherapy cycle 2, and post-cycle 4. Cardiac dysfunction was defined by a decrease in LVEF $\geq 10\%$ or a GLS reduction $\geq 15\%$. **Results:** No cardiac dysfunction was observed pre-chemotherapy, but 34.5% and 50.9% of patients developed dysfunction after cycles 2 and 4, respectively. Galectin-3 levels increased significantly post-cycle 4 (mean: 46.89 ± 18.34 ng/mL; $p < 0.05$). Receiver operating characteristic analysis showed that post-cycle 4 Galectin-3 levels predicted cardiac dysfunction with an area under the curve of 0.767 (95% CI: 0.638–0.897; $p = 0.001$), 92.9% sensitivity, and 59.3% specificity at a cut-off of ≥ 37.28 ng/mL. Significant correlations were observed between Galectin-3 and GLS ($r = 0.54$; $p = 0.00$) but not LVEF. **Conclusion:** Plasma Galectin-3 levels, particularly after chemotherapy cycle 4, are sensitive biomarkers for detecting cardiac dysfunction in patients receiving doxorubicin. Integrating Galectin-3 with GLS may provide better detection of subclinical cardiotoxicity. Additionally, monitoring Galectin-3 levels may help identify high-risk patients requiring cardioprotective strategies.

Keywords: Galectin-3, cardiotoxicity, doxorubicin, cardiac dysfunction, echocardiography, global longitudinal strain

INTRODUCTION

Doxorubicin remains a cornerstone chemotherapeutic agent for various malignancies, including breast cancer and lymphoma.¹ Despite its therapeutic efficacy, doxorubicin is associated with dose-dependent cardiotoxicity that may progress to irreversible heart failure.² The incidence of cardiac dysfunction due to doxorubicin is estimated to reach up to 37.5%, contributing to morbidity among cancer survivors and imposing considerable healthcare burdens.³ The mechanisms of doxorubicin-induced cardiotoxicity include oxidative stress, genetic dysregulation, and cardiomyocyte apoptosis.⁴ These effects increase both morbidity and mortality among cancer patients, thus raising substantial healthcare costs.⁵

Current monitoring approaches rely primarily on conventional left ventricular ejection fraction (LVEF) measurements using echocardiography, which often detect dysfunction only after clinically significant cardiac damage has occurred.⁶ This limitation underscores the urgent need for more sensitive biomarkers capable of identifying subclinical cardiac dysfunction and predicting future adverse cardiac events before irreversible damage ensues.

Emerging evidence highlights Galectin-3, a β -galactoside-binding lectin, as a key mediator of myocardial fibrosis, inflammation, and ventricular remodeling.⁷ Its expression is significantly upregulated in cardiac injury and may serve as a biomarker for predicting chemotherapy-induced cardiotoxicity.⁸ Several studies have established Galectin-3 as a critical biomarker involved in fibrosis, inflammation, and ventricular remodeling in the failing myocardium.^{9,10} Importantly, elevated Galectin-3 levels negatively correlate with LVEF and positively correlate with N-terminal pro-B-type natriuretic peptide (NT-proBNP), positioning it as a potential predictive biomarker for cardiac dysfunction.¹¹

A study by Christenson et al. (2010) showed that Galectin-3 demonstrates greater stability compared to alternative biomarkers, maintaining consistent levels over time.¹² Galectin-3 also shows no significant association with age, body mass index, or gender, reducing

confounding variables in clinical interpretation.¹² Furthermore, it exhibits a lack of circadian variation, eliminating the need for time-specific blood sampling.¹² Finally, galectin-3 demonstrates relatively low biological variability in both healthy individuals and patients with stable heart failure, enhancing its potential for reliable serial monitoring.¹³

Despite the theoretical promise of Galectin-3, conflicting evidence exists regarding its utility as a predictor of cardiac dysfunction in chemotherapy patients. A systematic review and meta-analysis by Wu et al. (2022) reported conflicting results regarding Galectin-3 as a positive predictor for cardiac dysfunction in this patient population.¹⁴ Additionally, investigations into alternative biomarkers have yielded inconsistent results, highlighting the absence of an established definitive predictor of cardiac dysfunction to date.

By combining Galectin-3 measurements with advanced echocardiographic parameters, this study aimed to enhance detection and prediction of subclinical cardiac dysfunction, potentially enabling earlier intervention and improved clinical outcomes for cancer patients receiving anthracycline therapy.

METHODS

Study Design and Setting

The study protocol was approved by the Ethics Committee of the Faculty of Medicine, University of Indonesia, Cipto Mangunkusumo National General Hospital. This prospective observational study was conducted from June 2024 to February 2025 at two tertiary care centers in Jakarta, Indonesia: Cipto Mangunkusumo National General Hospital (RSCM) and Dharmas National Cancer Hospital (RSKD). Ethical clearance was obtained from the institutional review boards of both institutions.

Study Participants

Eligible participants were adult patients (≥ 18 years) newly diagnosed with breast cancer or lymphoma and scheduled to receive doxorubicin-based chemotherapy. The inclusion criteria comprised patients with normal baseline

left ventricular function (LVEF $\geq 53\%$), no prior exposure to anthracyclines, and willing to undergo serial biomarker and echocardiographic evaluations. The exclusion criteria included pre-existing cardiac dysfunction (defined as a $\geq 10\%$ decline in LVEF or a $\geq 15\%$ reduction in GLS from baseline), known coronary artery disease, or renal impairment (eGFR < 30 mL/min/1.73 m²).

Sample Size and Enrollment

A total of 113 patients initially met the inclusion criteria. However, 21 patients were excluded due to early dropout: six were referred due to drug unavailability, eight died after the first chemotherapy cycle, and seven were lost to follow-up. Of the remaining 92, further attrition due to mortality and loss to follow-up resulted in a final sample size of 55 patients who completed all three evaluation points.

Variables and Data Collection

Clinical demographics, anthropometric data, and cancer diagnosis were recorded at baseline. Plasma Galectin-3 concentrations were measured using standardized enzyme-linked immunosorbent assay (ELISA) kits at three time points: pre-chemotherapy, post-cycle 2, and post-cycle 4. Certified cardiologists performed transthoracic echocardiography using Philips Epiq 7 and GE Vivid E95 ultrasound systems to assess LVEF and GLS. Cardiac dysfunction was defined as a $\geq 10\%$ decline in LVEF or a $\geq 15\%$ reduction in GLS from baseline.

Statistical Analysis

Changes in Galectin-3, LVEF, and GLS across time points were analyzed using Wilcoxon's signed-rank and paired t-tests. Receiver operating characteristic (ROC) analysis determined the predictive accuracy of Galectin-3 for cardiac dysfunction, reporting the area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Correlation analyses between Galectin-3 and echocardiographic parameters were performed using Pearson's or Spearman's tests as appropriate. A p-value < 0.05 was considered statistically significant. Missing data were handled through complete case analysis. Analyses were conducted using SPSS version 26 (IBM Corp.).

RESULTS

Participant Flow and Baseline Characteristics

A total of 113 eligible patients were obtained initially. Subsequently, 55 patients completed all three study evaluations. The mean age was 47.87 ± 12.15 years, with 76.4% female participants. Breast cancer accounted for 56.36% of cases, with lymphoma representing 43.63%. The average body weight and height were 54.72 ± 10.56 kg and 156.55 ± 8.36 cm, respectively. The median pre-chemotherapy Galectin-3 level was 34.38 ng/mL (IQR: 26.38–45.48). No cardiac dysfunction was observed at baseline. (Table 1)

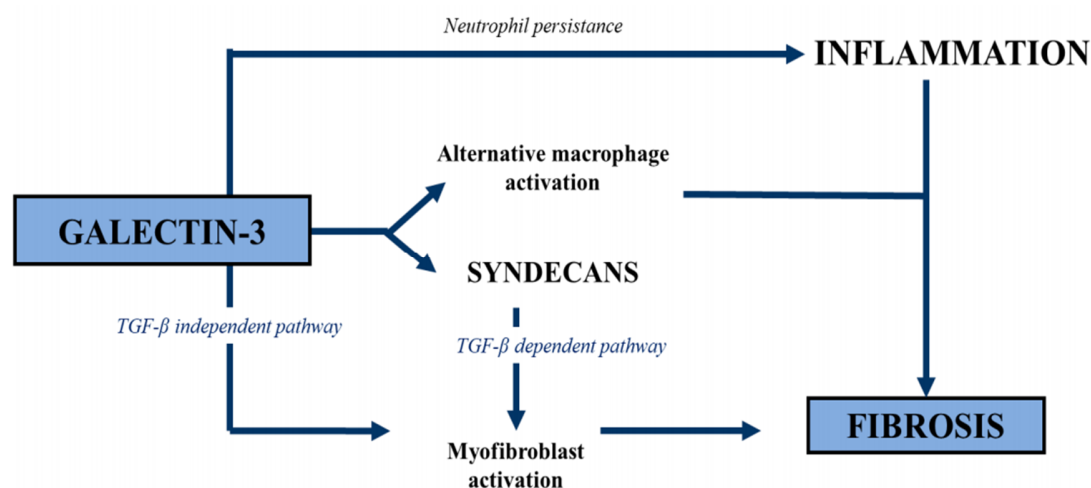


Figure 1. Galectin-3's role in fibrosis.¹⁰

Table 1. Subjects' baseline characteristics.

Variable	Number (n = 55)
Age (years), mean (SD)	47.87 (12.15)
Gender, n (%)	
- Male	13 (23.6)
- Female	42 (76.4)
Tumor Type, n (%)	
- Breast	31 (56.36)
- Lymphoma	24 (43.63)
Biomarker	
- Galectin-3 (ng/ml) pre-chemotherapy, median (IQR)	34.38 (26.38–45.48)
Cardiac dysfunction	0

SD: standard deviation; IQR: interquartile range.

Changes in Galectin-3 and Echocardiographic Parameters

Galectin-3 levels remained stable after the second cycle (median: 34.22 ng/mL; IQR 27.50–44.84) but showed significant elevation post-cycle 4 (mean: 46.89 $\pm$ 18.34 ng/mL; $p < 0.01$). LVEF decreased progressively from 67.1 $\pm$ 5.52% at baseline to 65.1 $\pm$ 5.62% post-cycle 2 and 63.68 $\pm$ 5.84% post-cycle 4 ($p < 0.01$). GLS declined significantly from a baseline median of -24.2% (IQR: -26 to -22.3) to $-23.32 \pm 2.28\%$ post-cycle 2 and $-22.53 \pm 2.34\%$ post-cycle 4 ($p < 0.01$).

Cardiac dysfunction developed in 34.5% of patients after cycle 2 and 50.9% after cycle 4. Patients with cardiac dysfunction exhibited greater increases in Galectin-3 post-cycle 4 (median Δ : 12.33 ng/mL vs. -0.08 ng/mL; $p < 0.0001$), greater declines in LVEF (Δ : -6.9% vs. -2.7% ; $p < 0.0001$), and greater GLS reduction (Δ : -4.0% vs. -1.2% ; $p < 0.0001$) compared to those without dysfunction. (Table 2)

Galectin-3's Diagnostic Performance

Post-cycle 4 Galectin-3 demonstrated the highest predictive value with an AUC of 0.767

(95% CI: 0.638–0.897; $p = 0.001$), sensitivity of 92.9%, and specificity of 59.3% at a cut-off of ≥ 37.28 ng/mL. Post-cycle 2 Galectin-3 yielded lower predictive accuracy (AUC of 0.592; $p = 0.265$). Pre-chemotherapy Galectin-3 levels were not significant predictors (AUC of 0.558; $p = 0.479$).

At the 37.28 ng/mL cut-off post-cycle 4, Galectin-3 had a sensitivity of 92.86%, a specificity of 59.3%, a PPV of 70.27%, and an NPV of 88.89%. The relative risk for dysfunction at Galectin-3 > 33.14 ng/mL post-cycle 2 was 2.17 (95% CI: 0.90–5.22; $p = 0.085$). Post-cycle 4, the relative risk increased significantly to 6.32 (95% CI: 1.66–24.05; $p = 0.007$).

Correlation Analysis

No significant correlation was found between Galectin-3 and LVEF at any time point ($p > 0.05$). In contrast, significant positive correlations were observed between Galectin-3 and GLS post-cycle 2 ($r = 0.35$; $p = 0.00$) and post-cycle 4 ($r = 0.54$; $p = 0.00$).

Table 2. Characteristics of plasma galectin-3 and echocardiographic parameters.

Examination Modality	Pre-Chemotherapy	Post-Chemotherapy Second Cycle	Post-Chemotherapy Fourth Cycle
Galectin-3	34.38 (26.38–45.48)*	34.22 (27.50–44.84)*	46.89 (18.34)
LVEF	67.10 (5.52)	65.10(5.62)	63.68(5.84)
GLS	$-24.2(-26-(-22.3))$	$-23.32(2.28)$	$-22.53(2.34)$

SD: standard deviation; median (IQR): interquartile range; LVEF: left ventricular ejection fraction; GLS: global longitudinal strain

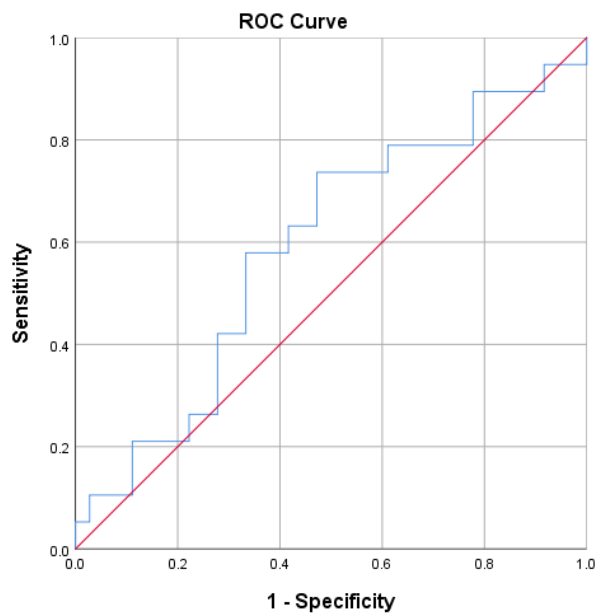


Figure 2. ROC curve post-chemotherapy (second cycle).

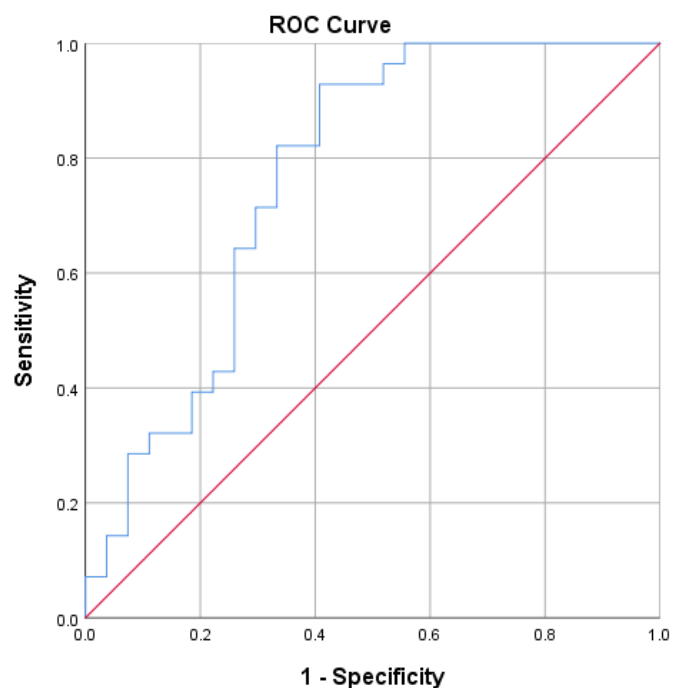


Figure 3. ROC curve post-chemotherapy (fourth cycle).

DISCUSSION

This prospective cohort study demonstrates that plasma Galectin-3 levels, particularly after the fourth cycle of doxorubicin-based chemotherapy, can significantly predict the development of cardiac dysfunction in cancer patients. The findings align with existing

literature underscoring the role of Galectin-3 in myocardial fibrosis and remodeling, particularly under oxidative stress and inflammation induced by anthracycline chemotherapy.⁷

Our observation that Galectin-3 did not predict cardiac dysfunction at baseline or after the second cycle suggests its utility is more

relevant in cumulative cardiotoxicity settings. The late elevation in Galectin-3 likely reflects progressive myocardial injury and fibrogenic activation, potentially preceding overt LVEF changes.⁹ Although LVEF remains a standard parameter, its changes are often delayed, limiting its utility for early detection.⁶ Conversely, GLS provides earlier and more sensitive detection of myocardial dysfunction. The significant positive correlation between Galectin-3 and GLS supports the biomarker's role in identifying early subclinical damage before conventional LVEF alterations become apparent.¹⁵

The ROC analysis yielded an AUC of 0.767 for post-cycle 4 Galectin-3, demonstrating diagnostic relevance with high sensitivity (92.9%) but moderate specificity (59.3%).³ This profile indicates that Galectin-3 serves as an excellent rule-out test or screening for cardiotoxicity risk due to its high sensitivity. Furthermore, it has a potential role as a single biomarker for cardiac dysfunction screening where echocardiography is not available. Nevertheless, due to its low specificity, it should not be used as a standalone test.

Ideally, Galectin-3 should be interpreted in conjunction with imaging modalities for optimal clinical decision-making.¹⁶ Indeed, recent cohort studies have similarly emphasized the importance of biomarker-imaging integration in cardiotoxicity surveillance.¹⁷ Building on this framework, the integration of Galectin-3 with GLS offers a biologically and functionally complementary approach to cardiotoxicity surveillance. Galectin-3 reflects underlying profibrotic and inflammatory activity, potentially identifying patients at risk before overt structural damage occurs, whereas GLS detects early impairment in myocardium. The combined interpretation of these parameters may therefore enhance sensitivity for early myocardial injury and improve risk stratification, particularly in populations exposed to cardiotoxic agents. In practical terms, patients with elevated Galectin-3 and concomitantly reduced GLS could be prioritized for intensified monitoring or early cardioprotective strategies.

In comparison, studies by Ky et al. and de Boer et al. also similarly reported the prognostic

significance of Galectin-3 in predicting adverse cardiac remodeling and heart failure.^{8,18} Thus, the findings of this study confirm these insights within the specific context of doxorubicin-induced cardiotoxicity in a Southeast Asian population, addressing a research gap in non-Western cohorts.

Importantly, dynamic changes in Galectin-3 and their delta values between chemotherapy phases conducted in this study provided more meaningful insights than absolute levels alone.¹¹ These findings emphasize the importance of longitudinal monitoring rather than isolated measurements. The significant relative risk increase in post-cycle 4 (RR = 6.32) suggests clinical utility in risk stratification after cumulative doxorubicin exposure. Nevertheless, future prospective studies should explore Galectin-3 thresholds for initiating cardioprotective interventions, such as angiotensin-converting enzyme inhibitors or beta-blockers.²

Limitations of this study include the relatively small sample size and single-center recruitment, which may limit generalizability to other populations. The high dropout rate due to mortality reflects the severity of underlying malignancies but may introduce selection bias. Thus, this study may lead to potential underestimation of cardiotoxicity incidence, as patients with severe outcomes (including death) were excluded from final analyses. Consequently, the final analyzed cohort (n = 55) may represent a healthier survivor subset, introducing a systematic difference between those retained in the study and those lost to follow-up. Nevertheless, this should not impact the diagnostic value of galectin-3 significantly, as its function is to detect cardiac dysfunction, not mortality.

An additional limitation is that this study did not assess other cardiotoxicity biomarkers, which limits comparative analysis of biomarkers. It is recommended that future larger multicenter studies with extended follow-up and cardiac outcome assessment are warranted to validate Galectin-3's predictive utility and optimize clinical implementation protocols.

CONCLUSION

Plasma Galectin-3 levels, particularly after chemotherapy cycle 4, may serve as a sensitive biomarker for predicting cardiac dysfunction in patients receiving doxorubicin. Elevated Galectin-3 levels significantly correlate with echocardiographic markers of myocardial injury, particularly GLS. Due to its high sensitivity and low specificity, Galectin-3 should be used as an adjunctive biomarker and in conjunction with other modalities. The combined use of Galectin-3 and GLS enhances detection of subclinical cardiotoxicity and may guide timely preventive strategies to mitigate heart failure risk for cancer patients.

We recommend further studies with larger cohorts and longer follow-up periods to validate Galectin-3's predictive power and explore its utility in therapeutic monitoring and planning cardioprotective interventions.

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CONFLICT OF INTERESTS

All the authors declare that there are no conflicts of interest.

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