Original Article

Serum Troponin-I Levels Facilitate Early Prediction of Cardiac Toxicity among High-Risk Patients Under Chemotherapy with Doxorubicin

Asaduzzaman M[1], Khatun N[2], Asaduzzaman M[3], Islam MR[4], Alam MJ[5]

ABSTRACT

A quasi-experimental study was conducted in the Department of Medical Oncology, National Institute of Cancer Research & Hospital (NICRH), Dhaka, Bangladesh, between September 2021 to August 2022, to evaluate troponin-I level as a biomarker to detect early-onset of cardiotoxicity among patients under chemotherapy with doxorubicin. We included patients having any malignancy (histopathologically confirmed) and receiving a dose of doxorubicin 45–75 mg/m² BSA 3 weekly in each cycle of chemotherapy. Exclusion criteria were: patients aged <18 years or >70 years, having pre-treatment level of troponin-I >0.08 ng/ml, any pre-existing cardiac disease detected through echocardiography, any significant change in ECG before treatment except sinus tachycardia, known case of hypertension, diabetes mellitus, chronic renal failure, chronic liver disease, obesity (BMI ≥25), previous exposure to chemotherapy or radiotherapy and WHO performance status 3 to 4. However, a non-probability, convenient and purposive sampling technique was adopted. A total of 71 patients were finally enrolled in this study. Multiple assessment were done at baseline and after 3 and 6 cycles of chemotherapy, which included systemic examination, laboratory investigations including complete blood count (CBC), serum troponin-I level, chest radiograph, ECG, echocardiography, ultrasonogram of the whole abdomen and CT scan/MRI, if needed. The mean age of the patients was 32.97±14.1 years. Most of the patients were in the 18–30 years age group (49.4%), followed by 31–40 years age group (22.5%) and 41–50 years age group (15.5%). A male predominance was observed; male-female ratio was 1.63:1. Cardiac toxicity was present in 21(29.6%) patients and absent in 50(70.4%) patients (403.71±42.358 mg/m² BSA vs. 368.36±44.53 mg/m² BSA of mean cumulative dose of doxorubicin; p<0.01). The mean serum troponin-I level at baseline was 0.035±0.025 ng/ml, which raised after three cycles of chemotherapy to 0.061±0.098 ng/ml (p<0.05) and further raised after six cycles to 0.248±0.395 ng/ml (p<0.001). The mean left ventricular ejection fraction (LVEF) at baseline was 64.46±3.749%; after three and six cycles of chemotherapy LVEF decreased to 62.87±3.902% and 60.14±7.112% respectively (p<0.001). Therefore, detection of increased levels of troponin-I facilitate early prediction of cardiac toxicity among high-risk patients under chemotherapy. Our study suggests the necessity of policy adjustment to incorporate routine cardiac screening in clinical practice for cancer patients.

Keywords: *Anthracycline, doxorubicin, cardiac toxicity, troponin-I, malignancy, chemotherapy.*

Mugda Med Coll J. 2026; 9(1): 43-47
DOI: https://doi.org/10.3329/mumcj.v9i1.90817

1. Dr. Mohammad Asaduzzaman, Assistant Registrar, Department of Medical Oncology, National Institute of Cancer Research & Hospital (NICRH), Dhaka-1212. Email: asaddr32@gmail.com (Corresponding author).
2. Prof. Nazrina Khatun, Professor & Head, Department of Medical Oncology, National Institute of Cancer Research & Hospital (NICRH), Dhaka-1212.
3. Dr. Mohammad Asaduzzaman, Associate Professor, Department of Medical Oncology, National Institute of Cancer Research & Hospital (NICRH), Dhaka-1212.
4. Dr. Muhammad Rafiqul Islam, Assistant Professor, Department of Medical Oncology, National Institute of Cancer Research & Hospital (NICRH), Dhaka-1212.
5. Dr. Mohammed Jahangir Alam, Medical Officer, Department of Medical Oncology, National Institute of Cancer Research & Hospital (NICRH), Dhaka-1212.

INTRODUCTION

Cancer chemotherapy has made remarkable advances in the treatment of both solid and hematologic malignancies, allowing in many patients the hope for a cure of their cancer. However, these therapies are not without their complications. Cancer treatment-associated cardiotoxicity (CTAC) is becoming an increasing health burden, as the number of cancer survivors increases due to early screening and modern anticancer treatment.[1,2] However, cardiotoxicity is a feared adverse effect that may limit the use of anthracyclines (e.g., doxorubicin) and affect the quality of life and the survival of patients with cancer regardless of oncological prognosis.[1-4] Therefore, clinicians must identify adverse events early and take suitable measures before permanent or irreversible dysfunction.

Anthracyclines either used alone, or in combination with other chemotherapy agents, are widely used agents for the treatment of cancer.[2,4] Anthracyclines e.g., doxorubicin, initiate cardiotoxicity in 5%–48% cases (dose-dependent) through ROS production, mitochondrial dysfunction, DNA damage, and activation of pro-apoptotic pathway leading to cardiomyocyte death.[3] Early detection of cardiotoxicity using biomarkers is critical to help prevent life-threatening cardiac events. The measurement of serum cardiac troponins is the gold standard for the diagnosis of acute myocardial events in humans and it has gained increasing recognition as a new tool for the assessment of cardiotoxicity in several previous studies.[4-7] Due to its unique high-definition technology, elevated serum cardiac troponin-I levels can be detected earlier with the ultrasensitive immunoassay technology.[4,5] Hence, any cardiotoxicity caused by anthracycline can be detected at preclinical phase or later. The role of biomarkers like troponin-I in identifying subclinical cardiotoxicity and its therapy with angiotensin-converting enzyme (ACE) inhibitor to prevent LVEF reduction is a recognized and effective supportive strategy for high-risk patients under chemotherapy.[4]

Following the standard guidelines, solid tumors like sarcomas are frequently treated with anthracyclines, e.g., doxorubicin, and many cancer survivors subsequently develop cardiotoxicity,[8,9] which is also true for Bangladeshi cancer patients.[10] There are ongoing searches for early detection of cardiotoxicity. Troponin-I may be an ideal biomarker to detect the early onset of cardiotoxicity, which is readily available, and inexpensive. Even in Bangladesh in any resource-strained settings, estimation of troponin-I in cancer patients may reduce morbidity and mortality from CTAC.[4,8,9] However, no such study has been conducted in our country to date. Therefore, we proposed this study to evaluate troponin-I level as a biomarker to detect early-onset of cardiotoxicity among patients under chemotherapy. It is expected that this study will play a significant role in the perspective of Bangladesh; in a resource-challenged country like Bangladesh, a simple blood test like troponin-I could be used for early-detection of chemotherapy-induced cardiotoxicity in cancer patients and help clinicians reduce further morbidity and mortality as well as treatment costs.

METHODS

This quasi-experimental study (before and after study) was conducted in the Department of Medical Oncology, National Institute of Cancer Research and Hospital (NICRH), Dhaka, Bangladesh, between September 2021 to August 2022. Malignant patients who were admitted under the Department of Medical Oncology and had planned chemotherapy with anthracycline (e.g., doxorubicin) within the time frame were the study population. Samples were selected through inclusion and exclusion criteria from those patients (following Chu & DeVita).[11] We included patients having any malignancy (e.g., sarcoma) that was histopathologically confirmed and those who received a dose of doxorubicin 45-75 mg/m² BSA 3 weekly in each cycle of chemotherapy. Exclusion criteria were: patients aged <18 years and >70 years, having pre-treatment level of troponin-I >0.08 ng/ml, any pre-existing cardiac disease detected through echocardiography, significant changes in ECG before treatment except sinus tachycardia, known case of hypertension, diabetes mellitus, chronic renal failure, chronic liver disease, obesity (BMI e"25), previous exposure to chemotherapy or radiotherapy and WHO performance status 3 to 4. A non-probability, convenient and purposive sampling technique was adopted.

The baseline evaluation included demographic characteristics, physical examinations and laboratory investigations, including complete blood count, diabetes panel, lipid profile, renal and hepatic function tests, serum troponin-I level (troponin was

considered positive for values e"0.08 ng/mL, according to Cardinale et al.),[12] ECG and echocardiography (2D, M-mode) report was done by cardiologist, chest x-ray postero-anterior (P/A) view, ultrasonography of the whole abdomen and other imaging modalities, immunohistochemistry, if needed, cytology and biopsy made the diagnosis of malignancies with histopathology (along with immunohistochemistry). Similar assessments were done following treatment (after 3 and 6 cycles of chemotherapy) including clinical response by systemic examination, WHO performance status, complete blood count (CBC), serum troponin-I level, chest x-ray P/A view, ultrasonogram of the whole abdomen, ECG, echocardiography, and CT scan/ MRI, if needed.

Data was recorded in the patient data sheet and after scrutinizing, cleaning and editing, relevant data was compiled in a master sheet in the computer. Statistical analysis was done by using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, NY, USA). Categorical data was expressed as frequency and percentage, while continuous data was expressed as mean±SD. Categorical variables were compared by using paired sample t-test and independent sample t-test where applicable. For all analyses, the significance level was set at 0.05, and a p-value <0.05 was considered statistically significant.

RESULTS

The mean age of the patients was 32.97±14.1 years. Most the patients were in the 18–30 years age group (49.4%), followed by 31–40 years age group (22.5%), 41–50 years age group (15.5%), 51–60 years age group (7%) and 61–70 years age group (5.6%). A male predominance was observed (62% were male and 38% were female); male-female ratio was 1.63:1 (Table-I). At baseline no patient had troponin-I level >0.08 ng/ ml. However, after completion of three cycles of chemotherapy with doxorubicin 5(7.0%) patients showed positive troponin-I levels (i.e., (>0.08 ng/ml) and after six cycles, a total of 21(29.6%) showed such positive results (Table-II). The mean serum troponin-I level at baseline, day after three and six cycles of chemotherapy were estimated 0.035±0.025 ng/ml, 0.061±0.098 ng/ml and 0.248±0.395 ng/ml respectively indicating a gradual rise over time. The differences were statistically significant (p<0.001) (Table-III). The mean left ventricular ejection fraction (LVEF) at baseline, after three and six cycles of chemotherapy were 64.46±3.749%, 62.87±3.902% and 60.14±7.112% respectively indicating a gradual decrease over time. The differences were statistically significant (p<0.001) (Table-IV). No cardiac toxicity was found in 50 patients and their mean cumulative dose of doxorubicin was 368.36±44.53 mg/m^2 BSA. In contrast, cardiac toxicity was observed in 21 patients and their mean cumulative dose of doxorubicin was 403.71±42.358 mg/m^2 BSA. This difference was statistically highly significant (p<0.01) (Table-V).

Table-I: *Age and gender distribution of the chemotherapy patients (N=71)*

Variables	Frequency (Percentage)
Age group (in years)	
18–30	35 (49.4)
31–40	16 (22.5)
41–50	11 (15.5)
51–60	5 (7.0)
61–70	4 (5.6)
Gender	
Male	44 (62.0)
Female	27 (38.0)

Table-II: *Distribution of troponin-I positive cases among chemotherapy patients (N=71)*

Serum Troponin-I (>0.08 ng/ml)	Frequency	Percentage
At baseline	0	0
After 3 cycles	5	7.0
After 6 cycles	21	29.6

Table-III: *Troponin-I at baseline, day after completion of 3 and 6 cycles of chemotherapy*

Serum Troponin-I (ng/ml)	Mean±SD	t-value	p-value
Baseline	0.035±0.025	-2.142	<0.05
After 3 cycles	0.061±0.098		
Baseline	0.035±0.025	-4.558	<0.001
After 6 cycles	0.248±0.395		
After 3 cycles	0.061±0.098	-4.432	<0.001
After 6 cycles	0.248±0.395		

Paired t-test was applied to reach p-value.

Table-IV: *Left ventricular ejection fraction (LVEF) at baseline, after 3 and 6 cycles of chemotherapy*

LVEF (%)	Mean±SD	t-value	p-value
Baseline	64.46±3.749	3.984	<0.001
After 3 cycles	62.87±3.902		
Baseline	64.46±3.749	4.011	<0.001
After 6 cycles	60.14±7.112		
After 3 cycles	62.87±3.902	5.421	<0.001
After 6 cycles	60.14±7.112		

Paired t-test was applied to reach p-value.

Table-V: *Association between cumulative dose of doxorubicin and cardiac toxicity*

Cardiac toxicity	Cumulative dose of doxorubicin (mg/m² BSA) Mean±SD	t-value	p-value
Absent (n=50)	368.36±44.53	-3.161	<0.01
Present (n=21)	403.71±42.358		

Independent-sample t-test was applied to reach p-value.

DISCUSSION

In the present study, 71 cancer patients were enrolled based on selection criteria. The mean age of the patients was 32.97±14.1 years. In similar studies, Sandri et al.[13] reported that the mean age of the participants was 47±11 years, while Sawaya et al.[14] reported average age 48 years and Cardinale et al.[7] found the mean age 50±13 years. Our result is comparatively lower than their study population. The underlying causes of such discrepancies might be due to inclusion of more patients of Ewing sarcoma. Besides, age reporting in our culture is still questionable as age verification is absent our healthcare settings, which might contribute to our finding.

In this study, at baseline no patient had troponin-I level >0.08 ng/ml. However, after completion of three cycles of chemotherapy with doxorubicin 5(7.0%) patients showed positive troponin-I levels (i.e., (>0.08 ng/ml) and after six cycles, a total of 21(29.6%) showed such positive results. In previous studies, Cardinale et al.[6] and Sandri et al.[13] observed similar proportion of troponin-I positive patients (30% and 32% respectively), which are comparable to our finding.

The mean serum troponin-I level at baseline, day after three and six cycles of chemotherapy were estimated 0.035±0.025 ng/ml, 0.061±0.098 ng/ml and 0.248±0.395 ng/ml respectively indicating a gradual rise over time. The differences were statistically significant (p<0.001). Cardinale et al.[12] studied on 703 patients using the same cut-off value of troponin-I (0.08 ng/ml) and reported 0.16±0.24 ng/ml as the mean troponin-I value after treatment completion, which is lower than the current study finding. The huge difference in sample size might be attributable to such different results. In contrast, Sandri et al.[13] reported a higher mean troponin-I value after treatment (0.63±0.54 ng/ml). Michel et al.[15] compared post-treatment and pre-treatment troponin levels described in 42 studies. Post-treatment troponins were significantly higher compared to pre-treatment troponins (OR 14.3, 95% CI 6.0-34.1; n=3049). Additionally, analysis of absolute serum troponins revealed increased post-treatment compared to pre-treatment values (SMD 1.0; 95% CI 0.6 to 1.3; n=811). Post-treatment troponins were elevated in 22.4% of patients. Those findings are in congruence with our results.

For cardiac functions, we compared the mean left ventricular ejection fraction (LVEF); at baseline, after three and six cycles of chemotherapy, LVEF were were 64.46±3.749%, 62.87±3.902% and 60.14±7.112% respectively indicating a gradual decrease over time. The differences were statistically significant (p<0.001). Cardinale et al.[7] reported baseline LVEF in patients with cardiotoxicity as 61±3.6% and 63±3.7% in patients with no cardiotoxicity (p<0.001), at the end of chemotherapy LVEF in patients with cardiotoxicity 55±4.6% and patients with no cardiotoxicity 61±4% (p<0.001). Sandri et al.[13] reported an 18% reduction of LVEF in troponin-I positive patients, while only 3% reduction in troponin-I negative patients. Their findings are comparable to our results as well.

In our study, cardiac toxicity was not observed in 50 patients and their mean cumulative dose of doxorubicin was 368.36±44.53 mg/m² BSA. On the other hand, cardiac toxicity was found in 21 patients and their mean cumulative dose of doxorubicin was 403.71±42.358 mg/m² BSA. The difference was statistically significant (p<0.01). Cardinale et al.[7]

reported cumulative anthracycline dose in patients with cardiotoxicity as 359±172 mg/m² and in patients with no cardiotoxicity as 299±144 mg/m² ($p<0.001$). This finding is comparable to our study result.

Our study has several limitations. Single-centre design and small sample size may limit generalizability. Besides, we studied only troponin-I as biomarker; however, using other biomarkers like troponin-T, topoisomerase 2β, myeloperoxidase, NT-proBNP could be employed to get comparable and better results. More follow-up visits were needed to precisely evaluate cumulative dose-related cardiotoxicity. These factors need to be addressed in future research.

CONCLUSION

Our data suggests that serum troponin-I levels increase with the cumulative dose of doxorubicin. Besides, increased dose of doxorubicin is associated with decreased level of left ventricular functions of the heart. Therefore, evaluating biochemical parameter like troponin-I can aid in diagnosing sub-clinical cardiac damage. Detection of increased concentrations of troponin-I can facilitate early prediction of cardiac toxicity among high-risk patients under chemotherapy.

Conflict of Interest: No potential conflict of interest was reported by the authors.

Funding Source: Self-funded.

Ethical Approval: Ethical approval for this study was obtained from the Ethics Committee of National Institute of Cancer Research & Hospital (NICRH), Dhaka, Bangladesh (Ref. No. NICRH/Ethics/2022/44).

Authors' Contribution: Concept and design: M Asaduzzaman, N Khatun; Patient selection, data collection, compilation, and analysis: M Asaduzzaman, MJ Alam; Manuscript preparation, editing and final submission: M Asaduzzaman, N Khatun, M Asaduzzaman, MR Islam, MJ Alam.

REFERENCES

1. Volkova M, Russell R 3rd. Anthracycline cardiotoxicity: prevalence, pathogenesis and treatment. Curr Cardiol Rev. 2011;7(4):214-20.
2. Bhagat A, Kleinerman ES. Anthracycline-induced cardiotoxicity: causes, mechanisms, and prevention. Adv Exp Med Biol. 2020;1257:181-92.
3. Narezkina A, Narayan HK, Zemljic-Harpf AE. Molecular mechanisms of anthracycline cardiovascular toxicity. Clin Sci (Lond). 2021; 135(10):1311-32.
4. Ananthan K, Lyon AR. The role of biomarkers in cardio-oncology. J Cardiovasc Transl Res. 2020;13(3):431-50.
5. Wu AH, Lu QA, Todd J, Moecks J, Wians F. Short- and long-term biological variation in cardiac troponin I measured with a high-sensitivity assay: implications for clinical practice. Clin Chem. 2009;55(1):52-8.
6. Cardinale D, Sandri MT, Martinoni A, Tricca A, Civelli M, Lamantia G, et al. Left ventricular dysfunction predicted by early troponin I release after high-dose chemotherapy. J Am Coll Cardiol. 2000;36(2):517-22.
7. Cardinale D, Colombo A, Bacchiani G, Tedeschi I, Meroni CA, Veglia F, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. Circulation. 2015;131(22):1981-8.
8. Khouri MG, Klein MR, Velazquez EJ, Jones LW. Current and emerging modalities for detection of cardiotoxicity in cardio-oncology. Future Cardiol. 2015;11(4):471-84.
9. Cardinale D, Cipolla CM. Chemotherapy-induced cardiotoxicity: importance of early detection. Expert Rev Cardiovasc Ther. 2016;14(12):1297-9.
10. Islam MR, Siddiqua SM, Islam R, Hossain A, Al Ayub SB, Islam MS, et al. Lung cancer in Bangladesh. J Thorac Oncol. 2023;18(8):972-80.
11. Chu E, DeVita Jr. VT. Physician's Cancer Chemotherapy Drug Manual 2021. Burlington, MA; Jones & Bartlett Learning; 2022.
12. Cardinale D, Sandri MT, Colombo A, Colombo N, Boeri M, Lamantia G, et al. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. Circulation. 2004;109(22):2749-54.
13. Sandri MT, Cardinale D, Zorzino L, Passerini R, Lentati P, Martinoni A, et al. Minor increases in plasma troponin I predict decreased left ventricular ejection fraction after high-dose chemotherapy. Clin Chem. 2003;49(2):248-52.
14. Sawaya H, Sebag IA, Plana JC, Januzzi JL, Ky B, Cohen V, et al. Early detection and prediction of cardiotoxicity in chemotherapy-treated patients. Am J Cardiol. 2011;107(9):1375-80.
15. Michel L, Mincu RI, Mahabadi AA, Settelmeier S, Al-Rashid F, Rassaf T, Totzeck M. Troponins and brain natriuretic peptides for the prediction of cardiotoxicity in cancer patients: a meta-analysis. Eur J Heart Fail. 2020;22(2):350-61.