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Original Article

Can Chemotherapy Induced Cardiomyopathy Be Detected from Pretreatment Platelets to Lymphocytes Ratio?

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ABSTRACT

Objective: In this study, we aimed to identify patients at risk of chemotherapy-induced cardiotoxicity with a simple method like platelet-to-lymphocyte ratio (PLR) before starting therapy.

Method: A total of 65 breast cancer patients who completed anthracycline or adjuvant trastuzumab treatment were evaluated retrospectively. Serial PLR calculations, echocardiographic examinations, and cardiac markers before treatment and after follow-up period were analyzed. Cardiotoxicity was determined according to Cardiac Review and Evaluation Committee Criteria.

Results: Patients were divided into two groups according to their baseline PLR levels as Group C—PLR $<$ 119 and Group D—PLR $\geq$ 120. The median follow-up of the study was 22.23 (12-42) months. Concomitant disease and baseline characteristics were similar in both groups. Symptomatic cardiotoxicity was not observed in both groups. Cardiotoxicity was occurred in one patient (2.3%) in Group C and in four patients (9.5%) in Group D ($P = .005$). Average mean left ventricular ejection fraction loss from baseline was 10.7 $\pm$ 7.0% in Group D vs 2.3 $\pm$ 6.4% in Group C ($P = .008$). Interpretation of cardiac markers that were present in nearly half of the patients revealed that serum hs-c-reactive protein and pro-brain natriüretic peptide levels were significantly higher in patients who developed cardiotoxicity compared to who did not develop cardiotoxicity. PLR $\geq$ 120 had 99% sensitivity and 85% specificity in predicting cardiotoxicity.

Conclusion: This study's results showed that high PLR levels were associated with chemotherapy-induced cardiotoxicity. To our best knowledge, this is the first study, examining the impact of whole blood test on chemotherapy-induced cardiotoxicity before starting the therapy and allowing doctors plot a route for these risky patients.

Keywords: Breast cancer, cardiotoxicity, chemotherapy, platelets-to-lymphocytes ratio

INTRODUCTION

Aged people are increasing as a consequence of better living conditions and improved technological development in our country as in the world. The incidence of malignancy especially breast cancer in women and, hence, the chemotherapy-treated patients is increasing with ages.[1] Apparently in the near future, cancer patients and also chemotherapy-treated patients will increase. The anthracycline and trasthuzumab therapy has been shown to improve survival in breast cancer patients.[2] According to the large retrospective studies, apparent reductions were recorded in mortality with these chemotherapeutic agents.[3–5] Although the drugs are highly effective in treatment, silent and severe cardiac side effects make to stop the therapy and limit the therapy effectiveness.[6,7] An effective parameter is not currently available to detect the cardiotoxicity.

PLR is a novel biomarker showing inflammation in cardiac and noncardiac patients. T and B lymphocytes and platelets secrete proinflammatory substances such as chemokines and cytokines are suggested to play a prominent role in the development and progression of many cancer types. PLR is a fast, simple, and cheap biomarker, showing inflammation in cardiac and noncardiac patients and widely studied in many subjects and found as an independent predictor for cardiac complications and prognosis.[8–15] In this study, we planned to find out patients with the risk of cardiotoxicity before starting the therapy with a simple whole blood test.

METHODS

Consent was obtained from the patients in accordance with the Declaration of Helsinki for participation. This study was approved by the Ankara Numune Education and Research Hospital Ethics Committee on March 5, 2017 (study number 2017E- 18)

The demographic characteristics including age, gender, history of arterial hypertension, diabetes mellitus, tobacco use, body mass index, past medications menopausal history, treatment history, beginning and ending time of treatments, timing of

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hormonal and chemotherapeutic treatments, and history of comorbid disease are presented in Table 1, and serum levels of fasting blood glucose, hemogram, c-reactive protein (CRP), and a lipid panel including low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride levels are all evaluated and shown in Table 2. Baseline and control echocardiographic left ventricular ejection fraction (LVEF) measurements and echocardiographic data are presented in Table 3. All data were analyzed retrospectively. Patients with heart failure, significant valvular disease, cardiomyopathy, uncontrolled hypertension, abnormal hepatic and renal functions, active infection, chronic inflammatory disease, chronic obstructive pulmonary disease, other malignancies, previous use of chemotherapy, and radiotherapy and immunotherapy patients were excluded. Recurrent or metastatic patients and severely ill patients were also excluded from the study. The PLR was calculated before and after 6 months of treatment. Institutional ethics committee approval was obtained. Cardiotoxicity was defined according to Cardiac Review and Evaluation Committee definition as an absolute decline of LVEF of 5% to <55% with symptoms of HF or an asymptomatic reduction of LVEF of 10% to <55%.[16]

The long and short axis parasternal and apical views, two-dimensional, M-mode, pulsed, and color flow Doppler echocardiographic examinations in the left lateral decubitus position were done using a Vivid 5, GE Vingmed, Horten, Norway, 2–4 mHz phased array transducer. Left ventricle end-diastolic (LVEDD), left ventricle end-systolic (LVESD), LVEF, mitral inflow indices as the peak early filling (E peak) and late diastolic filling (A peak) velocities, the E/A ratio, deceleration time (DT) of early filling velocity, and the isovolumic relaxation time (IVRT) were present in echocardiography reports.

An automated blood cell counter (ADVIA 2120i Hematology System, Siemens Healthcare Diagnostics, Deerfield, IL) was used in hematology laboratory. A Cobas E-601 analyzer (Roche Diagnostics, Mannheim, Germany) using electrochemiluminescence immunoassay was used in vitro CK-MB, pro-brain natriüretic peptide (BNP), and Troponin I and high-sensitive (hs) Troponin T analyses. A Hitachi Modular P800 analyzer (Roche Diagnostics, Mannheim, Germany) was used to measure the hs-CRP.

Main Points

- We aimed to identify patients at risk of chemotherapy-induced cardiotoxicity with a simple method like platelet-to-lymphocyte ratio (PLR) before starting therapy. Because cardiotoxicity is a therapy limiting factor in cardio-oncology.
- We planned this study to find out any possible association between PLR and cardiac complications.
- For the first time, the study results showed a possible correlation between PLR and cardiotoxicity.
- With this knowledge, we can predict the patients at cardiotoxicity risk and change if possible the chemotherapeutic agent or lower the dose.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) version 18.0 (IBM SPSS Corp.; Armonk, NY, USA) was used for statistical analysis. Variables were analyzed using the Kolmogorov–Smirnov test. Categorical variables were presented as percentages, and parametric variables were presented as mean ± standard deviation. Nonparametric variables were expressed as median (minimum – maximum). The normally distributed numeric variables were analyzed using the Student's t-test, and non-normally distributed variables were evaluated by the Mann–Whitney U test variance analysis. The categorical variables were compared with Chi-square test. P value $< .05$ was accepted as statistically significant.

RESULTS

This study was consisted of a total of 65 patients with breast cancer completed at least ≥6 months an anthracycline-containing regimen setting weekly doxorubicin (24 mg m^{-2} IV) with daily oral cyclophosphamide (60 mg m^{-2} PO) for 12 weeks, and in 11 of 65 patients, taxanes were added to the regimen. Patients' demographic characteristics were listed in Table 1. The median follow-up of the study was 22.23 (12-42) months and was not significant between two groups ($P = .34$). Of the enrolled patients, 29 (28.57%) patients were PLR < 119 in Group C and 36 (47. 61%) patients were PLR ≥ 120 in Group D. The median age was 48.1 ± 7.7 years (35-69) for Group D, whereas it was 46.2 ± 8.6 years (32-67) for Group C ($P = .47$). These accompanying chronic diseases were similar in both treatment groups. Histology of the primary tumor, lymphovascular invasion, perineural invasion, extracapsular extension, and histological grade and type of surgery were similar and not statistically significant in both groups.

Baseline LVEF values were 65.5 ± 3.4% and 67.1 ± 4. 5% in Group C and Group D, respectively ($P = .13$). Symptomatic heart failure was not observed during treatment in both groups. All echocardiographic results were presented in Table 2. Asymptomatic LVEF decline was observed in one (2.3%) and four (9.5%) patients in Group C and Group D, respectively ($P = .005$). The incidence of LVEF decline was significantly higher in Group D ($P < .001$). The lowest LVEF values during treatment were 64.3 ± 3.9% and 58.6 ± 6.7% in Group C and Group D, respectively ($P = .01$). Mean LVEF values decreased below 50% for two patients in Group D, and all of them had been treated with heart failure medications. In the subgroup analyses, no association was found between cardiotoxicity and hypertension ($P = .54$), hyperlipidemia ($P = .69$), diabetes ($P = .59$), obesity ($P = .79$), total anthracycline dose ($P = .68$), and family history of coronary artery disease ($P = .68$). Despite the risk of cardiotoxicity was increased with advanced age >60 years ($P = .08$) and with a combination of taxane and anthracycline regimens ($P = .07$), this risk was not significant. Baseline mean LVEF values were similar in Group C and Group D. Mean LVEF was 64.3 ± 2.7% and 63.8 ± 3.2% in Group C and Group D ($P = .29$), respectively. Average mean LVEF loss from baseline was significantly higher in Group D than Group C (10.7 ± 7.0% vs 2.3 ± 6.4%, HR: 1.46; 95% CI: 1.17 to 1.73; $P = .008$). As shown in Figure 1, patients with cardiotoxicity had significantly higher PLR values lower lymphocyte counts than those with cardiotoxicity not observed group. In the subgroup

Table 1. Baseline Demographic Characteristics of the Study Population

Variables	Group C, n (%); 29 (44.61%)	Group D, n (%); 36 (55.38%)	*P*
Age, years; median	48.1 ± 7.7 (35-69)	46.2 ± 8.6 (32-67)	.47
Diabetes mellitus, n (%)	5 (7.65)	7 (10.7)	.24
Hypertension, n (%)	17 (26.15)	19 (29.23)	.19
Hyperlipidemia, n (%)	5 (7.69)	6 (9.03)	.23
Family history with cancer, n (%)	14 (21.53)	13 (20.0)	.32
Grade, n (%)			
I	4 (6.15)	3 (4.61)	.67
II	8 (12.30)	13 (20.0)	.48
III	17 (26.10)	20 (30.70)	.56
T-Stage at diagnosis, n (%)			
T1	2 (3.07)	3 (4.61)	.56
T2	15 (23.07)	17 (26.15)	.67
T3	7 (10.7)	13 (20.20)	.65
T4	5 (7.65)	3 (14.61)	.54
Chemotherapy, n (%)			
Anthracycline	18 (27.69)	24 (36.9)	.65
Anthracycline + taxanes	11 (16.9)	13 (20.0)	.47
Hormonal treatment, n (%)			
No	9 (13.8)	13 (20.0)	.23
Yes	20 (30.7)	23 (36.38)	.45
Prior medication, n (%)			
Beta-blocker, ACE inhibitor	4 (6.67)	7 (10.7)	.32
ARB	5 (7.69)	4 (6.67)	.65
Calcium-channel blocker	2 (3.07)	3 (4.61)	.56
Statin	1 (1.65)	2 (3.07)	.67
	4 (6.67)	3 (4.61)	.45

Data are expressed as mean ± standard deviation (SD) for continuous variables and as percentages for dichotomous variables. P-values denote overall differences between groups.

analyses, mean LVEF was significantly lower in patients who developed cardiotoxicity during treatment compared to who did not develop (61.9 ± 3.6% vs 64.4 ± 2.6%, $P = .01$). Baseline LVEF values were significantly higher in patients who developed cardiotoxicity compared to who did not develop cardiotoxicity (69.0 ± 5.5% vs 65.6 ± 3.3%, $P = .01$). No significant differences were found in other echocardiographic measurements between both groups. Cardiac biomarkers such as hs-CRP, CK-MB, troponin I, troponin T, and pro-BNP were present in nearly half of the patients, and levels were shown in Table 4. Serum hs-CRP and pro-BNP levels were significantly higher in patients who developed cardiotoxicity compared to who did not develop cardiotoxicity (HR: 1.58; 95% CI: 1. 25 to 2. 01; $P = .001$) as shown in Figure 2.

Table 2. Biochemical and Hematological Measurements of the Study Population

Variables	Group C (n = 29)	Group D (n = 36)	*P*
Hemoglobin (g dL^{-1}) median (IQR)	14.3 (12.7–15.8)	13.9 (12.1–16)	.184
WBC ($\times 10^3$ μL^{-1}), mean ± SD	8.4 ± 3.9	7.2 ± 3.7	.062
Lymphocyte ($\times 10^3$ μL^{-1}), mean ± SD	2.0 ± 1.1	1.7 ± 1.2	.035
Platelet ($\times 10^3$ μL^{-1}), mean ± SD*	213 ± 65	254 ± 59	.001
PLR, median (IQR)	100 (86–119)	129 (120–154)	<.001
Creatinine (mg dL^{-1}), mean ± SD	1.1 ± 0.4	1.1 ± 0.3	.655

Data are expressed as mean ± SD, number (percentage), or median (interquartile range).
IQR, interquartile range; PLR, platelet-to-lymphocyte ratio; SD, standard deviation; TG, triglyceride; WBC, white blood cell.

Table 3. Comparison Echocardiographic Findings between Group C and Group D

Characteristics	Group C (n = 29)	Group D (n = 36)	*P*
LVEDD (3.5–5.8 cm)	4.2 ± 0.4	4.0 ± 0.4	.87
LVESD (2.45–4.1 cm)	2. 7 ± 0.3	2.9 ± 0.3	.26
Baseline LVEF (%)	65.5 ± 3. 4	67.1 ± 4.5	.13
Control LVEF (%)	65.3 ± 3. 1	62.8 ± 3. 2	.29
Average LVEF loss (%)	2.3 ± 6.4	10.7 ± 7.0	.008
E peak velocity (m sn^{-1})	10. 4 ± 0.48	1.03 ± 0.38	.31
A peak velocity (m sn^{-1})	0.77 ± 0.19	0.75 ± 0.15	.46
E/A ratio	0.85 ± 0.22	0.87 ± 0.28	.85
IVRT (msn)	95.5 ± 20.0	94.9 ± 16.7	.31
PAP (mm Hg^{-1})	26.4 ± 5.8	28.0 ± 4.7	.59

A peak, late diastolic filling velocity; E peak, early diastolic filling velocity; IVRT, isovolumic relaxation time; LVEDD; left ventricle end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricle end-systolic diameter; PAP, pulmonary artery pressure.
Values are median (interquartile range) or n (%).

Finally, ROC analysis was performed in cardiotoxicity and non-cardiotoxicity groups to detect the cutoff value of PLR for predicting cardiotoxicity. The cutoff value of PLR on admission to predict cardiotoxicity in all study population was 96, with a sensitivity of 69% and 68% and a specificity of 65% and 66%, respectively (area under curve = .675 and .700, *P* <.001 and <.001, respectively; Figure 3).

DISCUSSION

Many chemotherapeutics agents like anthracyclines have been associated with severe early and late cardiovascular side effects that started mainly in the early stage of therapy within a wide range of symptoms from nonspecific symptoms to cardiogenic shock. Clinicians' subsequent experience with anthracyclines has demonstrated considerable cardiotoxicity even at low doses, making them frightened to use them at therapeutic level. Consequently, patients were left with incomplete therapy and added new cardiovascular problems. Diagnosis of acute and late cardiotoxicity from cancer therapeutics has become increasingly important, and several studies were done to evaluate the risk, as cancer evolved into a chronic disease with new drugs and surgery techniques that require a life-long lasting therapy and need a long-term follow-up for ongoing cardiovascular toxicity. As more patients with cancer are treated, achieve remission, and enter survivorship, there is a need to monitor those at risk and to design best therapy for them.

Figure 1. PLR values of the study groups.

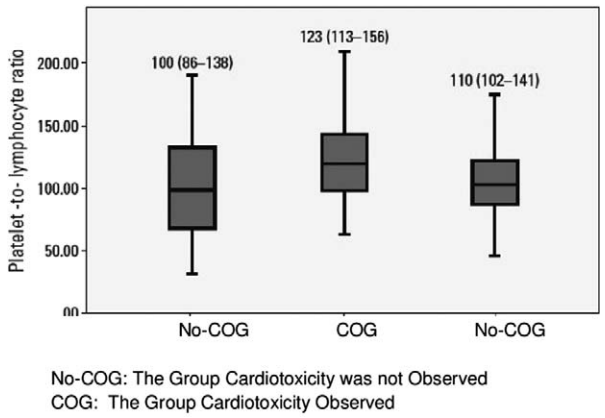
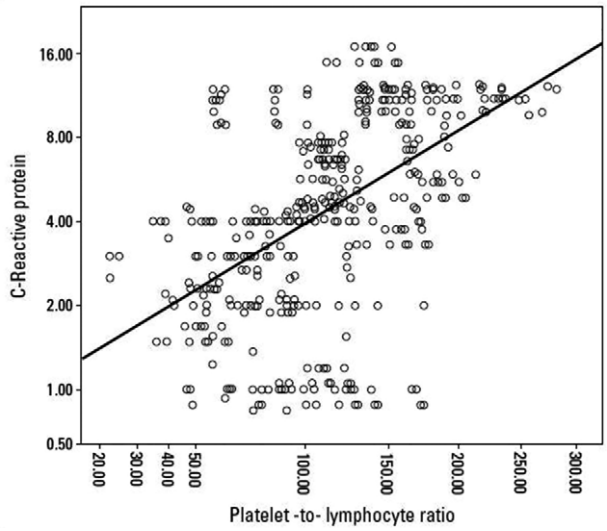


Figure 2. Correlation of PLR and hs-CRP values.



In the United States, cancer survivors are estimated to be by nearly 11 million: it will be 26.1 million in 2040, and only 18% of patients will be between the ages of 50 and 64 years and 8% will be younger than age 50 years.[17] Thus, the older population became the largest proportion of survivors requiring more imaging and treatment approaches for diagnosis and follow-up.

The incidence of toxicity reported in the larger trials is 4.1-35.4%.[18–24] There are insufficient data about predicting the cardiotoxicity in these patients. Although many studies were done to define the risky group, any clear evidence was not present at the moment.[25,26] Newly completed study results showed a correlation between cardiac and inflamamtory markers as troponins (TnI), myeloperoxidase and hs-CRP, and cardiotoxicity, but study investigators claimed that their study results needed more confirmative studies.[27]

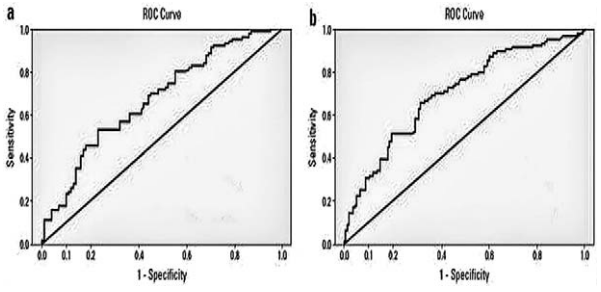
Although the exact mechanism of cardiac toxicity is not yet fully understood, autopsy studies of patients' cardiotoxicity showed myocarditis with the infiltration of predominantly platelets, macrophages, and lymphocytes, and the chemokines causing the cell death. These inflammatory molecules are overexpressed, which might contribute to cardiac injury.[28] Patients with multiple diseases hemograms demonstrated increased neutrophil, monocyte, and platelet counts. Several studies reported a strong association between inflammation and cancer and various other chronic diseases and correlate positively with other markers of systemic inflammation, particularly with NLR and PLR.[29,30] They served as a laboratory marker for predicting various neoplastic, prothrombotic, and metabolic diseases in clinical practice.[31] In fact, PLR gives information about both aggregation and inflammatory pathways that can be superior to the platelet or lymphocyte counts alone for the prediction of cardiotoxicity since both inflammation and endothelial damage play a role in the pathogenesis of the disease. Some small studies also have shown an association between high PLR and NLR levels and heart failure.[32]

Table 4. Comparison Long-Term Cardiac Biomarkers in Group C and Group D

Characteristics	Group C (n = 29)	Group D (n = 36)	*P*
Troponin I (ng mL^{-1})	0.5 (0.0-0.1)	0.3 (0.0-0.1)	.15
CK-MB (ng mL^{-1})	1.57 (0.53-6.0)	1.61 (0.5-7.1)	.43
hs-CRP (mg L^{-1})	3.24 (0.5-29.7)	4.12 (0.27-41.3)	.001
pro-BNP (pg mL^{-1})	64.8 (33-550)	116 (69-880)	.001

hs-CRP, high-sensitive CRP; CK-MB, creatine kinase MB; pro-BNP, pro-brain natriüretic peptide.

Figure 3. ROC analysis of PLR for predicting cardiotoxicity in patients with (a) no change in LVEF values and (b) in patients with decreased LVEF values.



We hypothesized that PLR could be associated with chemotherapy-induced cardiotoxicity. There are no prior data testing pretreatment PLR and detection of cardiotoxicity. Our findings suggested that a PLR of >96 was significantly correlated with chemotherapy-induced cardiotoxicity. Besides its close relation with chemotherapy-induced cardiotoxicity, PLR also had a positive correlation with serum CRP and BNP level in our study, which supported its role in systemic inflammation. From a clinical point of view, PLR may be used as a predictor of chemotherapy-induced cardiotoxicity as a new inflammatory marker in daily clinical practice.

Our study had some limitations; first it is a retrospective study; therefore, we could analyze the available parameters in data for cardiotoxicity and also could not analyze the follow-up data adequately. Second, only a small number of our patients had the cardiac enzymes and inflammatory markers other than CRP, such as IL-6, TNF-a, and MMP, which were not analyzed and, therefore, not compared with PLR. Third, we had analyzed one blood sample, and repeated analysis was not done. This study is not the first to use echocardiography to assess cardiac functions, but we did not employ speckle tracking techniques like strain parameters to evaluate the cardiotoxicity and RV function, and this is another limitation. Finally, our study group was a relatively small group, that is why our subgroup analysis was inadequate.

Besides, chemotherapy-induced cardiac side effects are more dramatic than other side effects; doctors avoid from chemotherapy and do not want their patient to compel with therapy-induced another disease at an expense of mortality.[33,34]

CONCLUSION

The need to diagnose cardiotoxicity rapidly and efficiently is of great concern to involved clinicians and must be aware of these adverse events due to their high fatality rate. A high level of clinical suspicion and early diagnosis indicators are required due to the rapid progress and fulminant course of the disease. The assessment of clinical features in combination with laboratory examinations, ECG, TTE, CMR, and EMB, contributes to the diagnosis of cardiotoxicity.

Our study has shown the relationship between pretreatment PLR level and the development of cardiotoxicity, demonstrating PLR is a powerful and independent predictor of cardiotoxicity in breast cancer patients. Patients were at greater risk of toxicity in the higher PLR vs lower PLR group (30.3% vs 1.9%, $P < .001$).

Finally, our results suggest that more sensitive methods needed to detect LVEF decrease, and a multimarker approach may increase the sensitivity of cardiotoxicity risk prediction in patients treated with chemotherapeutic agents.

Ethics Committee Approval: This study was approved by the Ankara Numune Education and Research Hospital Ethics Committee on March 5, 2017 (study number 2017E- 18).

Informed Consent: Consent was obtained from the patients in accordance with the Declaration of Helsinki for participation.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The author have no conflicts of interest to declare.

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