D-Dimer is a Predictive Factor of Cancer Therapeutics-Related Cardiac Dysfunction in Patients Treated With Cardiotoxic Chemotherapy

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Research

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**Abstract**

**Background:** D-dimer is a sensitive biomarker for cancer-associated thrombosis, but little is known about its significance on cancer therapeutics-related cardiac dysfunction (CTRCD).

**Methods:** Consecutive 169 patients planned for cardiotoxic chemotherapy were enrolled and followed up for 12 months. All patients underwent echocardiography and blood test at baseline, as well as at 3-month, 6-month, and 12-month.

**Results:** The patients were divided into 2 groups based on the level of D-dimer (> 1.65 µg/ml or ≤ 1.65 µg/ml) at baseline before chemotherapy: High D-dimer group (n = 37) and low D-dimer group (n = 132). Left ventricular ejection fraction (EF) decreased at 3-month and 6-month after chemotherapy in high D-dimer group (baseline, 65.2% [62.8%-71.4%]; 3-month, 62.9% [59.0%-67.7%]; 6-month, 63.1% [60.0%-67.1%]; 12-month, 63.3% [58.8%-66.0%], P = 0.03), but no change was observed in low D-dimer group. The occurrence of CTRCD within the 12-month follow-up period was higher in high D-dimer group than in low D-dimer group (16.2% vs. 4.5%, P = 0.0146). Multivariable logistic regression analysis revealed that high D-dimer level at baseline was an independent predictor of the development of CTRCD (odds ratio 3.93, 95% CI [1.00-15.82], P = 0.047).

**Conclusion:** Elevated D-dimer is a pivotal biomarker to predict CTRCD.

**Background**

Recent advances in the diagnosis and treatment of cancers improves its prognosis. However, anti-cancer drugs, including anthracyclines, monoclonal antibodies, tyrosine kinase inhibitors, and etc., induce cardiac dysfunction, resulting in poor prognosis in cancer survivors [1]. Several cardiac biomarkers and echocardiographic parameters, including troponins, myeloperoxidase, and reduced global longitudinal strain, are proposed to detect early phase of cancer therapeutics-related cardiac dysfunction (CTRCD), and prompt cardioprotective treatment can improve cardiac function [2–5]. Although those parameters are useful, careful monitoring is required to all patients to detect early sign of CTRCD. Thus, a novel biomarker that identifies high-risk patients before chemotherapy is desirable to perform effective clinical monitoring.

D-dimer is a sensitive biomarker for cancer-associated thrombosis, but accumulating evidence suggests that pretreatment D-dimer can be used as a prognostic biomarker for the patients with solid tumors [6]. In cardiovascular fields, elevated D-dimer is associated with not only thromboembolic events but also heart failure mortality in heart failure patients with reduced and preserved ejection fraction [7, 8].

Although D-dimer is a promising biomarker in cardio-oncology field, little is known about the relationship between D-dimer and CTRCD. The aim of the present study was to evaluate a predictive impact of D-dimer before chemotherapy on the development of CTRCD.
Methods

Study subjects and protocol

We enrolled 202 consecutive cancer patients, planned for cardiotoxic chemotherapy, including anthracyclines, human epidermal growth factor receptor 2 (HER2) inhibitors, tyrosine kinase inhibitors, and proteasome inhibitors at Fukushima Medical University hospital from November 2016 to March 2019 (Figure 1). Patients were excluded if they were died or transferred to other hospitals within 12 months follow-up period (n=33). Remaining 169 patients were divided into 2 groups based on the cut-off value of D-dimer, which was defined by receiver operator characteristic curve analysis to detect the occurrence of CTRCD (Figure 2).

Hypertension was defined as a history of use of antihypertensive drug or systolic blood pressure of $\geq 140$ mmHg, and/or diastolic blood pressure $\geq 90$ mmHg. Diabetes was defined as a recent use of insulin treatment or hypoglycemic drug, or hemoglobin A1c $\geq 6.5\%$. Dyslipidemia was defined as a history of use of cholesterol-lowering drugs, or triglyceride was $\geq 150$ mg/dl, low density lipoprotein cholesterol was $\geq 140$ mg / dl, and/or high-density lipoprotein cholesterol was $\leq 40$ mg/dl. Cumulative dose of anthracycline was expressed as a doxorubicin equivalent [1]. HER2 inhibitor included trastuzumab and pertuzumab. Tyrosine kinase inhibitors included dabrafenib, trametinib, lenvatinib, sorafenib, dasatinib, bevacizumab, and pazopanib. Proteasome inhibitors included carfilzomib and bortezomib. Radiation therapy was defined as a irradiation to the mediastinum and/or the heart field within follow-up period. Transthoracic echocardiography and blood sampling test were performed at baseline, as well as at 3 months, 6 months, and 12 months after administration of cardiotoxic chemotherapy. All procedures used in this research were approved by the Ethical Committee of Fukushima Medical University.

Echocardiography

Transthoracic echocardiography was performed by a trained sonographer, and images were checked by another trained sonographer and an echo-cardiologist. We measured cardiac function using EPIQ 7G (Philips Healthtech, Best, Netherland). Left ventricular ejection fraction (EF) was calculated using the modified Simpson's method according to the guideline from the American Society of Echocardiography and the European Association of Cardiovascular Imaging [9]. The left ventricular (LV) mass was calculated using the following formula

\[
\text{Left ventricular mass} = 0.8 \times \left[ 1.04 \times \left\{ \left( \text{LV diastolic diameter} + \text{interventricular septum wall thickness} + \text{LV posterior wall thickness} \right)^3 - \left( \text{LV diastolic diameter} \right)^3 \right\} + 0.6 \, \text{g} \right].
\]

CTRCD was defined as a decrease in EF more than 10% points, to a value less than 53% [10]. LV end-diastolic volume index, LV end-systolic volume index, LV mass index, and left atrial volume index were
measured using B-mode ultrasound.

**Blood sampling**

High sensitivity cardiac troponin I (TnI) was measured using an assay based on Luminescent Oxygen Channeling Immunoassay technology, and run on a Dimension EXL integrated chemistry system (Siemens Healthcare Diagnostics, Deerfield, IL, USA). B-type natriuretic peptide (BNP) levels were measured using a specific immunoradiometric assay (Shionoria BNP kit, Shionogi, Osaka, Japan). D-dimer was measured using a latex agglutination method (Lias Auto D-dimer Neo, Sysmex, Kobe, Japan).

**Statistical analysis**

All statistical analyzes were performed using Prism 9 (GraphPad Software, San Diego, USA) or R software packages version 3.6.3 (R core team 2020, Vienna, Austria). We used the Shapiro-Wilk test to discriminate which variables were normally or not normally distributed. Normally distributed variables were shown as mean ± standard deviation. Non-normally distributed variables were indicated by median with interquartile range. Category variables were shown in numbers and percentage. Student’s t-test was used for variables following a normal distribution, the Mann-Whitney U-test was used for variables of the non-normal distribution, and the χ²-square test was used for categorical variables. The time course of EF (baseline, 3-month, 6-month, and 12-month after the administration of anthracyclines) was evaluated using the Friedman test.

Logistic regression analysis was performed to identify the variables to predict the occurrence of CTRCD. We selected variables relating to general condition and cardiac function, including age, echocardiographic parameters, use of anthracyclines, BNP, hemoglobin, estimated glomerular filtration ratio, and the elevation of D-dimer. The variables presenting P value less than 0.05 in the univariable analysis were entered into the multivariable analysis. Receiver operating characteristic curve analysis was performed to determine the optimal cut-off value of D-dimer for predicting the occurrence of CTRCD. The P value of 0.05 or less was defined as significant.

**Results**

First, we performed receiver operating characteristic curve analysis to identify the threshold level of D-dimer to predict the occurrence of CTRCD (Fig. 2). A total of 12 patients suffered CTRCD within 12 months follow-up period. When we set the cut-off value of D-dimer at 1.65 µg/ml, sensitivity, specificity, and area under the curve to predict CTRCD were 50.0%, 80.3%, and 0.661, respectively. Then, we divided the patients into 2 groups based on the cut-off value. Table 1 shows patient characteristics at the baseline before chemotherapy. There were no statistical differences in age, sex, and the usage of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers and β-blockers. High D-dimer group included lower rate of breast cancer (35% vs. 67%, P = 0.0005), higher rate of ovarian/uterine cancer (19% vs. 6%, P = 0.0151), and higher rate of leukemia (16% vs. 4%, P = 0.0068) than low D-dimer group. Echocardiographic data demonstrated that EF was slightly higher in high D-dimer group (67 ± 5%...
vs. 64 ± 5%, P = 0.0019). In laboratory data, high D-dimer group showed lower hemoglobin values and higher BNP values.
Table 1
Baseline clinical characteristics of patients with elevated or non-elevated D-dimer

| Variable                                    | Entire cohort (n = 169) | Low D-dimer (n = 132) | High D-dimer (n = 37) | P value |
|---------------------------------------------|------------------------|-----------------------|-----------------------|---------|
| Age, years                                  | 57 ± 12                | 56 ± 12               | 58 ± 14               | 0.6265  |
| Female, n (%)                               | 146 (86%)              | 117 (89%)             | 29 (78%)              | 0.1078  |
| Medications                                 |                        |                       |                       |         |
| Use of ACEi or ARB                          | 23                     | 18                    | 5                     | 0.9846  |
| Use of β-blockers                           | 4                      | 3                     | 1                     | 0.8791  |
| Cancer types                                |                        |                       |                       |         |
| Breast cancer, n (%)                        | 101 (60%)              | 88 (67%)              | 13 (35%)              | 0.0005  |
| Lymphoma, n (%)                             | 28 (17%)               | 20 (15%)              | 8 (22%)               | 0.3495  |
| Ovarian or uterine cancer, n (%)            | 15 (9%)                | 8 (6%)                | 7 (19%)               | 0.0151  |
| Leukemia, n (%)                             | 11 (7%)                | 5 (4%)                | 6 (16%)               | 0.0068  |
| Bone cancer, n (%)                          | 2 (2%)                 | 2 (2%)                | 0 (0%)                | 0.4513  |
| Other cancers, n (%)                        | 12 (7%)                | 9 (7%)                | 3 (8%)                | 0.7872  |
| Cancer therapy                              |                        |                       |                       |         |
| Anthracyclines                              | 138 (82%)              | 104 (79%)             | 34 (92%)              | 0.0687  |
| HER2 inhibitors                              | 36 (21%)               | 31 (23%)              | 5 (14%)               | 0.1905  |
| Tyrosine kinase inhibitors                  | 8 (5%)                 | 6 (5%)                | 2 (5%)                | 0.8277  |
| Proteasome inhibitors                       | 5 (3%)                 | 5 (4%)                | 0 (0%)                | 0.2295  |
| Dose of anthracyclines (doxorubicin equivalent), mg/m² | 200 [161–240]         | 200 [180–240]         | 180 [112–300]         | 0.3874  |
| Radiation therapy, n (%)                    | 20 (12%)               | 15 (11%)              | 5 (14%)               | 0.7205  |
| Cardiovascular risk factors                 |                        |                       |                       |         |
| Hypertension, n (%)                         | 40 (24%)               | 31 (24%)              | 9 (24%)               | 0.9154  |
| Smoking history, n (%)                      | 47 (28%)               | 37 (28%)              | 10 (27%)              | 0.9042  |
| Diabetes mellitus, n (%)                    | 16 (10%)               | 13 (10%)              | 3 (8%)                | 0.7493  |

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; HER2, human epidermal growth factor receptor 2; LV, left ventricular
| Variable                                      | Entire cohort (n = 169) | Low D-dimer (n = 132) | High D-dimer (n = 37) | P value |
|----------------------------------------------|------------------------|-----------------------|-----------------------|---------|
| Dyslipidemia, n (%)                          | 44 (26%)               | 38 (29%)              | 6 (16%)               | 0.1235  |
| Atrial fibrillation, n (%)                   |                        |                       |                       |         |
| Echocardiographic parameter                  |                        |                       |                       |         |
| LV end-diastolic volume index, mm/m²         | 45 [36–55]             | 45 [36–55]            | 46 [36–55]            | 0.6517  |
| LV end-systolic volume index, mm/m²          | 15 [13–20]             | 15 [13–19]            | 16 [12–20]            | 0.6431  |
| LV mass index, g/m²                          | 70 [59–85]             | 70 [59–85]            | 75 [60–87]            | 0.4644  |
| LA volume index, ml/m²                       | 23 [17–30]             | 23 [17–28]            | 23 [19–32]            | 0.3159  |
| LV ejection fraction, %                      | 65 ± 5                 | 64 ± 5                | 67 ± 5                | 0.0019  |
| E/A                                          | 1.0 [0.8–1.2]          | 1.0 [0.8–1.2]         | 0.9 [0.8–1.1]         | 0.5788  |
| Laboratory data                              |                        |                       |                       |         |
| Aspartate aminotransferase, IU/L             | 19 [15–23]             | 19 [16–23]            | 19 [15–26]            | 0.7973  |
| Alanine aminotransferase, IU/L               | 15 [12–22]             | 15 [12–21]            | 15 [12–23]            | 0.7960  |
| eGFR, ml/min/1.73m²                          | 72 [64–85]             | 73 [65–82]            | 69 [57–88]            | 0.3472  |
| Hemoglobin, g/dl                             | 13 [11–14]             | 13 [12–14]            | 11 [9–13]             | 0.0001  |
| Uretic acid, mg/dl                           | 4.7 ± 1.4              | 4.6 ± 1.3             | 4.7 ± 1.7             | 0.8197  |
| B-type natriuretic peptide, pg/ml            | 12 [7–22]              | 11 [7–20]             | 17 [9–38]             | 0.0440  |
| Troponin I, ng/ml                            | 0.017 [0.017–0.017]    | 0.017 [0.017–0.017]   | 0.017 [0.017–0.017]   | 0.5440  |
| D-dimer, µg/ml                               | 0.6 [0.5–1.4]          | 0.5 [0.5–0.7]         | 3.1 [2.2–8.1]         | < 0.0001|

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; HER2, human epidermal growth factor receptor 2; LV, left ventricular

Time-dependent changes in EF are displayed in Fig. 3. Low D-dimer group showed no changes in EF within follow-up period, but EF was decreased at 3-month and 6-month after chemotherapy in high D-dimer group (baseline, 65.2% [62.8%-71.4%]; 3-month, 62.9% [59.0%-67.7%]; 6-month, 63.1% [60.0%-67.1%]; 12-month, 63.3% [58.8%-66.0%], P = 0.03, Fig. 3A and 3B).
The occurrence of CTRCD during the 12-month follow-up period was higher in high D-dimer group than in low D-dimer group (16.2% vs. 4.5%, \( P = 0.0146 \)). Multivariable logistic regression analysis revealed that LV end-diastolic volume index (odds ratio 0.95, 95% CI [0.91–0.99], \( P = 0.0122 \)) and high D-dimer levels (odds ratio 3.93, 95% CI [1.00-15.82], \( P = 0.0469 \)) before chemotherapy were independent predictors of the development of CTRCD (Table 2).

### Table 2
Parameters associated with the occurrence of CTRCD

| Parameter                                      | Univariate          | Multivariate        |
|------------------------------------------------|---------------------|---------------------|
|                                                | OR (95% CI)         | \( P \) value       | OR (95% CI)         | \( P \) value       |
| Age, per 1 year increase                      | 1.01 (0.96–1.05)    | 0.8470              |                     |                     |
| Male                                           | 1.79 (0.32–33.57)   | 0.5852              |                     |                     |
| Use of anthracyclines                          | 1.18 (0.29–7.94)    | 0.8353              |                     |                     |
| BNP, per 1 pg/ml increase                     | 0.99 (0.98–1.02)    | 0.4239              |                     |                     |
| LV ejection fraction, per 1% increase          | 1.07 (0.95–1.22)    | 0.2591              |                     |                     |
| LV end-diastolic volume index, per 1 ml/m\(^2\) increase | 0.95 (0.91–0.99) | 0.0099              | 0.95 (0.91–0.99) | 0.0122              |
| E/A, per 1 increase                            | 0.24 (0.05–1.39)    | 0.0934              |                     |                     |
| Left atrial volume index, per 1 ml/m\(^2\) increase | 0.99 (0.94–1.05) | 0.7157              |                     |                     |
| Hemoglobin, per 1 g/dl increase                | 1.13 (0.85–1.45)    | 0.3539              |                     |                     |
| Estimated GFR, per 1 ml/min/1.73m\(^2\)        | 0.98 (0.95–1.02)    | 0.2989              |                     |                     |
| Elevated D-dimer (1.65 mg/dl)                  | 4.07 (1.20–13.84)   | 0.0218              | 3.93 (1.00-15.82)   | 0.0469              |

CTRCD, cancer therapeutics-related cardiac dysfunction; BNP, B-type natriuretic peptide; LV, left ventricular; GFR, estimated filtration ratio

**Discussion**
In the present study, we revealed the predictive features of D-dimer in patients treated with cardiotoxic agents. First, the threshold level of D-dimer was 1.65 µg/ml to predict the development of CTRCD. Second, EF was decreased time dependently in high D-dimer patients. Third, the occurrence CTRCD was significantly higher in high D-dimer patients.

D-dimer is a pivotal biomarker of hypercoagulability and thrombosis. Fibrin-bound plasmin degrades the fibrin network into soluble fragments D-dimers and E fragments, thus increased levels of D-dimer represent a global activation of coagulation and fibrinolysis [11]. Cancers produce hypercoagulable and prothrombotic situation by secreting several pro-thromboembolic factors such as mucins, cysteine protease, and tissue factors [12]. Therefore, thrombi are easily generated in cancer patients, and thromboembolism is the second leading cause of cancer related morbidity and mortality [13, 14]. Although D-dimer is an established and widely used biomarker for the screening of thrombus formation in cancer patients, prognostic features of D-dimer become clinically overt recently. The link between D-dimer and cancer progression is reported in several papers [15, 16], and higher levels of D-dimer is associated with poor prognosis in cancer patients [16]. Although the precise mechanisms are still complex and uncovered, pro-coagulable state may produce a suitable milieu for cancer progression by recruitment of pro-metastatic leukocytes, adhesion to the endothelium, transendothelial migration, and restriction in natural killer cell-mediated clearance of micrometastasis [17, 18]. Accumulating evidence showed that abnormal inflammation and oxidative stress are key factors to the development of heart failure, and those also play important roles in cancer progression and thrombus formation [19–23]. The inflammatory microenvironment is now recognized as an important participant or a regulator of all stages of tumor development, from an early stage of carcinogenesis to tumor promotion and metastatic spread to distant organs [22]. Regarding to thrombus formation, Gomes et al. reported that blockade of IL-1 receptor abolished the neutrophil extracellular traps-dependent prothrombotic state and attenuated cancer-associated thrombosis in murine breast cancer model [23]. Consider the facts that inflammation is a major contributor of cardiac dysfunction and thrombus formation, cancer patients with high D-dimer may be predispose to cardiac dysfunction due to chronic inflammatory state. Cardiotoxic chemotherapeutic agents are crucial and indispensable to perform cancer treatment. Anthracyclines induce pro-inflammatory response by increasing TNF-α, IL-1β, and IL-6, leading to tumor cell death [24]. Not only anthracyclines, but targeted chemotherapy, such as trastuzumab and bevacizumab, also increased inflammatory cytokines after the treatment [25, 26]. In the present study, the patients with high D-dimer group may already had been exposed to inflammatory state before chemotherapy, and were vulnerable to additional inflammatory stress by cardiotoxic agents, resulting in the development of CTRCD. To elucidate the precise mechanisms was beyond of this study, but the importance of D-dimer should be noted in cardio-oncology field. LIPID study revealed that elevated D-dimer levels predict long-term risk of arterial and venous events, cardiovascular disease mortality, in addition to that, increased cancer incidence and mortality rate [27]. To the best of our knowledge, this is the first report of assessing the relationship between D-dimer levels and the development of CTRCD. The importance of D-dimer should be taken into account when managing cancer patients treated with cardiotoxic chemotherapy.
Conclusions

Elevated D-dimer is a pivotal biomarker to predict CTRCD. D-dimer should be taken into account when managing cancer patients treated with cardiotoxic chemotherapy.

Limitations

This study was performed using a relatively small number of patients and short follow-up period by a single center. Longer follow-up and larger population data were needed to confirm the importance of D-dimer to the development of CTRCD and cardiovascular prognosis.

List Of Abbreviations

CTRCD
Cancer therapeutics-related cardiac dysfunction; EF:Left ventricular ejection fraction; HER2:human epidermal growth factor receptor 2; LV:Left ventricular; TnI: Troponin I; BNP:B-type natriuretic peptide.

Declarations

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Authors’ contributions

MO created the study design, analyzed the data, and drafted the manuscript; DY created the study design and analyzed the data; TM, TS, TK, and AK aquired the data. AY, KN, TI, and YT interpreted the data, revised the manuscript. All authors contributed to the conception, design, critical revision and final approval of this manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

We obtained prior approval that the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki from the Ethics Committee of Fukushima Medical University (approval number 2839). Written consent was acquired from all patients.
Consent for publication

Not applicable.

Competing interests

None of the authors have any competing interest to disclose.

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Figures

Figure 1

- Cancer patients treated with cardiotoxic agents-containing chemotherapy between November 2016 and March 2019
- D-dimer was assessed before chemotherapy (n=202)

Exclude:
- Death or transferred to other hospitals within follow-up period (n=33)

Patients treated with cardiotoxic agents-containing chemotherapy with a follow-up of 12 months (n=169)

- Low D-dimer (<1.65 µg/ml) n=132
- High D-dimer (≥1.65 µg/ml) n=37
Figure 2

ROC curve analysis of D-dimer predicting the occurrence of cancer therapeutics-related cardiac dysfunction.
Figure 3

Time-dependent changes in EF after chemotherapy. (A) Changes in EF in low D-dimer group. (B) Changes in EF in high D-dimer group.