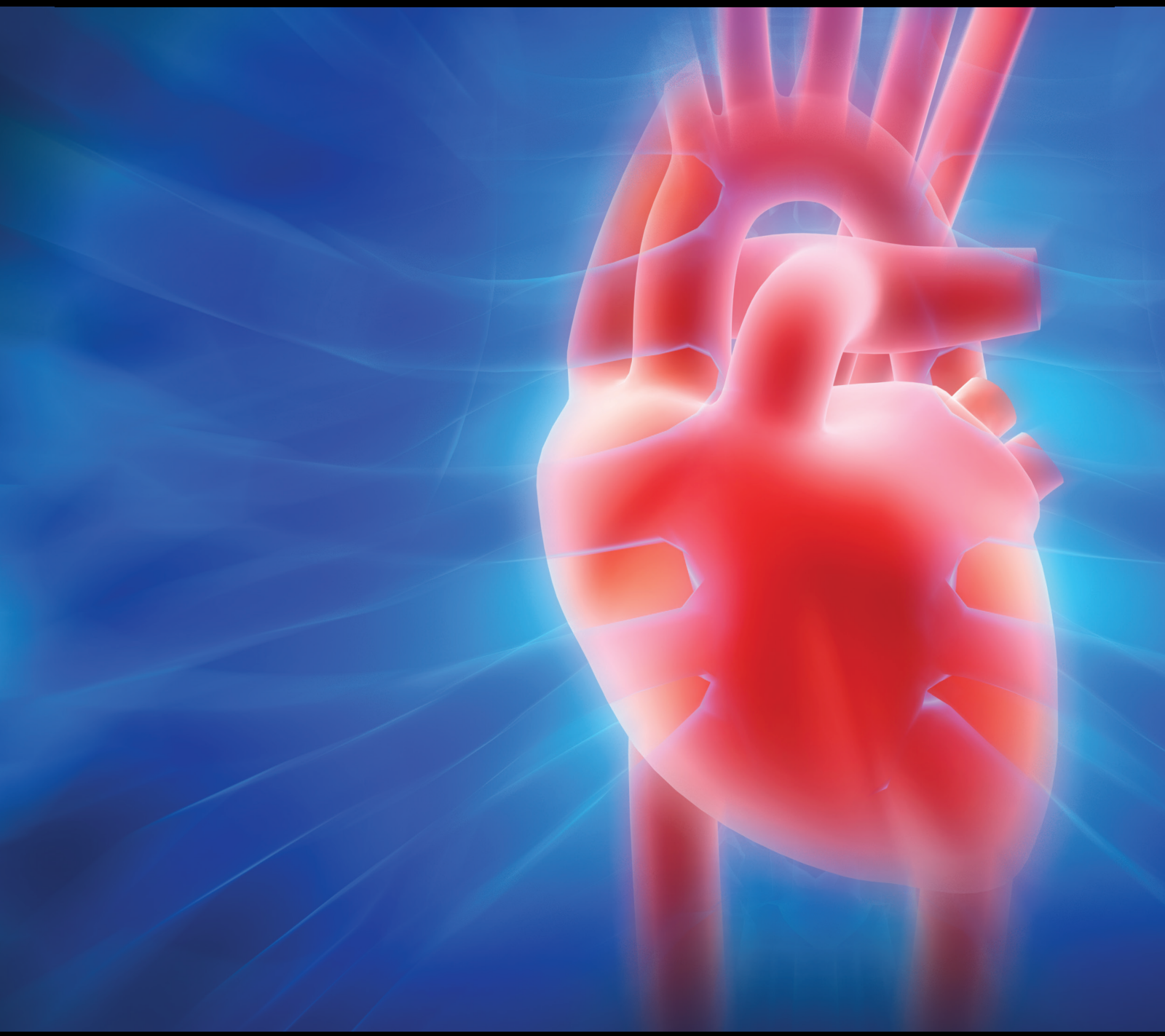
Cardiology Research and Practice

Cardio-oncology

Lead Guest Editor: Tong Liu
Guest Editors: Yun-Long Xia, Fei Ma, Jiwei Liu, Xiaoyuan Chu, and Leonardo Roever



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Contents

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Research Article

Preexisting Cardiovascular Risk Factors and Coronary Artery Atherosclerosis in Patients with and without Cancer

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Cancer survivors suffer a higher risk of coronary artery atherosclerosis (CAA). Whether cancer patients had increased baseline CAA burden prior to cardiotoxic therapy remains unclear. We conducted a case-control study, and 286 consecutive patients were finally included. Among these patients, 181 had newly diagnosed cancer and 105 had nonmalignant diseases. Cancer was confirmed by biopsy. The severity of CAA was determined by coronary angiography and evaluated using the percentage of stenosis or Gensini scoring (GS). Patients with cancer versus cancer-free controls were older (OR = 1.052, 95% CI: 1.021–1.084, $p < 0.001$), more commonly male (OR = 0.048, 95% CI: 1.004–2.676, $p = 0.048$), and more severely exposed to smoking (OR = 1.020, 95% CI: 1.007–1.033, $p = 0.003$). Cancer patients were significantly more commonly complicated by ≥90% coronary stenosis than the gender- and age-matched cancer-free controls (9/93 versus 1/93, OR = 4.875, 95% CI: 1.024–23.213, $p = 0.047$). After adjustment for age, gender, hypertension, diabetes, smoking history, blood glucose, and total cholesterol, cancer was significantly associated with high GS (adjusted OR = 2.208, 95% CI: 1.077–4.524, $p = 0.031$). Our study demonstrated that cancer patients had increased CAA burden prior to cardiotoxic therapy. Further study is necessary to investigate the link between CAA and cancer.

1. Introduction

Cardiovascular disease (CVD) and cancer are the leading causes of death worldwide with utterly different treatment strategies [1, 2]. In recent years, emerging evidence suggests a relation between the two seemingly disconnected diseases [3]. Survivors of cancer suffer a higher risk of CVD [4–7], while cohort studies also found that patients with CVD are more likely to develop cancer [8–10]. However, how the two appealingly separated diseases are linked is not clear.

Oncocardiology is a new field of clinical medicine that addresses the overlap between cancer and CVD [11]. During the decade of research of oncocardiology, the cardiotoxicity of the chemo-, radio-, and immunotherapy of cancer remains the principal focus [5, 12–14]. Accumulating evidence has shown that cardiovascular injury caused by cancer therapy is associated with poor prognosis, especially in patients with preexisting cardiovascular risk factors and cardiovascular diseases [15, 16]. Adding to the challenge is the fact that preexisting cardiovascular diseases in cancer patients are quite common and many patients with cancer show cardiac injury even before cardiotoxic treatments [7, 17, 18]. In 2015, S. G. Al-Kindi et al. first found that cancer patients had higher prevalence of preexisting CVD than the age-matched general population [7]. However, this finding was not the major content of their study, and to our knowledge, there were no other studies confirming this finding since then. Whether cancer patients had increased

CVD burden prior to cardiotoxic therapy and the reason behind remain unclear.

It is currently assumed that the shared risk factors of CVD and cancer play a role in the association between the two diseases [19–21]. Actually, many risk factors, such as smoking and diabetes, may cause CVD and cancer at the same time. This might partly explain the increased burden of preexistence of CVD in cancer patients. However, currently, almost all related studies are focused on cancer survivors [22, 23]. Studies evaluating the cardiovascular risk factors and CVD burden in cancer patients before active treatment are lacking.

Coronary artery atherosclerosis (CAA) is one of the most common CVDs. Here, we undertook a case-control study to investigate the distribution of preexisting cardiovascular risk factors and severity of CAA in patients with cancer and cancer-free controls. We aimed to compare the severity of CAA between cancer patients and cancer-free controls and provide clues for further research to investigate the reason behind the increased preexisting CVD burden in cancer patients.

2. Materials and Methods

2.1. Data Source and Study Design. We performed a real-world database analysis complied with the Declaration of Helsinki, and it was approved by the hospital's ethical review board (Tongji Hospital, Huazhong University of Science and Technology, Wuhan, China). Written informed consent was not obtained because the data were analyzed retrospectively and anonymously. Potential eligible patients were identified by screening lists of admissions from the departments of thoracic surgery, general surgery, urinary surgery, and orthopedics of Tongji Hospital between 4/2012 and 4/2018. The majority of the patients were found lung, liver, gastrointestinal, or urinary mass and admitted to hospital for suspected cancer. Initially included in the study were 439 consecutive patients who received coronary artery angiograph during hospitalization. While most patients received established diagnoses by pathologic examination, several patients had indeterminate lesions. In total, 84 patients were excluded for indefinite pathological diagnosis. Among these patients, 73 patients were excluded for the absence of histopathological results to identify the nature of the mass. Eleven patients were excluded because they had borderline tumor with malignant potential. Other exclusion criteria included history of cancer therapy ($n = 23$) and stent implantation (because the existence of stents made us unable to make accurate evaluation of the real stenosis, $n = 46$). Our final study included 286 patients, among whom 181 were diagnosed with cancer and 105 were cancer free (Figure 1).

2.2. Definition of Risk Factors. Data were retrieved from the medical records and electronic databases of Tongji Hospital. History of hypertension and diabetes was reported by patients themselves, taken by their residents, and recorded in patients' hospital medical records. The self-reported hypertension/diabetes was defined by answering "yes" to the question "Do you have hypertension/diabetes?" The history of smoking was defined as having consumed tobacco at least once in the past years and was quantified by the smoking index, which was calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked.

2.3. Coronary Angiography and Gensini Score Assessment. Coronary angiographies were performed using transradial or transfemoral approaches by experienced cardiologists. The extent of coronary stenosis was evaluated by at least two independent physicians, and a final written report was signed after discussion. The Gensini score was calculated according to the previously published method [24]. Briefly, reduction in lumen diameter was evaluated as different scores, and each vascular segment was weighed by a different coefficient. Reductions of 25%, 50%, 75%, 90%, and 99% and complete occlusion were evaluated as 1, 2, 4, 8, 16, and 32, respectively. The left main coronary artery was weighed by 5, proximal segment of the left anterior descending (LAD) coronary artery and the proximal segment of the circumflex artery by 2.5, the midsegment of the LAD by 1.5, the right coronary artery, the distal segment of the LAD, the middistal region of the circumflex artery, the posterolateral artery, and the obtuse marginal artery by 1.0, and other segments by 0.5. The enrolled patients were classified into the two groups (low group 0–18 points; high group >18 points).

2.4. Statistical Analyses. The data were analyzed by SPSS version 24.0 for Mac (SPSS Inc., Chicago, IL, USA). Continuous variables with normal distribution were presented as mean ± SD. Nonnormal variables were reported as median (Q1–Q3 quartiles). The normality of distribution of continuous variables was tested by the one-sample Kolmogorov–Smirnov test. Categorical variables were expressed as number (percentage). Means of 2 continuous normally distributed variables were compared by independent-sample Student's t-test. The Mann–Whitney U test was run to determine if there were differences between two nonnormal variables. The frequencies of categorical variables were compared using Pearson χ^2 (with or without continuity correction) or Fisher's exact test, when appropriate. Some covariates (smoking index, total cholesterol, and blood sugar) had missing values, and we applied max likelihood by expectation maximization and built imputation data to replace the missing values. Since there existed an imbalance in gender and age between patients in the malignant group and nonmalignant group, we used the case-control matching method and sampled 186 patients from the 286 patients. The binary logistic regression analysis was used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for the association between cancer and severity of coronary artery atherosclerosis. A p value of <0.05 was set as the level of statistical significance.

3. Results

3.1. Clinical Characteristics in Patients with Malignant and Nonmalignant Diseases. A total of 286 patients were finally included in this study. To assess the distribution of

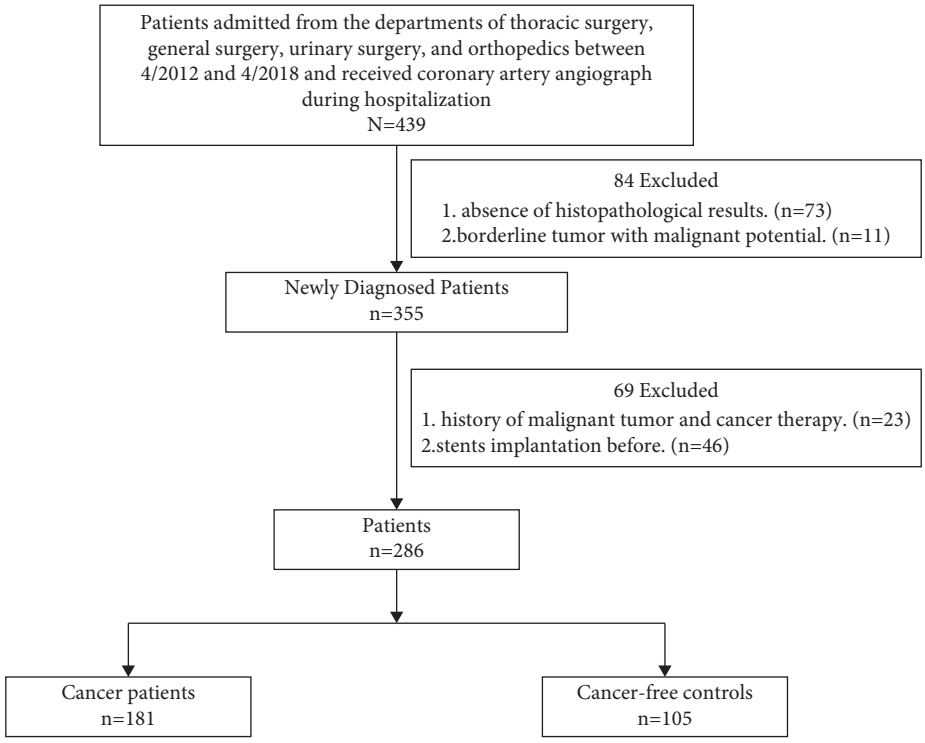

Figure 1: Patient inclusion and exclusion details.

conventional CVD risk factors in cancer patients and their cancer-free controls, patients were classified into two groups based on their pathological examination results. It turned out that 181 (65.2%) patients had cancer, while 105 (53.3%) patients were cancer free. Among the cancer patients, 83 patients had lung cancer, 41 had esophagus cancer, 18 had colorectal cancer, 12 had gastric cancer, 6 had kidney cancer, 6 had hepatobiliary cancer, 5 had bladder cancer, and 10 had other cancers (Supplementary Figure 1a). According to the TNM classification system of the International Union Against Cancer (8^{th} edition), 68 patients had stage I cancer, 48 stage II, 40 stage III, 8 stage IV, and 25 patients had unknown stage (Supplementary Figure 1b). For the total 286 patients, the median age was 64 years (59–69), including 174 (60.8%) men. Patients with cancer were older (OR = 1.052, 95% CI: 1.021–1.084, $p < 0.001$), more commonly male (OR = 0.048, 95% CI: 1.004–2.676, $p = 0.048$), and more severely exposed to smoking (OR = 1.020, 95% CI: 1.007–1.033, $p = 0.003$). There were no significant differences in the history of hypertension (OR = 1.379, 95% CI: 0.849–2.236, $p = 0.194$) and diabetes (OR = 0.572, 95% CI: 0.281–1.165, $p = 0.124$) between the two groups. Blood sugar (OR = 1.066, 95% CI: 0.892–1.272, $p = 0.661$) and total cholesterol (OR = 1.081, 95% CI: 0.827–1.413, $p = 0.575$) showed no significant differences between the patients with and without cancer (Table 1).

3.2. Severity of CAA in Patients with Malignant and Non-malignant Diseases. We next evaluated the incidence and severity of CAA in the both groups (Figure 2(a)). As shown in Figure 2(b), 42% of the cancer patients and 35.2% of cancer-free controls turned out to have ≥50% coronary stenosis. More cancer patients had ≥75% coronary stenosis compared to patients with no cancer (25.4% versus 16.2%, Figure 2(c)). Also, more cancer patients had ≥90% coronary stenosis compared to the cancer-free patients (8.3% versus 3.8%, Figure 2(d)). There was significant difference in age and gender between the two groups. Using Case-Control Matching function of SPSS, 93 cancer patients were gender and age (±2 years old) matched by 93 cancer-free controls. Basic characteristics of the gender- and age-matched 186 patients are presented in Table 2. The average age was 62 ± 8 years, and 96 (52%) were male. There were no significant differences in all common risk factors. Slightly fewer cancer patients had ≥50% coronary stenosis compared to the cancer-free controls (31/93 versus 33/93, OR = 0.909, 95% CI: 0.496–1.665, $p = 0.758$). As shown in Figure 2(g), 23/93 cancer patients and 14/93 of patients with no cancer had ≥75% stenosis (OR = 1.854, 95% CI: 0.886–3.879, $p = 0.101$). Notably, cancer patients were significantly more commonly complicated by ≥90% coronary stenosis than the cancer-free controls (9/93 versus 1/93, OR = 4.875, 95% CI: 1.024–23.213, $p = 0.047$, Figure 2(h)).

3.3. Association between Cancer and Worse CAA. Since age, gender, hypertension, diabetes, smoking history, blood glucose, and total cholesterol are all significant long-term risk factor for CAA [19], to verify whether or not there are correlations between cancer and worse CAA besides the shared risk factor association, a binary logistic regression analysis was then performed using the entry process. Variables included in the model were age, gender, hypertension,

Table 1: Basic characteristics of patients included.

Parameter	All patients, $n = 286$	Cancer patients, $n = 181$	Cancer-free controls, $n = 105$	OR (95% CI) for cancer	P value
Age	64 (59, 69)	65 (61, 70)	61 ± 10	1.052 (1.021–1.084)	< 0.001
Male	174 (60.8%)	118 (65.2%)	56 (53.3%)	1.639 (1.004–2.676)	0.048
Hypertension	137 (47.9%)	92 (50.8%)	45 (42.9%)	1.378 (0.849–2.236)	0.194
Diabetes	35 (12.2%)	18 (9.9%)	17 (16.2%)	0.572 (0.281–1.165)	0.124
Smoking history/bag-year	12 (0, 27)	17 (0, 30)	0 (0, 17)	1.020 (1.007–1.033)	0.003
Blood sugar/mmol/L	5.35 (4.92, 5.94)	5.41 (4.97, 5.95)	5.34 (4.81, 5.97)	1.066 (0.892–1.272)	0.661
Total cholesterol/mmol/L	4.02 ± 0.91	4.05 ± 0.89	3.98 ± 0.95	1.081 (0.827–1.413)	0.575

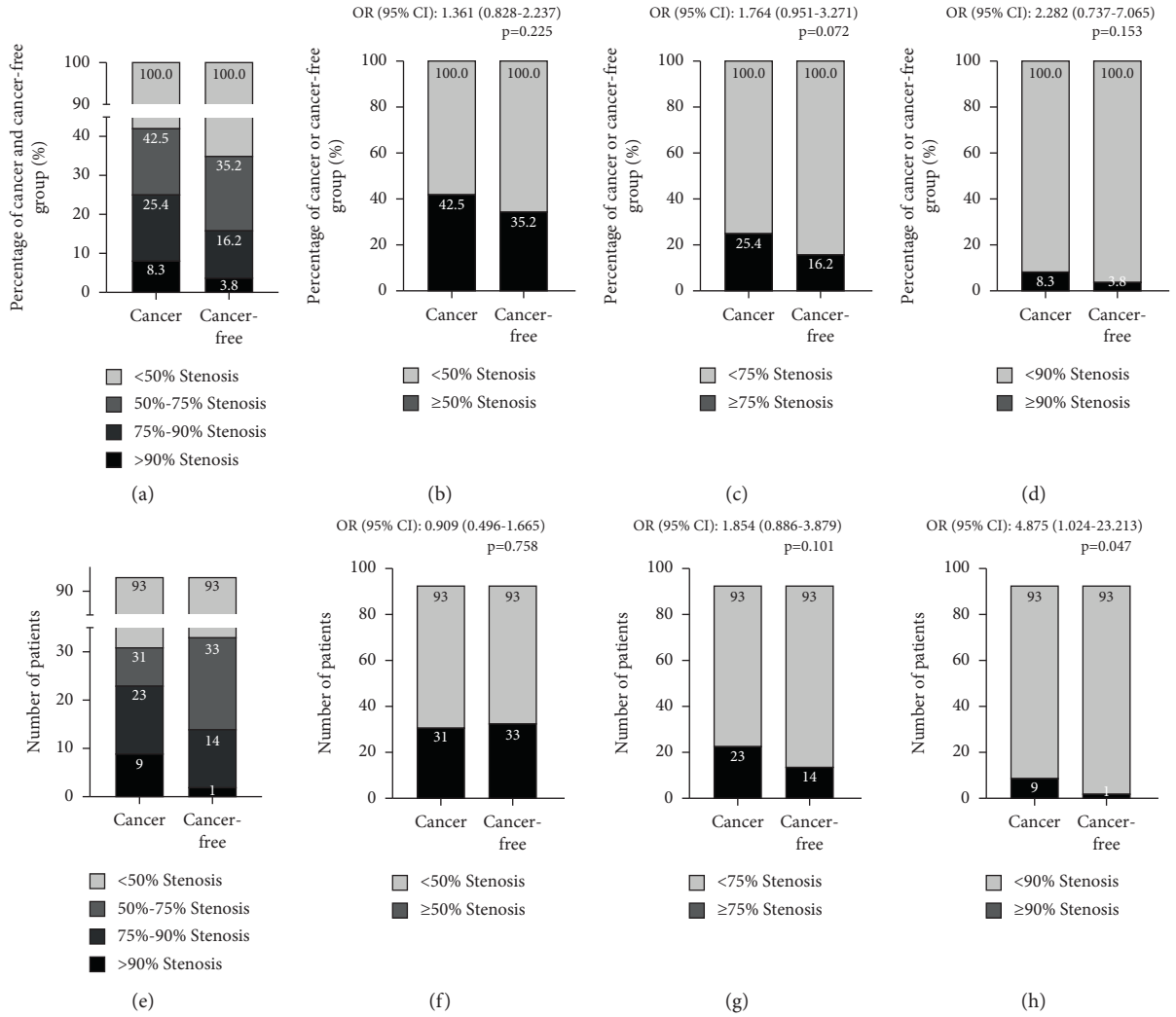

Figure 2: Severity of CAA in cancer and no-cancer patients. (a–d) Comparison of severity of CAA between cancer and no-cancer patients. (a) Cancer patients were more likely to have worse CAA compared with the cancer-free controls. (b), (c), (d) Cancer patients were slightly more likely to have ≥50%, ≥75%, and ≥90% coronary stenosis compared with the cancer-free controls. (e–h) Comparison of severity of CAA between gender- and age-matched cancer and no-cancer group. (h) Patients in the cancer group were significantly more commonly complicated by ≥90% coronary stenosis than patients in the no-cancer group (9/93 versus 1/93, OR = 4.875, 95% CI: 1.024–23.213, $p = 0.047$).

Table 2: Basic characteristics of patients matched by gender and age.

Parameter	All patients, $n = 186$	Cancer patients, $n = 93$	Cancer-free controls, $n = 93$	OR (95% CI) for cancer	P value
Age	62 ± 8	63 ± 7	62 ± 8	1.007 (0.970,1.047)	0.704
Male	96 (52%)	48 (52%)	48 (52%)	1.000 (0.563,1.777)	1.000
Hypertension	103 (55%)	51 (55%)	52 (56%)	0.649 (0.364,1.158)	0.143
Diabetes	24 (13%)	9 (10%)	15 (16%)	1.795 (0.743,4.336)	0.194
Smoking history/bag-year	0 (0, 20)	0 (0,30)	0 (0,17)	1.013 (1.000,1.027)	0.051
Blood sugar/mmol/L	5.41 (4.99,6.11)	5.47 (5.07,6.16)	5.35 (4.86,6.08)	1.098 (0.882,1.367)	0.402
Total cholesterol/mmol/L	4.03 ± 0.95	4.02 ± 0.95	4.03 ± 0.95	0.977 (0.717,1.331)	0.884

diabetes, smoking history, blood glucose, total cholesterol, and cancer. As shown in Figure 3, after adjusting for other risk factors, cancer was found to be still significantly associated with worse CAA (adjusted OR = 2.208, 95% CI: 1.077–4.524, $p = 0.031$).

4. Discussion

In this case-control study, we assessed the distribution of preexisting cardiovascular risk factors and severity of CAA in 286 consecutive patients with or without cancer. We found patients with cancer versus cancer-free controls were significantly older, more commonly male, and more severely exposed to smoking. Cancer patients were more likely to have worse CAA compared to the gender- and age-matched cancer-free controls before active treatment. Multivariate analyses revealed that, after adjustment for age, gender, hypertension, diabetes, smoking history, blood glucose, and total cholesterol, cancer was significantly associated with worse atherosclerosis.

Advances in medical therapies and technologies have prolonged the survival time of patients with cancer and increased the overlap between cancer and CVD. Several previous cohort studies have shown that cancer survivors have increased risk for CAA compared to the general population [22, 25]. However, to our knowledge, few studies ever estimated the baseline CAA burden in cancer patients before active treatment. We found that cancer patients were more likely to have worse CAA even before cardiotoxic cancer treatment, which should draw more attention from oncologists, since many antitumor treatments, such as fluoropyridines, cisplatin, nilotinib, VEGF inhibitors, and radiotherapy, may accelerate coronary artery atherosclerosis or plaque rapture [12, 26]. This result is consistent with the prior findings that preexisting CVDs (CAA, carotid artery disease, peripheral vascular disease, cerebrovascular disease, and heart failure) are more common in untreated cancer patients than the gender- and age-matched general population [7]. However, different from the previous study, our research focused on CAA and tried to further assess the distribution of cardiovascular risk factors between the two groups.

CAA and cancer possess several similar risk factors, which should lead to the concurrence of CAA and cancer in the same individuals [19]. However, most of the existing studies are focused on cancer-free patients or cancer survivors. We compared the distribution of cardiovascular risk factors in newly diagnosed patients and no-cancer controls and found that cancer patients were significantly older, more commonly male, and more severely exposed to smoking. This finding might partly explain the previous result that cancer patients were also more likely to have worse CAA even before cardiotoxic cancer treatments.

In our gender- and age-matched model, the distribution of common CAA risk factors showed no significant difference between the cancer and no-cancer group after the match, but the extent of CAA was still worse in cancer patients. Our multivariate analysis also demonstrated that cancer was associated with worse atherosclerosis after adjustment for some of the common CVD risk factors. This may be explained by that there are still many other risk factors which were not accounted for by the study. On the other hand, it may also suggest that the correlation between cancer and CAA can be pathophysiological [19–21]. There are many shared molecular factors critical to CAA and cancer. For example, chronic inflammation is a common cause for both atherosclerosis [27] and cancer [28]. Besides, it is interesting to mention that an analysis of the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) showed that selective inhibition of interleukin-1β with canakinumab decreased the rate of recurrent cardiovascular events and showed its most pronounced effect on reducing lung cancer mortality at the same time [29].

There are several inevitable limitations in our study. First, the case-control design of the study inherently limits our ability to make causal conclusions about the findings. Second, the small sample size limits the generalizability of our conclusions. Moreover, despite our efforts to adjust for many available confound factors, we did not assess the current use of cardiovascular medications and some other confounding factors of interest to clinicians, such as low-density lipoprotein and body mass index, due to the lack of clinic data. We hope to expand the sample size and try to collect multicenter data to obtain more reliable achievements in future.

In summary, our study demonstrated that cancer patients were more likely to have worse CAA before active treatment compared to the general population, which should draw attention from clinicians. A new strategy targeting the shared risk factors and the potential shared pathophysiological process may have synergistic benefits in the prevention and treatment of both CAA and cancer.

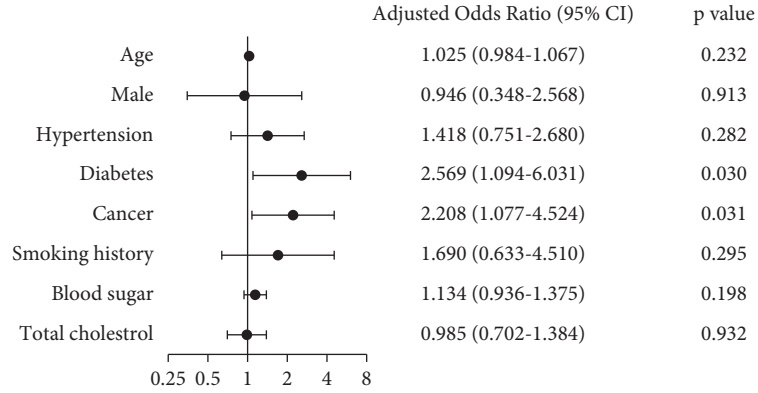

Figure 3: Forest plot of the multivariable logistic regression model. Cancer is significantly associated with high Gensini score (adjusted OR = 2.208, 95% CI: 1.077–4.524, $p = 0.031$). CI indicates confidential interval.

5. Conclusions

Cancer patients have a heavier baseline CAA burden than cancer-free controls before active cancer treatment. Further study is necessary to investigate the reason behind the increased preexisting CAA burden in cancer patients.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

Acknowledgments

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Supplementary Materials

Supplementary Figure 1: cancer type and cancer stage of patients. (a) Pie chart showing the cancer type distribution of patients. (b) Pie chart showing the cancer stage distribution of patients. (*Supplementary Materials*)

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Research Article

Identification of Subclinical Myocardial Dysfunction in Breast Cancer Patients with Metabolic Syndrome after Cancer-Related Comprehensive Therapy

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Background. Breast cancer patients with metabolic syndrome have an increased risk of cardiovascular disease. These patients are more prone to suffer from cardiotoxicity after anticancer therapy. Patients after completion of cancer-related comprehensive therapy, who show normal myocardial function, may already have subclinical myocardial dysfunction. We sought to evaluate the subclinical myocardial dysfunction in breast cancer patients with metabolic syndrome after cancer-related comprehensive therapy. Methods. In this study, 45 breast cancer patients with metabolic syndrome after completion of cancer-related comprehensive therapy, 45 non-breast cancer patients with metabolic syndrome, and 30 breast cancer patients without metabolic syndrome after therapy were enrolled. Left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS) were measured using echocardiogram. *Results.* All the patients had normal LVEF. However, nine breast cancer patients with metabolic syndrome (20%) had GLS that was lower than –17%, while all the noncancer patients had normal GLS. Breast cancer patients with metabolic syndrome had a decrease of GLS and LVEF, compared with noncancer patients with metabolic syndrome. Furthermore, we found that decrease of age was associated with reduction of LVEF and that use of trastuzumab for 1 year was a significant factor associated with reduction of GLS. In addition, breast cancer patients with metabolic syndrome had a decrease of GLS, compared with breast cancer patients without metabolic syndrome after cancer-related therapy. *Conclusions.* Breast cancer patients with metabolic syndrome after completion of cancer-related comprehensive therapy suffered from subclinical myocardial dysfunction. GLS should be routinely performed to early identify subclinical myocardial damage of patients, in order to prevent the cardiotoxicity of cancer-related comprehensive therapy.

1. Introduction

The incidence of metabolic syndrome has increased year by year with the unhealthy lifestyle. Previous study has estimated that 24.5% of Chinese subjects over 15 years old had suffered from metabolic syndrome [1]. Recently, several studies have shown that metabolic syndrome is involved in the occurrence, recurrence, and metastasis of breast cancer, thus affecting the prognosis of breast cancer patients [2]. In China, there are a large number of breast cancer patients with metabolic syndrome, especially those with abdominal obesity. It is known that patients with metabolic syndrome have an increased risk of cardiovascular disease [3]. Furthermore, most of these breast cancer patients need to have cancer-related comprehensive therapy, including chemotherapy, targeted therapy, and radiotherapy, which may result in the further damage of their myocardium.

Recent studies have shown that chemotherapy, targeted therapy, and radiotherapy in breast cancer patients can cause injury of the myocardium. Use of anthracyclines, one of most widely used chemotherapeutic drugs, can lead to acute and chronic toxic damage to myocardium [4]. In addition, trastuzumab is often used in combination in HER2 or ErbB2 positive breast cancer patients. Although trastuzumab improves clinical outcomes by targeting the tumor, trastuzumab also causes an increased risk of cardiovascular adverse events, the most common of which is the left ventricular systolic dysfunction [5]. Furthermore, radiation therapy for left breast cancer can also cause cardiotoxicity, including cardiac insufficiency, due to its radiation to the heart [6].

The European Society of Cardiology have defined that cancer therapy-related cardiac dysfunction (CTRCD) is that the reduction of left ventricle ejection fraction (LVEF) is over 10% or LVEF is decreased to a value below 50% [7]. However, the decrease of LVEF that can be detected by echocardiogram may occur after sever damage of myocardium in patients. In more than half of these patients, left ventricular dysfunction has been permanently impaired and cannot be restored [8]. It was found that measurement of GLS using two-dimensional speckle tracing echocardiography (STE) can detect early change of left ventricular function, thus predicting the occurrence of CRTCD [9]. However, due to the insufficient understanding of GLS, it is not routinely used in cancer patients [10]. In this study, we aim to evaluate the cardiotoxicity of patients by both LVEF and GLS, together.

Rare studies focused on the cardiotoxicity of cancer-related therapy in patients with metabolic syndrome. Therefore, our study observed the cardiac function in breast cancer patients with metabolic syndrome, compared with that in noncancer patients with metabolic syndrome. We aimed to find the subclinical myocardial dysfunction of these patients and related risk factors, so as to early prevent cardiotoxicity in these patients.

2. Methods

2.1. Study Design and Population. In our study (http://www.chictr.org.cn Identifier: ChiCTR1900022108), 45 breast cancer patients with metabolic syndrome who were admitted to Breast Center of Peking University People's Hospital from November 2018 to February 2019 were consecutively enrolled. The inclusion criteria were as follows: (1) patients were ≥18 and ≤60 years old; (2) patients were diagnosed with stage I-III breast cancer; (3) patients have completed breast cancer surgery, chemotherapy, targeted therapy, and radiotherapy in Breast Center; (4) patients had a body weight change of less than 10% in the past 6 months; (5) patients had a waist circumference ≥80 cm with at least one abnormal indicator, including high blood glucose, high blood pressure, and dyslipidemia. The exclusion criteria included the following: (1) patients had heart-, liver-, or kidney-related diseases; (2) Patients had history of other caner. Age, height, weight, radiotherapy, targeted therapy and chemotherapy regimen, and cardiovascular risk factors were collected for each patient. Meanwhile, serum type B natriuretic peptide (BNP) and troponin I (TnI) were also collected. In addition, 45 noncancer patients with metabolic syndrome were enrolled as matches. The inclusion criteria were (1), (4), (5), that the same with breast cancer patients, and no history of cancer, as well as no heart, liver, and kidney related disease. Moreover, 30 breast cancer patients without metabolic syndrome were enrolled as well. The inclusion criteria were (1), (2), and (3), but without (5).

2.2. Image Acquisition. All patients were examined by transthoracic echocardiography and contrast-enhanced echocardiography using GE95. All echocardiographic exams were performed by the same technician using the same machine. All images were interpreted by the same cardiologist. Contrast-enhanced echocardiography for left ventricular opacification (LVO) was used to improve the accuracy of quantitative assessment of LVEF. LVEF was calculated by the two-plane Simpson method. GLS was measured in all patients. The specific measurement is as follows. When the images were collected, we made an optimization of the gain, compress, and time-gain compensation controls to get clear appearance of the left ventricle. Then, apical views (4, 2, and 3 chambers) were collected using high frame rate (>50 frames/s). The GLS was measured, and the boundary tracking was optimized by manual corrections. The images of each patient had no or just one segment of poor display.

All participants provided written informed consent. The study was approved by the Medical Ethics Committee of Peking University People's Hospital.

2.3. Statistical Analysis. Continuous variables were represented by mean ± standard deviation. Categorical variables were expressed by percentage of patients in each group. Categorical variables were compared using Person's chi-square test. Continuous variables were compared using independent sample t-test. Multiple linear regression was used to analyzed the risk factors related to GLS and LVEF. $P < 0.05$ was considered to have statistical significance. All the analyses were performed by SPSS 20.0 software.

3. Results

Baseline characteristics of the 45 breast cancer patients with metabolic syndrome and the 45 noncancer patients with metabolic syndrome are shown in Table 1. The mean age of breast cancer patients was 49 years. The mean BMI of breast cancer patients was 27.8 kg/m^2. There were no significant differences in age, BMI, waist circumference, and cardiovascular risk factors between breast cancer patients and noncancer patients. All of the breast cancer patients with metabolic syndrome showed TnI and BNP levels within normal range.

All patients had normal LVEF. However, four breast cancer patients with metabolic syndrome had LVEF that was lower than 60%, while no noncancer patients with metabolic syndrome had LVEF that was lower than 60%. Furthermore, among the breast cancer patients with metabolic syndrome, nine patients (20%) had GLS that was lower than −17%, which

Table 1: Baseline characteristics of breast cancer and noncancer patients with metabolic syndrome.

	Breast cancer patients with metabolic syndrome	Noncancer patients with metabolic syndrome	P value
Demographics			
Age (years)	49 ± 8	52 ± 10	0.442
BMI (kg/m^2)	27.8 ± 3.2	27.3 ± 2.6	0.674
Waist circumference (cm)	92.6 ± 7.4	93.2 ± 8.3	0.542
Cardiovascular risk factors			
Coronary heart disease	0	0	—
Hypertension	9 (20%)	11 (24%)	0.342
High blood glucose	13 (29%)	15 (33%)	0.573
Dyslipidemia	26 (58%)	24 (53%)	0.483
Beta-blockers	2 (4%)	3 (7%)	0.231
ACE inhibitors	3 (7%)	2 (4%)	0.323
Vital sign			
Systolic blood pressure (mmHg)	122 ± 18	125 ± 15	0.673
Diastolic blood pressure (mmHg)	78 ± 10	76 ± 11	0.523
Cholesterol level (mmol/L)			
Total cholesterol	4.88 ± 0.97	5.02 ± 1.14	0.734
LDL-c	3.11 ± 0.79	3.15 ± 0.98	0.634
TG	1.82 ± 1.00	1.79 ± 1.15	0.667
Fasting glucose (mmol/L)	5.40 ± 0.97	5.56 ± 1.03	0.782
Breast cancer side			
Left	22 (49%)	—	—
Right	22 (49%)	—	—
Both	1 (2%)	—	—
Comprehensive therapy			
Chemotherapy	45 (100%)	—	—
Anthracycline use	31 (69%)	—	—
Trastuzumab use	20 (44%)	—	—
Both of anthracycline and trastuzumab	11 (24%)	—	—
Left-side radiotherapy	16 (36%)	—	—

Values as mean ± SD, or n (%). LDL-c: low density lipoprotein cholesterol; TG: triglyceride.

is the normal lower limit of GLS. In contrast, there was no abnormality of GLS in the noncancer patients with metabolic syndrome. In addition, we found that the breast cancer patients with metabolic syndrome had a decrease of GLS and LVEF (GLS −19.95 ± 2.98%, LVEF 67.19 ± 5.92%), compared with the noncancer patients with metabolic syndrome (GLS −21.53 ± 2.32%, LVEF 70.63 ± 3.24%) (Figures 1(a) and 1(b)).

Multivariate linear regression analysis was performed to identify possible factors that affected LVEF and GLS in breast cancer patients. Age, BMI, use of anthracycline, use of trastuzumab, and left-side radiotherapy were included. We found that age was a significant factor that affected LVEF (Table 2). Specifically, decrease of age was associated with decrease of LVEF. Moreover, use of trastuzumab was a significant factor that was associated with reduction of GLS (Table 3).

In addition, we also enrolled the breast cancer patients without metabolic syndrome after cancer-related comprehensive therapy (Supplementary Table S1) and compared them with the breast cancer patients with metabolic syndrome. The mean BMI of the breast cancer patients without metabolic syndrome was 22.8 kg/m^2, which was much lower than that of the breast cancer patients with metabolic syndrome (27.8 kg/m^2). We found that there was no significant difference in LVEF between the two groups. However, GLS decreased in breast cancer patients with metabolic syndrome (GLS −19.95 ± 2.98%, LVEF 67.19 ± 5.92%), compared with breast cancer patients without metabolic syndrome (GLS −21.43 ± 2.73%, LVEF 66.69 ± 6.93%) (Figure 2). Only 3 of the breast cancer patients without metabolic syndrome (10%) had GLS <17%, and the proportion was lower than the that of breast cancer patients with metabolic syndrome (20%).

4. Discussion

In this study, we observed the subclinical myocardial dysfunction of breast cancer patients with metabolic syndrome after completion of cancer-related comprehensive therapy. We measured LVEF and GLS in these patients, compared those with noncancer patients with metabolic syndrome, and identified risk factors that may be associated with subclinical myocardial dysfunction.

Our main findings are as follows: (1) breast cancer patients with metabolic syndrome after completion of cancer-related comprehensive therapy have decreased LVEF and GLS, compared to those without cancer, even though their LVEF are all within normal range; (2) decreased age is the

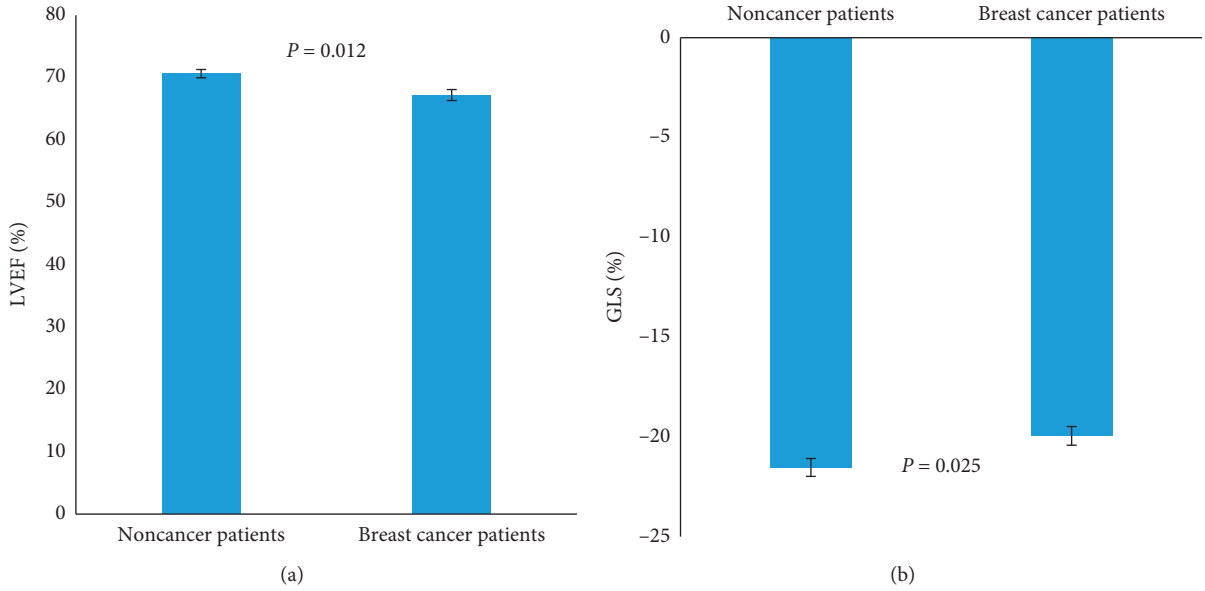

Figure 1: LVEF (a) and GLS (b) in breast cancer patients with metabolic syndrome and noncancer patients with metabolic syndrome.

Table 2: Multivariate analysis for LVEF in breast cancer patients with metabolic syndrome after treatment.

Factor	β	SE	P value
Age	0.328	0.127	0.014
BMI	0.343	0.270	0.211
Anthracycline	−0.020	2.073	0.992
Trastuzumab	−1.442	1.901	0.453
Left-side radiotherapy	2.133	1.802	0.244

Table 3: Multivariate analysis for GLS in breast cancer patients with metabolic syndrome after treatment.

Factor	β	SE	P value
Age	0.014	0.076	0.855
BMI	−0.222	0.154	0.160
Anthracycline	0.767	1.194	0.525
Trastuzumab	2.489	1.107	0.031
Left-side radiotherapy	0.578	1.077	0.595

risk factor of LVEF reduction in breast cancer patients with metabolic syndrome, while use of trastuzumab is associated with the reduction of GLS.

Our study used both LVEF and GLS to observe the myocardial injury of breast cancer patients with metabolic syndrome. LVEF is the regular method to be used in evaluation of myocardial function in cancer patients with tumor-related therapy. In contrast, echocardiography-based myocardial strain is a novel way to detect subclinical dysfunction of left ventricle. GLS may be a more sensitive predictor of toxicity of heart, compared to LVEF. This may be explained by the following reasons. Chemotherapy may affect just certain segments of left ventricle, resulting in the early reduction of GLS. Other region of left ventricle may have compensatory enhanced movement, leading to unchanged LVEF [11]. In addition, LVEF may be affected by many other conditions including preload, heart rate, etc. [12]. Tracing process is often used in measurement of LVEF. In contrast, GLS may adopt more accurate measurement through STE (speckle tracking echocardiogram). Therefore, 2014 ASE/EACVI Expert Consensus recommend that GLS can be used to early detect subclinical dysfunction of left ventricle in the patients with chemotherapy [13]. Indeed, we observed that there was a reduction of GLS in the breast cancer patients with metabolic syndrome after treatment and that 9 breast cancer patients with normal EF, however, had GLS below normal lower limit, indicating that GLS can be effective in finding early subclinical myocardial dysfunction [14, 15].

In addition, the average time after the completion of cancer-related comprehensive therapy of the breast cancer patients in our study was 33 months. Although TnI, BNP, and LVEF of these patients were in the normal range, 20% of these patients had an abnormal GLS, suggesting that the subclinical myocardial injury may persist for a long time after completion of anticancer therapy. Therefore, GLS should be used to monitor the early myocardial injury over a long period of time even after completion of cancer-related comprehensive therapy.

In our study, we found that the reduction of age was associated with LVEF reduction. Previous studies have shown that age >65 years is a risk factor for cardiotoxicity of cancer therapy [16]. However, we found that LVEF reduction more easily occurred in younger patients. This may be due to the fact that the average age of the patients in our study was 49 years old, with the youngest being 34 years old. Similarly, some studies have shown that the incidence of cardiotoxicity was elevated in younger patients. It was also found in a study with patients younger than 41 years old that there was a 6-fold increased risk of death resulting from cardiovascular diseases in patients treated for Hodgkin's Disease before age 21, and that this elevated mortality

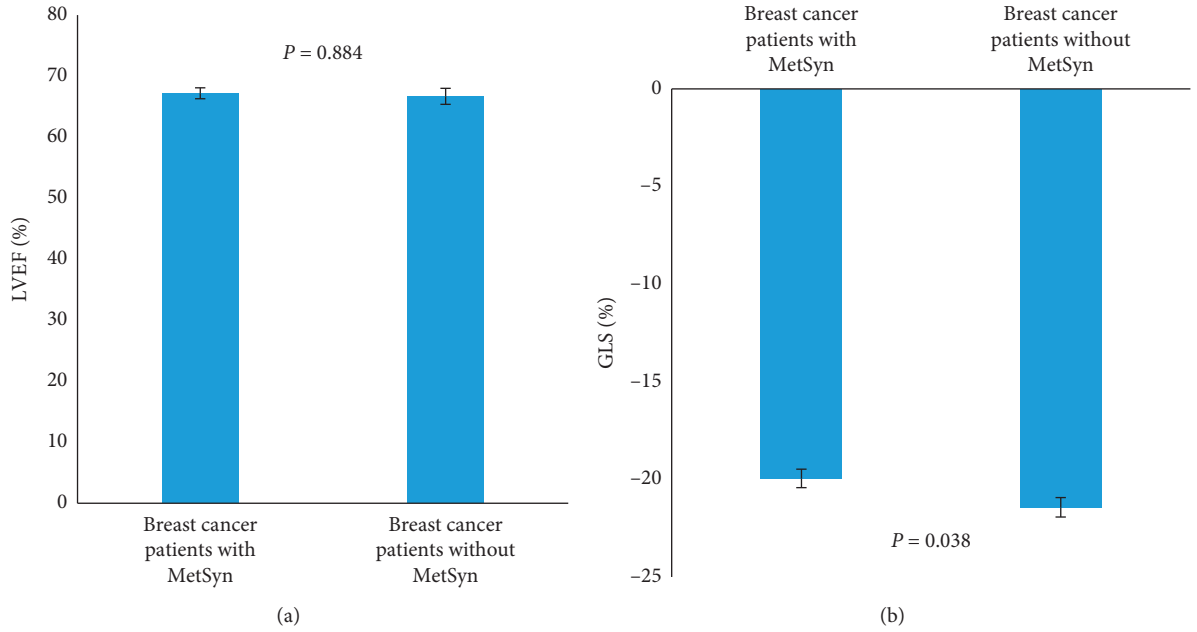

Figure 2: LVEF (a) and GLS (b) in breast cancer patients with metabolic syndrome (MetSyn) and breast cancer patients without metabolic syndrome (MetSyn) after cancer-related therapy.

decreased with increase of age [17]. The higher risks in patients treated at a younger age may be explained by a cardiovascular tissue more vulnerable to cancer-related therapy. In addition, the average age of patients treated with both anthracycline and trastuzumab in our study was 43 years, while the average age of the other patients was 51 years. This indicates that more younger patients received chemotherapy containing anthracycline plus targeted therapy in our study, while older patients chose non-combination therapy of anthracycline and trastuzumab. This may also explain the association of the reduction of age with LVEF reduction.

Our study found that trastuzumab can cause a decrease in GLS, which has been confirmed by many other studies. The mechanism of GLS reduction induced by trastuzumab is that it binds to HER-2 receptor of myocardial cells, which leads to the imbalance of Bcl-xL and Bcl-sL and sequential activation of mitochondrial apoptotic pathway. These result in myocardial injury and the decrease of GLS. Myocardial injury induced by trastuzumab, which is classified as type II CTRCD, leads to indirect cell injury and may be partly recovered after withdrawal of trastuzumab [5]. We do not find a relationship between use of anthracycline and cardiotoxicity. This may be explained by the fact that the cumulative dosage of anthracycline for all patients that receive anthracycline therapy in our study is 400 mg/m^2, which is below the waning dose of cardiotoxicity [18]. In addition, the number of patients in our study is small, and large-scale studies are still needed to further verify.

In our study, we did not find the effect of left-side radiotherapy on the LVEF and GLS, which may be related to the use of intensity-modulated radiation therapy (IMRT) in our breast center. IMRT is a new radiotherapy technology that can reduce adverse events of radiotherapy [19]. IMRT allows for the radiation dose to conform more precisely to the three-dimensional (3D) shape of the breast cancer by modulating the intensity of the radiation bean in multiple small volumes. IMRT also allows higher radiation doses to focus on the tumor while minimizing the dose to surrounding normal critical structures, including heart. Previous studies have shown that IMRT could effectively reduce clinical toxicities compared with conventional breast radiotherapy [20, 21].

We included patients with metabolic syndrome in our study and found that breast cancer comprehensive therapy caused subclinical myocardial dysfunction, compared with those without anticancer therapy. The metabolic syndrome has become a worldwide problem. The metabolic syndrome includes abdominal obesity, hyperlipidemia, hypertension, and hyperglycemia. Previous studies have shown that obesity is associated with progression of breast cancer, due to the augmented level of enzyme aromatase and increased production of estrogen caused by obesity [22, 23]. At the same time, patients with metabolic syndrome have a higher risk of cardiovascular disease. Obesity has been found to be a risk factor for cardiotoxicity of anthracyclines and trastuzumab in breast cancer patients [24]. Although we did not find a correlation of obesity with GLS or LVEF, further study with large scale of people is needed to be designed to confirm this correlation.

In addition, we compared difference of LVEF and GLS between the breast cancer patients with metabolic syndrome after cancer-related therapy and those without metabolic syndrome after therapy. We found that although there was no significant difference in LVEF between the two groups, the breast cancer patients with metabolic syndrome had a decrease of GLS, compared with those without metabolic syndrome, indicating that the breast cancer patients with metabolic syndrome were more prone to suffer from the

subclinical myocardial dysfunction. The patients with metabolic syndrome were susceptible to the toxicity of cancer-related therapy, possibly due to many mechanisms. Firstly, patients with obesity and dyslipidemia often have myocardial steatosis, which could be a reason of deterioration of myocardium [25, 26]. Secondly, obesity and hypertension in patients with metabolic syndrome could lead to increased preload and after-load of the heart, resulting in the impairment of left ventricular function [27]. Thirdly, oxidative stress was increased in patients with metabolic syndrome, which may cause the heart to be more sensible to the toxicity of the cancer-related therapy [28]. Therefore, we should closely monitor the possible subclinical myocardial damage in breast cancer patients, especially those with metabolic syndrome, during cancer-related therapy.

There are several limitations of our studies. Firstly, our study is a single-center, cross-sectional study, although consecutive patients were enrolled in our study. Secondly, the number of the patients in our study is small; therefore, other factors may not be found by multivariate linear regression analysis. Thirdly, we investigated patients at different time points after completion of treatment, possibly resulting in a loss of data with change of GLS and LVEF. Therefore, further studies with large scale of people are needed.

5. Conclusions

We found that breast cancer patients with metabolic syndrome after cancer-related comprehensive treatment have a reduction of GLS and LVEF. GLS should be routinely performed to early identify subclinical myocardial damage of patients, in order to prevent the cardiotoxicity of cancer-related comprehensive therapy.

Abbreviations

LVEF: Left ventricular ejection fraction
GLS: Global longitudinal strain
BNP: Type B natriuretic peptide
TnI: Troponin I.

Data Availability

The data used in the study can be provided upon request. This manuscript is available as a preprint on Research Square.

Ethical Approval

The study was approved by the Medical Ethics Committee of Peking University People's Hospital (2018PHB032-02) and was registered by Chinese Clinical Trial Registry (ChiCTR1900022108).

Conflicts of Interest

The authors declare that they have no conflicts of interest in this work.

Authors' Contributions

Feng Zhang and Siyuan Wang contributed equally to this work. FZ, SW, and TZ contributed to the concept and designed the study. FZ and SL analyzed the data. FZ and SW drafted the manuscript. SL, CY, SL, and HC revised the manuscript. TZ and SW approved the final version of the manuscript.

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Supplementary Materials

Table S1: baseline characteristics of breast cancer patients with and without metabolic syndrome after therapy. (*Supplementary Materials*)

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Review Article

Atrial Cardiomyopathy and Atrial Fibrillation in Cancer

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The number of patients with oncologic and cardiologic comorbidities is increasing. A growing number of evidence shows an inextricable link between cancer, atrial fibrillation, and atrial cardiomyopathy. Cancer itself and resultant inflammation, anticancer treatment, and other comorbidities lead to atrial remodeling and fibrosis, which increases the tendency to develop atrial cardiomyopathy and atrial fibrillation. The scarcity of current literature and ambiguous results make its relationship difficult to fully understand. In this review, we will summarize existing evidence of the relationships and interactions among cancer, atrial cardiomyopathy, and atrial fibrillation and discuss the underlying mechanisms, and provide better information for the management of these patients.

1. Introduction

Cancer patients have better survival nowadays due to multiple emerging therapies such as immunotherapy and target treatment. Therefore, cancer patients are more likely to suffer from cardiovascular disease (CVD) comorbidity. Cancer patients have more than twice the risk of fatal heart disease comparing to the general population [1]. A population-based study of CVD mortality risk shows that cancer patients are at elevated risk of dying from CVDs compared to the general population [2]. Recognition of the interaction between cancer and CVD has shifted from focusing on the cardiovascular toxicity of anticancer therapy [3] to the fact that they may share biological mechanisms that promote both malignancy and CVD development. One of the supporting evidence is that cancer survivors could have more cardiovascular abnormalities than the general population even without exposure to cardiotoxic treatment [4]. This naturally raises a question of whether this relationship is an association or causation between these two diseases, implying a new and exciting research realm in cardio-oncology.

Atrial cardiomyopathy, a term firstly described by Brigden in 1957 [5], affects the atria and atrioventricular system with the potential to produce arrhythmias [6, 7]. The term has evolved for years. EHRA/HRS/APHRS/SOLAECE jointly published a consensus on atrial cardiomyopathies: "any complex of structural, architectural, contractile, or electrophysiological changes affecting the atria with the potential to produce clinically relevant manifestations" [8]. Medical community now agree that atrial fibrillation has strong causality with atrial cardiomyopathy because some instances of genetic diseases provide convincing evidence that underlying atrial tissue abnormalities may be the cause of AF rather than merely impact [9].

Several lines of evidence show that there is an inextricable connection between cancer and atrial fibrillation; however, no study has ever mentioned that this association may also exist in cancer and atrial cardiomyopathy. This

review aims to summarize the existing evidence of the relationships and interactions among cancer, atrial cardiomyopathy, and AF, and we discuss the underlying mechanisms and provide useful information to improve the management of these patients.

2. Atrial Fibrillation in Cancer

AF is the most common type of heart arrhythmia. Here, we summarize the evidences supporting the relationship between AF and cancer (Table 1). AF can be induced by multiple cancer treatments such as immunotherapy, radiotherapy, surgery, and anticancer drugs [10]. Within 90 days after cancer diagnosis, the risk of AF was highest and this risk decreases over time [11].

Among all treatments, surgery may be the most frequently studied form of cancer-related AF. Several studies suggest that various types of cancer are associated with postoperative AF. A prospective study of 2588 thoracic surgery patients shows that malignant lung or esophagus cancer patients are more likely to develop postoperative AF than patients with benign disease [12]. About 4%–30% of patients after noncardiac surgery for malignancy would develop new-onset AF [12–16]. Meanwhile, the emerging of postoperative AF could predict a poorer long-term survival in lung cancer patients after receiving pulmonary lobectomy [17].But malignant tumor makes patients tending to suffer heavier burden of CVD and more invasive surgery form, making this association requiring more evidence to support.

In addition, cardiotoxicity of AF is a well-recognized adverse effect of certain chemotherapeutic drugs. For example, AF is a common complication induced by anthracyclines with the frequency of 2%–10% [18]. Persistent AF induced by anthracyclines is common and the first episode of AF event often occurs between 8 and 36 months after starting therapy [19]. AF could also occur in patients treated with other anticancer drugs such as fluorouracil, methotrexate, alkylating agents, antimicrotubule agents (docetaxel, paclitaxel), tyrosine kinase inhibitors (imatinib, lapatinib, sunitinib), proteasoma inhibitor (bortezomib), bevacizumab (blocker of the vascular endothelial growth factor), trastuzumab (angiogenesis inhibitor), and immune-checkpoint inhibitors [10, 20–22], and this cardiotoxicity complication has been shown related to poor prognosis. A prospective study investigated 249 lymphoma patients treated with anthracyclines showing that new-onset AF may predict unfavorable outcomes after chemotherapy [19].However, the lack of cardiac monitoring before chemotherapy makes it difficult to distinguish whether there was a preexisting undiagnosed arrhythmia or accompanying arrhythmia caused by chemotherapy. However, some evidenceshows that the incidence of AF is higher in cancer patients even without treatment, which indicates that cancer itself may make patients vulnerable to AF [23].

Meanwhile, recent studies have demonstrated that the manifestation of the arrhythmia could occur preceding the diagnosis of the malignancy, implying that patients of AF are prone to a higher risk of cancer than the general population. In a follow-up cohort study (1980–2011) of 269,742 patients with new-onset AF based on a Danish registry database, 2.5% of the patients were diagnosed with cancer within 3 months, exceeding the expected rate based on national cancer incidence during the period [24]. A similar cohort study including 34,691 initially healthy women also demonstrated that new-onset atrial fibrillation was associated with a higher risk of subsequent cancer diagnosis [25]. A retrospective cohort study of 5130 patients with new-onset AF also confirms this conclusion with a 41% increase in cancer risk compared with the general population [26]. Of note, the risk is highest in the first three months following the diagnosis of AF while the risk declines after that. Thus, the existing evidence cannot support that AF could cause cancer, but only can suggest a correlation. There could be several interpretations for these data. Firstly, occult cancer may exist before patients were diagnosed of AF due to shared corisk factors. Regular medical follow-up and treatment for AF would increase the chance of early detection of potential cancer. Secondly, it is well known that patients of AF are prone to bleeding after anticoagulant drug therapy, which could promote the screening and intervention of early diagnosis of colorectal cancer. It is worth noting that antiarrhythmic drugs such as digoxin have estrogen-like effects and increase the risk of breast cancer in female AF patients [27].

Not all studies are in agreement with this correlation: a population-based, retrospective, matched cohort study suggests that women patients with early breast cancer may not have a higher prevalence of AF before cancer diagnosis [28]. However, such observation should be interpreted with caution since the prevalence of CVD and its risk factors is well known to be lower in women population.

The magnitude and mechanism of the interaction between AF and cancer are still unclear. Proposed mechanisms involved cancer-related inflammation, shared risk factors, anticancer treatment, and other related comorbidities, causing atrial remodeling and increasing the tendency to develop AF for cancer patients [29].

3. Atrial Cardiomyopathy in Cancer

There is no direct evidence for the association of atrial cardiomyopathy and cancer; however, several studies may provide some insights in this respect. Recent studies indicate that some embolic strokes of unknown source (ESUS) cases result from subclinical AF and atrial cardiomyopathy [30]. About 50% of cancer-associated strokes are ESUS [31]. A large population-based cohort study suggests that some cryptogenic strokes may be caused by occult cancer [32]. Hence, the stroke events of cancer patients may relate to subclinical AF and atrial cardiomyopathy.

Left atrial enlargement (LAE) on echocardiogram, evidence of left atrial abnormality demonstrated by increased p-wave terminal force in lead V1 (PTFV1) on ECG, and increased serum levels of a form of brain natriuretic peptide (NT-proBNP) and other markers for atrial disease have been used to define atrial cardiomyopathy [30]. The abnormality of these markers has been shown to be related to the cardiotoxicity and prognosis of cancer patients (Table 2).

Table 1: Epidemiological evidence of AF in patients with cancer.

Author	Cancer type	Study type	Patient number	Treatment	Correlation or hypothesis
Ji-Hyun Chin	Esophageal cancer	Retrospective observational study	583	Esophagectomy	Postoperatively developed AF was associated with mortality in esophageal cancer patients after esophagectomy
Satoshi Higuchi	Head and neck; lung cancer; gastrointestinal cancer	Prospective cohort study	799	Noncardiac surgery for definitive/suspected malignancy	Perioperative atrial fibrillation in noncardiac surgery was strongly associated with perioperative complications
Ara A. Vaporciyan	Thoracic cancer	Prospective study	2588	Thoracic surgery	The overall incidence of atrial fibrillation was 12.3%
Chung-Wah Siu	Colorectal cancer	Retrospectively study	563	Elective abdominal surgery	4.4% patients developed postoperative AF
Andrea Imperatori	Lung cancer	Retrospectively cohort study	454	Pulmonary lobectomy	AF predicts poorer long-term outcome in 5-year survivors

Table 2: Atrial cardiomyopathy associated markers in patients with cancer

Marker	Cancer	Anticancer therapy	Correlation	Reference
Left atrial enlargement	HER2-positive breast cancer	Trastuzumab (TZ) therapy	LA dilatation associated with the development of cardiotoxicity	Corinna Bergamini
	Breast cancer	Anthracycline therapy	Maximum LA volume significantly increased in the patients	Yalin Tolga Yaylal
	Solid cancer (gynecological, breast, gastrointestinal, sarcoma, lungs)	Therapy-naive	LA reservoir and conduit functions were deteriorated in the cancer group	Marijana Tadic
	Breast cancer	Chemotherapy and trastuzumab therapy	Left atrial longitudinal strain as a predictor of cancer therapeutics-related cardiac dysfunction	Hyukjin Park
ECG abnormalities	Breast cancer	Anthracycline therapy	Left intraatrial and interatrial electromechanical intervals were prolonged	Yalin Tolga Yaylal
	Chronic lymphocytic leukemia (CLL)	Ibrutinib	Left atrial abnormality identified by EKG can identify patients at increased risk for this toxicity.	
	Multiple cancer	Cardiac-directed radiation; anthracycline and/or alkylating chemotherapies	ECG abnormalities are common among childhood cancer survivors and predictive of both cardiac and all-cause mortality	Daniel A. Mulrooney
	Left atrial myxoma	Tumor excision	Increased PTFV1 correlates with the tumor size	Norihiro Komiya
NT-proBNP	Coronary artery disease free of cancer	—	NT-proBNP is an independent predictor of malignancies in patients with CAD	José Tuñón
	Neuroendocrine tumor (NET)	—	NT-proBNP are important markers in the diagnosis and survival	Catharina M. Korse
	Multiple myeloma (MM)	Chemotherapy	Elevated levels of NT-proBNP are associated with disease severity	Noemi Pavo
	Differentiated thyroid carcinoma	Total thyroidectomy and radioiodine ablation	NT-proBNP associated with an increased risk for cardiovascular events and all-cause mortality	Esther N. Klein Hesselink
	Cancer	—	BNP levels are elevated and an indicator of heart failure	Sachiko Bando
	Breast cancer	Not-high-dose chemotherapy	NT-proBNP detects high risk of developing cardiotoxicity	S. Romano
	Non-Hodgkin lymphoma	Chemotherapy	NT-proBNP is a marker for risk assessment for NHL patients	Eva Gimeno
	Metastatic renal cell carcinoma	Sunitinib	NT-proBNP predicts for clinical benefit to sunitinib treatment	Konstantinos T. Papazisis

LA enlargement and dysfunction may relate with higher risk of cardiotoxicity during therapy in breast cancer [33, 34]. Furthermore, a retrospective study including 92 therapy-naive cancer patients and their matched controls suggests that LA reservoir and functions are deteriorated in the cancer group [35]. Peak atrial longitudinal strain decline is a useful indicator of cancer therapeutics-related dysfunction in patients of breast cancer [36].

ECG abnormalities are common among cancer survivors, which can predict cardiac-cause mortality [37]. Although the major abnormalities are isolated ST/T wave abnormalities (7.2%), evidence of myocardial infarction (3.7%), and left ventricular hypertrophy with strain pattern (2.8%) in this study, the markers for assessing atrial mechanical dysfunctions can also be detected in cancer patients. Moreover, left intraatrial and interatrial electromechanical intervals were prolonged in patients with breast cancer after anthracycline therapy [34]. A retrospective case-control study of chronic lymphocytic leukemia patients treated with ibrutinib indicated that left atrial abnormality identified by EKG is a predictor of atrial fibrillation [38]. In addition, the increasing size of left atrial myxoma brings about the broad negative P terminal force in lead V1 (PTFV1) [39].

NT-proBNP is a common and valuable marker regarding not only cancer but also therapy-related cardiac damage or prognosis. Firstly, NT-proBNP could be induced by oncologic diseases (such as invasive squamous cell carcinoma, malignant pericardial effusion, and small cell lung cancer) or related proinflammatory cytokines without cardiac failure [40, 41]. Secondly, NT-proBNP is an independent predictor of malignancies [42, 43]. Its levels are related to disease severity of multiple myeloma (MM) without cardiac disease [44]. A study shows that NT-proBNP levels increased in patients with differentiated thyroid carcinoma and is associated with an elevated risk of cardiovascular events [45].Furthermore, some studies discovered a potential value of NT-proBNP as biomarker for cardiovascular events in cancer during anticancer therapy [43]. Normally NT-proBNP level could increase in cancer patients' plasma within 24 hours after the starting of chemotherapy without significant changes in the echocardiographic parameters and clinical sign [46, 47]. The persistence of increased levels of NT-proBNP after the treatment may be helpful for the detection of patients with high risk of cardiotoxicity [47]. In addition, NT-proBNP was an independent indicator of survival time in patients of non-Hodgkin lymphoma [48] and a predictor for the progression of metastatic renal carcinoma [49].

The pathophysiologic mechanisms underlying the abnormal markers in cancer patients remain unclear. While it is frequently thought to be anticancer therapy-induced, cancer survivors without treatments can also present with abnormalities of these markers. Since there is no report on cancer patients complicated with atrial cardiomyopathy, it could raise a question of whether there is an underlying association between them. Existing research enrolled limited number of patients with various types of cancer and adopted different types of treatment in most studies. Well-standardized studies will be needed to better define the role of atrial cardiomyopathy and related markers in cancer.

4. Mechanisms of Increased AF and Atrial Cardiomyopathy in Cancer

As mentioned above, the risk of developing AF is increased for patients with cancer due to shared risk factors, treatments, and disease itself [50].

Oncologic and cardiologic diseases share many risk factors, such as advanced age, obesity, diabetes, and smoking, making the number of patients with comorbidities constantly increasing [51–54].

Antitumor therapy, including surgery, medication, and radiation, can result in atrial fibrillation. The exact mechanisms remain unclear, though it has been proposed that inflammation and apoptosis may be the decisive factors of cardiotoxicity during the treatment [29]. Fibrosis is a consequence of a nonspecific response to cardiomyocyte necrosis or apoptosis [55]. Anticancer therapy may contribute to AF through atrial fibrosis by apoptosis and inflammation.

For therapy-naïve cancer patients with increased incidence of AF, one alternative explanation is that proinflammatory states resulting from cancer itself can promote atrial fibrillation through atrial restructuring [23, 56–58]. Supportive evidence is that circulating levels of CRP, a marker representing the inflammatory state in cancer patients, is not only associated with the presence of AF but can also predict the risk of future development of AF [56, 59]. In addition, pain, malnourishment, infections, and metabolic abnormalities are prevalent in patients with cancer and can result in dysregulated autonomous nervous system, which could also contribute to AF [52, 60]. Moreover, tumors or metastases adjacent to atrial tissues can directly cause AF by compressing the left atrium [61].

Over the past years, the investigation of AF has yielded fundamental insights into the pathophysiology of the electrical, mechanical, and structural abnormalities of the atrium [62]. The fundamental characteristic of the structural pathology associated with AF is atrial fibrosis and structural remodeling [55, 63]. Atrial cardiomyopathy associated with AF includes myocyte degeneration and fibrotic changes of the connective extracellular matrix [55]. Therefore, it can be considered that atrial cardiomyopathy is the substrate for AF. As the atrial cardiomyopathy progresses, atrial dysfunction and eventually the AF develop [63]. Potential factors known to promote atrial fibrosis include aging, inflammation, and oxidative stress, which also could occur in cancer patients [63].

Based on the abovementioned theory, we can reasonably infer that atrial cardiomyopathy, AF, and cancer may interplay with each other on pathophysiological levels (Figure 1). Firstly, shared risk factors make cancer patients a high-risk group of atrial cardiomyopathy. Secondly, cancer itself and anticancer therapy may have direct effects on the LA substrate mediated by resultant systemic inflammation and apoptosis. Then, this pathological state would promote or result in fibrosis and structural remodeling of LA, which leads new-onset or existing atrial cardiomyopathy progress to atrial fibrillation.

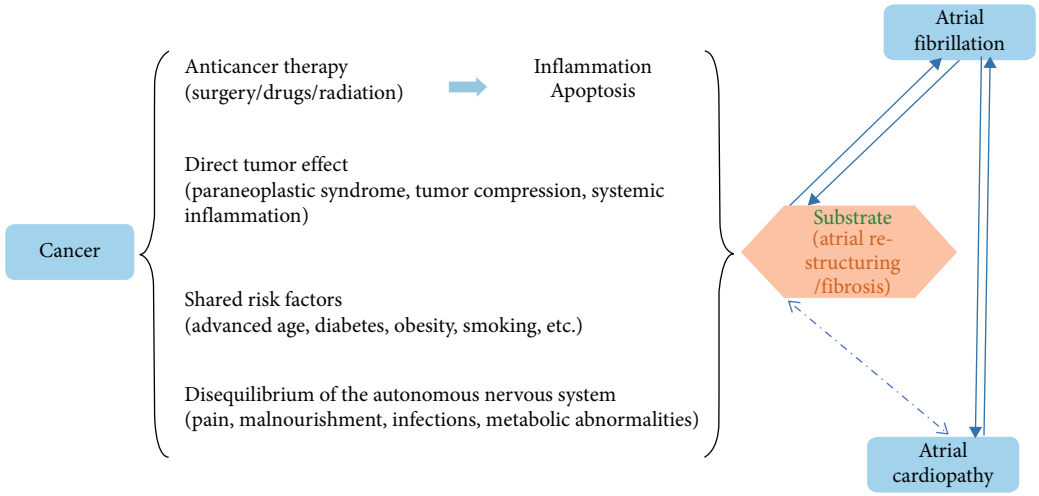

Figure 1: Schematic overview of the link between cancer, atrial fibrillation, and atrial cardiomyopathy. Shared factors may predispose to a comorbidity state of cancer, atrial cardiomyopathy, and atrial fibrillation. Cancer may cause atrial fibrillation and atrial cardiomyopathy by anticancer therapy, autonomous nervous system (ANS) imbalance, direct tumor effect, and other abnormalities. These factors may have direct effects on the left atria (LA) substrate and lead to systemic inflammation and apoptosis. Then, they promote or result in fibrosis and structural remodeling, leading new-onset or existing atrial cardiopathy progress to atrial fibrillation.

More studies are needed to explore the interaction between Cancer, AF, and atrial cardiomyopathy, which will provide crucial information on more individualized treatments.

5. Challenges and Managements

Given the increasing occurrence of the coexistent CVD in cancer patients, challenges of therapeutic strategies and management are vaster and more complicated than expected. The status of comorbidities and the deleterious effects of anticancer treatments often contribute to less effective treatment, poor life quality, and decreased survival.

The first problem is anticoagulation. Although it is recognized that cancer can lead to hypercoagulable state, the exact effect of cancer on thrombotic risk in patients with AF remains unknown [29]. The clinical recognition of atrial cardiomyopathy suggests a potential value on the identification of individuals at risk of stroke [64] and assessment of novel interventions designed for the prevention of AF [63]. Both atrial cardiomyopathy and cancer are involved in the prethrombotic state. A study showed that cancer patients, whether or not having AF, have an elevated risk of stroke than the general population [65]. However, the existing risk-models that aid to starting anticoagulant therapy do not take the malignant tumor into account. Although the exact extent is not clear now, further related studies are needed to provide some insights in this respect. The clinical recognition of atrial cardiomyopathy in the cancer patients may help with better identification of high-risk patients with hypercoagulable state, which will improve their quality of life and overall survival.

Besides, the presence of CVD comorbidity would affect the clinical decision of cancer treatment and prognosis. Cancer patients with higher risk require cardiologic specialists' review and benefit assessment of anticancer therapy [66]. Multidisciplinary treatment (MDT) including both oncologic and cardiologic specialists would be best choice for patients of such comorbidity.

6. Conclusion and Prospect

With the increasing number of cancer patients with CVD, oncocardiology has become an emerging medical subspecialty focusing on cardiovascular effects of cancer and its treatment [67]. Even though the interaction of AF, atrial cardiomyopathy and cancer has been widely documented, the exact mechanism is still unclear. Cancer, possibly through inflammation or effects of the autonomic nervous system, predisposes patients to atrial cardiomyopathy and AF via atrial remodeling and fibrosis. Common risk stratification tools of anticoagulant therapy currently do not take cancer into account as a variable. The clinical value of looking into the atrial cardiomyopathy will provide new insights of this discipline but also the individualized treatment of disease, which will have meaningful implications for future anticancer and supportive treatment.

Conflicts of Interest

Authors declare no conflicts of interest in this article.

Authors' Contributions

Mengdi Ren and Yang Yan drafted the manuscript. Yuye Ning, Yu Yao, Xin Yue, and Yang Yan provided critical review and revision of the manuscript and YangYan approved the final draft for publication.

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Research Article

Electrocardiographic Characteristics of Breast Cancer Patients Treated with Chemotherapy

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Introduction. Patients receiving chemotherapy for breast cancer may be at risk of developing cardiac dysfunction and electrophysiological abnormalities. The aim of this study is to evaluate alterations in electrocardiographic (ECG) parameters in breast cancer patients receiving chemotherapy. *Materials and Methods*. This was a prospective single-center cohort study conducted in the Fourth Hospital of Hebei Medical University, China. Participants with breast cancer referred for chemotherapy from May 1, 2019, to October 1, 2019, were invited to participate in the study. Standard 12-lead ECG and echocardiography were performed at baseline or before chemotherapy (prechemotherapy) (T0), after 1 cycle (T1), after 3 cycles (T2), and at the end of chemotherapy (T3). *Results*. A total of 64 patients with diagnosed breast cancer undergoing chemotherapy were included. Echocardiographic parameters showed no significant variation during the entire procedure (all $P > 0.05$). The incidence of abnormal ECG increased from 43.75% at baseline to 65.63% at the end of chemotherapy, of which only the prevalence of fragmented QRS (fQRS) was significantly increased after the drug regimen (26.56% to 53.13%). At the end of the treatment, heart rate, P-wave dispersion, corrected QT interval, T-peak to T-end, RR, SV1, RV5, Sokolow–Lyon index (SLI), and index of cardioelectrophysiological balance deteriorated markedly (all $P < 0.05$). The area under the curve for SLI and QT dispersion (QTd) derived by ECG was 0.710 and 0.606, respectively. The cutoff value with 2.12 of SLI by ECG had a sensitivity of 67.2% and specificity of 71.9% for differentiating patients after therapy from baselines. The cutoff value with 0.55 of QTd had a sensitivity of 60.9% and specificity of 60.9%. *Conclusions*. The current study demonstrated that ECGs can be used to detect electrophysiological abnormalities in breast cancer patients receiving chemotherapy. ECG changes can reflect subclinical cardiac dysfunction before the echocardiographic abnormalities.

1. Introduction

One of the important side effects of chemotherapeutic agents used in patients with breast cancer is cardiotoxicity, which refers to cardiac dysfunction and heart failure [1]. Anti-HER2 agents and chemotherapies (specifically anthracyclines, which are frequently used to treat HER2+ breast cancer) have been associated with increased risk of cardiotoxicity [2, 3]. As treatment efficacy increases, there is an increasing number of patients who survive for extended periods and may receive chemotherapies for longer durations. Therefore, cancer patients increasingly require long-term management of chemotherapy-related morbidities. It is imperative to detect chemotherapy-induced cardiac injury in the early stage in order to, with the help of early pharmacologic intervention, prevent the occurrence of clinical heart failure. It has been reported that standard 12-lead electrocardiogram (ECG) enables the detection of different findings of cardiotoxicity such as sinus tachycardia, ST-T wave abnormalities, cardiac conduction disorders, QT prolongation, fragmented QRS, and cardiac arrhythmia during chemotherapies in cancer patients [1, 4, 5]. The 12-lead ECG remains a routine screening tool owing to its noninvasive, rapid, and inexpensive properties, and it has demonstrated promise as a tool for measuring subclinical cardiotoxicity [6]. The identification of patients at risk for

cancer therapy-induced malignant arrhythmias is of exceptional clinical importance.

Previous studies have mainly focused on global left ventricular function changes during chemotherapy. However, in fact, the administration of chemotherapeutic agents may affect the cardiac electrophysiological properties before significant mechanical impairment. Therefore, we aimed to evaluate the presence or absence of ECG abnormalities in patients newly diagnosed with breast cancer following chemotherapies.

2. Materials and Methods

2.1. Study Population. In total, 64 eligible female patients with early-stage breast cancer were included in this single-center, prospective observational clinical study between May 2019 and December 2019. 35 patients had left-sided breast cancer, and 29 patients had right-sided breast cancer. All patients received adjuvant chemotherapy after breast cancer surgery. The exclusion criteria were age under 18 years or over 80 years, other malignancies, a previous history of chemotherapy and radiation therapy (RT), pregnancy or breastfeeding, acute myocardial infarction within the previous 6 months, symptomatic heart failure (New York Heart Association Functional Classification III-IV), left ventricular ejection fraction (LVEF) <50%, structural heart disease, serious cardiac arrhythmias, chronic use of drugs known to induce cardiac damage or arrhythmia, dialysis, permanent anticoagulation, and severe psychiatric disorders life expectancy less than 6 months. The study complied with the Helsinki Declaration, and the local institutional board of ethics approved the protocol. All participants signed informed consent before enrolment. Fourth Hospital of Hebei Medical University Research Ethics Committee approved the protocol (2020011).

2.2. Echocardiography. Echocardiography was performed by a cardiologist with experience in advanced echocardiography and trained for the requirements of the study, using standard parasternal and apical views with the frame rates of 45–75 frames/s and a GE Vivid E9 ultrasound system (GE Vingmed Ultrasound, Horten, Norway) equipped with a 2.0–4.5 MHz transducer and following current recommendations for cardiac chamber quantification in adults. Echocardiography data were collected from the department of function database [7–9]. Echocardiography was performed by the same cardiologist, who was blinded to the clinical data and electrocardiographic data.

2.3. Electrocardiography. Twelve-lead ECGs were recorded before the chemotherapy for breast cancer was started at the resting and supine position (filter: 45 Hz, alternating current filter: 50 Hz, paper speed: 25 mm/s, and amplitude 10 mm/mV; Huanan Medical, Zhengzhou, China). All of the ECGs were transferred to a personal computer to decrease error measurements and then used for 400% magnification by Adobe Photoshop software. All of the measurements were performed on the screen by manual method. No patient had fewer than nine measurable leads, and all precordial derivations were included in the measurements.

The following automated ECG measurements were extracted: heart rate (HR), P-wave amplitude (PWA), QT interval (QTI), RR interval (RR), corrected QT interval (QTc), QRS duration (QRSD), PR interval (PRI), QRS axis, and index of cardioelectrophysiological balance (iCEB: QT/QRS [10]). The following variables were manually measured: P-wave dispersion (Pd), QT dispersion (QTd), and T-peak to T-end (TpTe). ST-T changes were analyzed according to the criteria of parameter measurement, and ECG diagnosis is based on the recommendation of the American Heart Association (AHA) (AHA/ACCF/HRS, 2007–2009) [11]. Criteria for ST-T changes were any of the following: (1) ST-segment abnormalities: the ST segment was measured at 80 ms after J point, and the meaningful change was described as ST-segment depression ≥0.05 mV, or ST-segment elevation ≥0.10 mV in the limb leads and/or ≥0.20 mV in the chest leads. (2) T-wave changes: (a) high and sharp T-wave: the peak of T-wave was >0.5 mV in the limb leads and/or >1.5 mV in the chest leads; (b) low and flat T-wave: the peak of T-wave was <0.1 mV in the limb leads or <0.2 mV in the chest leads; (c) bidirectional T-wave; and (d) inversed T-wave (inversion depth ≥0.1 mV). Fragmented QRS (fQRS) is defined as the presence of an additional R-wave (R′), R-wave, or the S-wave notching, or the presence of more than one R′-wave in two consecutive leads [12]. An ECG is classified as abnormal if the following features were detected: sinus arrhythmia, atrial fibrillation, premature atrial or ventricular contraction, atrioventricular block, fQRS, ST segment, or T-wave changes. ECG parameters of the patients were measured by two blinded independent cardiologists (Y. W and Z. C), and ECGs were evaluated by a third independent reviewer (X. G) when there was a discrepancy between the evaluations of the two readers. For each study patient, these values were calculated on average three times.

2.4. Statistical Analysis. Continuous variables were summarized by the median and interquartile range or mean ± standard deviation and compared by one-way analysis of variance (ANOVA) or Fisher's exact test; otherwise, median and interquartile range (IQR) were reported. Categorical variables were expressed as frequencies and percentages and compared using the chi-square tests. The area under the receiver operating characteristic (ROC) curve was calculated to determine the capability of various ECG parameters to discriminate patients after chemotherapy from baselines. IBM SPSS Statistics 22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, version 22.0. Armonk, NY: IBM Corp.) was used for statistical analyses. A P value of <0.05 was considered significant.

3. Results

3.1. Baseline Clinical Characteristics of Study Population. The study enrolled 64 women (mean age, 49.09 ± 9.61 years) with breast cancer treated with chemotherapy. The mean body mass index was 24.02 ± 3.18 kg/m^2. Among

comorbidities, diabetes mellitus was present in 4.69%, hypertension in 12.5%, and coronary artery disease in 3.13% of the included cases. Patients received antihypertensive drugs: angiotensin-converting enzyme inhibitor or angiotensin receptor antagonist (1.56%) and calcium channel blockers (9.38%). Baseline clinical characteristics of all participants are presented in Table 1.

3.2. Echocardiography. Echocardiographic parameters are shown in Table 2. There was no statistically significant difference ($P > 0.05$) between baseline and each follow-up point during chemotherapy.

3.3. Electrocardiography. The incidence of abnormal ECG increased from 43.75% at baseline to 65.63% at the end of the treatment (Table 3). This was mainly due to a higher proportion of patients with fQRS after chemotherapy (26.56% to 53.13%, $P < 0.01$).

After three cycles of chemotherapy, heart rate (HR) (76.66 ± 11.99 to 81.23 ± 13.28 bpm, $P = 0.037$), QRS dispersion (QTd) (21.25 ± 10.95 to 27.50 ± 13.50 ms, $P < 0.01$), SV1 (1.18 ± 0.41 to 1.42 ± 0.49 ms, $P < 0.01$), and Sokolow–Lyon index (SLI) (1.92 ± 0.59 to 2.26 ± 0.69 mV, $P < 0.01$) increased significantly. At the end of the treatment, HR (76.66 ± 11.99 to 82.14 ± 12.74 bpm, $P = 0.013$), P-wave dispersion (Pd) (20.38 ± 9.76 to 16.81 ± 9.41 ms $P = 0.029$), corrected QT interval (QTc) (411.38 ± 26.83 to 421.69 ± 21.30 ms, $P = 0.032$), T-peak to T-end (TpTe) (73.63 ± 14.20 to 80.13 ± 14.37 ms, $P = 0.024$), RR (0.80 ± 0.12 to 0.75 ± 0.11 s, $P = 0.011$), SV1 (1.18 ± 0.41 to 1.49 ± 0.48 mV, $P < 0.01$), RV5 (0.74 ± 0.33 to 0.88 ± 0.40 mV, $P = 0.037$), SLI (1.92 ± 0.59 to 2.37 ± 0.65 mV, $P < 0.01$), and iCEB (4.29 ± 0.59 to 4.03 ± 0.53, $P = 0.011$) deteriorated markedly (all $P < 0.05$) (Table 4).

3.4. Receiver Operating Characteristic (ROC) Analysis. Table 5 shows the ROC curves generated using two ECG parameters to discriminate between before and after chemotherapy. Compared with the QTd, SLI had a greater area under the ROC curve and a cutoff value with 2.12 had a sensitivity of 67.2% and specificity of 71.9% for differentiating patients after chemotherapy from baselines. For QTd, the area under the ROC curve was 0.61 and a cutoff value with 0.55 had a sensitivity of 60.9% and specificity of 60.9% for differentiating patients after chemotherapy from baselines (Figure 1).

4. Discussion

Cardiotoxicity following chemotherapy in patients with breast cancer is a potentially life-threatening complication. Cardiac function can be assessed with echocardiography and cardiac biomarkers. However, there are few studies on electrocardiographic characteristics following chemotherapy in patients with cancer, especially breast cancer. To the best of our knowledge, no study has assessed

Table 1: Baseline clinical characteristics and cardiovascular risk factors in breast cancer patients.

Characteristics	
Age, years, mean ± SD	49.09 ± 9.61
Females, *n* (%)	64 (100)
BMI, kg/m^2	24.02 ± 3.18
Systolic pressure, mmHg	124.91 ± 14.86
Diastolic pressure, mmHg	81.63 ± 11.01
Medical history, *n* (%)	
Hypertension	8 (12.50)
Diabetes mellitus	3 (4.69)
Dyslipidemia	0 (0)
Coronary heart disease	2 (3.13)
Smoking, *n* (%)	
Current smoker	0 (0)
Former smoker	0 (0)
Nonsmoker	63 (100)
HR status, *n* (%)	
ER– and PR–	27 (42.19)
ER+ and/or PR+	36 (56.25)
HER-2+	24 (37.50)
Histology type, *n* (%)	
Ductal carcinoma	3 (4.69)
Lobular carcinoma	59 (92.19)
DCIS	2 (3.13)
Cancer stage, *n* (%)	
I	23 (35.94)
II	37 (57.81)
III	4 (6.25)
IV	0 (0)
Surgery, *n* (%)	
Lumpectomy	41 (64.06)
Mastectomy	23 (35.94)
Cardiovascular medications, *n* (%)	
Beta-blockers	0 (0)
Calcium channel antagonist	6 (9.38)
Antiplatelet medicines	1 (1.56)
ACEI/ARBs	1 (1.56)
Statins	0 (0)
Cancer therapy, *n* (%)	
Anthracycline	49 (76.56)
Taxane	60 (93.75)
Anti-HER2	21 (32.81)
Anthracycline and anti-HER2	15 (23.44)
Cumulative dose of anthracycline, mg	
Median (range)	354.29 ± 149.22
<430	37 (57.81)
≥430	12 (18.75)
Cumulative dose of taxane, mg	
Median (range)	771.00 ± 345.93
<760	40 (62.50)
≥760	20 (31.25)
Endocrine therapy, *n* (%)	
AI	16 (25.00)
TAM	20 (31.25)
None	28 (43.75)

BMI, body mass index; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; HER2, human epidermal growth factor receptor 2; DCIS, ductal carcinoma in situ; AI, aromatase inhibitor; BMI, body mass index; DCIS, ductal carcinoma in situ; ER, estrogen receptor; HR, hormone receptor; PR, progesterone receptor; TAM, tamoxifen.

Table 2: Echocardiographic parameters before and at each follow-up point during chemotherapy in breast cancer patients.

Variable	T0	T1	P value	T2	P value	T3	P value
LVIDd (cm)	4.60 ± 0.29	4.64 ± 0.29	0.422	4.67 ± 0.30	0.184	4.58 ± 0.27	0.711
LA (cm)	3.00 ± 0.31	3.05 ± 0.39	0.458	3.06 ± 0.27	0.425	3.01 ± 0.32	0.919
LVEF (%)	67.00 ± 4.07	66.09 ± 3.94	0.201	65.95 ± 3.96	0.139	65.34 ± 4.00	0.052
E/A ratio	1.10 ± 0.35	1.16 ± 0.48	0.389	1.11 ± 0.41	0.873	1.03 ± 0.38	0.334
E/E′ ratio	7.64 ± 1.74	7.99 ± 1.99	0.298	7.86 ± 1.93	0.519	7.28 ± 1.96	0.310

Values are mean ± SD. *Compared with T0 $p < 0.05$. T0, baseline before chemotherapy; T1, after 1 cycle of chemotherapy; T2, after 3 cycles of chemotherapy; T3, end of chemotherapy; LVIDd, left ventricular internal dimension diastole; LA, left atrial diameter; LVEF, left ventricle ejection fraction.

Table 3: ECG changes before and at each follow-up point during chemotherapy in BC patients.

ECG changes	T0	T1	P value	T2	P value	T3	P value
Abnormal ECG, n (%)	28 (43.75)	36 (56.25)	0.157	41 (64.06)	0.021*	42 (65.63)	0.013*
ST-T changes, n (%)	7 (10.94)	10 (15.63)	0.435	10 (15.62)	0.435	10 (15.62)	0.435
ST changes	6 (9.38)	7 (10.94)	0.770	7 (10.94)	0.770	7 (10.94)	0.770
T-wave changes	1 (1.56)	6 (9.38)	0.052	8 (12.50)	0.016*	6 (9.38)	0.052
Arrhythmias, n (%)	13 (20.31)	11 (17.19)	0.651	13 (20.31)	1.000	14 (21.88)	0.828
Sinus tachyarrhythmia	1 (1.56)	3 (4.69)	0.310	5 (7.81)	0.094	6 (9.38)	0.052
Ventricular premature beats	2 (3.13)	2 (3.13)	1.000	2 (3.13)	1.000	3 (4.69)	0.310
First-degree AVB	3 (4.69)	2 (3.13)	0.648	1 (1.56)	0.310	1 (1.56)	0.310
Intraventricular block	1 (1.56)	1 (1.56)	1.000	1 (1.56)	1.000	1 (1.56)	1.000
QTc prolongation, n (%)	3 (4.69)	4 (6.25)	0.697	1 (1.56)	0.310	2 (3.13)	0.648
fQRS, n (%)	17 (26.56)	27 (42.19)	0.063	30 (46.88)	0.017*	34 (53.13)	<0.01*

Values are mean ± SD. *Compared with T0, $p < 0.05$. T0, baseline before chemotherapy; T1, after 1 cycle of chemotherapy; T2, after 3 cycles of chemotherapy; T3, end of chemotherapy; AVB, atrioventricular block; QTc, corrected QT interval; fQRS, fragmented QRS.

Table 4: Electrocardiographic parameters before and at each follow-up point during chemotherapy in BC patients.

Variables	T0	T1	P value	T2	P value	T3	P value
HR (bpm)	76.66 ± 11.99	78.83 ± 11.30	0.321	81.23 ± 13.28	0.037*	82.14 ± 12.74	0.013*
PWA (mV)	0.11 ± 0.03	0.12 ± 0.03	0.454	0.12 ± 0.04	0.623	0.12 ± 0.04	0.438
PWD (ms)	95.53 ± 12.05	95.61 ± 11.60	0.973	94.06 ± 11.87	0.529	96.19 ± 16.58	0.779
PRI (ms)	148.97 ± 20.37	148.05 ± 21.29	0.835	147.78 ± 21.54	0.788	149.58 ± 34.16	0.890
Pd (ms)	20.38 ± 9.76	18.38 ± 9.66	0.218	18.31 ± 8.75	0.204	16.81 ± 9.41	0.029*
QRS axis (°)	39.33 ± 30.13	37.83 ± 30.28	0.769	40.29 ± 24.74	0.853	37.49 ± 29.51	0.720
QRSD (ms)	87.05 ± 13.88	87.02 ± 12.88	0.989	89.14 ± 12.66	0.371	91.64 ± 13.43	0.050
QTc (ms)	411.38 ± 26.83	415.61 ± 26.67	0.378	414.94 ± 32.45	0.458	421.69 ± 21.30	0.032*
QTd (ms)	21.25 ± 10.95	24.75 ± 11.92	0.102	27.50 ± 13.50	<0.01*	24.94 ± 11.71	0.085
TpTe (ms)	73.63 ± 14.20	76.31 ± 18.64	0.386	76.69 ± 21.64	0.323	80.13 ± 14.37	0.037*
RR (s)	0.80 ± 0.12	0.78 ± 0.11	0.252	0.76 ± 0.12	0.042	0.75 ± 0.11	0.011*
SV1 (mV)	1.18 ± 0.41	1.30 ± 0.41	0.144	1.42 ± 0.49	<0.01*	1.49 ± 0.48	<0.01*
RV5 (mV)	0.74 ± 0.33	0.79 ± 0.38	0.512	0.84 ± 0.42	0.158	0.88 ± 0.40	0.037*
SLI (mV)	1.92 ± 0.59	2.08 ± 0.61	0.151	2.26 ± 0.69	<0.01*	2.37 ± 0.65	<0.01*
iCEB	4.29 ± 0.59	4.26 ± 0.54	0.781	4.10 ± 0.62	0.069	4.03 ± 0.53	0.011*

Values are mean ± SD. *Compared with T0, $p < 0.05$. T0, baseline before chemotherapy; T1, after 1 cycle of chemotherapy; T2, after 3 cycles of chemotherapy; T3, end of chemotherapy; HR, heart rate; PWA, P-wave amplitude; PWD, P-wave duration; PRI, PR interval; Pd, P-wave dispersion; QRSD, QRS duration; QTc, corrected QT interval; QTd, QRS dispersion; TpTe, T-peak to T-end; SLI, Sokolow–Lyon index; iCEB: index of cardioelectrophysiological balance.

electrocardiographic parameters immediately after completion of chemotherapy infusion.

Our study used ECGs to evaluate the cardiac electrophysiological changes in patients with breast cancer who received chemotherapy. The main findings of this study are as follows: (1) the incidence of abnormal ECG increased from 43.8% at baseline to 65.6% during follow-up, and this was mainly due to a higher proportion of patients with fQRS; (2) HR, Pd, QTc, TpTe, RR, SV1, RV5, SLI, and iCEB deteriorated markedly along with chemotherapy; and (3) QTd and SLI had high sensitivity and specificity in differentiating patients after therapy from baselines. These findings indicate the development of both depolarization and repolarization abnormalities following chemotherapy.

Table 5: ROC curve analyses of electrocardiographic parameters.

Variable	AUC	95% CI	Cutoff value	Sensitivity	Specificity
SLI	0.710	0.620–0.799	2.12	0.672	0.719
QTd	0.606	0.507–0.704	0.55	0.609	0.609

ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval; SLI, Sokolow–Lyon index; QTd, QRS dispersion.

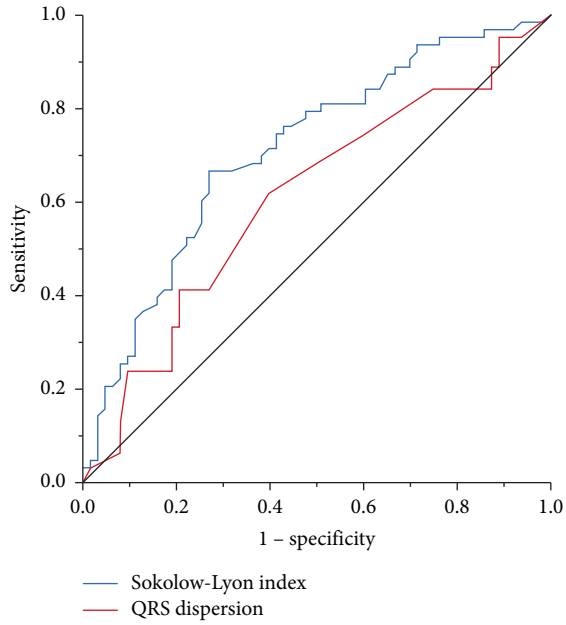

Figure 1: ROC curve for two electrocardiographic parameters to discriminate between pre- and posttherapy.

fQRS is a surrogate marker of myocardial conduction delay or heterogeneity with a prevalence ranging from 1% to 30% of the general population [13–15]. 26.6% (67/252) of breast cancer patients had fQRS after anthracycline-based chemotherapy [16]. At 1-year follow-up, 19 of 52 (37.4%) breast cancer patients receiving locoregional radiotherapy had developed fQRS on ECG [17]. Moreover, the prevalence of fQRS significantly increased in large B-cell lymphoma patients treated with anthracycline-based chemotherapy (15.8% to 28.9%, $P = 0.041$) [18]. We found fQRS in 53.1% of breast cancer patients after chemotherapy. In patients with coronary artery disease, fQRS has been shown to be associated with all-cause mortality and cardiac events [19]. Myocardial fibrosis may disrupt QRS morphology and lead to fragmentation of QRS on 12-lead ECG. Chemotherapeutic agents can trigger apoptosis or cause necrotic myocyte death. fQRS occurs when ventricular depolarization (VD) becomes abnormal and has been identified as an ECG biomarker of myocardial fibrosis and can be used to predict adverse cardiovascular events [12, 20].

In the ECG, ventricular repolarization (VR) is represented by QTc intervals, and QTc prolongations relate to a higher risk of ventricular arrhythmias in different conditions. As a risk factor for torsades de pointes (TdP) and sudden cardiac death, QTc prolongation is a toxicity of significant concern [21, 22]. Puppe et al. found a significant increase in QTc intervals after breast cancer treatment with 4 cycles of EC-Doc regimen (epirubicin, cyclophosphamide, and docetaxel) [23]. Several investigations already demonstrated significant QTc prolongation induced by anticancer therapies, especially in anthracycline regimens [24–26]. Similar to our study, in patients with breast neoplasms undergoing chemotherapy regimen with anthracycline (A; doxorubicin), cyclophosphamide (C), and taxane (T; paclitaxel), Veronese et al. also observed prolongation of the QTc interval [27]. In addition, in our study, 25.0% and 31.3% of breast patients were treated with aromatase inhibitor (AI) and tamoxifen (TAM), respectively. Several studies reveal the potential for endocrine therapy to induce ventricular arrhythmias, particularly TdP [28–30].

In this study, our results revealed a significantly increased QTd after chemotherapy. The QTd is defined as the difference between maximal and minimal QT intervals on a 12-lead surface ECG and reflects the regional heterogeneity of VR. Prolonged QT dispersion was even shown to predict acute heart failure in patients after high-dose cyclophosphamide therapy [31]. Further, it has been regarded as an index of ventricular arrhythmia, which may lead to sudden cardiac death [32]. Patients with breast cancer treated with trastuzumab after an anthracycline-based regimen exhibited a significantly higher QTd than nontreated patients (0.064 ± 0.023s vs. 0.051 ± 0.016 s, respectively, $P = 0.034$) [33].

SLI is recommended as diagnostic screening method for left ventricular hypertrophy. In this study, we found SLI increased through chemotherapy and thus appears to represent a transitional state from a normal healthy heart to heart failure with preserved ejection fraction. iCEB can provide information about both the depolarization and repolarization phases of the cardiac action potential and is a surrogate marker of excitation wavelength. In experimental studies, a 10% variation (either increase or decrease) of iCEB values from baseline showed to be a promising marker for drug-induced arrhythmic risk [32, 34]. However, data from clinical trials are scarce. To date, there is no comprehensive, easy to measure, and widely available risk marker available. High iCEB values are associated with TdP and low values with non-TdP-mediated VT/VF [10]. In this study, our results revealed a decreased iCEB after chemotherapy in breast cancer. In this study, chemotherapy did not induce a significant change in LVEF. Importantly, LVEF measurement shows a low sensitivity for the early detection of subclinical cardiotoxicity [35]. This might explain why in our observation period we could not detect any decrease in LVEF despite significant electrocardiographic abnormities. Therefore, echocardiography might be suboptimal for detecting acute cardiac complications. These data supported the idea that ECG could identify mild cardiotoxicity in an earlier stage than echocardiography Whilst strain imaging can also be used for early detection of myocardial damage, the advantage of electrocardiography is their rapid and wide availability for routine clinical use. Regular ECG monitoring after initiation of chemotherapy hence is great of importance and may help cardiologists and oncologists tailor treatments during clinical works.

Several limitations of the present study should be noted. Firstly, our study investigated a small number and short follow-up of patients in a single center. Further studies are needed to verify our findings. Secondly, baseline thyroid function and history of heart failure were not collected, which may influence the ECG changes of the patients. Thirdly, the cardiac biomarkers, such as brain natriuretic peptide and troponin, were not tested in most of the included patients because it is limited by medical insurance.

Finally, patients in this study are treated with multiple chemotherapeutics such as anthracyclines and cyclophosphamide, which may cause cardiotoxicity that is indistinguishable. Larger prospective studies examining the roles of ECG parameters for risk stratification purposes are needed in the future.

5. Conclusions

In this prospective study of patients with breast cancer who underwent chemotherapy, cardiotoxicity can also manifest as the emergence of ECG abnormalities, specifically abnormal ventricular repolarization. With further study, SLI and QTd ratio could potentially be used for differentiating patients after therapy from baselines. The data from this study demonstrated that ECG can be conducted to evaluate the subclinical cardiac damage for breast cancer patients after chemotherapy. ECG could help to detect subclinical cardiac dysfunction earlier than echocardiography. Regular ECG monitoring may help to detect early cardiotoxicity during follow-up following chemotherapy.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest

Authors' Contributions

Xufei Liang and Yueying Wang contributed equally. Xufei Liang and Yueying Wang investigated the study, wrote the original draft, and performed formal analysis. Xi Yin, Xiaohong Gong, Shuo Pan, and Ziliang Chen investigated the study. Xuhong Geng conceptualized the study, contributed to methodology, reviewed and edited the manuscript, and supervised the study.

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