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Process analysis of anthracycline adverse reactions in breast cancer patients with postoperative chemotherapy

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ABSTRACT

This study aimed to explore the clinical adverse effects of anthracyclines on patients undergoing chemotherapy after breast cancer surgery. A total of 118 patients who received anthracycline chemotherapy after breast cancer surgery were selected as the research object, and the changes of echocardiogram, ECG, myocardial enzymes and blood biochemical indices before, during and after chemotherapy were studied. SPSS V.20 was used to conduct statistical analysis. The differences in heart rate, ST-segment abnormalities, creatine kinase, lactate dehydrogenase, hemoglobin, albumin, triglycerides and high-density lipoprotein were statistically significant. Heart rate and triglycerides increased significantly in the early stage of chemotherapy; ST-segment abnormality increased during the entire chemotherapy period; creatine kinase and lactate dehydrogenase increased significantly in the late stage of chemotherapy; hemoglobin and albumin decreased in the early stage of chemotherapy. The magnitude is large; high-density lipoprotein decreases throughout the chemotherapy period. In anthracycline chemotherapy regimens, bone marrow suppression and dyslipidemia occur in the early stage of chemotherapy, and the risk of cardiotoxicity is higher in the late stage of chemotherapy.

Significance of this study

What is already known about this subject?

- Global Cancer Statistics (GLOBOCAN) 2020 show that breast cancer is the most common malignancy and a leading cause of cancer-related death among women worldwide.

What are the new findings?

- In anthracycline chemotherapy regimens, bone marrow suppression and dyslipidemia occur in the early stage of chemotherapy, and the risk of cardiotoxicity is higher in the late stage of chemotherapy.

How might these results change the focus of research or clinical practice?

- Our findings might be helpful for the clinical treatment of breast cancer.

INTRODUCTION

Global Cancer Statistics (GLOBOCAN) 2020 show that breast cancer is the most common malignancy and a leading cause of cancer-related death among women worldwide.[1] Depending on the tumor stage and the physical conditions of patients, the treatments may include surgery, chemotherapy, radiotherapy, endocrine therapy, and so on, among which chemotherapy is the primary one of breast cancer treatments. Anthracycline is currently the first-line drug in the clinical treatment of breast cancer and the first-class recommended drug for neoadjuvant chemotherapy. It plays an important role in the postoperative adjuvant chemotherapy of breast cancer, with a strong positive impact on breast cancer prognosis and survival.[2] However, anthracycline has toxic side effects such as myelosuppression and cardiotoxicity, especially cardiotoxicity with significant clinical symptoms, which limits their clinical use and affects the treatment course and survival prognosis of patients with cancer.[3] In the meantime, cardiovascular disease is the main cause of death for many elderly patients with breast cancer.[4] As the treatment progresses, the survival time of patients is extended while cardiovascular disease-related complications become an important lethal factor for patients with malignancies, with increasing incidence year by year.[5] It is not yet clear whether anthracyclines increase the risk of cardiovascular disease by altering patients' glucose lipid metabolism.

Current studies on anthracycline toxicity mainly focus on the changes in patients before and after chemotherapy, with few reports on the changes of cardiac-related indicators during anthracycline chemotherapy. In this study, we examine the changes of indicators in patients with breast cancer before, during, and after anthracycline chemotherapy to determine and predict myocardial damage and its associated risk factors in patients caused by anthracycline. This will reduce the risk of cardiovascular complications resulting from anthracycline used among postoperative breast cancer patients and thus improve the survival and prognosis.

MATERIALS AND METHODS

This study was conducted in accordance with the Declaration of Helsinki. This study was conducted with approval from the Ethics Committee of

Table 1 The basic information of patients (n=118)

Items	Cases
Sex	
Female	118
Male	0
Age	
≤40 years old	12
40 years old and ≤60 years old	62
>60 years old	44
Therapeutic regime	
AT	75
TAC	43
Patients with hypertension, coronary heart disease or diabetes before chemotherapy	0
The total number of patients	118

Tianjin Fourth Central Hospital. Written informed consent was obtained from the participants.

Subjects

We selected 118 patients who were diagnosed with breast cancer from January 2007 to September 2020 and received anthracycline chemotherapy after operation at the Tianjin No. 4 Central Hospital.

Inclusion criteria

Adult patients with breast cancer who received radical mastectomy; chemotherapy with an anthracycline regimen; no radiation therapy in the meantime; no patients with distant metastases.

Exclusion criteria

Pregnant patients; patients combined with other tumors; patients with significant abnormalities in echocardiograms, electrocardiograms, and lipid glucose index before chemotherapy.

Observed indicators

We observed the general condition of patients and analyzed various indicators before, during (after the third chemotherapy), and after (the entire six) chemotherapies, including echocardiograms (left ventricular ejection fraction, left atrial maximum anteroposterior diameter, right atrial transverse diameter, left ventricular end-diastolic internal diameter, left ventricular end-systolic internal diameter, right ventricular internal diameter), electrocardiograms (heart rate, P-wave time, P-R interval, QRS wave group, Q-T interval, ST segment, T wave), myocardial enzymology (creatine kinase, creatine kinase isoenzyme, lactate dehydrogenase) and blood biochemical indices (hemoglobin, albumin, fasting glucose, total cholesterol, triglycerides, low-density lipoprotein, high-density lipoprotein).

Statistical analysis

SPSS V.20 software was used for statistical analysis, and the measurement data were expressed as mean±SD if they conformed to normal distribution. If all the parameters of each group were normal distribution and the variance was homogeneous, one-way analysis of variance was used to compare the parameters between groups, and LSD-t test for comparison between two groups. Otherwise, the Brown-Forsythe test was used for the former, and the Dunnett T3 test for the latter. Differences were considered statistically significant at $p<0.05$. Count data were analyzed by the χ^2 test using a two-way contingency table, and differences were considered statistically significant at $p<0.05$.

RESULTS

General information

All patients were female, aged 28–79 years, with a mean of 56.2±10.3 years. Among them, 75 cases were treated with AT regimen (pirarubicin 50 mg/m^2, docetaxel 75 mg/m^2) for 21 days for 6 cycles, and 43 cases were treated with TAC regimen (docetaxel 75 mg/m^2, pirarubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2) for 21 days for 6 cycles. In the adjuvant regimen, the patients did not receive other drugs that might affect echocardiograms, ECGs, myocardial enzymology and blood biochemical indices. The basic patient information is shown in table 1.

Echocardiography

We recorded and analyzed the echocardiograms of the patients before, during and after chemotherapy. Compared with the pre-chemotherapy period, there were no significant changes in the echocardiographic indices of the patients during and after chemotherapy, and none of them were statistically significant ($p>0.05$), as shown in table 2.

Table 2 Analysis of the echocardiograms of the patients before, during and after chemotherapy

Clinical characteristics	Before chemotherapy ($\bar{x}$±s)	During chemotherapy ($\bar{x}$±s)	After chemotherapy ($\bar{x}$±s)	F(B) or χ^2	P_{12}	P_{13}	P_{23}
LVEF (%)	64.458±3.713	64.169±3.314	63.992±3.636	0.598(B)	0.896	0.700	0.971
LAMAD (mm)	31.508±3.486	31.915±3.988	31.966±4.118	0.610(B)	0.789	0.734	1.000
RAMD (mm)	29.619±2.276	29.644±2.567	29.542±2.395	0.945(B)	1.000	0.992	0.985
LVEDD (mm)	42.203±3.014	42.115±3.346	41.915±3.107	0.773(B)	0.995	0.851	0.951
LVESD (mm)	26.822±2.797	27.000±2.897	27.195±2.596	0.585(B)	0.950	0.640	0.929
RVID (mm)	14.627±1.642	14.814±2.335	15.093±3.320	0.363	0.571	0.158	0.396

P_{12}, P_{13} and P_{23} represent the calculation results of corresponding tests for indicators before and during chemotherapy, before and after chemotherapy, and during and after chemotherapy, respectively.

LAMAD, left atrial maximum anteroposterior diameter; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; RAMD, right atrial mediolateral diameter; RVID, right ventricular internal dimension.

Table 3 Analysis of the echocardiograms of the patients before, during and after chemotherapy

Clinical characteristics	Before chemotherapy ($\bar{x}\pm s$)	During chemotherapy ($\bar{x}\pm s$)	After chemotherapy ($\bar{x}\pm s$)	F(B) or χ^2	P_{12}	P_{13}	P_{23}
Heart rate (times/min)	74.017±11.195	80.627±13.391	81.373±13.312	<0.001(B)	<0.001	<0.001	0.963
P-wave time (s)	0.107±0.010	0.106±0.013	0.105±0.011	0.193(B)	0.632	0.153	0.875
P-R interphase (s)	0.152±0.020	0.153±0.019	0.151±0.018	0.696(B)	1.000	0.871	0.801
QRS complex (s)	0.086±0.010	0.086±0.008	0.086±0.008	0.968(B)	0.995	1.000	0.993
Q-T interphase (s)	0.399±0.036	0.398±0.040	0.397±0.040	0.891(B)	0.989	0.948	0.989

P_{12}, P_{13} and P_{23} represent the calculation results of corresponding tests for indicators before and during chemotherapy, before and after chemotherapy, and during and after chemotherapy, respectively.

Electrocardiogram

We recorded and analyzed the electrocardiograms of the patients before, during and after chemotherapy. The values of each index at the three time points, as well as the test results calculated by a two-by-two comparison of the values at the three time points, are as follows.

Compared with the pre-chemotherapy period, patients had an elevated heart rate in the middle period of chemotherapy after three chemotherapies, and the difference was statistically significant (P_{12} <0.001); there were no noticeable changes in P-wave time, P-R interval, QRS complex, Q-T interval and T-wave abnormalities. The incidence of ST-segment abnormalities increased, but none of the differences were statistically significant (P_{12} >0.05).

After the entire six chemotherapy sessions, the patients' heart rate and ST-segment abnormality ratio were increased compared with those before chemotherapy, and the differences were statistically significant (P_{13} <0.001, P_{13}=0.002); there were no noticeable changes in P-wave time, P-R interval, QRS complex, and Q-T interval, while the proportion of T-wave abnormality increased and the differences were not statistically significant (P_{13} >0.05). Compared with those in the period after the third chemotherapy, the heart rate, P-wave time, P-R interval, QRS complex, and Q-T interval did not change significantly after the end of chemotherapy, although the proportion of ST-segment and T-wave abnormalities increased, and the differences were not statistically significant (P_{23} >0.05), as shown in tables 3 and 4. We observed that the heart rate increased more in the pre-chemotherapy period, accounting for the majority of the increase throughout chemotherapy, and the probability of ST-segment abnormalities increased during whole the chemotherapy period.

Blood tests

Cardiac enzymes

We recorded and analyzed the patients' cardiac enzymes before, during and after chemotherapy, and the values of each index at the three time points, as well as the test results calculated by a two-by-two comparison of the values at the three time points, shown as follows.

Compared with the pre-chemotherapy indices, the patients' creatine kinase was elevated after the third chemotherapy, while creatine kinase isoenzyme and lactate dehydrogenase did not significantly change, with no statistically significant difference (P_{12} >0.05). Creatine kinase and lactate dehydrogenase in patients, after all six chemotherapy sessions, were higher than those before chemotherapy, with statistically significant differences (P_{13}=0.003, P_{13}=0.048); creatine kinase isoenzyme did not change significantly, with no statistically significant differences (P_{13} >0.05). Creatine kinase and lactate dehydrogenase in patients, after all six chemotherapy sessions, were higher than those after the third chemotherapy session, with statistically significant differences (P_{23}=0.009, P_{23}=0.042); creatine kinase isoenzymes did not change significantly, with no statistically significant differences (P_{23} >0.05), as shown in table 5. We therefore observed that the increase in lactate dehydrogenase was greater in the late stage of chemotherapy and even greater than the increase in the whole chemotherapy.

Hemoglobin and albumin

We recorded and analyzed the patients' hemoglobin and albumin before, during and after chemotherapy. Both hemoglobin and albumin decreased after the third chemotherapy compared with the pre-chemotherapy values, with statistically significant differences (P_{12} <0.001, P_{12} <0.001). Both values after all six chemotherapy sessions were lower than before chemotherapy, and the differences were statistically significant (P_{13} <0.001, P_{13} <0.001). Compared with the values after the third chemotherapy, the patients' hemoglobin slightly increased after all six chemotherapy sessions, and albumin did not change noticeably, with no statistically significant differences (P_{23} >0.05), as shown in table 6. It was found that the decrease of hemoglobin level in the early stage of chemotherapy was greater than that in the whole course of chemotherapy, and the decrease of albumin level in the early stage of chemotherapy was greater even than that in the whole course of chemotherapy.

Table 4 Statistical analysis results of ST-segment abnormalities and T wave abnormalities

Clinical characteristics	Before chemotherapy (%)	During chemotherapy (%)	After chemotherapy (%)	P_{12}	P_{13}	P_{23}
ST-segment abnormalities	16.95	25.42	34.75	0.111	0.002	0.118
T wave abnormalities	27.12	26.27	37.29	0.883	0.095	0.069

P_{12}, P_{13} and P_{23} represent the calculation results of corresponding tests for indicators before and during chemotherapy, before and after chemotherapy, and during and after chemotherapy, respectively.

Table 5 Statistical analysis of myocardial enzymes

Clinical characteristics	Before chemotherapy ($\bar{x}\pm s$)	During chemotherapy ($\bar{x}\pm s$)	After chemotherapy ($\bar{x}\pm s$)	F(B) or χ^2	P_{12}	P_{13}	P_{23}
Creatine kinase (U/L)	42.555±15.340	43.892±25.467	53.331±37.024	0.005	0.708	0.003	0.009
Creatine kinase isoenzyme (U/L)	11.678±6.787	11.794±6.107	11.748±5.857	0.990(B)	0.999	1.000	1.000
Lactate dehydrogenase (U/L)	180.118±36.402	179.927±35.885	192.522±42.150	0.016(B)	1.000	0.048	0.042

P_{12}, P_{13} and P_{23} represent the calculation results of corresponding tests for indicators before and during chemotherapy, before and after chemotherapy, and during and after chemotherapy, respectively.

Fasting blood glucose

We recorded and analyzed the fasting blood glucose of patients before, during and after chemotherapy. Compared with that before chemotherapy, there was no significant change in fasting blood glucose after the third chemotherapy and after all six chemotherapy sessions; compared with that after the third chemotherapy session, there was no significant change in fasting blood glucose after all six chemotherapy sessions in patients and the differences were not statistically significant ($p>0.05$), as shown in table 7. Therefore, fasting blood glucose did not change much during anthracycline chemotherapy.

Blood lipids

We recorded and analyzed the patients' blood lipids before, during and after chemotherapy. Compared with the values before chemotherapy, triglycerides increased after the third chemotherapy, with a statistically significant difference ($P_{12}<0.001$); total cholesterol and high-density lipoprotein decreased, with no statistically significant difference ($P_{12}>0.05$); low-density lipoprotein increased slightly, with no statistically significant difference ($P_{12}>0.05$). Compared with the values before chemotherapy, there was a triglyceride increase with a statistically significant difference ($P_{13}<0.001$) after all six chemotherapy sessions, a statistically significant difference in high-density lipoprotein decrease ($P_{13}<0.001$), a statistically significant difference in total cholesterol decrease ($P_{13}>0.05$), and a statistically significant difference in low-density lipoprotein increase ($P_{13}>0.05$). Compared with the values after the third chemotherapy, total cholesterol remained almost unchanged after all six chemotherapy sessions, with no statistically significant difference ($P_{23}>0.05$); triglycerides and low-density lipoprotein increased, with no statistically significant difference ($P_{23}>0.05$); high-density lipoprotein decreased, with no statistically significant difference ($P_{23}>0.05$), as shown in table 8. It was found that the increase in triglyceride levels was greater in the pre-chemotherapy period and accounted for the majority of the increase in the whole chemotherapy course; high-density lipoprotein tended to decrease in the whole chemotherapy course.

DISCUSSION

Increased cardiac risk in patients with breast cancer

The number of women with breast cancer incidence has increased dramatically worldwide from 2000 to 2020, from 1.05 million in 2000 to 2.26 million[1] in 2020. Various factors contribute to the increase in incidence, among which age is known to be an important risk factor. The incidence of breast cancer increases with age and the risk increases by about 50% in postmenopausal women.[6] In addition, blood type, diets, and lifestyle also constitute the risk factors for the increased incidence of breast cancer.[7 8] With the improvement of treatment methods, the mortality rate of breast cancer decreased year by year, and the survival time was prolonged as well.[9]

Anthracycline is a first-line chemotherapeutic drug used in the treatment of breast cancer and is the basis of postoperative chemotherapy regimens for breast cancer. Anthracyclines are cardiotoxic, but the mechanism by which they trigger cardiotoxicity is not well understood. Current studies suggest that they are associated with the production of reactive oxygen radicals that leads to oxidative stress and cardiomyocyte death.[10] Anthracyclines may cause heart failure and severe irreversible loss of mobility, which thus increased mortality in patients. The cardiotoxicity of anthracyclines limits their use in clinical chemotherapy.[11] In addition to chemotherapy, radiation or targeted therapies received by patients with breast cancer have similar toxic effects that damage the cardiovascular system. Therefore, patients with breast cancer are exposed to a higher risk of cardiovascular disease than the overall population.[12–14]

Effects of anthracyclines on cardiac function

Current studies on the adverse effects of anthracyclines have focused on cardiotoxicity, but almost exclusively on the results in the early phase and after all the end, with little

Table 6 Statistical analysis of blood tests

Clinical characteristics	Before chemotherapy ($\bar{x}\pm s$)	During chemotherapy ($\bar{x}\pm s$)	After chemotherapy ($\bar{x}\pm s$)	F(B) or χ^2	P_{12}	P_{13}	P_{23}
Hemoglobin (g/L)	129.280±12.762	115.381±12.752	116.881±12.900	<0.001(B)	<0.001	<0.001	0.749
Albumin (g/L)	42.636±3.932	39.973±3.633	40.080±4.127	<0.001(B)	<0.001	<0.001	0.995

P_{12}, P_{13} and P_{23} represent the calculation results of corresponding tests for indicators before and during chemotherapy, before and after chemotherapy, and during and after chemotherapy, respectively.

Table 7 Statistical analysis of blood tests

Clinical characteristics	Before chemotherapy ($\bar{x}\pm s$)	During chemotherapy ($\bar{x}\pm s$)	After chemotherapy ($\bar{x}\pm s$)	F(B) or χ^2	P_{12}	P_{13}	P_{23}
Fasting blood glucose (mmol/L)	5.632±2.180	5.391±1.385	5.660±2.004	0.484(B)	0.672	0.999	0.544

P_{12}, P_{13} and P_{23} represent the calculation results of corresponding tests for indicators before and during chemotherapy, before and after chemotherapy, and during and after chemotherapy, respectively.

monitoring of indicators during the process. In this study, by analyzing the results of chemotherapy in the middle stage, we can more clearly recognize the pattern of the process of cardiotoxicity and intervene more timely in the treatment of patients at risk. This study explored the effects of early anthracyclines on cardiac function and other associated metabolic functions in patients undergoing chemotherapy after breast cancer surgery, with multiple samples, at multiple stages, and through multiple indicators. By comparing echocardiography, electrocardiography, cardiac enzymology and blood biochemistry before, during and after chemotherapy, we analyzed and studied the changing trends in more concrete situations and with the help of more indicators. As suggested by the changes of data mentioned above, the findings of this study are as follows.

Two-by-two comparisons of the echocardiogram indices in the three stages did not reveal a noticeable difference, and the data changed very little in further cycles of chemotherapy. Among these indices, heart rate and ST-segment abnormalities were statistically significant. The heart rate was elevated more in the pre-chemotherapy period and accounted for most of the elevation throughout chemotherapy; the probability of ST-segment abnormalities continued to increase throughout the chemotherapy. Both heart rate and ST-segment abnormalities are hallmarks of cardiac injury, and they changed significantly in this study, with heart rate deteriorating more rapidly in the pre-chemotherapy period than in the post-chemotherapy period. Among the indices of the cardiac enzymes, the changes of creatine kinase and lactate dehydrogenase were statistically significant. Creatine kinase increased more in the late phase of chemotherapy and accounted for most of the elevation throughout chemotherapy; lactate dehydrogenase increased more in the late phase of chemotherapy, even more than that throughout chemotherapy.

Echocardiography, electrocardiography, and cardiac enzymes offer important evidence to cardiac injury. It is considered as cardiotoxic when there is a decrease in left ventricular ejection fraction of at least 10% from baseline values, along with absolute values <53%.[15] Pudil *et al* reported that the incidence of electrocardiography abnormalities such as non-specific ST changes, QT interval prolongation and QRS low voltage in anthracycline chemotherapy was 10%–30% in anthracycline chemotherapy.[16] The echocardiographic indices in this study were not statistically significant, suggesting that echocardiography is less sensitive to monitoring cardiotoxicity during chemotherapy and therefore is not suitable as evidence of cardiac injury from anthracyclines; heart rate, ST segment abnormality rate, creatine kinase and lactate dehydrogenase were statistically significant and can effectively reflect the process of myocardial injury. The changes of these four data in the study indicate that as chemotherapy proceeds and anthracycline accumulates in human body, myocardial injury gradually worsens in a dose-dependent manner and exacerbates more rapidly in the late stage of chemotherapy.

Effects of anthracycline drugs on metabolism

Abnormalities in glucose and lipid metabolism may lead to diabetes, hyperlipidemia and even cardiovascular abnormalities. It is not yet clear whether chemotherapy increases the risk of cardiovascular disease by altering patients' glucose and lipid metabolism.[17 18] In a study of 106 patients with breast cancer, Sheng *et al*[19] discovered that post-chemotherapy levels of total cholesterol, triglyceride and low-density lipoprotein were higher than pre-chemotherapy, while no significant difference was found in high-density lipoprotein levels. In a study of 12 patients with breast cancer, Sharma *et al*[20] found that post-chemotherapy levels of high-density lipoprotein were lower than pre-chemotherapy, while total cholesterol and triglyceride levels were not significantly different. This study not only analyzed the changes in glucose lipids before and after chemotherapy, but also concretely delineated the changes in glucose lipids throughout the chemotherapy period by investigating the midterm results of chemotherapy,

Table 8 Statistical analysis of blood tests

Clinical characteristics	Before chemotherapy ($\bar{x}\pm s$)	During chemotherapy ($\bar{x}\pm s$)	After chemotherapy ($\bar{x}\pm s$)	F(B) or χ^2	P_{12}	P_{13}	P_{23}
Total cholesterol (mmol/L)	5.695±4.042	5.557±1.032	5.566±1.050	0.892(B)	0.978	0.982	1.000
Triglyceride (mmol/L)	1.360±0.637	1.903±1.071	1.939±0.843	<0.001	<0.001	<0.001	0.748
Low-density lipoprotein (mmol/L)	3.388±0.863	3.461±0.928	3.506±0.901	0.594(B)	0.895	0.663	0.975
High-density lipoprotein (mmol/L)	1.519±0.356	1.451±0.324	1.396±0.340	0.021(B)	0.325	0.020	0.494

P_{12}, P_{13} and P_{23} represent the calculation results of corresponding tests for indicators before and during chemotherapy, before and after chemotherapy, and during and after chemotherapy, respectively.

which provides a basis for timely intervention in the treatment of glucose lipid abnormalities.

Among the indicators of blood tests, hemoglobin, albumin, triglycerides and high-density lipoprotein were statistically significant. Hemoglobin level decreased more in the pre-chemotherapy period, and even more than the whole chemotherapy course; albumin level decreased more in the pre-chemotherapy period, and even more than the whole chemotherapy period. The change of hemoglobin in the pre-chemotherapy period proved myelosuppression caused by anthracycline chemotherapy, and the change of albumin in the meantime indicated that the patients were too exhausted in poor nutritional conditions. The change of the two proteins in the late chemotherapy period was presumed to be a result of alleviated side effects after nutritional supplies. Triglyceride levels increased more in the pre-chemotherapy period and accounted for most of the increase throughout chemotherapy; high-density lipoprotein showed a decreasing trend throughout chemotherapy.

Triglyceride has been considered to be a risk factor for cardiovascular disease,[21] and its change indicates that anthracycline may lead to disorders of lipid metabolism and increased risk of cardiovascular disease, without dependence on the dose accumulation; high-density lipoprotein is an independent predictor of cardiovascular disease,[22] and its change indicates that anthracyclines may lead to disorders of lipid metabolism and increased risk of cardiovascular disease. Some studies have reported that chemotherapy has adverse effects on blood glucose in patients with breast cancer,[19] which is also an indirect risk factor for cardiovascular disease. However, fasting blood glucose was not statistically significant in this study, suggesting that changes in blood glucose are not statistically significant as chemotherapy proceeds.

In summary, we can conclude from the changes of the above indices: anthracycline drugs for breast cancer, at the early stage of treatment, can cause myelosuppression and lipid metabolism disorders that elevate the risk of cardiovascular disease; also, higher risk of cardiotoxicity as well as a reduced cardiac function would appear at the late stage of chemotherapy. Therefore, patients with underlying diseases or poor cardiac function need to be more carefully observed in the late stage of chemotherapy, with close monitoring of the various indices of patients. This will help clinicians to modify the ongoing treatment plan in time, and reduce the incidence and severity of complications as far as possible without harm to the antitumor efficacy.

Contributors CL and HY conceived and designed the study; CL, BC, and GZ collected the data; CL, BC, and GZ analyzed and interpreted the data; CL wrote the manuscript; HY provided critical revisions that are important for the intellectual content; CL, BC, GZ, and HY approved the final version of the manuscript. HY is responsible for the overall content as the guarantor.

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Competing interests None declared.

Patient consent for publication Obtained.

Ethics approval This study was conducted in accordance with the Declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Tianjin Fourth Central Hospital (SZXLL-2018-KY0308). Written informed consent was obtained from the participants. Participants gave informed consent to participate in the study before taking part.

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REFERENCES

1 Sung H, Ferlay J, Siegel RL, *et al*. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021;71:209–49.
2 , Peto R, Davies C, *et al*, Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. *Lancet* 2012;379:432–44.
3 Curigliano G, Cardinale D, Dent S, *et al*. Cardiotoxicity of anticancer treatments: epidemiology, detection, and management. *CA Cancer J Clin* 2016;66:309–25.
4 Bradshaw PT, Stevens J, Khankari N, *et al*. Cardiovascular disease mortality among breast cancer survivors. *Epidemiology* 2016;27:6–13.
5 Gernaat SAM, Ho PJ, Rijnberg N, *et al*. Risk of death from cardiovascular disease following breast cancer: a systematic review. *Breast Cancer Res Treat* 2017;164:537–55.
6 Engmann NJ, Golmakani MK, Miglioretti DL, *et al*. Population-Attributable risk proportion of clinical risk factors for breast cancer. *JAMA Oncol* 2017;3:1228–36.
7 Meo SA, Suraya F, Jamil B, *et al*. Association of ABO and Rh blood groups with breast cancer. *Saudi J Biol Sci* 2017;24:1609–13.
8 Shetty PJ, Sreedharan J. Breast cancer and dietary fat intake: a correlational study. *Nepal J Epidemiology* 2019;9:812–6.
9 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA A Cancer J Clin* 2020;70:7–30.
10 Carvalho FS, Burgeiro A, Garcia R, *et al*. Doxorubicin-Induced cardiotoxicity: from bioenergetic failure and cell death to cardiomyopathy. *Med Res Rev* 2014;34:106–35.
11 Patnaik JL, Byers T, DiGuiseppi C, *et al*. Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study. *Breast Cancer Res* 2011;13:R64.
12 Boekel NB, Duane FK, Jacobse JN, *et al*. Heart failure after treatment for breast cancer. *Eur J Heart Fail* 2020;22:366–74.
13 Cheng Y-J, Nie X-Y, Ji C-C, *et al*. Long-Term cardiovascular risk after radiotherapy in women with breast cancer. *J Am Heart Assoc* 2017;6:e005633.
14 Johnson CB, Davis MK, Law A, *et al*. Shared risk factors for cardiovascular disease and cancer: implications for preventive health and clinical care in oncology patients. *Can J Cardiol* 2016;32:900–7.
15 Plana JC, Galderisi M, Barac A, *et al*. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of echocardiography and the European association of cardiovascular imaging. *J Am Soc Echocardiogr* 2014;27:911–39.
16 Pudil R, Horacek JM, Horackova J, *et al*. Anthracycline therapy can induce very early increase in QT dispersion and QTc prolongation. *Leuk Res* 2008;32:998–9.
17 Guenancia C, Lefebvre A, Cardinale D, *et al*. Obesity as a risk factor for anthracyclines and trastuzumab cardiotoxicity in breast cancer: a systematic review and meta-analysis. *JCO* 2016;34:3157–65.
18 Li X, Liu Z-li, Wu Y-tuan, *et al*. Status of lipid and lipoprotein in female breast cancer patients at initial diagnosis and during chemotherapy. *Lipids Health Dis* 2018;17:91.
19 Dieli-Conwright CM, Wong L, Waliany S, *et al*. An observational study to examine changes in metabolic syndrome components in patients with breast cancer receiving neoadjuvant or adjuvant chemotherapy. *Cancer* 2016;122:2646–53.
20 Sharma M, Tuaine J, McLaren B, *et al*. Chemotherapy agents alter plasma lipids in breast cancer patients and show differential effects on lipid metabolism genes in liver cells. *PLoS One* 2016;11:e0148049.
21 Silbernagel G, Scharnagl H, Kleber ME, *et al*. Ldl triglycerides, hepatic lipase activity, and coronary artery disease: an epidemiologic and Mendelian randomization study. *Atherosclerosis* 2019;282:37–44.
22 Ouimet M, Barrett TJ, Fisher EA. Hdl and reverse cholesterol transport. *Circ Res* 2019;124:1505–18.