Curr Probl Cardiol 49 (2024) 102187

Contents lists available at ScienceDirect

Current Problems in Cardiology

journal homepage: www.elsevier.com/locate/cpcardiol

Cardiac dysfunction and their determinants in patients treated for breast cancer and lymphoma: A cardio-oncology center experience

Sheeren Khaled [a,b,*], Seham Abdelkhalek [a,c], Rawan Aljuwaybiri [d], Jana Almatrafi [d], Abdulelah AlHarbi [e], Reem Almarhabi [f], Fatma Alyamani [d], Magda Soliman [a], Eman Jubran [a], Ghada Shalaby [a,g]

[a] Cardiac center, King Abdullah Medical City, Makkah, Saudi Arabia
[b] Benha University, Benha, Egypt
[c] Mansoura University, Mansoura, Egypt
[d] Umm Al-Qura University, Makkah, Saudi Arabia
[e] University of Ha'il, Ha'il, Saudi Arabia
[f] Umm Al-Qura University, AlQunfidhah, Saudi Arabia
[g] Zagazig University, Zagazig, Egypt

ARTICLE INFO

Keywords:
Cancer
Cardiac dysfunction
In-hospital outcomes

ABSTRACT

Objective: Cancer and cardiovascular diseases both have adverse effects on each other. We aim in the current study to investigate cardiac dysfunction including its prevalence, and associated factors in patients treated for breast cancer and lymphoma in a unique cardiac oncology center.
Methods: A single-center retrospective study included 180 patients with cancer breast and lymphoma who presented and were treated at our oncology center from January 2019 to February 2022.
Result: Out of 180 consecutive patients, 155 patients (86 %) were diagnosed with cancer breast and 25 patients (14 %) were diagnosed with lymphoma. Patients with lymphoma were older age, less obese, and showed more prevalence of diabetes mellitus (DM) ($P = 0.026$, 0.05, and 0.04 respectively). They also showed more post-therapy left ventricular (LV) dilatation and lower values of global longitudinal strain (GLS); however, they did not develop more LV dysfunction compared to cancer breast patients. Moreover, lymphoma patients showed poor in-hospital outcomes ($P = 0.04$, 0.001, and 0.015 for infection, pericardial effusion, and mortality respectively). Cancer therapy-related cardiac dysfunction (CTRCD) was observed in 41 patients (23 %) of our population. The independent predictors of CTRCD in the current study were DM, low body mass index (BMI), and the use of trastuzumab.
Conclusions: Some patients treated for breast cancer and lymphoma develop LV dysfunction. Lymphoma patients showed more subclinical LV dysfunction and poor in-hospital outcomes compared to patients with cancer breast. DM, low body mass index (BMI), and the use of trastuzumab were the independent predictors of cardiac dysfunction among our patients.

Key message

* Corresponding author at: Cardiac center, King Abdullah Medical City, Makkah, Saudi Arabia.
E-mail address: sheeren.khaled@gmail.com (S. Khaled).

https://doi.org/10.1016/j.cpcardiol.2023.102187

Available online 30 October 2023

Cancer therapy-related cardiac dysfunction was not uncommon and implementation of cardiac function monitoring at pre-therapy and each treatment stage for high-risk patients is advised. Secondary prevention interventions in patients with pre-existing cardiovascular risk factors and following a healthy lifestyle are recommended. Moreover, our study suggests the fact that early detection of subclinical cardiac dysfunction could lead to an early start of heart failure therapy, thus preventing poor cardiac outcomes.

Introduction

Cardiovascular disease (CVD) is the leading cause of death and morbidity worldwide. Moreover, it is considered the second leading cause of both morbidity and mortality in cancer survivors. Cancer and cardiovascular diseases both have adverse effects on each other. Treatments that improve cancer prognosis and survival are frequently linked to cardiovascular risks.[1,2] A guiding principle of cardio-oncology is integration, and cardio-oncology providers must know the broad scope of cardiology, oncology, and hematology.[3]

Breast cancer is metastatic cancer that can commonly transfer to distant organs leading to manifestations that are more systematic and making it difficult to treat and manage with the increased rate of deaths.[3,4] Furthermore, it remains the most prevalent cancer in developing countries such as Saudi Arabia, accounting for 29 % of new cancer cases for women and 14 % of new cancer cases for both sexes in 2020.[5] On the other hand, lymphomas are a group of diseases caused by malignant lymphocytes that accumulate in lymph nodes and other lymphoid tissue higher in highly developed regions of the world associated with a raised mortality rate.[6] In Saudi Arabia, lymphoma is a common type of cancer with an increased incidence and a total death rate of up to 7.5 %.[5]

Cardiovascular risks are dependent on several variables, such as the types of chemotherapy regimens, the concurrent use of other medications, radiotherapy, or the patient's comorbidities.[7] Cancer treatment increases the risk of cardiovascular diseases by directly damaging heart structures or indirectly promoting accelerated atherosclerosis.[8] Cardiotoxicity is generally used to refer to dysfunction of the left ventricle (LV) which is defined by a decline in left ventricular ejection fraction (LVEF) of more than 10 %. To detect early myocardial damage before LVEF changes, a decline of >15 % of the global longitudinal strain (GLS) is a useful tool.[9,10]

Our center is one of the largest unique cardio-oncology centers in the western region of Saudi Arabia and hence receives most of the oncology patients deemed suitable for treatment with proper cardiac mentoring. Our study aims to investigate the cardiovascular outcomes including the prevalence, and factors associated with left ventricular (LV) dysfunction in patients treated for breast cancer and lymphoma.

Method

This retrospective descriptive study collected clinical data from electronic health records of patients with cancer breast and lymphoma who presented and were treated at our oncology center from January 2019 to February 2022. This study is designed to be part of the standard of patient care and has received approval from the ethics committee/institutional review board of our institution.

Inclusion criteria

Patients fitting the inclusion eligibility criteria of our center and have been diagnosed with breast cancer or lymphoma with at least available two echocardiograms, one pre-exposure to cancer therapy, and one post-exposure.

Exclusion criteria

Patients outside the scope of the service of our center, those who had significant baseline LV dysfunction, and those who did not have completed recorded data.

Data collection

**Clinical data*

Baseline patient's demographics, characteristics, cardiovascular risk factors, and occurrence of any cardiac insult (chest pain, arrhythmias, heart failure…etc). Oncology data include age at diagnosis, stage of cancer, and different lines of treatment (chemotherapy, hormonal, biological, radiotherapy, and surgical intervention). Laboratory data included troponin levels. Outcome parameters include infection rate, pericardial effusion, shock, cardiac arrest, and mortality.

**Echocardiography*

All patients underwent a baseline standard transthoracic Doppler echocardiography and a follow-up study within 6 months to two-year post-therapy. It was performed with a Vivid 7 ultrasound system assessing the slandered parameters. (a) Left ventricular ejection fractions (LVEF) are the fraction of chamber volume ejected in systole (stroke volume) concerning the volume of the blood in the ventricle at the end of diastole (end-diastolic volume). Stroke volume (SV) is calculated as the difference between end-diastolic volume (EDV) and end-systolic volume (ESV). LVEF is calculated from LVEF: [SV/EDV] x 100. (b) The early (E) and late diastolic velocities (A) of the mitral inflow were measured by using pulsed wave Doppler from the apical 4-chamber view. (c) TDI was performed by activating

the TDI function. Spectral waveforms from pulse wave tissue Doppler are used to measure peak myocardial velocities (Sm) at different LV sites, and then an average value was used to assess the global systolic function. Normal reference values for (Sm) should be interpreted according to age and gender.[11] (d) Myocardial deformation (strain) using automated function imaging (AFI) software to measure LV GLS from three standard apical views (the apical 4- chamber, apical 2-chamber, and apical long axis views). Each apical view assessment produced segmental values of peak systolic longitudinal strain. Thus, LV GLS was defined as the mean of the peak systolic longitudinal strain of all the LV segments from three apical views.[12]

A comparison between patients treated for breast cancer and lymphoma was done regarding all the above-mentioned data.

**Cancer therapy-related cardiac dysfunction (CTRCD) is defined as*

1- ⩾10 % decline in LVEF to a final value less than 53 % confirmed on subsequent imaging performed 2 to 3 weeks after the initial measurement (Clinical)
2- >15 % relative decline in global longitudinal strain (GLS) compared with baseline strain (subclinical) (14).

However, the need to harmonize the proper definitions has frequently been stated and recognized and resulted in the recent international definitions of CTRD supported by an updated guideline.[3]

Statistical analysis

Patients were divided into two groups; patients with cancer breast and lymphoma. A 10 % reduction in LVEF was considered the cut-point of LV dysfunction. Statistical analysis was performed by use of the SPSS software package (SPSS Inc.; Chicago, Ill), version 21.0. Continuous data were expressed as mean± standard deviation and compared using the Student t-test. Categorical data were given as a percentage and compared with a chi-square test. Also, a regression analysis was done to identify the predictors of CTRCD. For all analyses a p-value, < 0.05 was considered significant and not significant if it is > 0.05.

Results

A total of 180 consecutive oncology patients who met the criteria were analyzed. Among these patients, 155 patients (86 %) were treated for cancer breast (Group I) and 25 patients (14 %) for lymphoma (Group II) (Fig. 1).

Patients and clinical characteristics

Patients with lymphoma were older age at the time of diagnosis, less obese, and showed more prevalence of diabetes mellitus (DM) ($P = 0.026$, 0.05, and 0.04, respectively). There are no detected other cardiovascular risk factors, advanced cancer stage, and/ or cardiac insult-related differences between both groups (Table 1).

There were no significant differences between both groups regarding the baseline echocardiographic parameters (LVEF, systolic myocardial velocity (Sm by TDI and/ or GLS). However more LV dilatation (increased both LV end-diastolic and end-systolic volumes), Lower values of GLS post-therapy were noted among lymphoma patients (Group II), and this reflects the occurrence of subclinical cardiac dysfunction. On the other side, they did not develop more clinical LV dysfunction compared to cancer breast patients (Table 2).

Radiotherapy and biological treatment are frequently utilized among patients with cancer breast ($P < 0.001$) (Fig. 2).

Different groups and in-hospital outcome

The in-hospital outcome parameters were different as lymphoma patients showed poor in-hospital outcomes reflected by higher

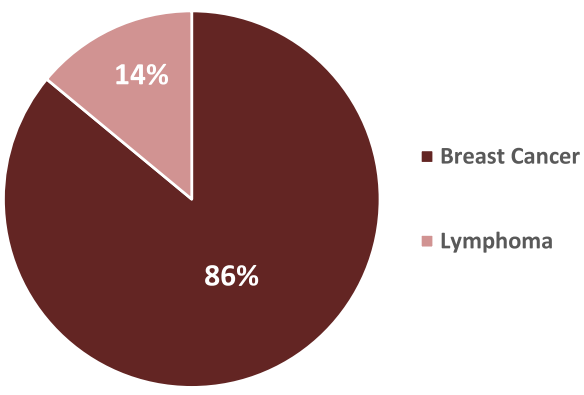

Fig. 1. Distribution of groups regarding frequency of breast cancer & lymphoma.

Table 1
Comparing demographic and clinical data between the two groups.

Variable	Group I Breast cancer $N = 155$ (86 %)	Group II Lymphoma $N = 25$ (14 %)	P value
Age at diagnosis (years) M ± SD	50.5 ± 11.3	53.7 ± 15.4	0.026
Female gender n, %	152 (98 %)	10 (40 %)	<0.001
Non Saudi patients n, %	26 (17 %)	5 (20 %)	NS
BMI M ± SD	30.5 ± 7.2	27.9 ± 5.5	0.05
DM n, %	37 (24 %)	12 (48 %)	0.04
HTN n, %	54 (35 %)	9 (30 %)	NS
CKD n, %	2 (1.3 %)	1 (4 %)	NS
Advanced stage n, %	108 (70 %)	20 (80 %)	NS
Cardiac insult n, %	31 (20 %)	4 (16 %)	NS

BMI: Body Mass Index; CKD: Chronic kidney disease; DM: Diabetes mellitus; HTN: Hypertension

Table 2
Comparing the echocardiography parameters between the two groups.

Variable	Group I Breast cancer $N = 155$ (86 %)	Group II Lymphoma $N = 25$ (14 %)	P value
LVEDV (mL) Mean ± SD (Pre- therapy)	51.6 ± 5.0	52.3 ± 6.6	NS
LVESV (mL) Mean ± SD (Pre- therapy)	22.9 ± 3.2	24.1 ± 4.6	NS
LVEF % Mean ± SD (Pre- therapy)	55.6 ± 3.9	54.2 ± 7.4	NS
Average Sm by TDI (cm/sec)) Mean ± SD (Pre-therapy)	10.7 ± 3.2	9.2 ± 2.6	NS
GLS % Mean ± SD (Pre-therapy)	17.9 ± 4.0	16.9 ± 4.5	NS
LVEDV (mL) Mean ± SD (Post therapy)	56.6 ± 16.0	72.3 ± 40.1	0.002
LVESV (mL) Mean ± SD (Post therapy)	27.9 ± 10.8	38.1 ± 29.5	0.004
LVEF % Mean ± SD (Post therapy)	54.1 ± 5.6	51.5 ± 7.2	0.07
Average Sm by TDI (cm/sec)) Mean ± SD (Post therapy)	9.8 ± 2.1	8.9 ± 2.2	NS
GLS % Mean ± SD (Post therapy)	17.09 ± 4.1	14.2 ± 3.4	0.05
CTRCD n, %	35 (23 %)	6 (24 %)	NS

CTRCD: Cancer therapy related cardiac dysfunction; GLS: Global longitudinal strain; LVEDV: Left ventricle end diastolic volume; LVEF: Left ventricular ejection fraction; LVESV: Left ventricle end systolic volume; TDI: Tissue Doppler imaging

rates of infection, pericardial effusion, and mortality compared to patients with breast cancer ($P = 0.04$,0.001, and 0.015, respectively) (Table 3).

Clinical profile and predictors of CTRCD group

Almost one-fourth (23 %) of our cancer-treated patients developed CTRCD (Fig. 3). The median time between cancer diagnosis and CTRCD diagnoses was 9 months.

The majority of patients with CTRCD were elderly, more than one-third had DM& HTN, more than a half had advanced cancer stage, one-fourth showed cardiac insult in their history, and 6 % died (Fig. 4). Among our patients, the independent predictors of further cardiac dysfunction were DM, lower BMI, and the use of trastuzumab ($P = 0.03$, 0.05, and 0.02, respectively) (Table 4).

Moreover, there was a positive correlation between baseline global longitudinal strain (GLS) and the follow-up LVEF post-cancer therapy ($P = 0.02$).

Discussion

Cancer treatment-related cardiotoxicity is a significant concern among a rising number of cancer patients and a proper definition& delivering appropriate prevention and surveillance plan for possible complications is highly recommended.[3] The majority of oncology patients presented and treated at our center are cancer breast and lymphoma. We seized this opportunity to conduct the current study comparing those two groups of cancer-treated patients defining their pre-existing cardiovascular risk factors, clinical data, and further development of CTRCD-related differences. This is considered a new addition as no similar study conducted in the region in this regard. However, our main concern was to focus on and evaluate the development of CTRCD among our cancer-treated patients exploring their clinical profile and associated independent predictors. This enables the oncology team to consider initial risk stratifications while

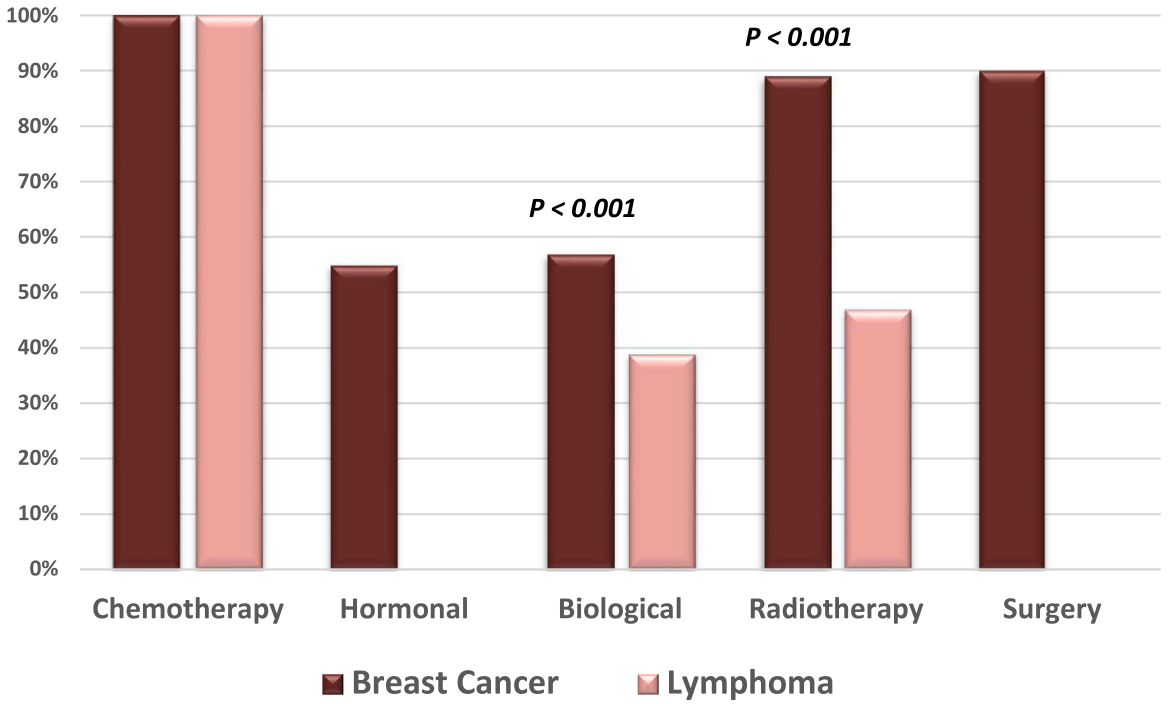

Fig. 2. Distribution of different types of cancer therapy received by both groups.

Table 3
Comparing the in-hospital outcome parameters between the two groups.

Variable	Group I Breast cancer $N = 155$ (86 %)	Group II Lymphoma $N = 25$ (14 %)	P value
Infection n, %	40 (26 %)	11 (44 %)	0.04
Pericardial effusion n, %	0	3 (12 %)	0.001
Shock n, %	23 (5 %)	3 (12 %)	NS
Cardiac arrest n, %	9 (6 %)	1 (4 %)	NS

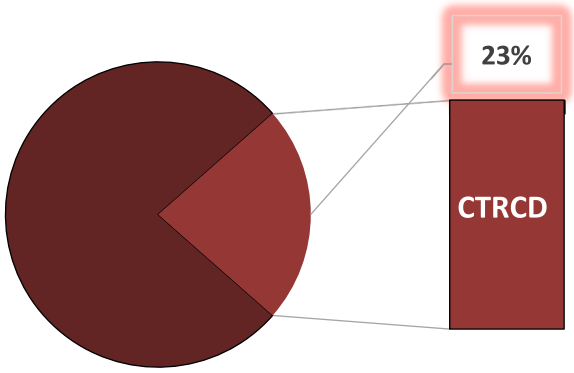

Fig. 3. Frequency of cancer treated patients developed further CTRCD.

making cancer treatment choices, educating patients regarding their risk, and personalizing the surveillance and follow-up strategy. The present study demonstrated several important findings. First, there were clinical variables, cardiac dysfunction, and complications-related differences between cancer breast, and lymphoma-treated patients. Second, CTRCD was not uncommon in the patients and detailed monitoring pathways during cancer therapy are highly recommended. Third, DM, lower BMI, and the use of trastuzumab were independent predictors of CTRCD in patients with breast cancer and lymphoma. Fourth, the current study shows that specialized care provided for cancer patients utilizing echocardiography (baseline and at follow-up stages) is necessary for early

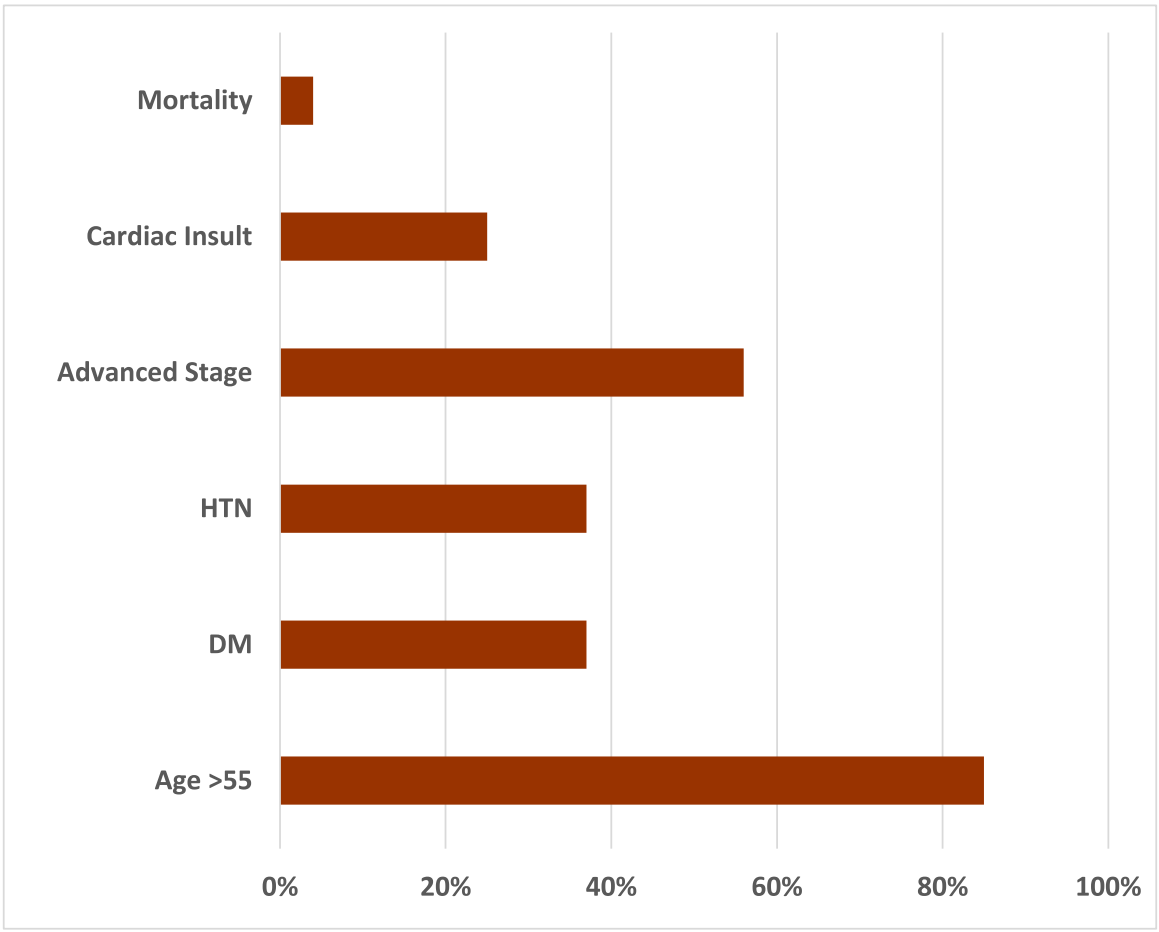

Fig. 4. Clinical profile of patients developed CTRCD.

Table 4
Binary regression analysis for independent predictors of CTRCD.

Variable	B	df	P value	EXP (B)	95 % lower	95 % upper
DM	0.991	1	0.033	2.693	1.085	6.685
BMI	-0.059	1	0.052	0.943	0.884	1.005
Trastuzumab	1.025	1	0.024	2.786	1.144	6.781

DM: Diabetes mellitus; BMI: Body Mass Index

recognition and detection of even subclinical cardiac dysfunction and reflects how our actual practice is following the existing guidelines.

Based on the literature, the comorbidity of cancer and cardiovascular diseases is increasing, given the aging population with preexisting cardiovascular risk factors[13,14] and this was similar to our current findings. Moreover, body mass index (BMI) predisposes to several site-specific cancers and this is affected by variable individual-level factors (gender, smoking, menopausal status, and age).[15] In this regard, present data show the same increase in BMI was associated with cancer breast. On the other side, lower values of BMI were noted more among lymphoma patients. This could be explained by the fast burning up of the body's energy caused by cancer cells while trying to fight these cells off. This can lead to sudden weight loss, especially since many lymphomas typically grow rapidly. Interestingly, this finding raises and highlights the idea of the "obesity paradox" in cancer patients which is well acknowledged in the cardio-metabolic literature but less so in oncology.

It is worth mentioning that the evaluation of the early impact of cancer therapy on cardiac function and the clinical implication of subtle LV dysfunction is challenging. In this study, there were no significant differences regarding baseline echocardiography parameters (LV size, LVEF, Sm by TDI or/ and GLS) between breast cancer and lymphoma. However, subclinical LV dysfunction was noted in lymphoma patients receiving cancer therapy during the follow-up stage. This was identified by post-therapy dilated LV size and reduced GLS values. Interestingly, these results are consistent with a recent study, which concluded that LV GLS is a feasible,

noninvasive, and objective modality for identifying early cardiac dysfunction in lymphoma patients receiving anticancer therapy.[16] Growing evidence has shown that LV GLS is a very potent prognostic predictor, not only for patients with cardiac disease but also for those with systemic diseases.[17,18] Here, we verified the prognostic value of LV GLS in patients with lymphoma undergoing cancer therapy. Treated lymphoma patients who had subtle LV dysfunction showed significantly poor in-hospital outcomes including mortality and this was consistent with the results of a recent study.[16]

During their treatment, oncology patients are frequently at risk for CTRCD, which occurred in approximately 23 % of our patients including breast cancer and lymphoma. Indeed, the incidence of CTRCD varies according to the definition and series.[19] Many factors might explain the variable prevalence of CTRCD including age, pre-existing cardiovascular risk factors, type of cancer, treatment schedule….etc.

The development of CTRCD dysfunction was associated with poor prognosis.[20] Therefore, the early identification of high-risk patients for CTRCD would be clinically important. In the present study, DM was one of the independent predictors of CTRCD in patients with breast cancer and lymphoma. It has known that the risk of a number of cancers and cancer mortality is increased in the presence of DM. On the other hand, some kinds of cancer and cancer therapies are associated with an increased risk of diabetes mellitus.[21] Many factors might explore the associations between these different diseases including genetic factors, inflammation, oxidative stress, hyperglycemia, hyperinsulinemia, cancer therapies, insulin, and some oral hypoglycemic medications. Moreover, low BMI was found as another independent risk factor of CTRCD in the present study, even though it was not a well-known CTRCD-related risk factor. This is consistent with a previous study, which concluded that Low BMI was an independent predictor of chemotherapy-induced LV dysfunction in patients with breast cancer.[8] In contrast to the result of the present study, a recent study demonstrated that elevated BMI was an independent predictor of cardiac function impairment in breast cancer.[22] This discrepant result regarding the association between BMI and CTRCD may come from a selection bias as we involved both groups of patients (breast cancer and lymphoma) in the present study. Moreover, low BMI may reflect a poor nutritional status, and hence more prone to the further development of heart failure. The strong independent predictor of CTRCD in the current study was the use of trastuzumab as a target therapy and this was similar to previous studies.[8] The benefits of trastuzumab are unfortunately associated with a significant risk of cardiac dysfunction however, the new guidance on continuing trastuzumab in cancer patients who develop asymptomatic moderate CTRCD (LVEF 40–49 %) whilst starting cardioprotective medication is provided.[3] Therefore, patients with these characteristics may be considered as a high-risk group and the development of CTRCD should be closely monitored.

Limitations

The present study has some potential limitations. The number of patients included is due to the nature of the single center and the limited selected period. It is a retrospective analysis that included both cancer breast and lymphoma patients; thus, selection bias would be a considerable limitation. Cardiac biomarkers, such as high-sensitivity cardiac troponin and brain natriuretic peptide were not investigated in this study due to deficient recorded data. The timing of the follow-up echocardiography was not the same among all patients, the onset of CTRCD could not be estimated accurately in the present study. No long-term follow-up was assessed including the prescription of heart failure medications after the diagnosis of CTRCD and further assessment of LV function recovery. We hope to reduce the effect of this limitation by sharing with other cardio-oncology centers in the region to conduct similar studies in the future including long-term follow-up data.

Conclusion

It is well-recognized that cancer therapy-related cardiac dysfunction represents an emerging problem for cancer survivors. Our study demonstrated that lymphoma patients showed more subclinical LV dysfunction and poor in-hospital outcomes compared to patients with cancer breast. DM, low body mass index (BMI), and the use of trastuzumab were independent predictors of cardiac dysfunction among our patients. Therefore, the development of CTRCD should be carefully monitored in patients with breast cancer and lymphoma who are receiving trastuzumab therapy, have DM, and have poor nutritional status. Communication between different healthcare professionals is critical to optimize the care of patients with cancer. Further larger prospective multicenter studies that include longer follow-ups even investigating the reversibility of CTRCD are needed.

Source of funding

None.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Hou Y, Zhou Y, Hussain M, et al. Cardiac risk stratification in cancer patients: a longitudinal patient–patient network analysis. *PLoS Med.* 2021;18(8), e1003736.
2. Tan TC, Scherrer-Crosbie M. Cardiac complications of chemotherapy: role of imaging. *Curr Treat options Cardiovasc Med.* 2014;16(4):1–19.

3. Lyon AR, López-Fernández T, Couch LS, et al. 2022 ESC guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS) Developed by the task force on cardio-oncology of the European Society of Cardiology (ESC). *Eur Heart J Cardiovasc Imaging*. 2022;23(10):e333–e465.
4. Van Diest PJ, van der Wall E, Baak JP. Prognostic value of proliferation in invasive breast cancer: a review. *J Clin Pathol*. 2004;57(7):675–681.
5. Sun YS, Zhao Z, Yang ZN, et al. Risk factors and preventions of breast cancer. *Int J Biol Sci*. 2017;13(11):1387.
6. World Health Organization. (2020). WHO report on cancer: setting priorities, investing wisely, and providing care for all.
7. - 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(3):209–249.
8. Yoon HJ, Kim KH, Kim JY, et al. Chemotherapy-induced left ventricular dysfunction in patients with breast cancer. *J Breast Cancer*. 2016;19(4):402–409.
9. Giza DE, Iliescu G, Hassan S, Marmagkiolis K, Iliescu C. Cancer as a risk factor for cardiovascular disease. *Curr Oncol Rep*. 2017;19(6):1–8. https://doi.org/10.1007/s11912-017-0601-x.
10. Nicol M, Baudet M, Cohen-Solal A. Subclinical left ventricular dysfunction during chemotherapy. *Card Fail Rev*. 2019;5(1):31–36.
11. Caballero L, Kou S, Dulgheru R, et al. Echocardiographic reference ranges for normal cardiac Doppler data: results from the NORRE Study. *Eur Heart J Cardiovasc Imaging*. 2015;16(9):1031–1041.
12. Marwick TH, Leano RL, Brown J, et al. Myocardial strain measurement with 2-dimensional speckle-tracking echocardiography: definition of the normal range. *JACC Cardiovasc Imaging*. 2009;2(1):80–84.
13. Gulati M, Mulvagh SL. The connection between the breast and heart in a woman: breast cancer and cardiovascular disease. *Clin Cardiol*. 2018;41(2):253–257.
14. Lim A, Jang H, Jeon M, Fadol AP, Kim S. Cancer treatment-related cardiac dysfunction in breast cancer survivors: a retrospective descriptive study using electronic health records from a Korean tertiary hospital. *Eur J Oncol Nurs*. 2022;59, 102163.
15. Bhaskaran K, Douglas I, Forbes H, dos-Santos-Silva I, Leon DA, Smeeth L. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5·24 million UK adults. *Lancet N Am Ed*. 2014;384(9945):755–765.
16. Chang HY, Lee CH, Su PL, et al. Subtle cardiac dysfunction in lymphoma patients receiving low to moderate dose chemotherapy. *Sci Rep*. 2021;11(1):1–9.
17. Lee WH, Liu YW, Yang LT, Tsai WC. Prognostic value of longitudinal strain of subepicardial myocardium in patients with hypertension. *J Hypertens*. 2016;34(6):1195–1200.
18. Arciniegas Calle MC, Sandhu NP, Xia H, et al. Two-dimensional speckle tracking echocardiography predicts early subclinical cardiotoxicity associated with anthracycline-trastuzumab chemotherapy in patients with breast cancer. *BMC Cancer*. 2018;18(1):1–8.
19. Ponikowski P, Voors AA, Anker SD, ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic Heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;37(27):2129–2200.
20. Esteban-Fernández A, Carvajal Estupinan JF, Gavira-Gómez JJ, et al. Clinical profile and prognosis of a real-world cohort of patients with moderate or severe cancer therapy-induced cardiac dysfunction. *Front Cardiovasc Med*. 2021;8, 721080.
21. Qu S, Zhu B. The relationship between diabetes mellitus and cancers and its underlying mechanisms. *Front Endocrinol*. 2022;75.
22. Guan J, Bao W, Xu Y, et al. Assessment of myocardial work in cancer therapy-related cardiac dysfunction and analysis of CTRCD prediction by echocardiography. *Front Pharmacol*. 2021;12.