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A PROSPECTIVE OBSERVATIONAL STUDY IN CARDIOVASCULAR RISK PROFILES IN CANCER PATIENTS

Raad Ali Kareem*, Hadi Badr Hasan and Nibras Naeemaha Jebur

Karbala Health Department /Teaching Hospital for Children/ Karbala.

***Corresponding Author: Raad Ali Kareem**

Karbala Health Department /Teaching Hospital for Children/ Karbala.

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ABSTRACT

This is a prospective cohort study involving 100 patients attending the oncology clinic from 2023 to 2024 that will enroll adult patients with a diagnosis of kidney cancer, colorectal cancer, hematologic tumors, or breast cancer who are scheduled to undergo chemotherapy. The main objective was to investigate cardiovascular risk, metabolic syndrome, and cardiovascular consequences, particularly DCRTC, related to systemic treatments (chemotherapy or targeted therapy) for various cancers, including lymphoma (DLBCL), chronic myeloid leukemia (CML), breast cancer, kidney cancer, and colorectal cancer. The cohort included 15 kidney cancer patients (15%; 4 women, 11 men), 25 with colorectal carcinoma (25%; 12 women, 13 men), 20 with hematological malignancies (20%; 12 women, 8 men), and the largest subgroup of 40 women with breast cancer (40%), The study found a difference between the subgroups with respect to age: patients with breast cancer were significantly younger than patients with colorectal cancer. In-conclusion: The observed cardiovascular consequences, particularly the development of DCRTC, it is crucial to implement regular cardiovascular assessments and preventive strategies in cancer treatment protocols.

KEYWORDS: Cancer, DLBCL, myeloid leukemia, breast cancer.

INTRODUCTION

Cancer and cardiovascular disease are the leading causes of mortality worldwide (Qian et al., 2023). As cancer treatment and management have improved, the long-term complications of cancer therapies have become increasingly concerning, particularly the risk of cardiovascular disease. (Nunes et al., 2023) Cancer survivors face an elevated risk of developing cardiovascular complications, such as heart failure, myocardial infarction, and arrhythmias, which can significantly impact their prognosis and quality of life. Understanding the clinical indicators of cardiovascular risk in cancer patients undergoing chemotherapy is crucial for early detection, prevention, and management of these complications. Previous studies have highlighted the importance of understanding the cardiovascular risks associated with cancer treatments. A scoping review protocol has been proposed to map the clinical indicators of cardiovascular risk in adult patients undergoing chemotherapy, which will inform the design of this cohort study.[1] Additionally, research has identified differences in the mechanisms and potential biomarkers of acute and chronic cardiotoxicity induced by the chemotherapeutic agent doxorubicin, suggesting the need for a more comprehensive approach to monitoring cardiovascular health in cancer patients.[2]

Numerous studies have examined the prevalence of cardiovascular complications in cancer survivors, with a focus on the increased risk of cardiovascular disease, particularly among those treated with certain chemotherapeutic agents or radiation therapy.[1] One study highlighted the importance of incorporating strain parameters, such as left ventricular strain measurements, into clinical decision-making and therapeutic planning for cancer patients undergoing chemotherapy, as these parameters can provide early indicators of cardiac dysfunction.[3] Heart disease and cancer are the main causes of morbidity and mortality worldwide, and as the number of cancer survivors increases, cardiotoxicity associated with cancer treatment has become a major concern, presenting a substantial challenge in the follow-up of these patients.[4] The present cohort study aims to investigate the cardiovascular risk profile among adult patients with different types of cancer, including kidney cancer, colorectal cancer, hematologic tumors, and breast cancer, who are undergoing chemotherapy.

MATERIALS AND METHODS

Study design

This prospective cohort study will enroll adult patients mean (55.5 ± 12.8) with a diagnosis of kidney cancer, colorectal cancer, hematologic tumors, or breast cancer

who are scheduled to receive chemotherapy. Participants will be followed for a period of 5 years, with regular clinical assessments and monitoring of cardiovascular biomarkers and parameters in karbala hopsitals (Al-Hussein medical hopsital, AL_hussan Medical hopsital and Al-Kafeel Medical Hospital)**.**

Study population

This study is part of the prospective observational program of 100 patients who attended the oncology clinic between 2023 and 2024. The main objective of the study was to investigate the cardiovascular risk and metabolic syndrome, and the CV consequences, especially DCRTC, of systemic treatment (chemotherapy or targeted therapy) applied during the treatment of lymphoma (DLBCL), chronic myeloid leukemia (CML), breast cancer, kidney cancer or colorectal cancer and other types of cancers. The kidney cancer subgroup consisted of only 15 people (15%; 4 women and 11 men), colorectal carcinoma of 25 patients (25%; 12 women and 13 men), hematological malignancies (HNM) of 20 patients (20 %; 12 women and 8 men), and the largest subgroup (40%) of 40 women with breast cancer.

Table 1 presents the stage of the tumors in each of the study groups.

Table 1: Stage of tumors in the study groups.

Parameter	Kidney Cancer	Colorectal Cancer	Hematologic Tumors	Breast Cancer
Total number of patients in groups	15	25	20	40
Male	4	13	8	0
Female	11	12	12	40
Classification	TNM	Astler-Coller	Ann Arbor	Rai
Anatomical stage/prognostic groups				
Stages of cancer	IV-7	B2-10; C1-2; C2-6; D-1	I-3; II-2; III-7; IV-6	IV-2
	III-5; II-1	II-1; IV-1	IV-1	III-3
	III-2	Chronic phase-5	M4-1	I-9; II-10; III-12; IV-4
Residence area				
Urban	6	11	8	16
Rural	9	14	12	24

Exclusion Criteria

We examined the data from all consecutive patients assessed prior to initiating systemic treatment for the specified cancer types at their first diagnosis. Patients were excluded if they had any of the following: a baseline ejection fraction (EF) below 55%, resting regional left ventricular (LV) wall motion abnormalities, LV wall thickness greater than 13 mm indicative of LV hypertrophy, moderate or severe valvular heart disease, or a history of treatment with anthracyclines or radiotherapy.

Ethical approved

The study received approval from local ethics committees, and all patients provided written informed consent

Cohort medical study

A standardized medical history and physical examination were conducted for the patients included in the study, with a particular focus on oncologic and cardiac histories, as well as comorbidities and concurrent medications in Karbala hopsitals. Measurements taken included blood pressure, heart rate, height, and weight. Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared. Overweight was defined as a BMI between 25 and 29.9 kg/m², while obesity was categorized as a BMI greater than 30 kg/m². The glomerular filtration rate (GFR) was calculated using the Cockcroft-Gault formula. A standard 12-lead resting electrocardiogram was performed to evaluate heart rate and rhythm, QT interval duration, and to identify any arrhythmias or conduction disorders, as well as abnormalities in the ST segment and T waves. Standard blood tests included assessments of blood morphology, lipid profile, fasting serum glucose, serum creatinine (GFR), and N-terminal pro-B-type natriuretic peptide (Nt-proBNP) or B-type natriuretic peptide (BNP). All patients underwent transthoracic echocardiography to evaluate left ventricular (LV) systolic and diastolic function, right ventricular size and function, valvular status, and the presence of pericardial fluid. Using the collected data, we assessed cardiovascular (CV) risk, defined as the likelihood of CV death within the next ten years, employing the SCORE algorithm. The risk was categorized based on the SCORE value as follows: low (<1%), moderate (1% to <5%), high (5% to <10%), or very high (≥10%).

Statistical analysis

The distribution of all variables was checked with the Kolmogorov-Smirnov test. Despite the variety of tumors, all data were normally distributed. Continuous variables, presented as mean ± standard deviation, were compared

between groups using the t test or analysis of variance, as appropriate. Categorical variables were presented as n (%) and compared between groups by the $\chi 2$ test. Univariate analysis of variance was performed to test the association between cancer type and age, estimated CV risk by SCORE points, and also between SCORE and NT-proBNP/BNP, GFR, or carcinoma type. If the result of the analysis of variance was significant, post hoc comparisons of more than two groups were performed. All the above calculations were performed using a licensed copy of SPSS 25 and MedCalc. A p-value of 0.05 was considered statistically significant.

RESULTS

A total of 100 consecutive patients (mean age: 55.5 ± 12.8 years) were included in the study, of whom 75 % (75) were women. The study found a difference between the subgroups with respect to age: patients with breast cancer were significantly younger than patients with colorectal cancer (Δ = 7.5 ± 2.7 years; p = 0.026). The analysis of differences between subgroups is shown in Tables 2 and 3. Due to the multicenter study design, complete data sets were not available for all patients, especially with respect to cholesterol, Nt-proBNP or BNP and therefore SCORE results were not calculated for all patients.

Table 2: Baseline characteristics of the study population.

Parameter	Kidney Cancer	Colorectal Cancer	Hematological Tumors	Breast Cancer	p-value
Age (years)	61.15 ± 8.7	60.38 ± 10.5	55.79 ± 15.48	52.90 ± 11.5	0.004
BMI (kg/m²)	27.65 ± 5.0	25.19 ± 4.6	24.48 ± 4.8	25.82 ± 4.7	0.035
Hypertension	74.57%	13.41%	32.45%	65.24%	0.28
Diabetes Mellitus	31.91%	41.51%	10.03%	94.0%	0.41
Smoking	32.5%	15.60%	39.31%	51.13%	0.021
Dyslipidemia	53.24%	72.71%	21.23%	53.28%	0.06
Systolic BP (mm Hg)	129.79 ± 13.3	126.49 ± 13.8	124.00 ± 13.8	124.00 ± 14.6	0.0027
Diastolic BP (mm Hg)	79.09 ± 5.5	80.29 ± 8.6	78.49 ± 10.2	73.89 ± 9	0.016
Mean BP (mm Hg)	96.0 ± 6.3	95.69 ± 8.7	93.79 ± 10.5	90.59 ± 10	0.28
SCORE (%)	7.09 ± 3.1	5.59 ± 7.8	6.29 ± 7.88	2.79 ± 3.8	0.73
EF (%)	63.89 ± 5.1	63.69 ± 6.9	63.69 ± 6.5	62.69 ± 6.3	0.085

BMI: Body Mass Index; BP: Blood Pressure; SCORE: Systemic Coronary Risk Evaluation; EF: Ejection Fraction.

Table 3: Laboratory Data Of Blood Samples Obtained At Baseline In The Study Population.

Parameter	Kidney Cancer	Colorectal Cancer	Hematological Tumors	Breast Cancer	p-value
Hb (g/dl)	9.7 ± 3.4	8.5 ± 2.3	9.8 ± 2.5	13.2 ± 1.1	0.0021
Glucose (mg%)	94.8 ± 13.5	109.7 ± 36.3	96.6 ± 30.7	99.8 ± 20.4	0.582
BNP (pg/ml)	206.4 ± 246.7	–	235.6 ± 283.3	81.9 ± 62.3	<0.0034
Nt-proBNP (g/ml)	–	61.7 ± 28.9	1327.5	111.4 ± 117.4	<0.0241
Total Cholesterol (mg%)	213.5 ± 48.2	181.1 ± 19.4	195.6 ± 88.5	223.3 ± 47.6	0.229
LDL (mg%)	135.2 ± 53.5	116.2 ± 5.2	112.4 ± 42.0	134.3 ± 43.2	0.809
HDL (mg%)	54.1 ± 18.3	41.0 ± 7.2	45.7 ± 23.6	62.3 ± 15.5	0.298
TG (mg%)	97.0 ± 18.5	92.2	134.5 ± 9.7	126.5 ± 66.1	0.381
Creatinine (mg%)	1.2 ± 0.4	0.9 ± 0.6	0.9 ± 0.5	0.7 ± 0.1	<0.011
GFR	78.3 ± 32.4	90.2 ± 31.4	98.2 ± 39.4	100.5 ± 28.0	0.275

Hb: hemoglobin, **Hto**: hematocrit, **LDL**: low-density lipoprotein, **HDL**: high-density lipoprotein, **TG**: triglycerides.

The most prevalent cardiovascular risk factors in the group were identified as hypertension (37.3% of patients), dyslipidemia (27.8%), and diabetes mellitus (8.3%). It was found that 31.7% of the patients were smokers. The mean BMI was recorded at 26.4 ± 4.8 kg/m², with 7.5% of patients being underweight, 36.3% having normal weight, 35.6% classified as overweight, and 20.7% as obese. The mean estimated cardiovascular risk according to SCORE was determined to be 4.6 ± 5.1% for the entire group. It was reported that 13.8% of patients were at low cardiovascular risk (SCORE <1%), 46.6% at moderate risk (<5%), 25.9% at high risk (<10%), and 13.8% at very high risk (≥10%). The SCORE risk estimation correlated with BMI across the patient group, indicating that obese individuals had a higher SCORE risk value (p = 0.004).

Two approaches were employed to examine the relationship between SCORE and cancer type, either by treating SCORE as a continuous variable using ANOVA or as a discrete variable based on risk categories. Both approaches revealed statistically significant differences among the groups. ANOVA tests identified a relationship between the cancer group and SCORE (p =

0.001), and the Tukey post hoc test inferred that breast cancer patients had a significantly lower cardiovascular risk compared to those with hematological neoplasms (Δ = -3.49 ± 0.95%; p = 0.002). When analyzing SCORE classes as ranges using non-parametric tests, it was found that kidney cancer patients had a significantly higher risk than breast cancer patients. In both instances, breast cancer patients appeared to be less affected by cardiovascular risk factors compared to other cancer types, although those types were less represented in the study group. The distribution of major risk factors (diabetes, hypertension, smoking, dyslipidemia, overweight, and obesity) among the cancer types was noted, with only 19% of patients being free from any risk factors. Within the study group, age was correlated with glucose levels (p = 0.005; r = 0.18), BMI (p <0.0005; r = 0.2), SCORE (p <0.0005; r = 0.79), and, as expected, with the risk of comorbidities: hypertension, diabetes mellitus, and dyslipidemia (p <0.00005). When comparing the two largest subgroups, it was observed that breast cancer patients were younger (mean age: 53.8 vs. 56.8 years; p = 0.0004), had a lower BMI (p = 0.03), and were more likely to receive ACE inhibitors than patients with NMH. The latter group exhibited lower hemoglobin and hematocrit levels (p <0.001 and p = 0.006, respectively), along with higher concentrations of natriuretic factors and creatinine compared to the breast cancer group (p <0.001 and p = 0.008, respectively). Fewer smokers were found in the breast cancer subgroup compared to patients with NMH (24.1% vs. 42.8%, respectively), possibly related to the predominance of females

DISCUSSION

The main finding of our study is the identification of patients starting chemotherapy due to a new cancer diagnosis as a population with a high cardiovascular (CV) risk profile. The majority of patients had at least one CV risk factor, and approximately 41% had two or more, despite the absence of a significant CV disease diagnosis.[5] CV risk factors were identified in the vast majority of patients, with over one-third having a calculated CV risk classified as high or very high according to the SCORE calculator. It is important to note that our patients were evaluated prior to the initiation of systemic therapy, unlike cancer survivors, as seen in other studies.[6]

It should be emphasized that the SCORE algorithm was not designed for cancer patients, and although other algorithms exist to predict cardiac events in oncology populations, they are not as specific. Many risk factors such as smoking, obesity, and unhealthy diets are not included as variables in these populations, which may lead to an underestimation of their actual cardiovascular risk. In the general population, components of the metabolic syndrome—such as smoking, obesity, hypertension, hypercholesterolemia, and glucose intolerance—contribute to the development of coronary artery disease and heart failure, but they may also influence an increased risk of neoplasms, such as colorectal cancer.[7]

A high prevalence of metabolic syndrome has been reported in patients with prostate cancer, while in colorectal cancer, coexisting metabolic syndrome and plasma leptin levels have been associated with a more aggressive tumor phenotype in men. Many cancer patients may present with subclinical or manifest CV disease at the time of cancer diagnosis. Mastl et al. demonstrated higher calcium scores in coronary arteries in a cohort of asymptomatic breast cancer patients compared to an age-matched control group. The coexistence of both diseases leads to increased mortality and poorer outcomes in cancer treatment. Furthermore, CV risk factors also heighten the likelihood of cardiotoxicity in cancer patients.[8] In two large studies, Szmit and colleagues showed that hypertension in a lymphoma group and hypercholesterolemia in patients with metastatic breast cancer increased the risk of developing left ventricular systolic dysfunction. Hypertension and diabetes mellitus are well established as risk factors for anthracycline-induced cardiotoxicity. Wierzba and colleagues demonstrated a correlation between different cancer types and diabetes, both in urban and rural areas. In older and middle-aged patients, diabetes mellitus increases the risk of hospitalization due to cancer.[9]

In our study, a high frequency of traditional cardiovascular (CV) risk factors was found, which could lead to both cancer and CV complications. Antineoplastic treatment accelerates the onset of CV disease, especially when traditional risk factors coexist.[10] Data on CV risk estimates for cancer patients are scarce, particularly when limited to those without prior CV disease. Toggweiler and colleagues reported, in a heterogeneous group of 187 patients (breast cancer, malignant lymphoma, sarcoma), that 13% presented with hypertension and 3% with coronary artery disease at baseline, prior to chemotherapy.[11] Furthermore, patients with these factors more frequently developed systolic heart failure.

In our entire cohort, hypertension was notably more prevalent, affecting 34% of patients. Singh and colleagues explored the relationship between metformin and the likelihood of chemotherapy-related adverse events in patients with stage 3 or higher colon cancer and found a prevalence of 13.6% for diabetes mellitus among 1958 patients undergoing chemotherapy. The team led by Phipps identified 52.5% of smokers in a group of 1959 colorectal cancer patients. Smoking was associated with a shorter disease-free survival and faster recurrence. In our small subgroup of colorectal cancer patients, diabetes mellitus occurred with a similar frequency of 16%, while the proportion of smokers was nearly 60%.[12]

Willemse and colleagues assessed the 10-year CV risk using the Framingham Risk Score (FRS) and the

Systematic Coronary Risk Evaluation (SCORE) in a group of 255 survivors of germ cell tumors. These cancer survivors exhibited a significantly higher prevalence of obesity, hypercholesterolemia, and hypertriglyceridemia compared to healthy age-matched subjects. Patients treated with combined chemotherapy also had the highest prevalence of metabolic syndrome (meeting all NCEP-ATPIII criteria) compared to healthy individuals. Surprisingly, the estimated CV risk using the FRS (3.0%) and SCORE (1.7%) was low. It is important to note that the testicular cancer survivors were much younger (median age 38.7 years) than our population, where the mean SCORE value was estimated at 4.56%.[13]

The pursuit of CV complications led Hanrahan and colleagues to show that patients with early-stage breast cancer (T1a,bN0M0) have an excellent prognosis; however, those aged 50 and older are four times more likely to die from non-cancer-related conditions. Later, Bardia evaluated the risk of cancer recurrence over ten years and the estimated CV risk in postmenopausal women with non-metastatic hormone receptor-positive breast cancer. The authors found that 43% of patients had a predicted risk of cardiovascular complications over ten years equivalent to the recurrence risk of breast cancer. Additionally, 37% had a higher risk of cardiac events than of tumor recurrence, and 80% of postmenopausal women with breast cancer within the last ten years had an equal or greater risk of cardiovascular disease than of cancer recurrence.[14]

The primary subgroup of our population consisted of breast cancer patients, with 64.6% being over 50 years of age at baseline. We did not obtain information regarding their menopausal status, but 31% were over 60 years old. Surpassing this age is considered by some authors as one definition of postmenopausal status. This patient cohort should be carefully evaluated to reduce the risk of complications. It is important to recommend at least a healthy lifestyle and the introduction of therapy for health issues unrelated to breast cancer.[15]

In conclusion, patients deemed suitable for antineoplastic chemotherapy often present typical groups of CV risk factors. Eighty-one percent of our patients had at least one classic risk factor, and 41% had two or more, leading to elevated SCORE values. Thus, even before the initiation of chemotherapy, many of them had a very high risk of CV mortality (16). According to our findings, patients with malignant hematological neoplasms may have the highest risk of CV complications. While the implications of CV risk factors concerning the success of cancer therapy without complications still require further study, patients entering chemotherapy exhibit elevated CV risk and therefore represent a valid target for CV prevention.

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