Cardiovascular Complications of Anticancer Therapy in Pashtun Ethnicity

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Abstract

Cancer treatment has evolved significantly over the years, leading to improved survival rates for many cancer patients. However, this progress has brought about a new concern - the cardiovascular complications associated with anticancer therapy. This project delves into the intricate relationship between cancer treatments and adverse cardiovascular effects, shedding light on the complexity of this emerging issue. The primary focus of this study is on the two major pillars of cancer treatment: chemotherapy-induced cardiotoxicity and radiation-related heart issues. Chemotherapy agents, such as anthracyclines and tyrosine kinase inhibitors, have shown a propensity to cause damage to the myocardium, leading to heart failure and reduced cardiac function. Similarly, radiation therapy, while crucial in eradicating cancerous cells, can inadvertently affect the heart, resulting in conditions like radiation-induced coronary artery disease and pericardial disease.

Our study identified effective chemotherapeutic drugs that can treat cancer cells, meanwhile can also cause cardiovascular complications. The complications can be of any type such as; angina, cardiomyopathy, heart ischemia, hypotension, bradycardia, tachyarrhythmia, myocarditis, cardiotoxicity, cardial blood vessel damage, thromboembolism, hypertension, atrial fibrillation, decreased left ventricular ejection fraction, ventricular fibrillation, fast heartbeat, shortness of breath, acute coronary syndrome and myocarditis. It was noted that majorly all the drugs prescribed to individual linked directly or indirectly with the complications related to heart but there were 28.5% complication observed. About 13.5% individual had SPO_2 less than 89% .The 36.5% individual had tachycardia while 1% had bradycardia. 37% individual were obese and 13% had diagnosed DM. 12.5% had sedentary lifestyle. All these parameter had correlation with the cardiac complications. First of all cardiosafe chemotherapeutic drugs should be prescribed and there should be keen observation while finding surface area because small variation in body surface area will directly alter the recommended dose which immediately cause cardiac complications, so complete concentration is necessary for estimating dosage.. It is highly recommended that minimum effective dose should be prescribe while treating who had diagnosed cancer in both chemotherapy and radiotherapy. In conclusion, the growing concern of cardiovascular complications associated with anticancer therapy necessitates proper review and monitoring using the integrated multidisciplinary patient care approaches.

INTRODUCTION

Cancer is a significant global public health issue, causing over 10 million fatalities, it is expected to exceed cardiovascular disease as the major cause of death by 2025–2030, making it a major worldwide public health concern[1].The Chemotherapeutic drugs and radiation therapy used to treat cancer can both induce Cardiovascular Complications(CCs)[2]among which; cardiac toxicity is a wide phrase that refers to the most clinically important side effects of cancer treatment and refers to all cardiac adverse effects caused by oncological treatment or specific cardiovascular disorders, such as hypertension or hypotension, left ventricular systolic dysfunction, myocardial infarction, rhythm and conduction disturbances, myocarditis and pericarditis [3],while radiation therapy cause coronary artery disease (CAD), valvular heart disease (VHD), heart failure (HF), myocarditis, cardiomyopathies, arrhythmias, and acute and chronic pericardial syndromes [2]**.**Traditionally, cardiotoxicity was classified into two categories: type I, which was produced by AC and was thought to be irreversible, and type II, which was thought to be reversible and was caused by other antineoplastics like trastuzumab. This classification has been abandoned nowadays since evidence suggests that, in any event, cardiotoxicity may be curable with early diagnosis and treatment [4], [5], [6], [7], [8]. The undesirable medication effects might occur when contractility, growth factor, mitochondrial toxicity, electrophysiosiology, and cytokine control are disrupted [9].

2 PATHOPHYSIOLOGY OF CARDIOVASCULAR COMPLICATIONS

The most frequent serious complication of anthracycline anticancer medications is cardiotoxicity, which can cause irreversibility, dose accumulation, and progression [11]**.**The specific mechanism of anthracycline-induced cardiotoxicity is unknown,but it disrupts the mitochondrial electron transport chainand the frequency of cardiomyopathy and heart failure in people treated with anthracyclines varies [12],[13].The onset of anthracycline-associated cardiotoxicity can be vary from immediately upto 1 year [14]. Comparing monotherapy with anthracycline to combination treatment with trastuzumab, the frequency of cardiac dysfunction was reduced .The occurrence of cardiotoxicity events was irrelevant of whether trastuzumab was used as a first line treatment or for metastatic breast cancer [15],[16]**.**

Many non-anthracycline chemotherapy drugs are expected to generate free radicals and cause inflammatory alterations, but at considerably lower rates than anthracyclines**..**According to the "American Society of Clinical Oncology" cardiac problems occur in 10-30% of radiation treatment (RT) patients. Radiation initially reacts with water molecules in the cell, producing ROS and damaging myocyte mitochondria and DNA, resulting in cardiac fibrosis. Cardiotoxicity is determined by the total radiation dose as well as the volume of the heart exposed [12]**.**In addition to causing capillary loss, inflammation, fibrosis, and microvascular endothelial damage, radiation therapy (RT) can have late-life side effects such as coronary heart disease (HF), valvular disease, constrictive pericarditis, conduction dysfunction, and stroke [17], [18]**.**Despite widespread potential to revolutionize cancer treatment, targeted cancer medicines are also associated with CCs such as development of LV dysfunction, HF, arrhythmias, QT interval prolongation, and arterial thrombosis [12].

3 LIST OF CARDIOTOXIC DRUGS, CLASS OF DRUG MECHANISM AND NATURE OF CARDIOVASCULAR COMPLICATIONS

Over the last 20 years, the area of cardiac adverse effects of chemotherapies has increased with the introduction of several regimens combining traditional cytotoxics and targeted treatments [19]**.**The development of cardiotoxicityassociated with antineoplastic is still a barrier to the completion of some chemotherapeutic protocols [20]**.** More recently, symptomatic and asymptomatic categories for Cancer-therapeutics Related Cardiac Dysfunction (CTRCD) were established by the International Cardio-Oncology Society 2021 Consensus [21].The CCs may be divided into three categories: drug-induced modifications to hemodynamics, drug-induced alterations to electrocardiograms, and drug-induced modifications to molecular signaling pathways [22]. The CCs is an important consideration for cancer patients since, while the majority of patients will recover from cancer, they will have increased long-term heart risks [23]**.**

Table 1
Cardiotoxic drugs, Class, Mechanism and nature of Cardiac Complications [24], [25], [26], [27], [28]

S.NO	CARDIOTOXIC DRUGS	Class of Drug	MECHANISM	NATURE OF CARDIOVASCULAR COMPLICATIONS
1	Paclitaxel	Antimicrotubule agent	Serves as a byproduct of the Purkinje system's direct chronotropic action	Bradycardia or Trachyarrhythmias, Arterio-ventricular and branch blockages heart ischemia, and hypotension (2.3% to 8%)
2	5- Fluorouracil	Antimetabolite	Inhibition of thymidylate synthase, an enzyme that plays a vital role in DNA synthesis	Arrhythmias, angina,myocardial infraction ,sudden death (4-6%)
3	Cyclophosphamide	Alkylating agent	Suppress the expression of carnitinepalmitoyltransferase-I and heart-type fatty acid-binding proteins in cardiac tissues	Cardiomyopathy, Cardiotoxicity, myocarditis, heart failure (7-28%)
4	Cisplatin	Alkylating agent	Involve in the generation of reactive oxygen species (ROS) and the subsequent damage to cardiac cells	Arrhythmias ,Cardiac dysfunction, Chest pain, dyspnea, and arrhythmias, cardial blood vessel damage, heart failure .
5	Bevacizumab	Antiangiogenic agent	Inhibit the binding of Vascular endothelial growth factor (VEGF)to cell surface receptor	Thromboembolism, Hypertension, Decreased left ventricular ejection fraction
6	Pertuzumab	Monoclonal antibody	Inhibitor of Human epidermal growth factor 2 (HER2)	Left ventricular dysfunction
7	Interferons alpha	Immunomodulator	Activation of genes,influencing cell growth and division	Atrial fibrillation, Ventricular fibrillation, Cardiomyopathy
8	Adriamycin	Anthracycline	Disruption b/w oxidants and antioxidants in heart	Reduce LVEF, fast heartbeat, shortness of breath
9	Imatinib	Tyrosine kinase inhibitor	Target proteins involved in the pathogenesis of specific cancer types	Cardiotoxicity
10	Dasatinib	Tyrosine kinase Inhibitor	Block the action of an abnormal protein that signals the cancer cells to multiply	Cardiotoxicity
11	Nilotinib	Tyrosine kinase inhibitor	Binds and stabilizes the inactive conformation of the kinase domain of ABL protein	Cardiotoxicity(QT prolongation)
12	Ponatinib	Tyrosine kinase inhibitor	Block the action of an abnormal protein that	Vascular occlusion, Myocardial infarction, Cardiomyopathy,

			signals cancer cells	Congestive heart failure
13	Sorafenib	Tyrosine Kinase Inhibitors	Block the action of an abnormal protein that signals cancer cells	Acute coronary myocardial infarction, in about 3% of patients
14	Doxorubicin	Anthracyclines	Increased reactive oxygen species (ROS) production , defects in iron handling and inhibition of topoisomerase 2β (Top2β)	Angina, shortness of breath.
15	Idrarubicine	Anthracyclines	Inducing breaks in DNA strand	Chest pain, shortness of breath, heart palpitation
16	Trastuzumab	Monoclonal antibodies	Inhibit the homodimerization of human epidermal growth factor (HER2)	Left ventricular dysfunction,arrhythmias,hypertension,myopathy
17	Sunitinib	Tyrosine kinase inhibitor	Inhibit the tyrosine kinase activity of vascular endothelial growth factor receptors	Hypertension, angina, left ventricular dysfunction
18	Mitoxantrone	Anthracenediones	Inhibitor of topoisomerase II	Cardiotoxicity is dose-dependent and occurs in 2% of cancer patients with systolic and diastolic dysfunction
19	Rituximab	Monoclonal antibodies	Cell lysis by triggering complement dependent and antibody mediated cytotoxicity	Arrhythmias,Cardiogenic shock, myocardial infarction
20	Daunorubicin	Anthracycline	Damage DNA by intercalating between base pairs	Myopericarditis, tachycardia, premature atrial and ventricular beats
21	Epirubicin	Anthracycline	Form complex with DNA by intercalation of its planar rings between nucleotide base pairs	Chest pain, shortness of breath
22	Carboplatin	Platinium-containing compound	Form reactive platinium complexes that cross-link with DNA	Cardiotoxicity
23	Ipilimiumab	Immune check point	Activating immune system against melanoma by T cells	Pericarditis, atrial fibrillation,heart failure
24	Nivolumab	Immune check point	Binds to protein PD-1on the surface of T cells thus blocking antibody	Myocarditis, cardiogenic shock,atrial fibrillation
25	Avelumab	Immune check point	Binds to protein PD-1on the surface of T cells thus blocking antibody	Cardiogenic shock, atrial fibrillation, myocarditis
26	Durvalumab	Immune check point	Binds to protein PD-1on the surface of T cells thus blocking antibody	Myocarditis, cardiogenic shock, atrial fibrillation
27	Bosutinib	Tyrosine kinase inhibitor	Block the action of abnormal protein that signals cancer cells to multiply	Impaired cardiac blood flow, heart failure

28	Sorafinib	Tyrosine kinase inhibitor	Inhibit tumor cell proliferation and angiogenesis via enzyme inhibition	Hypertension, ischemia, congestive heart failure
29	Pazopanib	Tyrosine kinase inhibitor	Inhibit tumor cell proliferation and angiogenesis via enzyme inhibition	Thrombotic events, hypertension, myocardial ischemia, Reduce LVEF
30	Pertuzumab	Proteasome inhibitor	Inhibit the ligand dependent HER2-HER3 dimerization	Left ventricular systolic dysfunction
31	Carfilzomib	Proteasome inhibitor	Inhibit the subunit of proteasome and immmunoproteasome	Acute coronary syndrome, hypertension, arrhythmias, heart failure
32	Bortezumab	Proteasome inhibitor	Prevent the degradation of various pro-apoptotic factors	Cardiomyopathy
33	Vincristine	Vinca alkaloid	Inhibition of microtubule formation in mitotic spindle	Ischemic heart disease
34	Methotrexate	Antimetabolites	Folate antagonist	Caradiomyopathy
35	Letrozole	Aromatase inhibitor	Blocking estrogen synthesis	Heart palpitation
36	Tamoxifen	Estrogen reception modulator	Bind to estrogen receptors, producing both estrogenic and antiestrogen effects	Ischemic heart disease

1.1 FACTORS RELATED TO CARDIOVASCULAR COMPLICATIONS

The risk of cardiotoxicity depend on the patient's cancer diagnosis, treatment, and risky health behaviors such as tobacco use, alcohol consumption, drug use (e.g., cocaine, diet pills, ephedra, mahuang), poor dietary habits, sedentary lifestyles, and comorbidities such as pre-existing cardiomyopathy and underlying congenital heart disease, hypertension, hyperlipidemia, diabetes, and obesity [12]**.** The SerpinA3, also known as -1-antichymotrypsin, was upregulated in HF patients and stimulated cell proliferation in colon tumors, among the five proteins thought to be implicated in the pathophysiological overlap between HF and cancer.C-reactive protein (CRP), interleukin-1 (IL-1) and interleukin-6 (IL-6) levels were linked to atherosclerosis and associated consequences, including plaque development, progression, and rupture. Increased CRP levels have also been linked to CV disease and cancer mortality**.** Both cancer and CV disease are caused by immune system dysregulation. An insufficient or inadequate immune response is responsible for tumor development and progression in cancer. The immune system's participation in CV disease is equally critical. Among the many pathophysiological processes of HF, the renin-angiotensin-aldosterone system (RAAS) plays a critical role, first as a compensatory mechanism and then as the illness develops, becoming maladaptive, leading to cardiac remodelling and sympathetic activation [29]**.**

1.2 RISK ASSESSMENT CHECKLIST:

In 2022, European guidelines included a baseline cardiovascular toxicity risk assessment checklist. This includes blood pressure, heart rate, height, weight, and BMI. Where accessible, cardiac biomarkers (troponin and natriuretic peptide) should be evaluated in patients at risk of cancer therapy-related cardiac dysfunction, and the results should be interpreted based on the patient's clinical condition, type of cancer treatment, and kidney function. Other cardiovascular supplementary tests to consider in chosen individuals include cardiac magnetic resonance, coronary computed tomography angiography, and cardiopulmonary exercise testing (in selected patients for pre-operative [lung, colon, and rectal cancer] risk stratification [30].

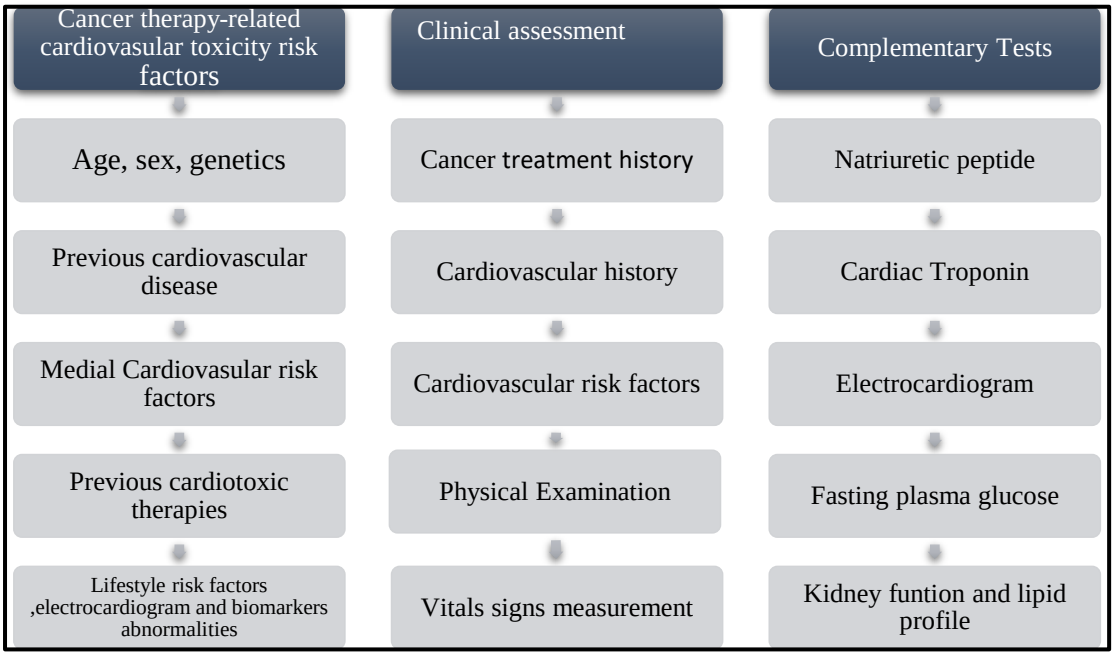

Fig 1 : Risk Assessment Checklist 2022 [30]

1.3 DIAGNOSIS OF CARDIOTOXICITY

Global Longitudinal Strain (GLS) has been investigated for its ability to identify early alterations in LV contractile performance in individuals receiving cardiotoxic chemotherapy. The identified range for cut-off for GLS that might indicate the development of cardiotoxicity. Identifying high-risk patients and diagnosing cardiotoxicity in individual before symptoms of HF appear necessitates a careful evaluation of CV risk factors prior to, during, and after cancer therapy using standard history, physical examination, clinical and laboratory tests for cardiac biomarkers, and imaging methods [31].In cancer patients undergoing cardiotoxic cancer therapy, serum biomarkers are a useful tool for assessing baseline risk and diagnosing cardiovascular disease. Increases in cardiac biomarkers, such as cardiac troponin and natriuretic peptides, can be used to guide the commencement of cardioprotective medications for cancer patients throughout therapy, as well as to monitor response to cardioprotective treatments, and they can also be used to predict prognosis [32].The diagnostic tests such as echocardiography(ECHO), cardiac catheterization, nuclear imaging, computed tomography (CT) and Cardiac Magnetic Resonance (CMR) recommended for diagnosis of Cardiotoxicity [12], [13].

1.4 CARDIOPROTECTIVE TREATMENTAND MANAGEMENT

In 2019, the American Heart Association unveiled the idea of CardioOncologyREhabilitation (CORE), multidisciplinary strategy aims to avoid or lessen cardiovascular events in patients who are at high risk of CVD, including cardiotoxicity from cancer treatments [34]. A multifactorial strategy is needed to prevent cardiotoxicity, which involves primary, secondary, and tertiary prevention. Three stages of pharmacological prophylaxis are possible: prior to cancer therapy, during pathologic cardiac remodeling, and, lastly, after the onset of structural heart disease [35].The several principles, such as prevention, serial monitoring, early diagnosis, and early treatment, are important elements of cardio-oncology to protect patients from unforeseen cardiotoxicity [36]. The Calcium channel blockers can be used to treat chest discomfort in normotensive individuals without cardiomyopathy or heart failure since fluoropyrimidines frequently cause vasospasm [37].Guidelines for adults suggest that individuals with pre-existing systolic dysfunction, including those without symptoms, should be treated with Angiotensin Converting Enzyme inhibitors (ACE-I) or β-blockers [38],[39]. To minimize cardiac damage while maintaining cancer treatment's therapeutic efficacy, independent risk factors for developing cardiotoxicity must be evaluated. By selecting extended infusion application over boluses, therapeutic strategies can be altered. Schemes can last from 6-96 hours, and the risk of cardiotoxicity is 4.13 times higher

with bolus administration than with sustained infusion. Drug administration in long-term regimens, such as weekly treatment regimens, results in decreased cardiotoxicity. Early introduction of cardioprotective medicine is especially crucial because myocardial function recovery appears to be restricted and transitory in individuals with established cardiomyopathy. Subclinical cardiotoxicity frequently precedes overt cardiotoxicity, offering an essential window for the introduction of cardioprotective medicines [1].The exercise has been studied as a non-pharmacological cardioprotective treatment in cancer patients. Several studies have shown that exercise training or physical activity can prevent or reduce heart dysfunction caused by chemotherapy-induced cardiotoxicity. Exercise's cardioprotective benefits may increase chemotherapy completion rates by reducing dose-limiting toxicity [40].

METHODOLOGY

1. STUDY DESIGN AND SAMPLING

A questionnaire based cross sectional survey was to determine the CCs of chemotherapy and radiotherapy in the general population of Afghanistan and Pakistan. Non-probability convenient sampling technique was used to include appropriate respondents for the study.

2. SAMPLING LAYOUT

The survey conducted was in the Anticancer hospital having patient belong to District Kabul of Afghanistan and Khyber Pakhtunkhwaof Pakistan. The study performed by final year student in hospital was based on proximity to the resident of these specialized areas. From each of the following areas, interview based questionnaires were collected.

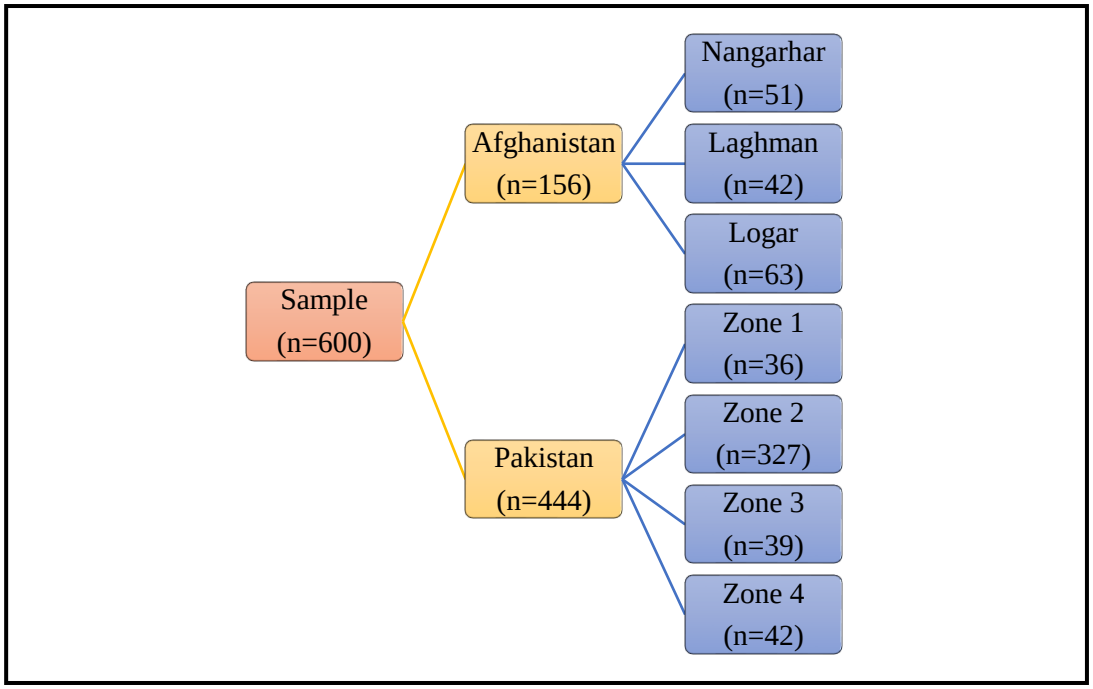

Fig 2 : Sampling Layout

3. INCLUSION AND EXCLUSION CRITERIA

The Individual with age range from 5 to 90 year were included in the study. The individuals unable to comprehend the asked questions and those who refused to participate were excluded from the study.

4. DATA COLLECTION

An interview-based questionnaire was used to collect the data which was chosen by the research students to ensure authentic and accurate questionnaire filling. The questions asked by the interviewers were in the native language of the participants or in a language easier for the interviewee to understand.

5. STUDY TOOL

The study tool developed was based on previously published articles and in consultation with experts. The validation and revision of the questionnaire was done by a focus group, experienced in the related field, 30 participants were selected to conduct a pilot test study. The reviewed questionnaire was used to collect the data for the survey. The individuals from the pilot test study were excluded from the study.

The questionnaire organized in the following 5sections was used to collect the data; 1. Socio-demographic factors, lifestyle, educational and financial status, 2.Patient History and Co-morbidities 3. Family History 4.

Medication prescription trends, adverse reactions and compliance 5. Laboratory workup and adherence to therapy

The first section consist of questions such as; gender, age, weight, height, body mass index(BMI), oxygen saturation(SPO_2), pulse, lifestyle, address, job, marital status. The second section consist of questions such as patient history and any other co-morbidities which may worsen the severity of concurrent diagnosis. The third section consist of questions related to family history which play an important role in genetic overview of individual. The fourth section consist of questions related to the dose, strength, route, frequency and duration of medication, adverse reactions and compliance of individual toward therapy while the fifth section have questions related to laboratory workup and adherence of individual to the medications.

RESULTS&ANALYSIS

1. BASIC CHARACTERISTICS

The frequency, cumulative frequency and percentage of basic characteristics such as gender, marital status, life style, address, education and occupation status regarding the individual involved in study is shown in table 3.1.The incidence of major cardiovascular events, including heart failure (HF), myocardial infarction, stroke, arrhythmias, and valvular disease, is greater in cancer patients than in age- and gender-matched controls [41], [42].The combined effects of the neoplastic therapy directly on the body and the indirect effects of lifestyle modifications, including decreased physical activity and bad eating habits, contribute to the medium-high CV risk among cancer survivors [43], [44], [45].

Table 2

Basic Characteristics

Basic Characteristics		Frequency(n)	Commulative Frequency(n)	Percent (%)	CommulativePercent(%)
Gender	Male	225	225	37.5	37.5
	Female	375	600	62.5	100
Marital Status	Married	519	519	86.5	86.5
	Single	81	600	13.5	100
Life Style	Active	525	525	87.5	87.5
	Sedentary	75	600	12.5	100
Address	Afghanistan	156	156	26.0	26.0
	Bajawar	09	165	1.50	27.5
	Khuram Agency	12	177	2.00	29.5
	Waziristan	06	183	1.00	30.5
	Khyber Agency	09	192	1.50	32.0
	Mardan	48	240	8.00	40.0
	Nowshera	42	282	7.00	47.0
	Peshawar	126	408	21.0	68.0
	Swabi	54	462	9.00	77.0
	Charsadda	57	519	9.50	86.5
	Bunir	09	528	1.50	88.0
	Chitral	06	534	1.00	89.0
	Dir	24	558	4.00	93.0
	Hangu	21	579	3.50	96.5
	Kohat	15	594	2.50	99.0
	Lakkimarwat	06	600	1.00	100
Education	Illiterate	342	342	57.0	57.0
	Primary	117	459	19.5	76.5
	Middle	45	504	7.50	84.0
	Matric	45	549	7.50	91.5
	Intermediate	27	576	4.50	96.0
	Bachelor	15	591	2.50	98.5
	Master	09	600	1.50	100
Occupation	Armed forces	09	09	1.50	1.50
	Bussiness	60	69	10.0	11.5
	Dailywager	30	99	5.00	16.5
	Farmer	66	165	11.0	27.5
	Government officer	06	171	1.00	28.5
	House wife	342	513	57.0	85.5
	Jobless	09	522	1.50	87.0
	Student	51	573	8.50	95.5
	Teacher	27	600	4.50	100

The age versus weight depicted in the figure 3.1. The incidence of cancer increases with age [46].Due to the cardiotoxicity of anticancer therapy, survivors of childhood cancer are more susceptible to cardiovascular

disorders (CVDs) [47], [48]. A recent study indicated that survivors of pediatric cancer had a 2-to 10-fold greater risk of cardiovascular diseases (CVDs) than the general population. This finding may be partially attributed to the high oxidative metabolism and low antioxidant defense level of cardiomyocytes [49].

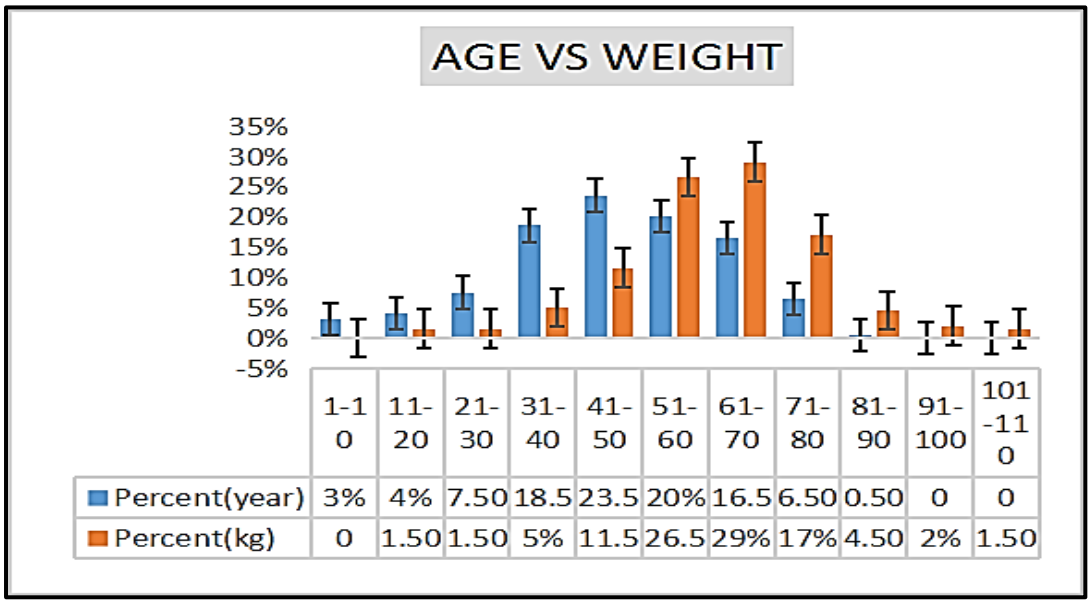

Fig 3 : Age versus Weight

The frequency, cumulative frequency, percent and cumulative percent of characteristics of the individuals such as; height, body mass index, body surface area, oxygen saturation and pulse were noted as shown in table 3.2.

In survivors of pediatric cancer, early management for modifiable risk factors such obesity, inactivity, diabetes, and smoking can lower the incidence of cardiovascular disease. Close monitoring and early identification of cardiotoxicity are crucial, in addition to addressing risk factors [50].

Table 3

Basic Characteristics

Basic Characteristics		**Frequency(n)**	**Commulative Frequency(n)**	**Percent%**	**CommulativePercent(%)**
Height(cm)	<101	06	06	1.00	1.00
	101-120	15	21	2.50	3.50
	121-140	69	90	11.50	15.0
	141-160	405	495	67.50	82.5
	161-180	102	597	17.0	99.5
	>180	03	600	0.50	100
Body Mass Index (BMI)	<18.5	30	30	5.00	5.00
	18.5-24.9	204	234	34.0	39.0

	25.0-29.9	144	378	24.0	63.0
	> 29.9	222	600	37.0	100
Body Surface Area(BSA)	< 0.8	09	09	1.50	1.50
	0.8-1.4	123	132	20.50	22.0
	1.5-2.0	453	585	75.50	97.5
	> 2.0	15	600	2.50	100
$\%SPO_2$	Normal Blood Oxygen Level (95-100%)	378	378	63.0	63.0
	Concerning Blood Oxygen Level (90-94%)	141	519	23.50	86.5
	Low Blood Oxygen Level(0-89%)	81	600	13.50	100
Pulse (HR)	Bradycardia (<60 bpm)	06	06	1.00	1.00
	Normal (60-100 bpm)	375	381	62.50	63.5
	Tachycardia (>100)	219	600	36.50	100

Hypertension was found to be a significant risk factor for the development of heart failure in the group that had undergone anthracycline chemotherapy, as was hypertension in conjunction with concomitant diagnoses of diabetes and dyslipidemia [51]**.** Primary preventive measures to lessen fluoropyrimidinecardiotoxicity are not being investigated. Statins and other medications as needed should be administered to patients with known coronary artery disease, those who have diabetes and are at high risk for developing coronary artery disease, and those who have an elevated 10-year risk because of concomitant conditions or advanced age, in accordance with evidence-based guidelines [52], [53], [54], [55].

The patient and family history depicted in figure 4.

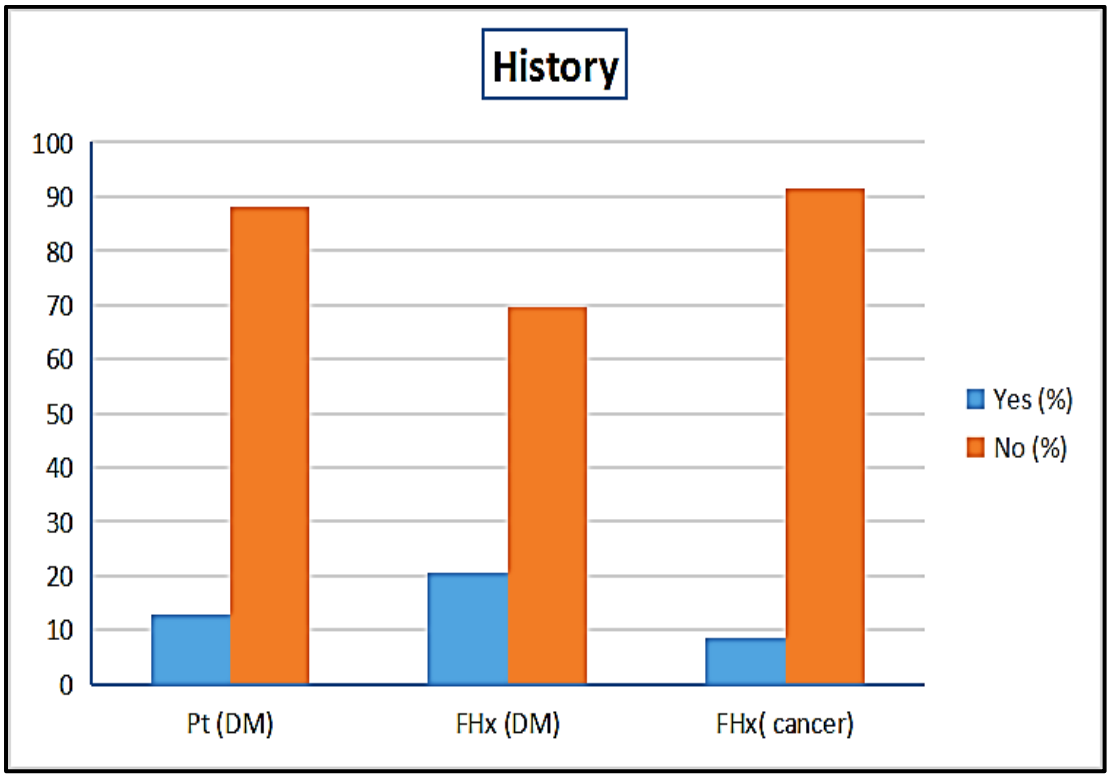

Fig 4 : Patient and Family History

The diagnostic tests which were played an important role in the detection of cancer stage and the organs affected by the chemotherapy and radiotherapy as shown figure 5.

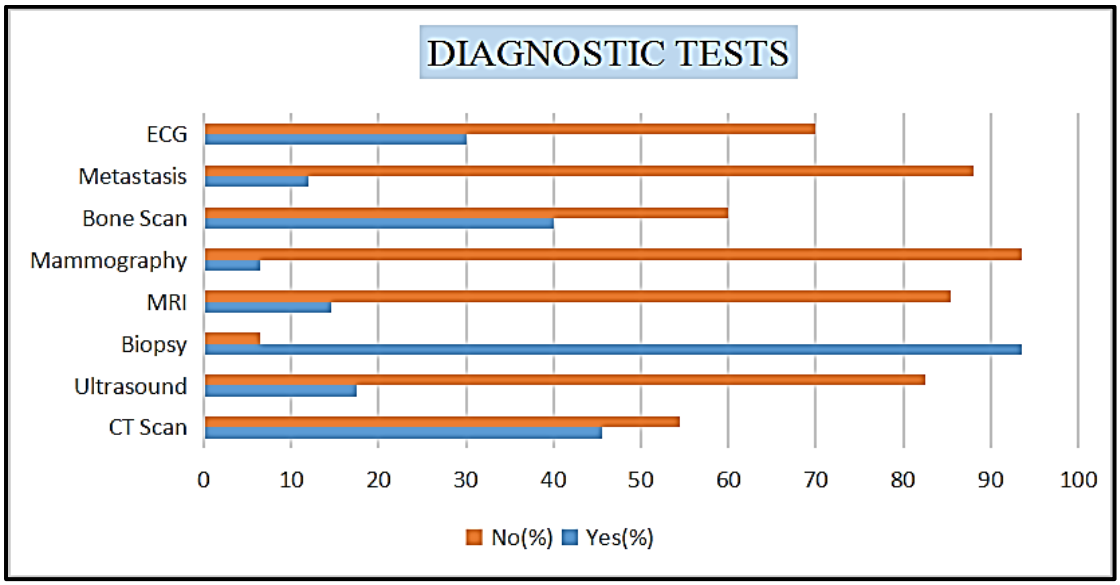

Fig 5 : Diagnostic Tests

The percent of various diagnosis of different individuals noted during the data collection are shown in the fig 3.4. Breast cancer is one of the most common kinds of cancer and comes in a number of forms, including estrogen receptor (ER) positive, progesterone receptor (PR) positive, and triple-negative cancer [56]**.** Cancer therapy improvements have drastically increased patient survival rates. At the same time, the issue of avoiding and controlling treatment-related chronic adverse effects has grown in importance. Cardiovascular problems, independent of cancer type, have been identified as one of the primary causes of mortality among cancer survivors [57] **.**

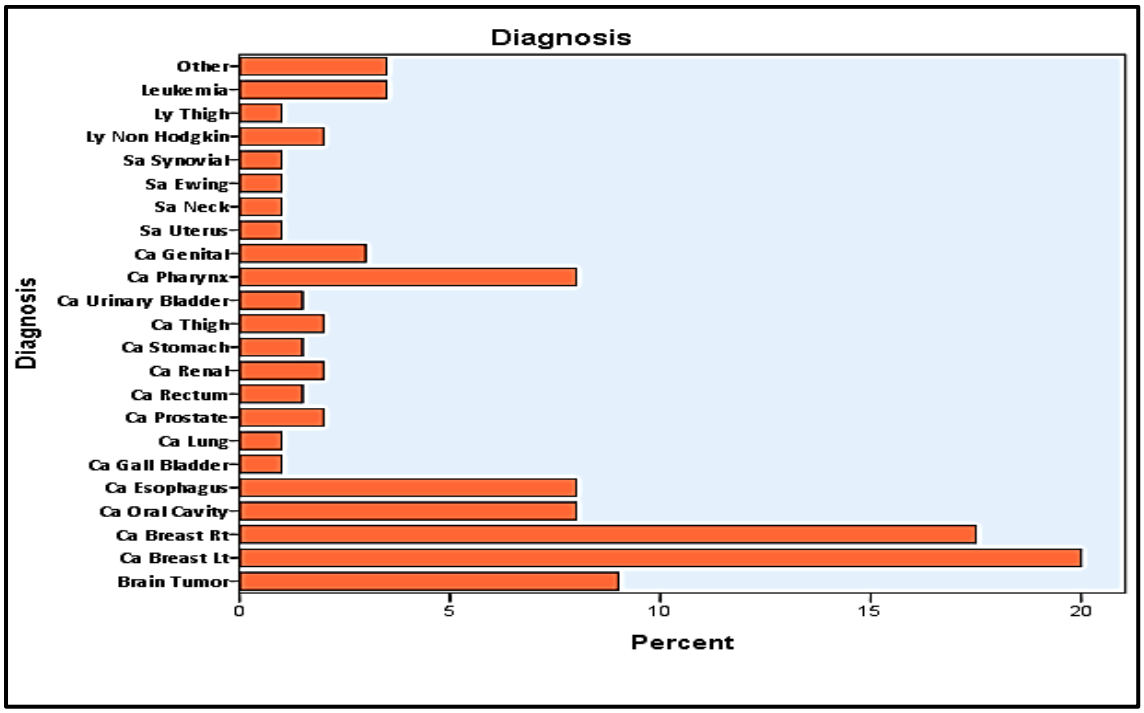

Fig 6 : List of Types of Diagnosis

The cancer tumor have different types such as; carcinoma, sarcoma, lymphoma and leukemia while it is also classified into various stages such as; stage1,stage 2, stage 3,and stage 4. The percent of tumor type and stage were noted as shown in figure 7.

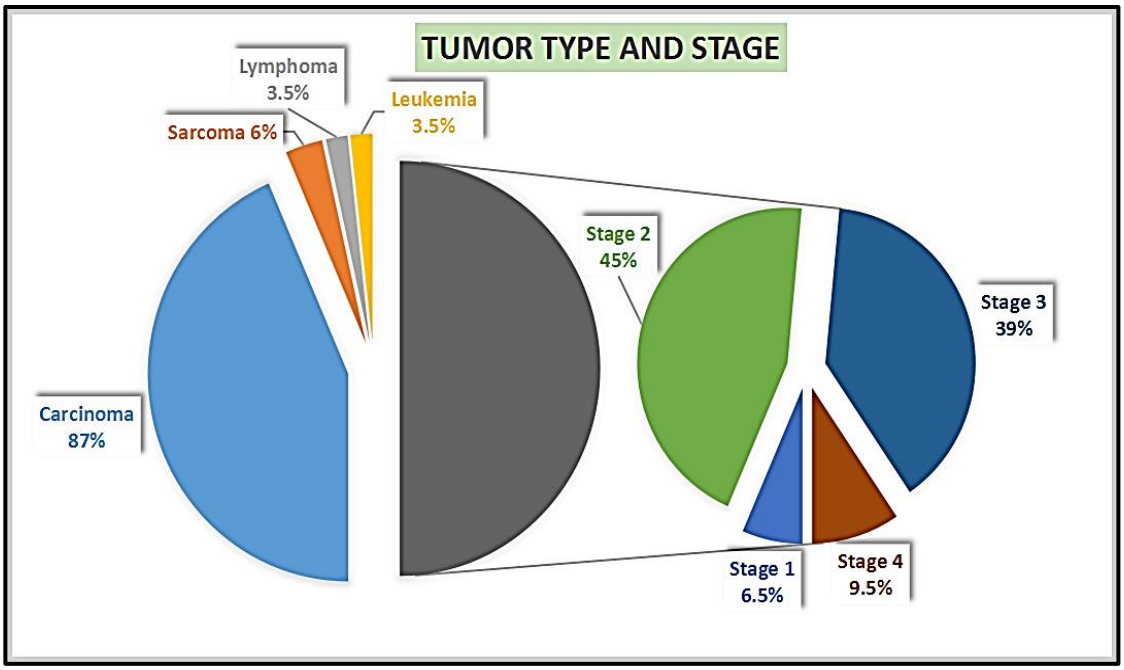

Fig 7 : Tumor types and Stages

The laboratory reports of the individual were collected and analyzed as shown. A high reduction trend was found in platelets counts due to the cytotoxicity nature of chemotherapy as shown in figure 8.

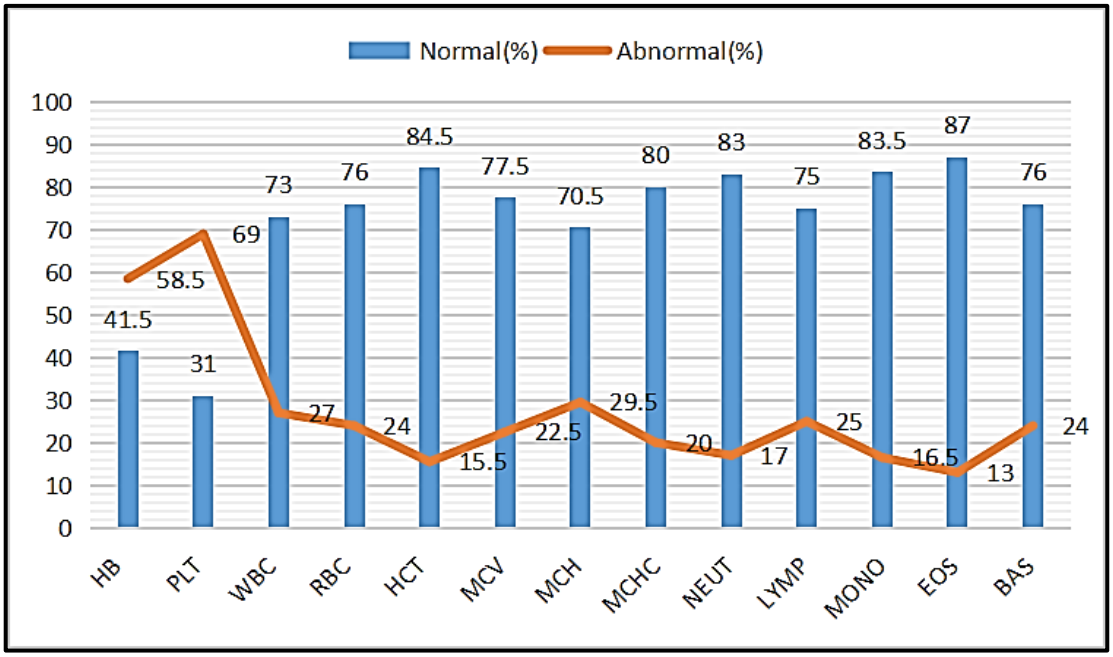

Fig 8 : Laboratory Values

The different stages of cancer were treated with different chemotherapy and radiotherapy in combination or alone. The percent of therapy were noted and as shown 3.7. Radiation cardiotoxicity is diagnosed using a multimodal method that includes clinical suspicion, imaging, and laboratory data. Following up with a cardio-oncology expert enables for longitudinal evaluation and therapy, which can result in optimal outcomes [58]. Chest RT combined with anthracycline therapy raises the risk of heart failure even at modest cumulative anthracycline dosages [59],[60].The high-dose chemotherapy was employed as a conditioning regimen but however, as predicted, the increased effectiveness was accompanied with increased toxicity while in survivors of Hodgkin's lymphoma, the mean radiation dosage to the left ventricle was linked to an elevated risk of heart failure (HF), with an extra risk in patients treated with both radiation and anthracycline treatment [61].

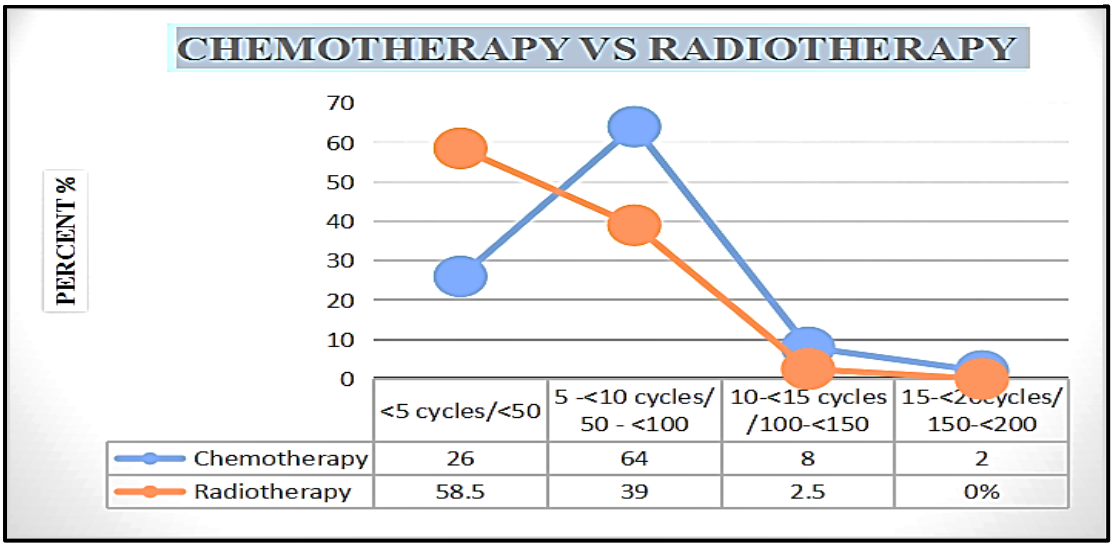

Fig 9 : Chemotherapy versus Radiotherapy

The dosage forms used in the treatment were categorized as ; infusion, injection, suspension, syrup, oral solution and tablet as shown in Figure 3.8. The injectable category mark high in percentage while suspension remained at lowest percentage.

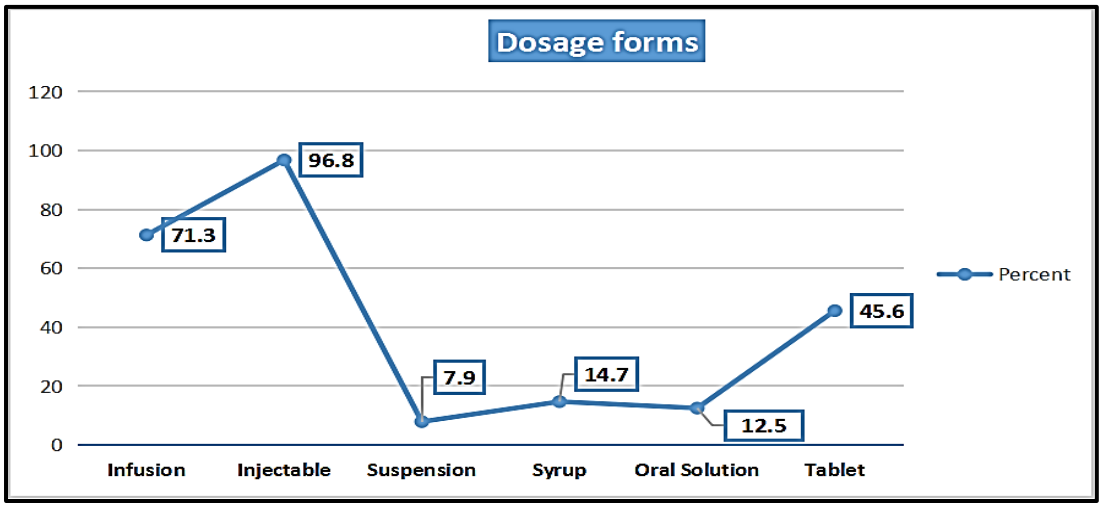

Fig 10 : Dosage forms

Chemotherapy and radiotherapy are two therapies for treatment of cancer. The different class of drugs which were administered by patient calculated by percentage and depicted in figure 11.

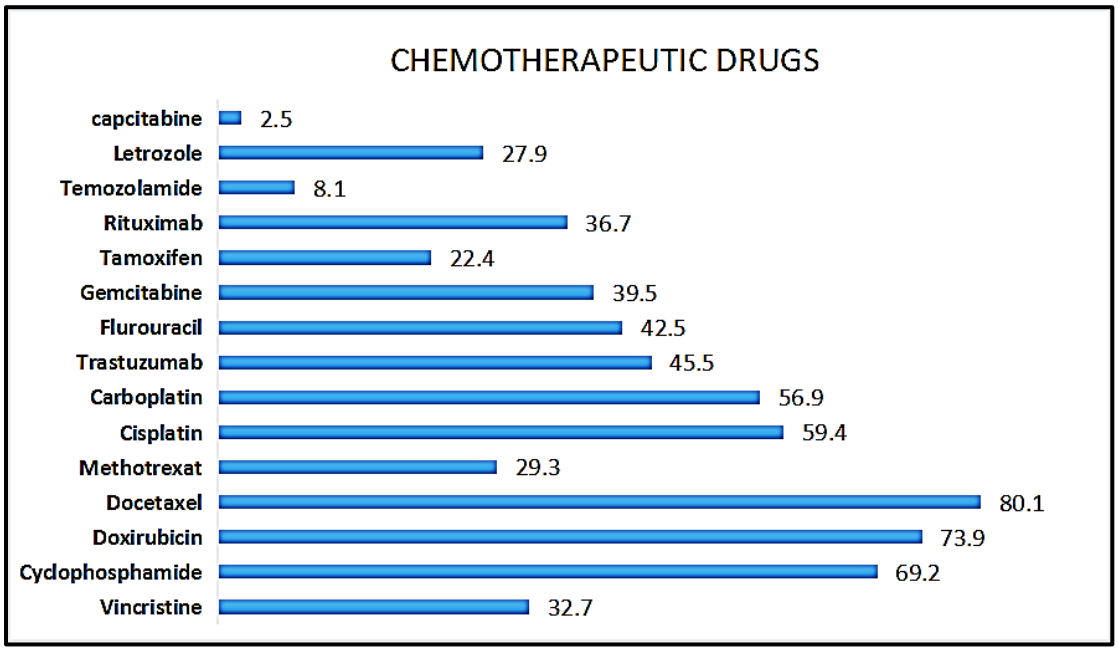

Fig 11 : Chemotherapeutic drugs

The cardiac complications observed in individuals along with family history were depicted in figure 12.

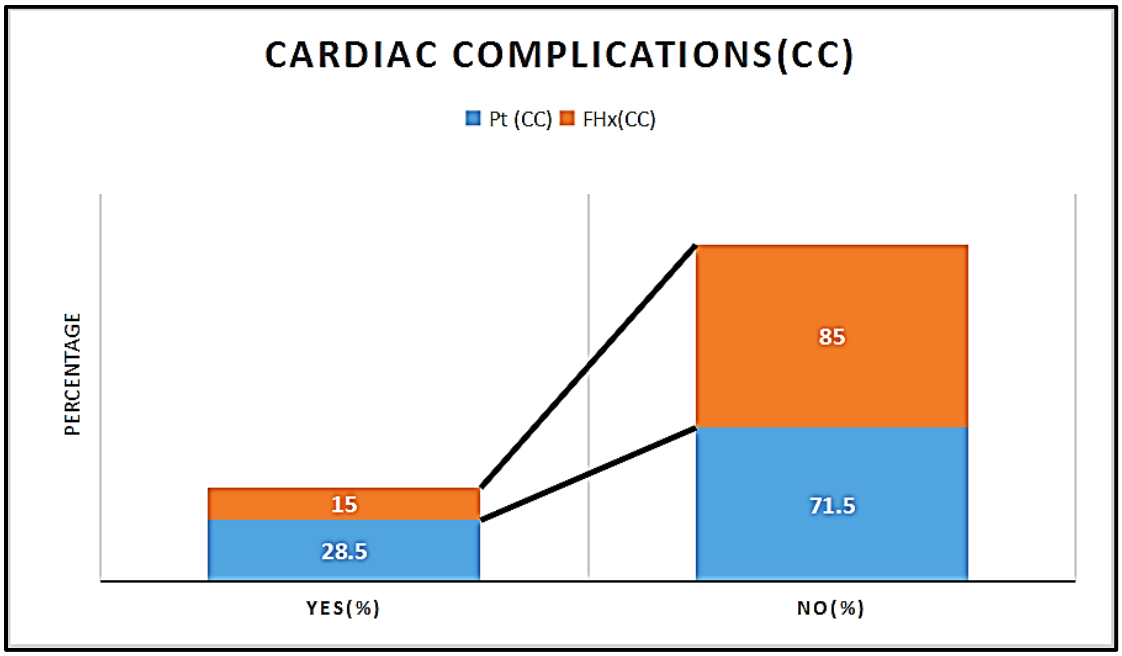

Fig 12 : Cardiac Complications

The Spearson Correlation among different factors were determined by Version 25 of SPSS software. The range from 0.6 to 1 value indicates "Strongest Correlation" while range from 0.3 to 0.5 value indicates "Moderate Correlation".

Table 4
Spearson correlation

Spearman's rho	%SP O2	Pulse (HR)	Patient CC	Family Hx CC	Family Hx Cancer	Diagnosis	Tumor Type	Tumor Stage	Chemo therapy (cycle)	Radio therapy Dose (cGy)
Age(years)	.836**	.822**	.766**	.595**	**.477****	.975**	.563**	.905**	.967**	.861**
%SPO2		.960**	.855**	.703**	.533**	.864**	.674**	.807**	.801**	.895**
Pulse(HR)			.826**	.549**	.399**	.846**	.504**	.787**	.780**	.892**
Patient Cardiac Complications (pt CC)				.665**	**.483****	.788**	.611**	.691**	.685**	.758**
Family Hx CC					.726**	.622**	.918**	.574**	.567**	.532**
Family Hx Cancer						**.487****	.820**	.519**	**.495****	**.418****
Diagnosis							.589**	.922**	.968**	.862**
Tumor Type								.568**	.560**	.502**
Tumor Stage									.938**	.849**
Chemo therapy (cycle)										.845**

**. Correlation is significant at the 0.01 level (2-tailed), Strongest Correlation=0.6-1, Moderate Correlation=0.3-0.5

DISCUSSION

The study exploresCCs associated with the anticancer therapy: chemotherapy and radiotherapy. These selection of therapy depend upon the stage of diagnosis. The study was performed in cancer specialized hospital where more than 1000 individual involved in treatment. The convenient sampling technique was used in the study. The sample size was calculated by using sample size formula. The result of formula depicted about 200 participant participation in the study. About 500 questionnaires were filled from the targeted sample size. The inclusion and exclusion criteria were applied as a result 200 individual met the criteria and process their data for statistical analysis. The sample size (n=200) were selected from two different country; Pakistan and Afghanistan. The individuals were belong to specific province in both country. There individual(n=52) belonged to province Kabul which were further distributed into three most populated districts such as; Nangarhar(n=17), Laghman(n=14), Loghar(n=21). A decreasing of participant was observed as Loghar>Nangarhar>Laghman in districts Kabul of Afghanistan. Meanwhile on the flip of the page, individuals belonged to Pakistan marked higher than Afghanistan, having n=148 which were residents of province Khyber Pakhtunkhwa, which was subdivided into four different zones such as Zone 1, Zone 2, Zone 3, Zone 4.The individual(n=12) belonged to zone 1 which encompassed on areas as; Agencies of Bajaur, Mohmand, Khyber, Kurram, Orakzai, North Waziristan, South Waziristan and frontier regions attached to the districts of Peshawar,Kohat,Bannu and Dera Ismail Khan. The participant(n=109) were residents of Zone 2 which consist of such areas as; Peshawar, Charsadda, Nowshera, Swabi and Mardan. The individuals(n=13) linked with the Zone 3 encircled such areas as; Swat, Upper Dir, Lower Dir, Chitral, Buner, Shangla, Kohistan and backward areas of Haripur, Mansehra, and Swabi Districts while individuals(n=14) lied in Zone 4 having areas such as; Dera Ismail Khan, Tank, Bannu, LakkiMarwat, Kohat and Karak. The only participants who met the inclusion criteria such as age range from 5 to 90 year were included in the study while all the other participants beyond the range, were excluded from the study due to the fact of precise statistical analysis. The mean and standard deviation calculated for address was 2.64 and 1.161. Childhood cancer survival has increased significantly as cancer medicines and healthcare systems have advanced.1 In high-income nations, the five-year survival rate for children with cancer has reached 80%, but it is only around 30% in low- and middle-income countries. The health equity of long-term survival among childhood cancer survivors has drawn attention, with the goal of increasing this ratio to 60% globally by 2030.Increasing focus. The WHO developed the Global Initiative for Childhood Cancer [62].

The basic characteristics consist of such parameters as; gender ,age, weight, lifestyle, marital status, , educational status and occupation. The selection of parameters was based on the relation with the CCsof anticancer therapy. There were two category in the gender parameter, such as male and female having frequency of 75 (37.5%) and 125 (62.5%). The age and weight parameter of individual strongly associated with the cardiovascular complication of therapy. There was broad variation observed in age and weight. The calculated value of mean and standard deviation of age was 5.17 and 1.684 The lowest age marked was 6 year while the highest age observed as 88 year .The age was measured in year and were classified into 9 class interval, each consist of 10 year range . The percentage of individualsupto 50 year was 56.5% while the remaining 43.5% lie in the age range above 50 years. There were 3% (=<10 year), 4%(=<20), 7.5%(=<30), 18.5%(=<40), 23.5%(=<50), 20%(=<60), 16.5%(=<70), 6.5%(=<80) and 0.5%(=<90) . The lowest and highest value of weight noted as 11 kg and 109 kg. The calculated value of mean and standard deviation of weight was 5.60 and 1.553. The weight have co-relation with the co-morbidities. The individuals fall in overweight category have high lipid profile and high CCs. The weight range was classified into various class interval of 10kg difference. There were1.50%(=<20kg), 1.50%(=<30), 5%(=<40), 11.5%=<50), 26.5%(=<60), 29%(70), 17%(=<80),4. 5%(=<90) 2%(=<100), 1.50%(=<110). The life style parameter was included in the study because it affect the physical and mental health of individual. . The calculated value of mean and standard deviation of life style was 1.13 and 0.332. There were two sort of life style such as active lifestyle and sedentary life style. There was low risk of CCs in active lifestyle as compared to sedentary lifestyle.

The marital status was included to determine the genetic co-relation .Among all sample size, there were 173 (86.5%) married and 27(13.5%) single individuals. . The calculated value of mean and standard deviation of marital status was 1.14 and 0.343. The frequency of married population in selected sample size were marked high as compared to single. The education parameter was added in the study in order to study the compliance of therapy. . The calculated value of mean and standard deviation of education was 1.97 and 1.461. The percentage of diagnosed cancer was more in illiterate individual as compare to educated. The education was categorized as; illiterate, primary, middle, matric, intermediate, bachelor and master. There trend from illiterate toward master

having frequency(percentage) were observed as, 114(57%) > 39(19.5%) > 15(7.5%) >15(7.5%) > 9(4.5%) >5(2.5%)> 3(1.5%).The parameter occupation was included in order to determine the financial status and work load of individuals. The government officer marked as lowest percentage while occupation related to house wife marked as high percentage. An increasing trend was observed as government officer, jobless, armed forces, teacher, dailywagers, student, busssiness, farmer and House wife having frequency and percentage were; 2(1%) < 3(1.5%) = 3(1.5%) < 9(4.5%)<10(5%)<17(8.5%)<20(10%)<22(11%)<114(57%).The height parameter is very important for chemotherapy because the dose of chemotherapy is based on body surface area whose equation] require height of individual. The minimum and maximum height observed were 81cm and 182cm respectively. The trend of class interval (%) were calculated as; <101cm (1.0%),101-120 (2.50%) ,121-140 (11.50%),141-160(82.5%), 161-180 (17%) , >180 (0.50%).

The parameter related to body mass index(BMI) was included to find out the lipid profile individual which have strong relation with CCs. Obesity is a risk factor for several chronic illnesses (type 2 diabetes, arterial hypertension, stroke, and many cancers) as well as early mortality. Leptin is a hormone that is largely generated by fat tissue, and its circulating levels are directly proportional to the amount of energy stored in the human body as fat. When leptin levels rise, immune cells such as macrophages and lymphocytes become proinflammatory. Furthermore, prolonged inflammation can modify deoxyribonucleic acid (DNA) and hence cause cancer [63]**.** The BMI had categorized according to the value derived from equation. Each value depicted the nature of lipid profile of individual. The first category of BMI had value <18.5 which showed the underweight nature of body, meanwhile there were only 5% individuals. The second category had value range from 18.5 to 24.9 imprinted 34% among all sample size. The value range from 25.0 to 29.9 showed third category(overweight) in which 24% individual lied. About 37% of selected sample size fell in fourth category which marked obesity and had value >29.9. The body surface area(BSA) was calculated from equation of BSA by putting values of weight and heigh for each individual. The numerical value of BSA is required in determination of chemotherapy dose while the trend of BSA were observed as(n%) as; <0.8(1.5%) , 0.8-1.4(20.50%) ,1.57-2.0(75.5%), >2.0(2.5%).The Oxygen saturation(SPO_2) is the fraction of oxygen-saturated hemoglobin relative to total hemoglobin in blood. The SPO2 were classified as normal level(95-100%) concerning level(90-94%) and low(0-89%).The trend observed as; 95-100% (n=126) > 90-94%(n=47) >0-89% (n=27). The low oxygen saturation level clarified the inability of heart to receive oxygen-rich blood from the lungs. The category (%) trend of Pulse (HR) observed as; bradycardia <60bpm (n=2), Normal 60-100bpm (n=125) Tachycardia>100 (n=73). The co-morbidity such as diabetes mellitus (DM) was included in study. The fact behind the inclusion of diabetes was its association with cardiac association.

Diabetes mellitus has an impact on cardiovascular disease and may raise the risk of cancer. This could be increased inflammation, increased oxidative stress, hyperinsulinemia and hyperglycemia. Studies has shown that cancer is more frequent in diabetic versus non-diabetic. Serum insulin growth factor (IGF) levels rise when persistent hyperinsulinemia reduces IGF-binding protein levels. Tumor cells express insulin receptors as well as IGF receptors . Increased IGF levels can promote cell proliferation, which can lead to the development of different forms of cancer (e.g., colorectal, prostate, esophageal, pancreatic, and premenopausal breast cancer). On the other hand, metformin (an insulin sensitizer) lowers it, but sulfonylureas (insulin secretagogues) appear to raise cancer risk in those with type 2 diabetes. Metformin's protective impact on cellular neoplasia was thought to be due to suppression of the adenosine monophosphate-activated protein kinase/liver kinase B-1 (AMPK/LKB1)-dependent growth pathway [63]. Among the individual 13% had DM while remainings were free from DM. There were 20.5% and 8.5% of family history of DM and Cancer. The individual involved in study were suffering from different types and stage of cancer. The trend of tumor type as; carcinoma(87%)>Sarcoma(6%)> lymphoma(3.5%) > leukemia(3.5%). While stage of cancer depicted trend as; stage 1(6.5%)<stage 4(9.5%)<stage 3(39%)<stage 2(45%).The diagnosis were varied and affect various parts of body observed as; brain,breast,oral cavity, esophagus, gall bladder, lung, prostate, rectum, renal, stomach, thigh, urinary bladder, pharynx, genital, uterus and neck. Breast cancer is the most frequent female cancer . However, breakthroughs in adjuvant therapy and earlier identification have resulted in gradually declining rates of breast cancer-related mortality . As a result of the million breast cancer survivors, breast cancer patients are surviving longer and are becoming more vulnerable to the late-occurring unfavorable effects of cancer therapy [64].

The diagnostic tests included in study were; computed tomography(CT) scan, ultrasound(U/S), biopsy, magnetic resonance imaging(MRI),mammography(M/G), bone scan, and electrocardiogram(ECG). The test recommended for individual depend upon the stage and type of tumor. The trend observed as Biopsy(93.5%)> CT scan(45.5%)> bone scan(40%),ECG (30%)> U/S(17.5%)> MRI(14.5%)> M/G).The complete blood count laboratory(Lab) reports

of all individual among selected population were noted. Mostly the individuals had normal value while some had abnormal value. The trend of normal lab values as : eosinophils(87%) >hematocrit(HCT)(84.5%) > monocytes(MONO)(83.5%) > neutrophil(NEU)(83%) >(mean corpuscular hemoglobin concentration(MCHC)(80%) >mean corpuscular volume (MCV)(77.5%), RBC(76%)= BASO(76%), LYM(75%)> WBC(73%)> MCH(70.5%)> HB(41.5%), PLT(31%). The trend of abnormal lab values were observed as ;PLT(69%)> HB(58.5%) > MCH(29.5%)> WBC(27%)> LYMP(25%) >BASO(24%) =RBC(24%)> MCV(22.5%)> MCHC(20%)>NEUT(17%)MONO > (16.5%) > HCT(15.5) >EOS(13%). Chemotherapy and radiotherapy are two of the mainstays of treatment for several types of cancer. These treatments have allowed for an increased number of patients to survive. However, their mechanism, doses, and frequency of use to achieve remission can generate side effects in patients, with cardiotoxicity as one of the most concerning**.**The selection of any sort of therapy depend upon stage and type of tumor. The 5 to 9 cycles of chemotherapy were prescribed to 64% of individual,less than 5 cycles to 26%,10 to 14 cycle to 8% and 15 to 19 cycles to 2% of all individual included in selected sample size. Radiotherapy dose (Gy) was prescribed in combination with chemotherapy or single therapy. The dose of radiotherapy depend upon the nature and size of tumor. Patients with locally advanced cancer treated with estimated mean heart doses > 10 Gy experienced an excess of major cardiac events compared to those treated with doses < 10 Gy [39]**.** About 58.5% individuals were prescribed with dose of <50Gy and 39% were prescribed with 50 to 99Gy. The highest dose such as 100 to 149 Gy were recommended to 2.5% of individual. The different dosage form were utilized in chemotherapy. There were more than one dosage forms observed in prescription of individuals. The trends were noted as injectable (96.8%)>infusion(71.3%)> tablets (45.65%)> syrup(14.7%)> Oral solutions(12.5%)> suspension(7.9%).

The therapy landscape for patients with a range of malignancies has altered due to T-cell treatments, including chimeric antigen receptor (CAR) T-cell, bispecific T-cell engager (BiTE), and tumor-infiltrating lymphocyte (TIL) therapies [65], [66], [67].

The trend of chemotherapeutics drugs mostly prescribed as; docetaxel(80.1)> doxorubicin(73.9)>cyclophosphamide(69.2%)>cisplatin(59.4%)>carboplatin(56.9)>transtuzumab(45.5)>fluorouracil(42.5%)>gemcitabine(39.5%)>rituximab(36.7)>vincristine(32.7%)>methotrexate29.3%>leterozole(27.9%)>tamoxifen(22.4%)>temozolamide(8.1)>capcitabine(2.5) while the other non chemotherapeutic drugs prescribed to such patients have no effect on tumor suppression which requires awareness session [68],[69],[70],[71],[72],73],[74],[75]. DOX are well-known and very effective antineoplastic medicines used to treat a variety of adult and pediatric malignancies, including breast cancer, leukemia, lymphomas, sarcomas, and others [76]. Cardiotoxicity is one of the worst adverse effects of antineoplastic therapy that causes significant morbidity and mortality worldwide [77]**.**and is most commonly characterized by an asymptomatic decrease in left ventricular ejection fraction (LVEF), but it can take many forms, including congestive heart failure (CHF), hypertension, arrhythmias, cardiac ischemia, venous thromboembolism, and pericardial and valvular diseases [78].Among the prescribed drug comparatively less cardiotoxic drugs were docetaxel and gemcitabine. The positive family history of cardiac complication noted among the individual were 15%. While the individual itself were marked as 28.5%.

2 CONCLUSION

Our study has identified the CCs associated with the anticancer therapy which marked at 28.5%.Individual having wide range of weight, age, marital status, life style, address, education and occupation were included in the study to observed the different cardiac complications. The height,body BMI and BSA were recorded for the dose calculations of chemotherapeutic agents. The pulse and oxygen saturation value of each individual were observed by using Pulse Oximeter. All individuals were asked about the family history of DM and Cancer which were marked upto 20% and less than 10% respectively. The analysis of different diagnostic tests such as ; ECG, MRI, CT scan, metastasis, bone scan, mammography, biopsy, ultrasound were observed for finding of CCs. A wide range of diagnosed cancer patient were included in the study which were; carcinoma, sarcoma, lymphoma and leukemia. All the values of laboratory tests were noted which had role in CCs. The doses of anticancer therapy ;chemotherapy and radiotherapy in different diagnosis were noted. In chemotherapy the percentage of dosage forms and drug class varied, depends upon the diagnosis and stage of cancer. Moreover, the development of new, targeted therapies that are less cardiotoxic is an area of active research and holds promise for reducing the CCs associated with anticancer treatments. These therapies may provide effective cancer control

while minimizing damage to the heart and blood vessels, thereby improving the overall quality of life for cancer survivors. The CCs of anti-cancer therapy are a complex and evolving challenge. As advancements in cancer treatment continue, it is essential to prioritize the cardiovascular health of cancer patients to ensure the best possible outcomes. By identifying high-risk patients, adopting preventive measures, and fostering collaboration among healthcare professionals, we can better manage and mitigate these complications.

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