EARLY DETECTION OF CHEMOTHERAPY INDUCED CARDIO-TOXICITY IN CANCER PATIENTS BY VARIOUS NON-INVASIVE TOOLS
A PROSPECTIVE OBSERVATIONAL STUDY

THESIS

Submitted to

ALL INDIA INSTITUTE OF MEDICAL SCIENCES, JODHPUR

In Partial fulfilment of the requirement for the degree of

DOCTORATE OF MEDICINE (DM)

(CARDIOLOGY)

JULY 2020

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This is to certify that the thesis titled "**Early Detection of Chemotherapy Induced Cardio-toxicity in Cancer Patients by Various Non-invasive Tools: A Prospective Observational Study"** is the bonafide work of **Dr Shubham Kumar Sharma** carried out under our guidance and supervision, in the Department of Cardiology, All India Institute of Medical Sciences, Jodhpur.

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DECLARATION

I declare that the thesis titled "**Early Detection of Chemotherapy Induced Cardio-toxicity in Cancer Patients by Various Non-invasive Tools: A Prospective Observational Study"** embodies the original work carried out by the undersigned in All India Institute of Medical Sciences, Jodhpur.

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RAJASTHAN

Acknowledgement

I would like to begin by expressing my heartfelt gratitude to my Guide ***Dr Surender Deora, Additional Professor and Head, Department of Cardiology, AIIMS Jodhpur*** who has great experience and knowledge and who has an art of encouraging, correcting, and directing me in every situation possible, which made me complete the work. I consider myself to be extremely privileged to have been his student.

I am immensely thankful to my Co-guide- ***Dr Rahul Choudhary & Dr Atul Kaushik, Associate professor, Department of Cardiology*** for their constant guidance and support without which I could not have completed this thesis.

I am also extremely grateful to my co-guide ***Dr Puneet Pareek, Additional Professor, Department of Radiation Oncology and Dr Kuldeep Singh, Professor and Dean (Academic)*** for sincere and valuable guidance and encouragement in both professional and personal life.

I would like to extend my sincere thanks to my friendly juniors - ***Dr Sourabh, Dr Vivek, Dr Rahul, Dr Gopal, Dr Narendra, Dr Amit, Dr Omprakash, Dr Saroj, Dr Mahendra*** for their constant encouragement.

Last, but not least my success would not be possible without the support of my family especially my parents ***Mrs Gaytri Sharma and Mr Mahendra Kumar Sharma***, who gave me the wings to fly high. My Love and gratitude for them can hardly be expressed in words. I dedicate my thesis to my parents.

I would like to extend my sincere thanks to the ***Nursing staff for*** their unfailing support and assistance throughout my DM period.

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LIST OF ABBREVIATIONS

CV	Cardiovascular
CS	Cancer survivors
CREC	Cardiac Review and Evaluation Committee
LVEF	Left ventricular ejection fraction
CTR-CVT	Cancer therapy-related cardiovascular toxicity
CTRCD	Cancer Therapeutic Related Cardiac Defects
HF	Heart Failure
STE	Speckle tracking echocardiography
GLS	Global longitudinal strain
GCS	Global circumferential strain
MUGA	Multiple- gated acquisition Scan
HER2	Human epidermal growth factor receptor 2 inhibitors
RDW	Red blood cell distribution width
ECG	Electrocardiography
ECHO	Echocardiography
TTE	Transthoracic echocardiography
PAP	Pulmonary arterial pressure
BNP	Brain natriuretic peptide
LPSS	Longitudinal peak systolic strain
GAS	Global area strain
GRS	Global radial strain
PCI	Percutaneous coronary intervention
CABG	Coronary artery bypass graft
ACS	Acute coronary syndrome
CKD	Chronic kidney disease
CAD	Coronary artery disease
HTN	Hypertension
DM	Diabetes mellitus
BMI	Body mass index
RFT	Renal function tests

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SUMMARY

Background: Cardiotoxicity in cancer patients receiving chemotherapy may lead to premature cardiovascular events leading to decreased quality of life and co-morbidities. It is the leading cause of mortality and morbidity in cancer survivors. The common manifestations of cardiotoxicity secondary to chemotherapy include subclinical decline of LVEF, new-onset heart failure, conduction disorders, hypertension, thrombotic events, and cardiovascular ischemia. Numerous non-invasive tools are used for the early detection of cardiotoxicity caused by chemotherapeutic agents, including cardiovascular imaging, hematological parameters, cardiac biomarkers, and ECG parameters. Transthoracic echocardiography (TTE) is the preferred imaging for detection of cardiotoxicity. When conventional echocardiographic parameters are close to normal, 2D-STE-derived global longitudinal strain (GLS) and global circumferential strain (GCS) could be used for significant cardiotoxicity detection. High Red blood cell distribution width (RDW) is strongly linked to poor prognosis in common cardiovascular diseases like acute coronary syndrome, heart failure, and pulmonary hypertension, but little is known about its connection to the onset of CTRCD. Therefore, the present study also evaluates the association of RDW and CTRCD. Electrocardiography (ECG) is used as non-invasive method; early identification of ECG abnormalities can predict cardiotoxicity.

Aim and Objectives

Aim: Early detection of cardiotoxicity in cancer patients after chemotherapy by various novel diagnostic markers. **Objectives:** 1. 2D-strain imaging to detect subclinical LV dysfunction. 2. To compare conventional and strain 2D-echo findings

for early diagnosis of chemotherapy induced cardiotoxicity during subclinical phase. 3. To find relation between RDW and associated cardiotoxicity by chemotherapy. 4. To study various ECG changes caused by cancer chemotherapy in patients with normal baseline ECG and also to determine if ECG changes precede echocardiographic findings of cardiomyopathy.

Methods: We enrolled the 193 patients from day of approval to 12 months at All India Institute of Medical Sciences, Jodhpur. After selection of cancer patients who are planned to go for chemotherapy, a pre and 1-month post chemotherapy hematological, cardiac and inflammatory biomarkers, ECG and 2D-transthoracic echocardiography was done.

Results: Out of total 193 patients, 123 were females and 70 were males with mean age were 45.17 ± 1.42 years. There was no significant association between the two groups based on age, sex, cardio-active medications and co-morbidities except hypertension. There was no significant difference in cardiotoxicity who were treated with different chemotherapy. Left ventricular end-systolic volume (LVESV) increased from 25.2±14.5 ml to 39±29.5 ml (p=0.0001) without any significant change in left ventricular end-diastolic volume (LVEDV) [90.1±8.3 ml to 91.8±7.4 ml (p=0.08). There was significant decline in Left ventricular ejection fraction (LVEF) after chemotherapy (66.9±8.3% vs. 54.2±12.2; P = 0.0001). Global longitudinal myocardial strain (GLS) was reduced significantly from -17.98±4.5% to -15.9±6.9%, P=0.0002). Global circumferential strain (GCS) was reduced significantly after chemotherapy from -27.7±11.7% to -16.5±2.6%, P=0.0001). There were significant changes in the main diastolic parameters. E/A ratio was decreased, de-acceleration time (DT) was increased, significant decrease in E' at mitral annuli and an increase in

the trans-mitral Doppler early filling velocity E/E' ratio. 36 patients were dead which was more in males. A significant difference in LVEF (by Simpson's), GLS and GCS were noted post-chemotherapy in dead patients. The LV GLS value of -15.9 % showed the sensitivity of 80% and specificity of 99% for predicting cardiotoxicity. The accuracy of the GCS value of -16.5 was assessed by use of its sensitivity and specificity (100% and 93%, respectively). This confirms GLS and GCS are excellent independent factor of cardiotoxicity. Laboratory data showed that hemoglobin and mean corpuscular volume were reduced post chemotherapy and RDW was increase significantly. Compared to previous studies, RDW can't predict the development of CTRCD. Heart rate, rhythm, QRS duration, QT interval, TpTe/QTc and ΣQRS(6L) didn't change after chemotherapy while there was highly significant change seen in, QTc interval, TpTe/QT and ECG score. There was significant difference in cardiotoxicity among QTc interval, TpTe (ms) and TpTe/QT of dead and alive patients.

Conclusion: The present study revealed that there was a significant worsening of LV systolic function as measured by the LVESV, LVEF and strain parameters (GLS and GCS) on STE in cancer patients on chemotherapy. STE may be a valuable tool in detecting early myocardial damage in cancer patients undergoing chemotherapy. ECG is also inexpensive and easily available tool that may aid in evaluating individual patient risk during and after therapy.

INTRODUCTION

Cardiotoxicity in cancer patients receiving chemotherapy may lead to premature cardiovascular (CV) events leading to decreased quality of life and comorbities.[1,2] It is the leading cause of mortality and morbidity in cancer survivors (CS). Since the 1990s, there has been a steady decline in cancer-related mortality mirrored by a steady increase in CS.[3,4] Therefore, it is of extreme importance to screen these patients for early cardiotoxicity so that early preventive measures can be instituted for substantial recovery of cardiac function.

According Cardiac Review and Evaluation Committee (CREC) criteria cardiotoxicity due to tumoricidal drug use is generally characterized by an asymptomatic reduction in left ventricular ejection fraction (LVEF) of ≥10% to <55% or, less often, as a reduction of the LVEF of ≥5% to <55% with symptoms of Heart Failure (HF).[5]

Newer guidelines defines CTR-CVT (cancer therapy-related cardiovascular toxicity)[6]: Asymptomatic Cancer Therapeutic Related Cardiac Defects (CTRCD) is graded on the basis of LVEF change and includes measures of Global longitudinal Strain (GLS) and/or biomarkers to help further determine severity. A reduction in LVEF to <40% indicates severe asymptomatic CTRCD, with an association with poor prognosis in multiple cancers and treatment regimens. Moderate asymptomatic CTRCD requires (i) a fall in LVEF into a clearly abnormal range (40–49%) with a change in LVEF beyond the described variability of the most commonly used Echo-based 2D LVEF measurements (i.e. by >10 percentage points), or (ii) a smaller change in LVEF but with a concomitant significant fall in GLS and/or new rise in cardiac biomarkers. Mild asymptomatic CTRCD is defined as preserved LVEF (i.e. LVEF ≥ 50%) with >15% reduction in GLS relative to baseline and/or new rise in troponin or Natriuretic Peptides (NPs).

High doses of chemotherapy drugs like anthracyclines, cyclophosphamide, 5-fluorouracil, and vincristine are linked to CTRCD. The likelihood that cardiotoxicity will manifest depends on the total dose, the patient's age, any concurrent or prior radiation therapy, any pre-existing cardiovascular conditions, and the concurrent use of HER2 inhibitors.[7] Subclinical LVEF decline, newly developed heart failure, conduction issues, hypertension, thrombotic events, and cardiovascular ischemia are common signs of cardiotoxicity secondary to chemotherapy.[8] The majority of chemotherapy-induced cardiotoxicity, which is difficult to treat and frequently worsens cardiac function, occurs within the first year of chemotherapy. By starting treatment for cardiotoxicity early, cardiac function may be restored or prevented from further declining. In order to identify patients who are predisposed to anthracycline-induced cardiotoxicity and to implement timely preventive measures, assessment of cardiac function should be performed to detect cardiotoxicity in its early stages.

Numerous non-invasive tools are used for the early detection of cardiotoxicity caused by chemotherapeutic agents, including cardiovascular imaging, hematological parameters, cardiac biomarkers, and ECG parameters. Excellent methods for identifying cardiotoxicity and adverse cardiac effects include the electrocardiogram, echocardiography, coronary angiography, ventriculography, and cardiac magnetic resonance imaging (MRI). Heart failure, chronic coronary syndrome, and myocardial infarction can all be detected early on using cardiovascular biomarkers like BNP, NT pro-BNP, and ECG. Arrhythmias are a common side effect of many cancer treatments, so every cardio-oncological evaluation must include an ECG analysis.

In order to identify patients with subclinical CV disease, to evaluate the level of cardiac comorbidity present before making cancer therapy decisions, and to serve as a reference for identifying changes during treatment and long-term follow-up, CV imaging is essential.[9-13] Transthoracic echocardiography (TTE) is the preferred imaging technique

for baseline risk stratification as it provides quantitative assessment of LV and right ventricular (RV) function, chamber dilation, LV hypertrophy, regional wall motion abnormalities, diastolic function, valvular heart disease, pulmonary arterial pressure (PAP), and pericardial disease, which may influence the therapeutic decision. Cardiotoxicity is typically detected using left ventricular volume and left ventricular ejection fraction (LVEF) as measured by conventional 2D-Echocardiography but it has technical limitations because it can't detect minute myocardial changes and LVEF declines over time.[14, 15] In order to adjust cancer therapy and prevent irreversible myocardial damage, speckle tracking echocardiography (STE) is a potentially more sensitive marker for detecting early myocardial dysfunction at an earlier stage.[16]

When conventional echocardiographic parameters are close to normal, 2D-STE-derived global longitudinal strain (GLS) and global circumferential strain (GCS) could be used for significant cardiotoxicity detection. In addition to being more accurate than a global LVEF evaluation at detecting silent myocardial impairment, global strain decline may be reversible and not linked to clinically significant cardiotoxicity or late LVEF decline.[17] Therefore, decreased global strain may detect early cardiac dysfunction in HF cancer survivors who are not exhibiting any symptoms and who could benefit from early medical intervention.

The American Society of Echocardiography and the European Association of Cardiovascular Imaging have agreed that deformity changes precede ventricular dysfunction. A reduction > 15% in GLS, immediately after or during anthracycline treatment, was the most useful parameter to predict cardiotoxicity; while a reduction < 8% might exclude its diagnosis.[18]

Red blood cell distribution width (RDW), a haematological parameter, is an easy and quick way to measure the heterogeneity of erythrocyte volume. High RDW is strongly

linked to poor prognosis in common cardiovascular diseases like acute coronary syndrome, heart failure, and pulmonary hypertension, but little is known about its connection to the onset of CTRCD.[19-21] Therefore, the present study also evaluates the association of RDW and CTRCD.

Electrocardiography (ECG) is used as non-invasive method for monitoring cardiac toxicity in cancer patients.[22] Early identification of ECG abnormalities associated with structural or electrical alterations is therefore of great importance. This may relate to pathologic contiguous Q waves, ECG markers of LV hypertrophy and left atrial enlargement, increased heart rate and heart rate variability, prolongation of the PR and QRS intervals, QRS fragmentations, left bundle branch blocks, JTc prolongation and contiguous T-wave inversion, which were shown to be associated with cardiac adverse events in the general population.[23-28] The role of ECG parameters in the prediction of mortality in cancer patients has been assessed previously.[29,30] Therefore, the present study also evaluated the ECG changes in patients undergoing chemotherapy and to relate it with mortality.

Management of CTR-CVT has a tremendous impact on the type of anticancer therapies that patients can receive as well as the long-term morbidity and mortality outcomes of patients with cancer. Effective management of patients with both cancer and CVD requires the unique interest and expertise of healthcare providers, which has led to the formation of a new discipline: cardio-oncology.[31,32] Appropriate criteria for the organization and implementation of cardio-oncology services are described in a recently released ESC-CCO document.[32]

REVIEW OF LITERATURE

1. Definition and classification:

Cancer survivorship has significantly increased over the past 40 years, in part due to earlier detection and better care.[33] An increasing cancer survivorship has created a community of patients in need of specialised healthcare to treat the long-term side effects of their medication and reduce their comorbidity and mortality.[34]

According to cardiac review and evaluation committee (CREC), cardiotoxicity due to tumoricidal drug use is generally characterized by an asymptomatic reduction in LVEF of ≥10% to <55% or, less often, as a reduction of the LVEF of ≥5% to <55% with symptoms of Heart Failure (HF).[5] The National Cancer Institute (NCI) developed the Common Terminology Criteria for Adverse Events (CTCAE), which are the most commonly used metrics for evaluating cardiovascular disease and events.[35] However, defining cardiac toxicity is challenging due to a variety of measurement techniques for LVEF parameters, varying degrees of LV dysfunction, an ambiguous definition of the possibility of reversibility of cardiac dysfunction, and enough variation in the risk of CV outcomes (Table).

Table: Criteria of cardiac toxicity

	Criteria of cardiac toxicity	Confirmation of cardiac toxicity
CREC	1. Cardiomyopathy with reduced LVEF (Global or more severe in septal region) 2. Symptomatic heart failure 3. Objective findings associated with HF (Tachycardia, raised JVP) 4. Reduced LVEF from baseline ≥5% to <55% with symptoms and signs of HF or reduction of the LVEF of ≥10% to <55% without symptoms of Heart Failure (HF)	Any of 4 criteria
LVEF criteria in routine practice	1. Reduced LVEF from baseline >10% to <55% 2. Reduced LVEF from baseline ≥10% to <50% 3. Reduced LVEF from baseline ≥ 20% or >15%, but remains > 50% in follow up 4. Any LVEF decline to <50%	Any of 4 criteria
CTCAE	1. Declining 10-19% from baseline when resting LVEF is 40-50% 2. Declining >20% from baseline, when resting LVEF is 20-39% 3. Resting LVEF <20% 4. Newly asymptomatic or symptomatic or life-threatening events related to HF	One of criterion

2. Cardiotoxicity of anti-cancer agents

2.1 Anthracyclines:

Anthracyclines were originally derived from Streptomyces peucetius and include daunorubicin, doxorubicin, epirubicin, idarubicin and valrubicin.[36] The incidence of late-onset anthracycline-induced cardiotoxicity has been reported to be as high as

20% in cancer survivors 15-20 years after exposure.[37,38] Proposed mechanisms to explain delayed cardiotoxicity include progressive impairment of sarcoplasmic reticulum calcium-handling mechanisms, oxidative lesions on mitochondrial DNA (mtDNA), free radical-derived DNA lesions and the removal of progenitor cells in young patients which will later limit the already restricted regenerative capacity of the heart.[39-42]

Doxorubicin induced cardio toxicity is known to be dose-dependent particularly in patients seen to be at risk of cardiac dysfunction dependent.[43,44] It is administered as an intravenous (IV) infusion of 40-75 mg/m2 at 3 to 4-week intervals, limiting the cumulative dose to 400-450 mg/m2. However, it is known that cardiac dysfunction can happen at cumulative doses much lower than this one.[44,45]

2.2 Tyrosine kinase inhibitors (TKIs)

Tyrosine kinase inhibitors' (TKIs) function in contemporary cancer research is rapidly changing.[46] TKIs specifically target the structure of tyrosine kinases' ATP-binding pocket and all rapidly dividing cells. Inhibiting other unintended kinases may lead to "off-target" cardio toxicity effects.[47] Although inhibiting tyrosine kinase signalling is beneficial for cancer treatment, inhibiting it in a healthy heart can lead to compromised function.

2.3 Vascular endothelial growth factor A (VEGF-A)

VEGF-A is a pro-angiogenic protein which is expressed in up to 60% of human tumors.[48] The proliferation, migration, and sprouting of endothelial cells as a result of its receptor signalling contribute to the growth of tumours. The drugs sorafenib and sunitinib, both of which have adverse cardiac effects, were developed as a part of a

strategy to target VEGF signalling pathways. (SU11248; also referred to as Sutent and STB).[49]

2.4 Human epidermal growth factor receptor 2 (HER2)

Doxorubicin is often used as part of combination therapies however this can also lead to synergistic cardio toxicity. Most commonly used combination agent that is associated with cardio toxicity is Doxorubicin with trastuzumab (also known as Herceptin, ERG-ERBB) which is a monoclonal antibody targeting human epidermal growth factor receptor 2 used in the treatment of breast cancer. Up to 30% of all breast cancer cases over-express HER2 and the development of trastuzumab was a significant breakthrough in the treatment of this type of breast cancer.[50] The mechanism behind cardio toxicity has yet to be elucidated but it is hypothesized that the neuregulin-1 (NRG-1)/ErbB signalling which is involved during cardiac development also plays an important role in adult cardiac physiology and therefore its inhibition may affect cardiac function.[51] Combination therapy may increase the risk of cardiac dysfunction because it causes a "dual hit," which worsens cardiac damage and places the myocardium under more strain.

2.5 Vinca Alkaloids

Catharanthus roseus produces vinca alkaloids, which bind to specific sites on tubulin dimers to prevent them from assembling into microtubules.[52] While vinorelbine and the investigational substance vindesine are produced semi-synthetically, vinblastine, vincristine, and vinorelbine are naturally occurring chemicals. Despite the fact that none have been FDA-approved for the treatment of breast cancer, their use in this clinical setting is reported in several publications.[53,74]

2.6 Taxanes

Taxanes inhibit cell proliferation through microtubule depolymerisation which interferes with chromosome segregation and leads to mitotic arrest.[55] Paclitaxel is a natural taxane extracted from the Tavus brevifolia Pacific Yew tree whereas docetaxel and cabazitaxel are semi-synthetic products. Paclitaxel and cabazitaxel exert their inhibitory functions at the boundary of the G2-S phases of the cell cycle in contrast to docetaxel which affects the S-phase.[56] All taxanes except cabazitaxel are indicated for the treatment of metastatic breast cancer.

2.7 Alkylating agents

Alkylating agents, which are highly reactive molecules, are used to treat cancers of the breast, brain, lung, testis, pancreas, and ovary as well as leukaemia, lymphoma, multiple myeloma, sarcoma, and Hodgkin disease by binding covalently to electron-rich nucleophilic positions on molecules like DNA, RNA, and proteins. Their impact is dose-dependent but independent of the cell cycle.[57] Alkylating agents are derived from nitrogen mustard include bendamustine, busulfan, chlorambucil, cyclophosphamide, ifosfamide, mechlorethamine, melphalan, and uramustine.

Alkylating agent cyclophosphamide has been linked to left ventricular dysfunction in 7–28% of patients, and case studies of pericardial effusions and pericarditis caused by the medication have also been published.[58] Cardiotoxicity risk appears to be dose related and is more common with individual doses ≥150 mg/kg and >1.5 g/m2/day 3.[59] Cyclophosphamide cardiotoxicity usually occurs within one to ten days after administration.[58] Concurrent doxorubicin and/or trastuzumab administration, and prior chest irradiation, are also cardiac risk factors.

Alkylating-like platinum-based agents act in a similar fashion to classical agents which are carboplatin, cisplatin and oxaliplatin.[60] They have the advantage of causing less long-term bone marrow damage, reducing the risk of leukemia following treatment when compared to other alkylating agents but have been associated with significant peripheral neuropathies.[61]

2.8 Antimetabolites

Antimetabolites have a structural resemblance to nucleosides and block the synthesis of RNA and DNA by incorporating into DNA and RNA during the S phase of the cell cycle, cause strand breaks or premature chain termination.[62] Antimetabolites subcategorised as anti-pyrimidines, anti-purines and anti-folates. 5-fluorouracil, capecitabine and gemcitabine are commonly used. Available anti-purine agents include cladribine, fludarabine, mercaptopurine, nelarabine, pentostatin and thioguanine. Methotrexate is the only folate antagonist with FDA-approval for breast cancer and is often used in combination with cyclophosphamide and 5-Fluorouracil (CMF) in that setting.[63]

3. Risk factors

The cardiovascular risk factors affecting cancer patients reflect those present in the general population. Patient-related factors include prior history of cardiovascular diseases, age, body mass index, decreased physical activity, comorbidities such as diabetes.[64-66]

Treatment-related factors include the cumulative dose, route of administration, schedule of delivery, sequence and combination of drugs, and prior radiotherapy or surgery. Cardiac exposure to ionizing radiation in breast cancer patients treated with

radiotherapy increases the risk of subsequent heart diseases for at least 20 years post-treatment.[67] In their treatment decisions, physicians should consider underlying risk factors and balance them against the potential benefit expected from the chosen therapy.

4. Clinical presentation:

Three different types of cardiotoxicity have been identified based on how the symptoms are presented: (1) **Acute onset** following a single drug dose or the onset of clinical manifestations within two weeks of the end of treatment (2) **early-onset chronic**, which usually manifests as a dilated and hypokinetic cardiomyopathy and causes heart failure within a year, is the most common type of cardiotoxicity (HF) (3) A **late-onset chronic** condition that appears years after chemotherapy has ended.

Arrhythmias, heart failure, vaso-occlusive diseases, and cardiomyopathy are the most serious complications that have been observed. Electrocardiographic abnormalities like supraventricular tachycardia, ventricular tachycardia, atrioventricular block, and signs of ventricular dysfunction are the most common early clinical manifestations. Patients who present with heart failure later often exhibit symptoms and signs like palpitations, orthopnoea, pedal edema, and dyspnea.

5. Risk assessment and monitoring

In every patient receiving chemotherapy baseline risk assessment is necessary for early identification of cardiotoxicity and early intervention which help in early identifying the signs of heart failure and improve the quality of life there by decreasing the mortality. Prior to and after completing cancer-directed therapy, routine surveillance with non-invasive and invasive cardiac and haematological

investigation may be warranted for these higher risk cancer survivors. This will allow for the implementation of the necessary interventions to slow or even reverse the progression of cardiac dysfunction.

ECG: Since arrhythmias are a common side effect of chemotherapy, ECG analysis is advised as a part of the cardio oncological evaluation. Although guidelines in this situation do not call for a baseline electrocardiogram, it aids in comparison when evaluating later cardiovascular symptoms.

Cardiovascular Imaging

As a reference for identifying changes during treatment and long-term follow-up, it plays a crucial role in identifying patients with subclinical CVD, assessing the degree of pre-existing cardiac comorbidity, and identifying patients with subclinical CVD.[68-71] TTE which provides quantitative assessment of LV and RV function, chamber dilation, LV hypertrophy, regional wall motion abnormalities, diastolic function, valvular heart disease (VHD), pulmonary arterial pressure (PAP), and pericardial disease, which may affect the therapeutic decision, is the preferred imaging technique for baseline risk stratification.[72] The preferred echocardiography technique for measuring cardiac volumes and LVEF is three-dimensional (3D) echocardiography.[73] The modified two-dimensional (2D) Simpson's biplane method is advised if 3D echocardiography is not practical. Multi-gated acquisition nuclear imaging (MUGA) can be utilised as a third-line modality if TTE and CMR cannot be used to evaluate LVEF.

Echocardiography: Due to its low price, widespread availability, and large body of published data, it is widely used for determining cardiac damage and has revealed the frequency of CTRCD linked to known cardiotoxic substances.[74] However, a reduction

in LVEF for the assessment of myocardial injury has limitations. The measurement of LVEF has high technique-related variability, which is higher than the threshold for detection of CTRCD.[75] Secondly, a reduction in LVEF often occurs when overt disease has occurred, with failure to recover systolic function despite use of pharmacological interventions.[76,77] Strain imaging is readily measured during routine echocardiography, which objectivity quantifies regional myocardial function and demonstrates value in detection of early myocardial injury.[78]

2D speckle-tracking echocardiography (STE) is the preferred method for assessing myocardial deformation, provides a more accurate strain assessment, and is less influenced by artefact and the ultrasound beam angle.[79] Apical long-axis images including four-chamber, two-chamber and three-chamber views are used to measure longitudinal strain whereas short-axis images, at basal, mid and apical levels are used for measuring radial and circumferential strain.[119] During offline analysis, using specialized software, the myocardial speckles are tracked from a selected region of interest. The unique speckle pattern is tracked with a search algorithm to recognize the most similar speckle pattern from frame to frame where the displacement of each speckle represents tissue deformation.[80] The LV myocardium is then divided into six segments in the apical long-axis images and the strain values for all the segments are recorded and averaged to obtain the GLS and strain rate (SR). The same process is performed with the short-axis images to derive the segmental and global radial and circumferential strain and SR.[81]

Baseline LVEF and GLS are recommended in all patients evaluated with TTE before cardiotoxic cancer treatment initiation to stratify CTR-CVT risk and to identify significant changes during treatment.[82] A baseline borderline (50–54%) or reduced

(<50%) LVEF is a risk factor for future CTR-CVT from most cardiotoxic cancer therapies, in particular with anthracyclines or trastuzumab.[83] Increased baseline indexed LV end-diastolic volume can be a predictor of major CV events (symptomatic HF or cardiac death) during anthracycline chemotherapy in patients with preserved LVEF.[84] A normal LVEF does not exclude CTRCD and deformation parameters can detect early systolic impairment with sufficient test reliability.[85]

It is advised to use three apical views to determine GLS at baseline, especially in patients with moderate- and high-risk conditions.[86] A future decline in LVEF was predicted by a median GLS change of 13.6% with a 95% upper limit of a 15% GLS reduction.[87] Since the 15% cut-off increases specificity, it is advised to use it when assessing GLS during cancer treatment. GLS has been reported to identify patients at risk of CTRCD, but data are currently insufficient to recommend its use routinely[88].

Cardiac MR: The decline in LV mass was linked to worsening HF symptoms when the echocardiography findings were comprehensive and it was used as the gold standard imaging to measure the Left ventricular mass and LVEF. Compared to other modalities, it also aids in the detection of asymptomatic LV dysfunction[89.90] but further research is required to confirm this.

Nuclear imaging: Technetium-labelled red blood imaging is a common clinical tool used to evaluate cardiac function; however, use is restricted due to the repeated radiation exposure involved.

Endomyocardial biopsy: It is both the invasive test and the gold standard for detecting cardiac injury following chemotherapy.

Serum biomarkers: The troponin levels and NT-pro BNP levels are not typically measured to determine cardiac injury. However, some studies have demonstrated that these two markers aid in the prediction of a decline in LVEF, though further research is required to confirm this.

Red cell distribution width: RDW may be a promising biomarker for assessing high-risk individuals and cardiac dysfunction caused by cancer therapy. Cardiotoxicity brought on by chemotherapy causes oxidative stress and mitochondrial dysfunction, which in turn causes bone marrow dysfunction, abnormal heme synthesis, and an increase in RDW. Cancer chemotherapy decreases ejection fraction and increases the risk of CTRCD in patients with high RDW.

6. Management and prevention of drug-induced cardiotoxicity

Pharmacological interventions, such as statins, beta-blockers, and angiotensin-converting enzyme inhibitors, have been used to manage drug-induced hyperlipidaemia, hypertension, myocardial infarction, and HF and to mitigate their detrimental cardiovascular effects.[91] Angiotensin-converting enzyme inhibitors[92] and β-blockers[93] have been administered prophylactically to patients scheduled to receive anthracycline to reduce the incidence of drug-induced cardiomyopathies. It is possible to lessen chemotherapy-related cardiotoxicity by increasing infusion duration time[94], lowering total cumulative dose[95], and giving cardio-protective chelator agents like dexrazoxane.[96] Aspirin has been demonstrated to increase survival in cancer patients with thrombocytopenia and acute coronary syndromes while lowering bleeding risk.[97] Discontinuation of the causative agents is often warranted as the cardiovascular symptoms often disappear once treatment is suspended.

Some studies regarding detection of chemotherapy induced cardiotoxicity

Taufan M et al[98] prospectively studied 63 patients with breast cancer who were deemed amenable for anthracycline chemotherapy from March 2013 to March 2015 in University Hospital settings. Global LVEF, fractional shortening and the strain over 17 segments of the LV were examined using 2- dimensional TTE before and after chemotherapy. More than 15% reduction in longitudinal peak systolic strain (LPSS) was considered significant. The study showed significant global and segmental reduction in LPSS.

Ciro Santoro et al[99] had shown both the potential superiority and the suboptimal viability of 3D EF and 3D strain in detecting subclinical anthracycline cardiotoxicity in breast cancer patients. Standard 2D-echo, 2D STE-derived left ventricular GLS, 3D volumetric echo, and 3D STE with measurements of GLS, GCS, global area strain (GAS), and global radial strain were used to examine 100 breast cancer patients both before and after chemotherapy. The study demonstrated the superiority of 2D GLS over conventional echo and its strong viability. The E/e' ratio is advantageous for identifying cardiotoxicity.

Emily Hoe et al[100] examined 70 women (chemotherapy group) aged 54±8 years who had received anthracycline treatment with (n=19) or without (n=51) adjuvant trastuzumab up to 6 years previously, and 50 women controls. Left ventricular systolic (ejection fraction (LVEF%), peak systolic myocardial excursion, (Sm)) and diastolic (peak mitral E and A velocities, six-point average of mitral annular E' velocities) function, 2D global and regional longitudinal and radial strain were determined using standard 2D Doppler and tissue Doppler echocardiographic methods and speckle tracking software. Despite normal LVEF% (62±4% vs 60±63%, p=0.051)

the chemotherapy group had reduced E/A ratios (0.9±0.3 vs 1.1±0.3, p=0.003), global E' (10.2±2 vs 11.2±2.3, p=0.036), global Sm (9.0±1.3 vs 9.6±1.3, p=0.029) and global longitudinal 2D strain (18.1±2.2 vs 19.6±1.8, p=0.0001) in comparison with controls. In 18 (26%) of the chemotherapy group, global longitudinal strain was below the lower limit of the control group. Cigarette smoking was a negative predictor of longitudinal strain, but only in the chemotherapy group. Radial strain did not differ significantly between the two groups. There were no significant differences in EF%, global Sm and longitudinal strain between trastuzumab-treated individuals and controls. Author concluded that subclinical systolic and diastolic myocardial abnormalities were present in asymptomatic breast cancer survivors up to 6 years after standard chemotherapy. Adjuvant trastuzumab treatment did not appear to have an additive adverse impact on myocardial function in the medium-long term.

Isaac B Rhea et al[101] studies Incremental Prognostic Value of Echocardiographic Strain and Its Association with Mortality. In this retrospective study, 120 patients with cancer undergoing or scheduled to undergo chemotherapy and with normal ejection fractions (>50%) underwent assessments of GLS. Over an average follow-up period of 21.6±13.9 months, 57 of 120 patients died. Multivariate analysis of all significant univariate variables showed that Eastern Cooperative Oncology Group performance status (hazard ratio, 2.12; 95% confidence interval, 1.54–2.92; P < .001), male sex (hazard ratio, 1.93; 95% confidence interval, 1.14–3.27; P = .014), and GLS (hazard ratio, 0.89; 95% confidence interval, 0.81–0.97; P = .012) were significantly and independently associated with mortality. Stepwise analysis of the multivariate associations showed an increase in the global χ^2 value after adding GLS (P = .011) to significant clinical variables. Author concluded that Eastern Cooperative Oncology Group performance status, male sex, and GLS were significantly associated with all-

cause mortality in patients with cancer with normal ejection fractions receiving chemotherapy. Adding GLS to significant clinical variables provided incremental prognostic information.

Paul W. stoodley et al[102] enrolled 52 women with histologically confirmed breast cancer. Echocardiographic LVEF (by Simpson's method), global and regional peak longitudinal, radial, and circumferential 2D systolic strain were measured 1 week before and 1 week after chemotherapy. Global and regional longitudinal LV systolic strain was significantly reduced after treatment; global longitudinal strain decreased from -17.7 to -16.3% ($P < 0.01$) with 48% of global measurements reduced by > 10%. Global and regional radial LV systolic strain after treatment was also significantly reduced; global radial strain dropped from 40.5 to 34.5% ($P < 0.01$) with 59% of global measurements reduced by > 10%. In contrast, no reduction in LVEF > 10% after chemotherapy was observed. This study concluded that reduced LV systolic strain after anthracycline treatment may indicate early impairment of myocardial function before detectable change in LVEF.

Anita Boyd et al[103] studied 140 patients by detailed echocardiography before and within seven days post treatment. LVEF, GLS, strain rate and radial and circumferential strain were assessed. Additionally, left atrial volumes and LV diastolic parameters were evaluated. LVEF although reduced after treatment, remained within the normal range (60±3% vs. 59±3%, $p = 0.04$). Triplane GLS was significantly reduced after treatment (-20.0±1.6% vs. -19.1±1.8%, $p<0.001$). Sub-clinical LV dysfunction (>11% reduction in GLS compared to before therapy) occurred in 22% (29/135). Impaired diastolic function grade significantly increased from 46% to 57% ($p<0.001$%) after treatment. Diastolic dysfunction was more

common in the subgroup with reduced systolic GLS compared to those without changes in GLS (30% vs. 11%; p = 0.04). Twenty two percent of patients had sub-clinical LV dysfunction by GLS, whilst none had cardiotoxicity defined by LVEF, demonstrating that GLS is more sensitive for detection of sub-clinical LV systolic dysfunction immediately after anthracycline therapy. Diastolic dysfunction increased, particularly in the group with reduced GLS, demonstrating the close pathophysiological relationship between systolic and diastolic function.

Singh DK et al[104] studied 30 patients with newly diagnosed malignancy and 15 aged- and gender-matched healthy controls. These patients underwent 2D-echocardiography and STE at baseline and after the completion of their treatment. Baseline characteristics and echocardiographic parameters were similar between the cases and controls. No significant difference in left ventricular ejection fraction was seen before and after cancer therapy (64.27 ± 3.25 vs. 62.6 ± 3.12; P = 0.63), whereas global longitudinal strain reduced significantly from –21.16 ± 2.50 before cancer therapy to –19.86 ± 3.22 after it (P < 0.01). The global circumferential strain was also reduced significantly from –23.60 ± 7.36 before cancer therapy to –21.33 ± 6.97 after it. A significant reduction in segment-wise longitudinal strain rate was observed among the cases after cancer therapy in all segments. This study revealed that there was a significant worsening of LV systolic function as measured by the strain parameters on STE in cancer patients on chemotherapy and/or radiotherapy which was not detected by 2D echocardiography alone.

Daiki Yaegashi et al[105] enrolled 202 cancer patients for anthracycline treatment and followed up for 12 months. The patients were divided into 2 groups based on the median value of baseline RDW before chemotherapy [low RDW group, n = 98, 13.0

[12.6–13.2]; high RDW group, n = 104, 14.9 [13.9–17.0]]. Cardiac function was assessed serially by echocardiography at baseline (before chemotherapy), as well as at 3, 6, and 12 months after chemotherapy with anthracycline. Baseline left ventricular end systolic volume index and LVEF were similar between two groups. After chemotherapy, LVEF decreased at 3- and 6-month in the high RDW group [baseline, 64.5% [61.9–68.9%]; 3-month, 62.6% [60.4–66.9%]; 6-month, 63.9% [60.0–67.9%]; 12-month, 64.7% [60.8–67.0%], P = 0.04], but no change was observed in low RDW group and concluded that CTRCD was higher in high RDW group than in low RDW group.

Lajja Desai et al[106] did a retrospective analysis of 589 pediatric cancer patients who received anthracyclines. ECG endpoints were sum of absolute QRS amplitudes in the 6 limb leads (ΣQRS(6 L)) and corrected QT interval (QTc). Cardiomyopathy was defined by echocardiogram as ejection fraction < 50%, fractional shortening < 26%, or left ventricular end-diastolic diameter z-score > 2.5. The authors reported that male sex, race, older age at first dose, and larger body surface area were associated with development of cardiomyopathy. A 0.6 mV decrease in ΣQRS(6 L) and 10 ms increase in QTc were associated with an increased risk of developing cardiomyopathy with hazard ratios of 1.174 (95% CI = 1.057–1.304, p = 0.003) and 1.098 (95%CI = 1.027–1.173, p = 0.006) respectively.

AIM AND OBJECTIVES

AIM:

- Early detection of cardiotoxicity in cancer patients after chemotherapy by various novel diagnostic markers.

PRIMARY OBJECTIVES

1. Two-dimensional (2D) strain imaging to detect subclinical left ventricular (LV) dysfunction.

2. To compare conventional and strain 2D-echo findings for early diagnosis of chemotherapy induced cardiotoxicity during subclinical phase.

SECONDARY OBJECTIVES

1. To find relation between RDW and associated cardiotoxicity by chemotherapy.

2. To study various ECG changes caused by cancer chemotherapy in patients with normal baseline ECG and also to determine if ECG changes precede echocardiographic findings of cardiomyopathy.

RESEARCH DESIGN AND METHODOLOGY

STUDY SETTING:

Patients attending the OPD and IPD of Department of Cardiology and Radiation Oncology, AIIMS, Jodhpur

STUDY DESIGN:

Prospective observational study

SAMPLING METHOD

Purposive Sampling

ELIGIBILITY CRITERIA

INCLUSION CRITERIA:

1. Age ≥ 18 years
2. Written informed consent
3. Previously normal cardiac function LVEF ≥ 50%
4. Estimated survival ≥ 6 months
5. Normal baseline ECG
6. Normal baseline hematological and cardiac biomarkers

EXCLUSION CRITERIA:

1. Patient who does not give informed written consent for participation in study.
2. Poor Image Quality

3. Concurrent radiotherapy

4. Prior h/o systemic cytotoxic agents

5. Prior history of percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG)

6. Patients presented with acute coronary syndrome (ACS)

7. Congestive heart failure

8. Atrial fibrillation

9. More than trivial valvular heart disease

10. Failure to assess all segments by speckle tracking

11. Sepsis

12. CKD

SAMPLE SIZE:

As this was a time-bound study, we enrolled the 193 patients from day of approval to 12 months at the outpatient and inpatient services of Department of Cardiology and Radiation oncology, All India Institute of Medical Sciences, Jodhpur, Rajasthan.

STUDY PROCEDURE

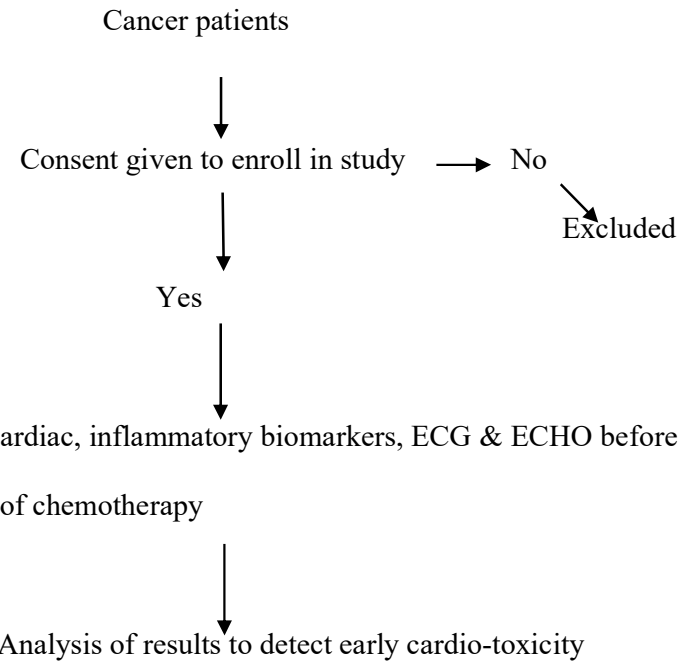
After seeking approval from the Institutional Ethics Committee recruitment of patients were selected based on the inclusion and exclusion criteria. Patients from the OPD & IPD of Department of Cardiology and Radiation Oncology, AIIMS Jodhpur were selected, who have been diagnosed with cancer. On the visit to hospital baseline assessment of various variables was done which includes:

- **Socio-demographic**: Name, age, gender

- **Clinical**: Presenting Complaints, past history of CAD/HTN/DM, smoking history, weight, height, BMI
- **Investigations**: CBC, RFT, Random blood sugar, HbA1c, Lipid profile, Cardiac Biomarkers (cTnT, cTnI, CK-MB, NT-Pro BNP), Electrocardiography, Echocardiography

After selection of cancer patients who are planned to go for chemotherapy, a pre and 1-month post chemotherapy hematological, cardiac and inflammatory biomarkers, ECG and 2D-transthoracic echocardiography was done.

STUDY ALGORITHM



Conventional 2D-Echocardiography and speckle tracking echocardiography (STE)

Echocardiography was performed with the patient at rest in the left lateral position at end-expiration, using the Phillips Epiq 7, with image acquisition with a S5-1

transducer and harmonic imaging. Initial echocardiogram was performed before chemotherapy and follow-up echocardiogram was done 1 month following completion of chemotherapy. The measurements were done initially by single observer which was reassessed by a second observer who was specialized in the method and was blinded to study. The measurements and image acquisition followed the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[107]

All standard measurements were recorded in the parasternal long- and short-axis views, and apical four-chamber view. The LVEF was calculated from the apical 4- and 2-chamber views by using a modified Simpson's biplane method. Diastolic function was evaluated by use of mitral flow with anterograde values of E wave and A wave, tissue Doppler of septal and lateral mitral annulus, and E/E' ratio. Diastolic function was categorized by the following previously described and validated criteria[108]: normal filling pattern (normal diastolic function), grade I (delayed relaxation), grade II (pseudo-normal pattern), or grade III diastolic dysfunction (restrictive pattern).

In our study, cardiotoxicity was defined as reduction of at least 5% of EF values < 55% in symptomatic patients, or a reduction of at least 10% of EF values < 55% in asymptomatic patients (CREC criteria).

STE and strain imaging were done using Philips QLAB, cardiac and vascular ultrasound quantification software. Standard B-mode images of the left ventricle were acquired in apical four-, two- and three-chamber views and in the parasternal short-axis view at mid-papillary, basal and apical level. After manual tracing of the endocardial border of LV in longitudinal and short-axis plane at end-systolic frame

and selecting the appropriate region of interest, the software automatically determined six segments in each view. Systolic longitudinal strain (LS) and circumferential stain (CS) were measured in all segments and global strain was calculated by software.

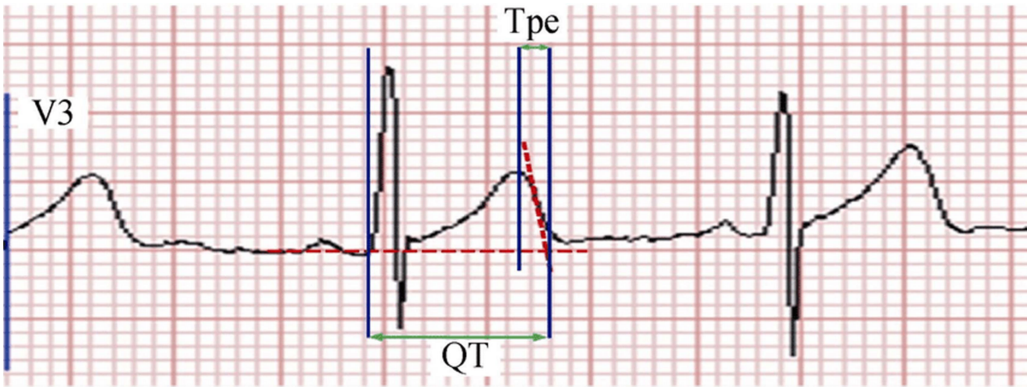
RDW was measured using a Sysmex XN-1000 hematology analyser. The patients were divided into 2 groups based on the median value of baseline RDW-CV before chemotherapy [low RDW group (<15) and high RDW group (≥15)].

Analysis of result was done to detect early cardiotoxicity.

ECG

All ECGs were recorded and analyzed on a digital system (Philips ECG machine). ECGs were digitized at 500 Hz, and measurements were verified manually by a single investigator, blinded to knowledge of the echocardiographic findings. We used a standard 12-lead ECG tracing at 25-mm/s paper speed and 10-mm/mV amplitude. Measurements of other ECG intervals were conducted manually using digital onscreen software. The following ECG complexes and intervals were analyzed: heart rate and rhythm, P, P-R, QRS, T, S-T, Q-T and QTc as well as the T peak to T end (TpTe) and absolute QRS amplitudes in the 6 limb leads (ΣQRS(6 L)). Amplitudes were measured in millivolts (mV) from peak to trough of the QRS.

QT and QRS intervals were measured manually with calipers and magnifying for decreasing the error measurements. The QT interval was measured from the beginning of the QRS complex to the end of the T wave. Heart rate corrected QT interval (QTc) was calculated using Bazett's formula.[109] Normal value of QTc is ≤430 ms for men and ≤450 ms for women).[110] The TpTe/QT ratio was calculated as the ratio of TpTe in that lead to the corresponding QT interval.[111]



The TpTe was measured from Tpeak to Tend. TpTe and QT intervals were measured in lead V5.[112] If V5 was not suitable, leads V4 and V6 in that order were measured.[113] The end of the T wave was defined as the intersection of the tangent to the down slope of the T wave and the isoelectric line[114] when not followed by a U wave or if distinct from the following U wave. If a U wave followed the T wave, the T-wave offset was measured as the nadir between the T and U waves. If the T-wave amplitude was 1.5 mm in a particular lead, that lead was excluded from analysis. Prolonged TpTe was defined as >85 ms.

The algebraic sum of positive and negative deflections of the QRS complex in the six limb leads (ΣQRS (6 L)) also measured in millivolts (mV) from peak to trough of the QRS to evaluate voltage magnitude of that complex.[115] The exclusive use of limb lead voltage in this study was of special importance because of the known distorting effect of surgical removal of the breast and chest wall on the precordial leads.[116]

ECG scoring was evaluated concerning the following parameters: contiguous Q wave, QRS duration, marker of LV hypertrophy and prolongation of the JTc interval. **Contiguous Q waves** were defined as a Q wave duration > 40 ms and/or a Q:R ratio amplitude >25% in any two contiguous leads.[117] The presence of a contiguous Q wave counted as 1 point. The **QRS duration** was measured in a standard manner in lead II.

A QRS duration of 110 ms for 2 points. The **LV hypertrophy** was assessed by the Sokolow−Lyon Index being positive (+1 point) if the sum of S in V1 and R in V5 or V6 was ≥3.5 mV.[118] The **JTc time** was calculated by QTc minus the QRS duration with QT being measured as the maximum value in leads II, V5 or V6 and QTc being calculated with Bazzett's formula.[119] A JTc prolongation > 360 ms accounted for 1 point. After assessment of all 4 parameters, the ECG score was calculated by summation[120] (Table).

Variables		**Points (maximum 5)**
Contiguous Q wave		+1
QRS duration	≤ 80 ms	0
	80 – 110 ms	+1
	>110 ms	+2
LV hypertrophy		+1
Prolonged JTc		+1

ETHICAL JUSTIFICATION

1. This study was undertaken only after obtaining the Ethical Clearance and receiving approval from the institute's Ethics committee.

2. Patients were enrolled after obtaining the proper informed consent.

STATISTICAL ANALYSIS

Data Entry was done in MS-Excel. Statistical Analysis was done using SPSS version 25.0. The results are presented in frequencies, percentages, and mean ± standard deviation and percentages. Measures of central Tendency were calculated of Quantitative Variables. We used the Shapiro-Wilk test to discriminate which variables were normally or not normally distributed. Normally distributed variables were shown as mean ± standard deviation. Non-normally distributed variables were indicated by median with interquartile range. Paired t-test or Wilcoxon signed-rank test was used for comparing baseline and follow-up markers. Paired t-test was used to compare LV strain parameters before and after chemotherapy. Linear regression analysis and Pearson's correlations were performed to examine the relationship of LV systolic strain parameters to cumulative anthracycline dose and age. A 2x2 analysis was used to assess the effect of baseline clinical risk factors on altered LV systolic function at follow-up, while univariate analysis was performed to evaluate the effect of alteration in strain to cumulative anthracycline dose, age, and clinical risk factors. Spearman correlation was calculated for the change (i.e., follow-up minus baseline) in LVEF with baseline and follow-up. $P<0.05$ was considered statistically significant.

OBSERVATION AND RESULTS

In 12 months, a total of 193 patients were included in the study and data were analyzed. The mean age was 45.17 ± 1.42 years. 123 were females and 70 were males.16 (8%) patients were hypertensive, 9 (5%) were diabetic, 3 (2%) had dyslipidaemia and 4 were smokers. 7 patients were on ACE-I/ARB and 5 were on β-blockers.

Table 1: Baseline characteristics of patients

Baseline characteristics		**Cardiotoxicity**	**No cardiotoxicity**	**P-value**
Age		44.61±19.7	43.65±18.7	0.7
Sex (N=193)	Female (N=123)	55 (44.7%)	68 (55.3%)	0.3
	Male (N=70)	44 (62.9%)	26 (37.1%)	
Hypertension, 16 (8%)		12 (75%)	4 (25%)	0.001
Diabetes mellitus, 9 (5%)		5 (55.5%)	4 (44.5%)	0.07
Hypercholesterolemia /Dyslipidaemia, 3 (2%)		2 (66.7%)	1 (33.3%)	0.1
Smoker, 4 (2%)		3(75%)	1(25%)	0.338
ACE-inhibitors/ARB, 11 (5.6%)		6 (54.5%)	5 (45.5%)	0.765
Beta-blockers, 6 (3.1%)		2 (33.3%)	4 (66.7%)	0.683
Statins, 6 (3.1%)		3 (50%)	3 (50%)	0.969

There was no significant association between the two groups based on age, sex, DM and hypercholesterolemia. While there was a highly significant association based on hypertension between two groups. The usage of angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB), β-blockers and statins were similar between the two groups without any significance.

Table 2: Type of cancer and chemotherapy

Baseline characteristics	Cardiotoxicity	No cardiotoxicity	P-value
Breast cancer, n=111 (57.4%)	51(26.4%)	60(31.0%)	0.08
Hematological cancers, n=54 (27.9%)	31(16%)	23(11.9%)	0.178
Gastro-intestinal cancers n=24 (12.4%)	12(6.2%)	12(6.2%)	0.97
Lung, n=4 (2%)	2(1%)	2(1%)	0.94
Chemotherapy			
Anthracyclines	64(33.1%)	68(35.2%)	0.64
Cyclophosphamide	51(26.4%)	61(31.6%)	0.08
Cisplatin	4(0.8%)	3(1.5%)	0.668

There was no significant difference in cardiotoxicity who were treated with different chemotherapy (Table 2). Majority of patients (33.1%) having cardiotoxicity belonged to those who took anthracycline, followed by cyclophosphamide.

Table 3: Conventional and strain echo parameters

Systolic Parameters	Before chemotherapy	After chemotherapy	P-value
LVEDV (ml)	90.1±8.3	91.8±7.4	0.08
LVESV (ml)	25.2±14.5	39.0±29.5	0.0001
LVEF (Simpson, %)	66.9±8.3	54.2±12.2	0.0001
GLS	-17.98±4.5	-15.9±6.9	0.0002
GCS	-27.7±11.7	-16.5±2.6	0.0001

Diastolic Parameters		Before chemotherapy	After chemotherapy	P-value
E/A		1.28±0.3	1.09±0.3	0.05
DT (ms)		156±26	179±21	0.03
E' (cm/s)		9.2.0±2.7	8.3±2.4	0.01
E/E'		8.4±3.3	9.6±4.0	0.04
LVDD	Normal	53	33	0.08
	I	102	113	
	II	30	33	
	III	8	14	

Left ventricular end-systolic volume (LVESV) increased from 25.2±14.5 ml to 39±29.5 ml (p=0.0001) during the study without any significant change in left ventricular end-diastolic volume (LVEDV) [90.1±8.3 ml to 91.8±7.4 ml (p=0.08). There was significant decline in Left ventricular ejection fraction (LVEF) before and after cancer therapy (66.9±8.3% vs. 54.2±12.2; P = 0.0001). Global longitudinal myocardial strain (GLS) was reduced from -17.98±4.5% to -15.9±6.9%) and the difference was statistically significant (P=0.0002). Global circumferential strain

(GCS) was reduced significantly after chemotherapy from -27.7±11.7% to -16.5±2.6% and the difference was statistically significant (P=0.0001). Diastolic function was categorized[18]: normal filling pattern (normal diastolic function), grade I (delayed relaxation), grade II (pseudo-normal pattern), or grade III diastolic dysfunction (restrictive pattern). There were significant changes in the main diastolic parameters. E/A ratio was decreased significantly while deacceleration time (DT) was increased after chemotherapy. There was a significant decrease in E' at mitral annuli and an increase in the trans-mitral Doppler early filling velocity E/E' ratio. The baseline LVDD grade was deranged in 140 of the study subjects but there was an increase in the grade of LVDD in 20 patients after chemotherapy. The difference was not significant with a P-value of 0.08.

Table 4: Association of mortality with baseline parameters

Variables	Cardiotoxicity		P-value
	Dead	Alive	
Mean age (year)	47.4±18.75	44.5± 19.5	0.41
Male	23	47	0.0001
Female	13	110	0.06
Breast cancer	12	99	0.0001
Haematological cancer	11	43	0.0001
GI Cancer	11	13	0.0001
Lung cancer	2	2	0.0001

In this study 36 patients were dead, whose mean age was 47.4±18.75, 23 were male and 13 were female. There was no significant difference in the mean age of dead and alive patients, while gender and type of cancer showed significant differences.

Table 5: Comparison of pre chemotherapy and post chemotherapy LVEF, GLS, GCS in dead patients

	Chemotherapy		
	Pre	Post	P-value
Simpson's LVEF	67.73±14.3	59.89± 9.2	0.0001
GLS	-23.67± 7.2	-14.24±3.2	0.0001
GCS	-34.4±7.8	-21.68±7.2	0.0001

The above table shows that there was a significant difference in LVEF (by Simpson's), GLS and GCS among pre and post-chemotherapy in dead patients.

Table 6: Comparison of cardiotoxicity in dead and alive patients

	Dead	Alive	P-value
Simpson's LVEF	54.2±12.2	59.89± 9.2	0.01
GLS	-12.24±3.2	-15.9±6.9	0.04
GCS	-16.5±2.6	-21.68±7.2	0.02

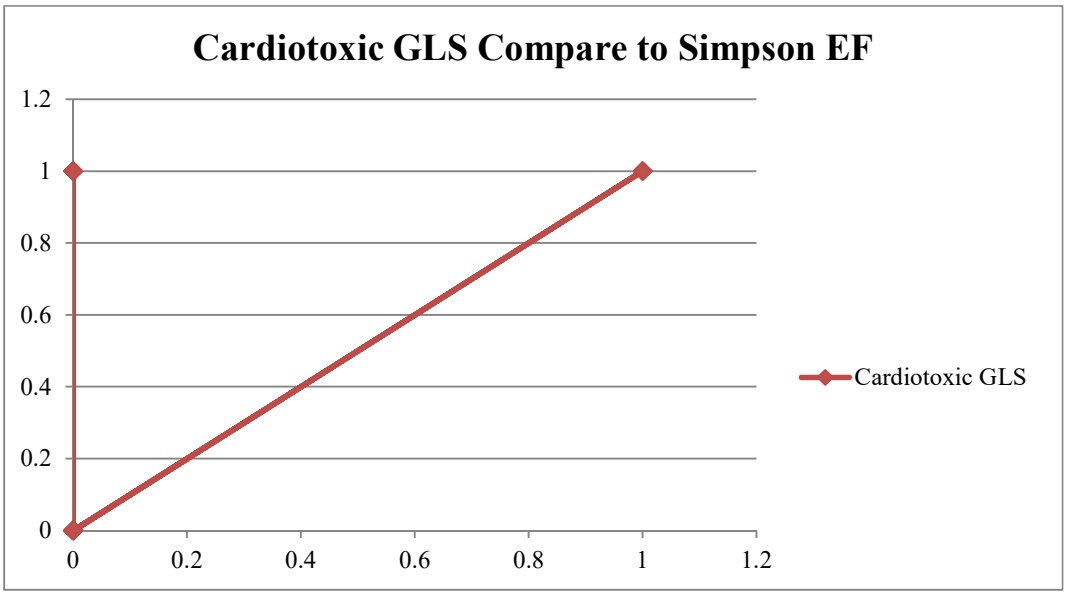
There was a significant difference in LVEF, GLS and GCS scores of dead and alive patients. The score was the dead patients were lower.

Table 7: Cox-Regression Model

	Baseline	Standard error	P-value
Cox regression model			
Simpson LVEF (%)	54.2	12.2	0.0001
GLS (%)	-15.9	6.9	0.0002
LVEDV	80.8	41.4	0.0003
Cox regression model			
LVEF (%)	54.2	12.2	0.0001
GCS (%)	-16.5	2.6	0.0001
LVEDV	80.8	41.4	0.0003

ROC curves to predict cardiotoxicity by use of LV GLS

To define the most accurate cut-off point of the absolute LV GLS value to predict cardiotoxicity, a ROC curve was built. The LV GLS value of -15.9 % showed the sensitivity of 80% and specificity of 99% for predicting cardiotoxicity. This confirms LV GLS as an excellent independent factor of cardiotoxicity, which can be assessed by use of the data from cox regression (p= 0.0002).



ROC curves to predict cardiotoxicity by use of GCS

To define the most accurate cut-off point of the absolute GCS value to predict cardiotoxicity, a ROC curve was built. The accuracy of the GCS value of -16.5 was assessed by use of its sensitivity and specificity (100% and 93%, respectively). This confirms GCS as an excellent independent factor of cardiotoxicity, which can be assessed by use of the data from cox regression (p= 0.0001).

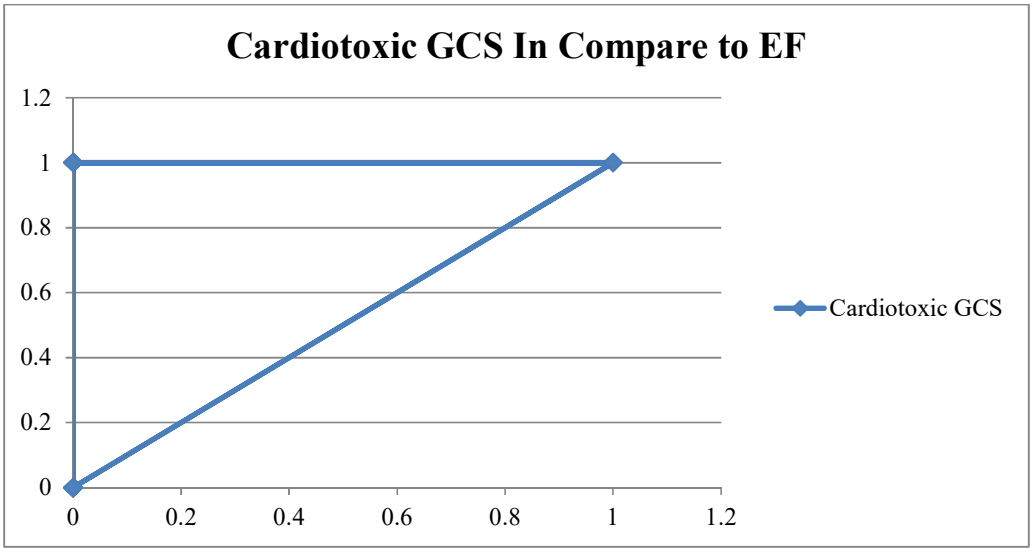


Table 8: Baseline characteristics according RDW

Demography (N=193)	Pre-chemotherapy		P-value
	Low RDW (N=95)	High RDW (N=98)	
Age (years)	46.82±17.8	44.92±19.5	0.3
Male	31(44.28%)	39(55.71%)	0.3
Female	64(52.03%)	59(47.96%)	(χ2 1.07)
Cardiovascular risk factors			
Hypertension, 16 (8%)	5	11	0.047
Diabetes mellitus, 9 (5%)	2	7	0.471
Hypercholesterolemia /Dyslipidaemia, 3 (2%)	1	2	0.351
Cardiovascular medications			
ACE-inhibitors/ARB	6	5	0.765
Beta-blockers	2	4	0.683
Statins	3	3	0.969

There were no statistical differences in age, sex, and cumulative anthracycline dose between the two groups at baseline. There was no significant difference in co-morbidities between two groups except hypertension. The usage of angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB), β-blockers and statins were similar between the two groups without any significance.

Table 9: Type of cancer according RDW

Oncological disease	Pre-chemotherapy		P-value	Post-chemotherapy		P-value
	Low RDW n=95	High RDW n=98		Low RDW n=59	High RDW n=134	
Breast cancer, n=111	59	52	0.20	35	76	0.14
Hematological cancer, n=54	21	33	0.22	19	35	0.89
GI Cancer, n=24	14	10	0.34	12	12	0.6
Lung, n=8	5	3	0.493	4	4	0.71

There was total of 193 patients, 111 were breast cancer, 54 were hematological cancer, 24 were GI cancers and 4 having lung cancer. There was no significant association of RDW in breast, lung, gastrointestinal and hematological cancer pre as well post chemotherapy.

Table 10: Hematological parameters before and after chemotherapy

Hematological parameters	Pre-chemotherapy	Post-chemotherapy	P-value
Haemoglobin (g/dl)	11.0±2.5	10.4±2.2	0.01
White blood cell (µl)	8693.8±902.7	8008.6±428.1	0.491
Platelet (X 10^3/ µl)	2.84±1.43	2.74±1.44	0.440
MCV (fl)	84.4±9.7	86.2±8.6	0.001
RDW	15.5±2.6	16.0±2.9	0.01

Laboratory data showed that hemoglobin and mean corpuscular volume were reduced post chemotherapy and RDW was increase significantly.

Table 11: Echocardiographic parameters before and after chemotherapy in relation with RDW

Echocardiographic parameters	Pre-chemotherapy			Post-chemotherapy		
	Low RDW	High RDW	P-value	Low RDW	High RDW	P-value
Diastolic parameters						
E (median) IQR	73.7 (59.2-91.7)	81 (66.6-88.7)	0.279	82.5 (70.22-94.1)	82.5 (75.7-93.6)	0.786
A (median) IQR	71.3 (56.8-88)	74.2 (61.2-84.4)	0.593	78.5 (67.7-98.5)	77.6 (67.3-94.7)	0.362
E' (median) IQR	8.41 (7.25-10.8)	8.9 (7.13-11.1)	0.681	8.9 (7.18-10.95)	9.8 (8.39-11.5)	0.02
E/E' (median) IQR	8.5 (6.43-11.11)	9.16 (7.35-11.46)	0.212	8.4 (6.8-11.38)	8.06 (6.93-10.4)	0.334
LVDD	28 (14.5%)	25 (13%)	0.986	16 (8.4%)	7 (3.7%)	0.646
	67 (34.7%)	73 (37.8%)		79 (41.4%)	81 (42.4%)	
Systolic parameters						
LVEDV (ml)	67.1 (56.6-83.5)	66.3 (52.6-88.7)	0.785	70 (54.8-105)	70 (49.5-96.8)	0.203
LVESV (ml)	22.3 (16.4-30.1)	22.65 (17.9-30.1)	0.791	33.3 (23.2-47.6)	33.3 (18.9-38.2)	0.158
LVEF (Simpson, %)	68.4 (59.7-75.2)	65.4 (59.6-73.8)	0.902	54.8 (49.9-60.1)	55.8 (52.4-62)	0.221

FS, %	37.4 (31.8-43.9)	37.4 (31.1-42.5)	0.405	29.25 (26.05-33.65)	29.1 (26.5-34)	0.651
GLS	-17.4 {(-20.0)-(-14.1)}	-16.95 {(-22.2)-(-15.4)}	0.51	-17.7 {(-19.2)-(-13.7)}	-17.7 {(-19.9)-(-12..7)}	0.899
GCS	-29.4 {(-32.2)-(-23.3)}	-28.65 {(-34)-(-23.5)}	0.584	-23 {(-26.7)-(-20.2)}	-23 {(-26.5)-(-20.2)}	0.913

LVEDV left ventricular end-diastolic volume; LVESV left ventricular end-systolic volume, EF ejection fraction, FS fractional shortening, GLS global longitudinal strain, GCS global circular strain

Diastolic parameters

Pre-chemotherapy there was no significant difference in the diastolic parameters between low and high RDW. The baseline LVDD grade was deranged in 140 (72.5%) of the study subjects but there was an increase in the grade of LVDD in 20 (10.3%) patients after chemotherapy. The difference was not significant with a P-value of 0.08. Post chemotherapy there was no significant difference in the diastolic parameters between Low and High RDW.

Systolic parameters

There was no significant difference in the systolic parameters between low and high RDW pre- and post-chemotherpay.

Table 12: Correlation of chemotherapy and cardiotoxicity with RDW

Echocardiographic parameters		Post-chemotherapy		P-value
		Low RDW n=78	High RDW n=115	
LVEF (Simpson)	No cardiotoxicity	68 (87.2%)	101 (87.8%)	0.894
	Cardiotoxicity	10 (12.8%)	14 (12.2%)	
GLS	No cardiotoxicity	47 (60.3%)	73 (63.5%)	0.651
	Cardiotoxicity	31 (39.7)	42 (36.5%)	
GCS	No cardiotoxicity	42 (53.8%)	67 (58.3%)	0.544
	Cardiotoxicity	36 (46.2%)	48 (41.7%)	

According to Simpson's method, cardiotoxicity developed in 10 (12.8%) patients in low RDW group and 14 (12.2%) patients in high RDW group with no statistical significance (p=0.894). According to global longitudinal strain (GLS) method, cardiotoxicity developed in 31 (39.7%) patients in low RDW group and 42 (36.5%) patients in high RDW group with no statistical significance (p=0.651). According to global circumferential strain (GCS) method, cardiotoxicity developed in 36 (46.2%) patients in low RDW group and 48 (41.7%) patients in high RDW group with no statistical significance (p=0.544).

Table 13: Comparison of ECG Parameters Before and After Chemotherapy

	Before chemotherapy	After chemotherapy	Paired t-test	95% CI
Heart rate (bpm)	84.9±19.3	85.9±18.5	0.5	-4.78 to 2.7
PR interval (ms)	141.6±29.9	140.08±30.13	0.4	-4.48 to 7.5
QRS axis (°)	44.6±31.8	44.3±32.9	0.3	-6.17 to 6.7
QRS interval (ms)	88±15.13	87.0±11.18	0.4	-1.66 to 3.66
QT interval (ms)	363.3±36.09	364.8±33.4	0.6	-8.45 to 5.45
QTc interval (ms)[a]	427.9±21.6	451.9±22.4	0.03	-5.40 to 3.40
ΣQRS(6 L)[a]	14.4±7.8	14.4±7.5	0.2	-1.53 to 1.53
TpTe (ms)	69.2±20.5	66.6±21.5	0.22	-1.60 to 6.80
TpTe/QT	0.20±0.65	0.18±0.05	.0001	-0.03 to -0.02
TpTe/QTc	0.15±0.04	0.15±0.05	1	-1.53 to 1.53

[a]Data presents as median (interquartile range) or mean ± SD

Changes in Heart Rate, PR, QRS and QTc Intervals

Heart rates in the whole study group were normal before therapy started and did not significantly increase or decrease after the start of therapy (84.9±19.3 bpm vs. 85.9±18.5 bpm, p = 0.5). All patients had sinus rhythm before and after therapy started, no patient developed new atrial fibrillation or atrial flutter during the follow-up. PR intervals did not significantly change after therapy started (141.6±29.9ms vs. 140.08±30.13ms, p= 0.4). QRS axis did not significantly change after therapy started (whole study group: 44.6±31.8ms vs. 44.3±32.9 ms, p = 0.3). QRS interval did not significantly change after therapy started (whole study group: 88±15.13ms vs. 87.0±11.18ms, p = 0.4). None of the patients developed a RBBB or LBBB. ΣQRS(6L) had no significant change after chemotherapy. It was same as before i.e.

14.4±7.8 vs. 14.4±7.5 (p=0.2). There was no significant prolongation of QT interval before and after chemotherapy (363.3±36.09 vs. 364.8±33.4, p=0.6). There was no significant change in TpTe/QTc (0.15±0.04 vs. 0.15±0.05, p=1.0). While there was highly significant (.0001) change seen in, QTc interval, TpTe/QT and ECG score (before chemotherapy-0.20±0.65, after chemotherapy -0.18±0.05).

Table 14: Comparison in ECG Parameters in Cardiomyopathy and No Cardiomyopathy Groups

	Cardiomyopathy	No Cardiomyopathy	P-value
Change in ΣQRS(6L)	12.9±6.3	14.4±7.8	1
Change in QTc	399.7±25.8	427.9±21.6	0.001

When comparing the change in ECG parameters before and after anthracycline therapy in the cardiomyopathy versus no cardiomyopathy group, there was a greater decrease in ΣQRS(6L) in the cardiomyopathy group although there was no statistically significant difference. There was statistically significant difference in the QTc interval change between these groups, the data trended in the expected direction with a greater decrease on average in patients who developed cardiomyopathy.

Table 15: Comparison of Cardiotoxicity in Dead and Alive Patients

	DEAD	ALIVE	P-value
QTc interval (ms)	416.9±18.6	399.7±25.8	0.01
TpTe (ms)	69.2±20.5	66.6±21.5	0.01
TpTe/QT	0.15±0.04	0.18±0.05	.0001

There was significant difference in cardiotoxicity among QTc interval, TpTe (ms) and TpTe/QT of dead and alive patients. These are positively associated with dead patients.

Table 16: Composition of ECG Score pre- and post-chemotherapy

Score Parameter		Pre Chemotherapy	Post Chemotherapy	P value
Contiguous Q wave		5	5	1
QRS (ms)	< 80	47 (24.9%)	49(25.3%)	0.9
	80-110	136(71%)	136(70.4%)	1
	>110	10(4.1%)	8(4.1%)	0.73
LV Hypertrophy		2(1.03%)	2(1.03%)	1
Prolonged JTc		40(21.2%)	41(21.2%)	0.92
ECG score	<2	168(87%)	162(84%)	0.08
	>2	25(13%)	31(16%)	0.02

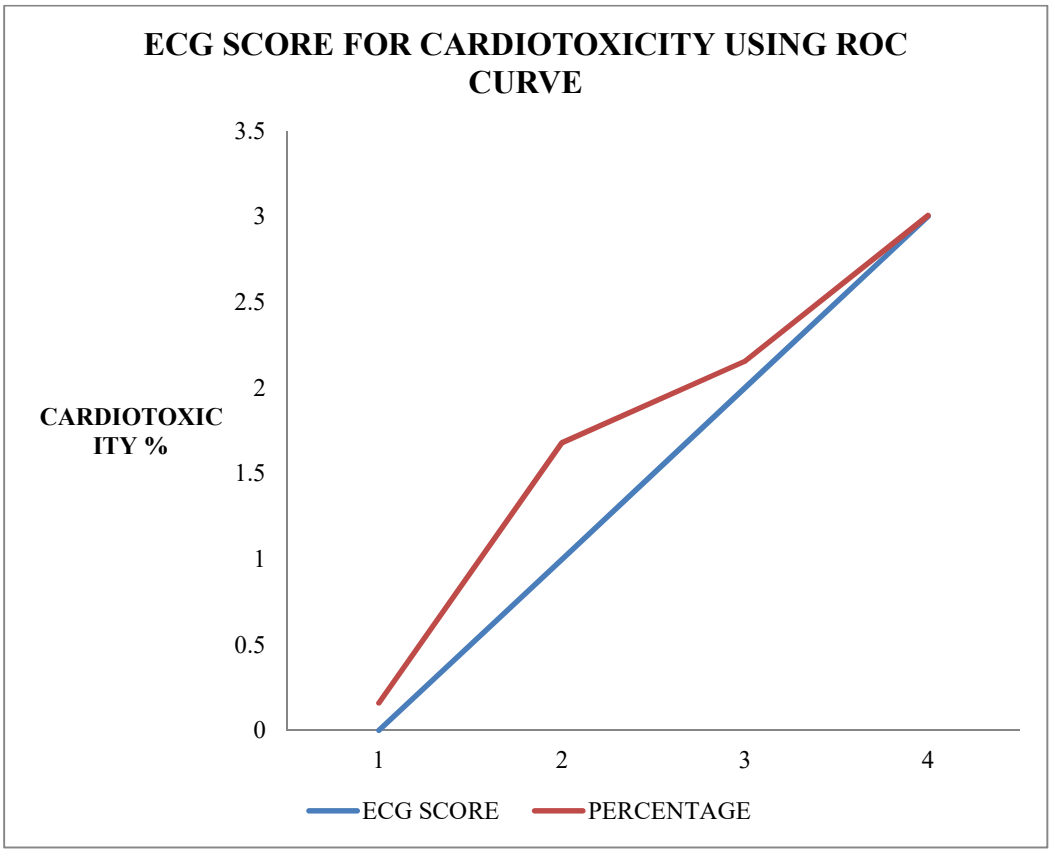
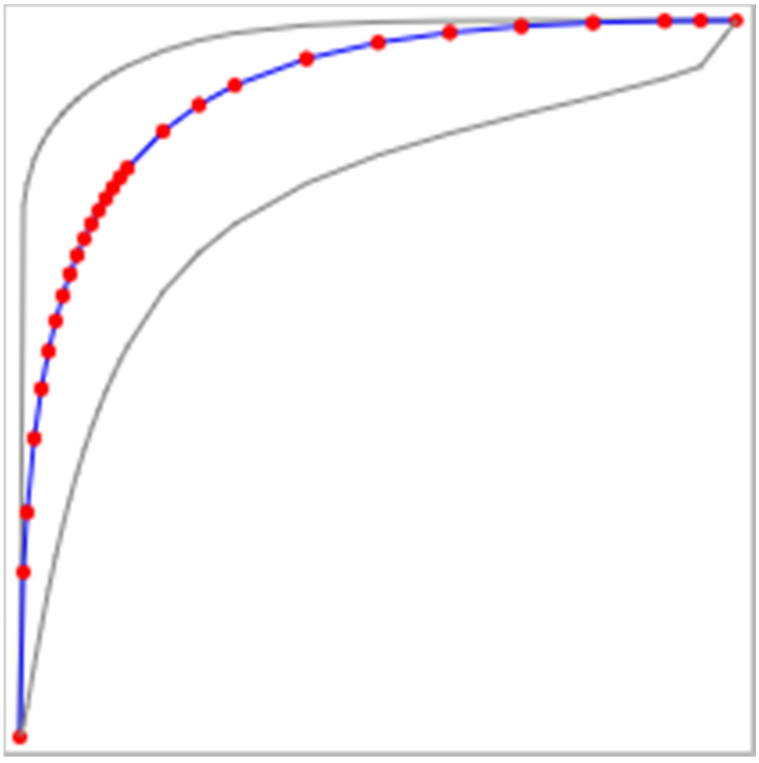


TABLE 17: Prediction of Cardio toxicity by use of ECG Score

a) TpTe

Variable	Value	95% CI
Sensitivity	88%	-0.75 to 2.5
Specificity	80%	-1.9 to 3.5
Accuracy	84%	-1.64 to 3.2

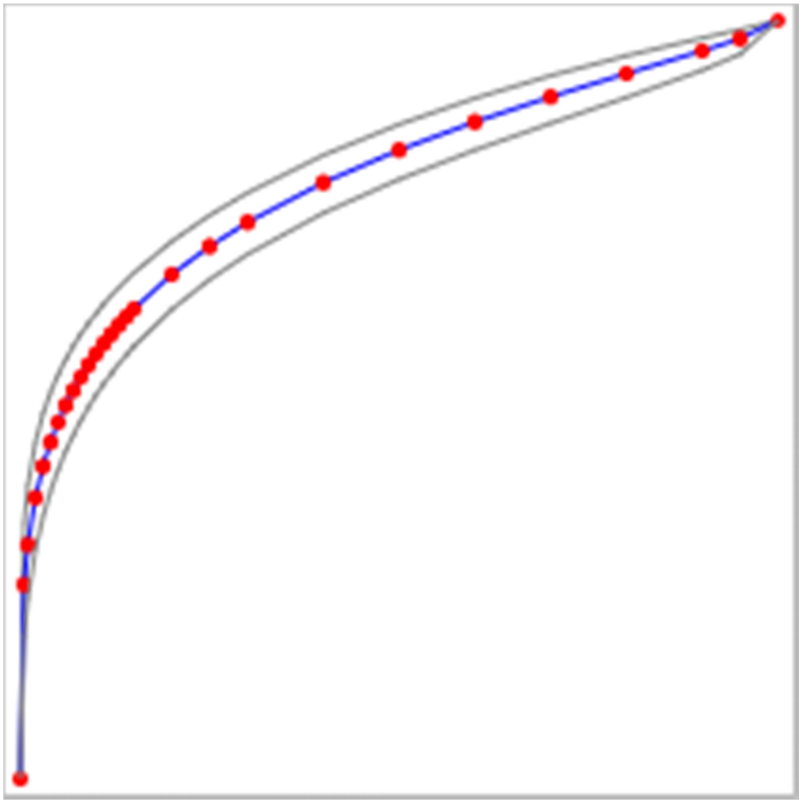
The ECG test showed sensitivity of 88% and specificity of 80%. To define the most accurate cut-off point of the absolute ECG value to predict cardiotoxicity, a ROC curve was built. The area under the ROC curve for TpTe was 0.905 (95% CI, 0.69 to 0.77).



b) QTc interval

Variable	Value	95% CI
Sensitivity	68.6%	-0.18 to 0.33
Specificity	79.2%	-0.28 to 0.38
Accuracy	73.9%	-0.34 to 0.48

Above test showed sensitivity of 68.6% and specificity of 79.2%. To define the most accurate cut-off point of the absolute ECG value to predict cardiotoxicity, a ROC curve was built. The area under the ROC curve for QTc was 0.79.



DISCUSSION

There has been a progressive improvement in the cancer survival rate due to the availability of effective remedial options. Cardiac dysfunction related to cancer therapeutics remains an important management issue in these cases. Hence it is important to assess the myocardial functions of cancer patients before starting chemotherapy and/or radiotherapy and during the treatment. Multiple mechanisms have been implicated in the pathophysiology of cancer-induced cardiotoxicity. However, the prolongation of life duration following cancer treatment is greatly improved, and techniques that ensure early detection and timely management of cardiotoxicity are essential. Early detection and prompt therapy of cardiotoxicity appear crucial for substantial recovery of cardiac function.

In 12 months, a total of 193 patients were included in the study and data were analyzed. The mean age was 45.17 ± 1.42 years. 123 were females and 70 were males. 16 (8%) patients were hypertensive, 9 (5%) were diabetic, 3 (2%) had dyslipidaemia and 4 were smokers. 7 patients were on ACE-I/ARB and 5 were on β-blockers. There was no significant association between two groups based on age, sex, DM and hypercholesterolemia. While there was a highly significant association based on hypertension between two groups ($p<0.001$). These findings were similar to the study done by Boyd et al[103] who found that there were no significant differences in LVEF, GLS, radial or circumferential strain before or after anthracyclines between this group and those not receiving these medications.

In this study, we have taken risk factors of cardiovascular disease as variables. It has been found that the incidence of myocardial damage after anthracycline chemotherapy may be enhanced by smoking[100], pre-existing cardiovascular disease, coexisting

damage or individual patient genetic predisposition.[121] Our study found that there was no significant difference in cardiotoxicity in patients who were treated with cyclophosphamide, anthracycline or cisplatin. Majority of patients (33.1%) having cardiotoxicity belonged to those who took anthracycline, followed by cyclophosphamide (26.4%). Our results were similar to study done by which Emily Hoe et al[100] which divided patients in 6 chemotherapy groups. There were no statistically significant differences in the chemotherapy regimens, including total anthracycline dose and time from last administered anthracycline dose, between the two trastuzumab-based chemotherapy subgroups.

In our study, metrics of LV systolic function (LVESV, LVEF and strain) deteriorated throughout study. Left ventricular end-systolic volume (LVESV) increased from 25.2±14.5 ml to 39±29.5 ml (p=0.0001) during the study without any significant change in left ventricular end-diastolic volume (LVEDV) [90.1±8.3 ml to 91.8±7.4 ml (p=0.08). Changes similar to these (2–6 ml increase in LVESV or a 5% drop from a normal resting LVEF) were associated with an adverse CV prognosis in a recent study by Draft BC et al of patients with heart failure and a preserved resting LVEF.[122] As a result of these changes in left ventricular volumes, LVEF (calculated by Simpson's method) diminished (66.9±8.3% vs. 54.2±12.2; P = 0.0001). The decline in LVEF was also paralleled with a rise in strain parameters GLS and GCS (less negative reflecting worsening regional systolic function). The global longitudinal myocardial strain (GLS) was reduced from -17.98±4.5% to-15.9±6.9% and the difference was statistically significant (P=0.0002). The global circumferential strain was also reduced significantly after chemotherapy from -27.7±11.7% to 16.5±2.6% and the difference was statistically significant (P=0.0001). Myocardial strain diminished with a decrement in LVEF. After multivariable analyses, the subclinical abnormalities we

observed in LVESV, LVEF, and strain parameters occurred regardless of gender, race and associated CV comorbidities. Our findings were similar to the study done by Boyd et al[103] who found that there was a significant increase in LVESV post anthracycline chemotherapy (p = 0.02) without increasing in LVEDV (p= 0.07). Also similar to our study changes in GLS and GCS were found to be significant (p <0.001 and p= 0.001 respectively. LVEF although reduced after treatment, remained within the normal range (60±3% vs. 59±3%, p = 0.04). Triplane GLS was significantly reduced after treatment (-20.0±1.6% vs. -19.1±1.8%, p<0.001).

These findings are similar to study done by Araujo-Gutierrez R[123] et al who investigated the cardiotoxicity of anthracycline based chemotherapy. In this single-centre study done on 188 patients, baseline 2D STE was compared before initiation of treatment and at follow-up after 3 months. It was concluded that baseline GLS or decreased baseline GLS was predictive of CTRD before anthracycline treatment in cancer patients having normal LVEF. Agha et al.[124] reported that declined 2D-STE derived global longitudinal strain and strain rate could be used for early detection of cardiotoxicity when global LVEF is near normal.

Our finding was also similar to the finding by Negishi *et al*,[125] and Singh DK et al[104]. In a study of Dinesh et al[104] there was no significant difference in LVEF (by M mode) before and after cancer therapy (64.27 ± 3.25 vs. 62.6 ± 3.12; P = 0.63), whereas GLS reduced from −21.16 ± 2.50 before cancer therapy to −19.86 ± 3.22 after it, and the difference was statistically significant (P < 0.01). The GCS was also reduced significantly from –23.60 ± 7.36 to –21.33 ± 6.97 after cancer therapy.

There were significant changes in the main diastolic parameters. E/A ratio was decreased significantly while deacceleration time (DT) was increased after

chemotherapy. There was a significant decrease in E' at mitral annuli and an increase in the trans-mitral Doppler early filling velocity E/E' ratio. The baseline LVDD grade was deranged in 140 of the study subjects but there was an increase in the grade of LVDD in 20 patients after chemotherapy. The difference was not significant with a P-value of 0.08. Similar results were also found by Upshaw JN et al[126], with persistent worsening of diastolic function was observed with breast cancer therapy. This study was conducted in 362 breast cancer patients treated with doxorubicin, doxorubicin followed by trastuzumab, or trastuzumab alone and changes in diastolic function were evaluated. Participants treated with doxorubicin or doxorubicin followed by trastuzumab demonstrated a persistent worsening in diastolic function, with reductions in the E/A ratio, lateral and septal e' velocities, and increases in E/e' ($p < 0.01$). Abnormal diastolic function grade was associated with a subsequent decrease in LVEF (-2.1%; 95% CI: -3.1 to -1.2; $p<0.001$) and worsening in longitudinal strain (0.6%; 95% CI: 0.1 to 1.1; $p=0.013$) over time.

Emily Ho et al[100] evaluated the long-term effects of standard chemotherapy on myocardial function in asymptomatic breast cancer survivors using 2D-STE. Despite normal EF% (62±4% vs 60±3%, $p=0.051$) the chemotherapy group had reduced E/A ratios (0.9±0.3 vs 1.1±0.3, $p=0.003$), global E' (10.2±0.2 vs 11.2±2.3, $p=0.036$), and global longitudinal 2D strain (-18.1±2.2 vs -19.6±1.8, $p=0.0001$). Subclinical systolic and diastolic myocardial abnormalities were present in asymptomatic breast cancer survivors up to 6 years after standard chemotherapy but failed to report a link between diastolic and systolic measurements. In this study 36 patients dead, whose mean age was 47.4±18.75, 23 were male and 13 were female. There was no significant difference in the mean age of dead and alive patients, while gender and type of cancer showed significant differences. In our study, mortality was observed more in males.

There was a significant difference in LVEF (Simpson's), GLS and GCS among pre and post-chemotherapy in dead patients. There was also a significant difference in cardiotoxicity among LVEF, GLS and GCS of dead and alive patients. These are positively associated with dead patients.

Isaac B. Rhea et al[101] studied the prognostic value of echocardiographic strain and its association with mortality in 120 cancer patients undergoing chemotherapy. It showed that male sex and GLS were significantly associated with all-cause mortality in patients with cancer with normal ejection fractions receiving chemotherapy. Other studies have also demonstrated that GLS was independently associated with all-cause mortality, major adverse cardiovascular events and cardiotoxicity.[127,128] Furthermore, early reductions in LVEF and GLS after chemotherapy persist at follow-up.[128] Longer-term multicentre studies are required to determine the extent of early change that best predicts future cardiotoxicity in such patients.

In our study, the LV GLS value of -15.9 showed the sensitivity of 80% and specificity of 99% and LV GCS value of -16.5 showed the sensitivity of 100% and specificity of 93% for predicting cardiotoxicity. This confirms LV GLS and GCS as an excellent independent factor of cardiotoxicity. Similar results were obtained in a study conducted by Eliza de Almeida Gripp[129] confirming GLS and GCS as an excellent independent predictor of cardiotoxicity ($p = 0.004$, HR = 2.77; 95% CI: 1.39-5.54). None of the patients assessed showed the GCS and GLS drop after the LVEF drop. Other studies were also done regarding the sensitivity and specificity of GLC and GCS for predicting cardiotoxicity.[125,128,130-133]

Red blood cell distribution width (RDW) is a simple and rapid measurement of the heterogeneity of erythrocyte volume. It is integral parameter of complete blood count

which is showing the variability in size of circulating erythrocytes (anisocytosis) expressed as either as the standard deviation (SD) of erythrocyte volumes (RDW-SD) or as the coefficient of variation (RDW-CV). The normal reference ranges of RDW-SD and RDW-CV are typically 39–46 fL and 11.5–15%, respectively, but often vary depending on the method of RDW calculation and the available hematological analyzers used.[134] Prognostic value of high RDW is strongly associated with widespread cardiovascular diseases such as acute coronary syndrome, heart failure, and pulmonary hypertension.[135-137] Prognostic value of RDW in cardiac-oncology has not been examined extensively therefore the present study also examined the relation between RDW and associated cardiotoxicity by chemotherapy.

The patients were divided into 2 groups based on the median value of baseline RDW-CV before chemotherapy [low RDW group (<15) and high RDW group (≥15)]. It has been reported that elevation of RDW is also seen with aging, inflammation, malnutrition, and renal dysfunction. In the present study, we revealed the trend of RDW in patients treated with chemotherapy and its correlation with 2D-TTE findings. There were no statistical differences in age, sex, co-morbidities and cardio-active medications between the two groups at baseline. There was no significant association of RDW in breast, lung, gastrointestinal and hematological cancer pre as well post chemotherapy. Laboratory data showed that hemoglobin and mean corpuscular volume were reduced post chemotherapy and RDW was increase significantly. There was no significant association of diastolic as well as systolic parameters between Low and High RDW group. Cardiotoxicity was developed in 10 (12.8%) patients in low RDW group and 14 (12.2%) patients in high RDW group by Simpson's method which was statistically not significant. On speckle tracking echocardiography, cardiotoxicity developed in 31 (39.7%) patients in low RDW group and 42 (36.5%) patients in high

RDW group according to GLS. According to GCS, cardiotoxicity was developed in 36 (46.2%) patients in low RDW group and 48 (41.7%) patients in high RDW group. Cardiotoxicity on basis of both GLS and GCS was not statistically significant in relation with RDW. Contrary to our study, D.Yaegashi et al[105] reported that the occurrence of CTRCD was higher in high RDW group than in low RDW group (11.5 vs. 2.0%, P = 0.008) and established RDW value as an independent predictor of the development of CTRCD. High RDW are associated with unfavourable survival in breast cancer, haematological tumor, gynecological cancer, and osteosarcoma.

Compared to previous studies, RDW can't predict the development of CTRCD. In the present study, the calculation of net reclassification index (NRI) and integrated discrimination index (IDI) demonstrated the significance of RDW for the prediction of CTRCD. The utility of RDW should be considered when managing cancer patients treated with anthracycline-containing chemotherapy.

Most of the studies to determine cardiomyopathy in cancer patients have focused on echocardiography as a screening tool to determine cardiomyopathy. Based on findings, ECGs is inexpensive and easily available tool that may aid in evaluating individual patient risk during and after therapy. ECGs should be considered as part of comprehensive cardio-oncology surveillance, but a specific protocol for screening cannot be established without prospective study design.

Heart rates in the whole study group were normal before therapy started and did not significantly increase or decrease after the start of therapy (84.9±19.3 bpm vs. 85.9±18.5 bpm, p = 0.5). All patients had sinus rhythm before and after therapy started, no patient developed new atrial fibrillation or atrial flutter during the follow-up. Our results are similar to study of Bokemeyer C et al[138] and Kucharz J et al[139] in

which changes in HR, both bradycardia and tachycardia, have been reported to be early complications of cisplatin-based therapy: bradycardia can occur as a rare early effect; on the other hand, also tachycardia was reported as an early complication. QRS axis and interval did not significantly change post cancer therapy.

In study by Bacharova L et al[140], ECG of 173 patients with the germ cell tumor were retrospectively analysed. The patients were divided into four groups: Group CT: Orchidectomy plus Cisplatin-based therapy CBT (n=133); Group AS: Orchidectomy only (n=18); Group RT: Orchidectomy plus adjuvant radiotherapy (n=14); Group CTRT: Orchidectomy plus adjuvant radiotherapy in combination with CBT (n=8). All patients were on the sinus rhythm. The heart rate and the time intervals under study were within normal limits, as well no significant differences were observed between the groups. The QT and QTc values were within normal limits. QRS complex parameters were within normal limits. On the other hand, in study of El-Hawwary AA et al[141] and Chowdhury S et al[142] in cisplatin-based treatment, as well as radiotherapy cause myocardial changes that might alter the electrical properties of myocardium, and consequently might affect the resultant QRS vector. Our finding is consistent with results documented in study of Alpert MA et al[143] and Eisenstein I[144], in which the leftward shift of the electrical axis in obese subjects was seen. The slight differences in QRSmax in the combination with the differences in the electrical axis were reflected in the changes in the individual leads of 12-lead ECG. Although these differences were within normal limits, they could indicate subtle changes in electrical impulse propagation in ventricles.

PR intervals did not significantly change after therapy started (141.6±31.8ms vs. 140.08±30.13ms, p= 0.4).There was non-significant prolongation of QT interval

before and after chemotherapy whereas there was highly significant change was seen in QTc interval, ΣQRS TpTe/QT and ECG score.

There are findings from the bench that link TpTe to mechanisms of ventricular arrhythmia. Using a canine myocardial wedge preparation model, Antzelevitch and coworkers[145,146] explored the genesis of TpTe as well as the potential mechanisms that link TpTe prolongation to increased risk of ventricular arrhythmogenesis. There are 3 electrophysiological distinct cell types in the ventricular myocardium: the endocardial, epicardial, and subendocardial M cells (Masonic mid-myocardial Moe cells). In study of Gupta P[147] and Liu T et al[148], during bradycardia or because of a repolarization-prolonging insult, M cells are more vulnerable to prolongation of action. TpTe corresponds with transmural dispersion of repolarization in the ventricular myocardium, a period during which the epicardium has repolarized and is fully excitable, but the M cells are still in the process of repolarization and are vulnerable to the occurrence of early after-depolarization. If conditions are favourable, these early after-depolarization can lead to re-entry and its perpetuation, resulting in polymorphic ventricular tachycardia or ventricular fibrillation. Hence, a prolonged TpTe likely corresponds to an extended vulnerable period, could increase risk of ventricular arrhythmogenesis.

Our findings are comparable with a smaller study of Watanabe N et al[149], in which 65 patients with organic heart disease were divided into three groups: VT inducible group (n=37), VT non-inducible group (n=25) and control group (n=65). V4 TpTe/√RR was significantly prolonged in the VT inducible group, as compared to the VT non-inducible group and the control group (118.9±26.1 vs. 103.9±25.7, 104.1±22.6 ms, $P<0.05$). Prolonged transmural dispersion (TDR) may be a useful

index for predicting ventricular tachyarrhythmias. In our study, TpTe value of 100 ms had a specificity of 97% but a sensitivity of only 27%. Hence, the cut-off for TpTe for SCD risk prediction in the community may be lower than values published earlier. This fact is supported from data by Lubinski et al[150], who reported that the TpTe duration was 74 ± 14 ms in the VT group versus 63 ± 16 ms in the control group ($P < 0.004$). TpTe was longer in patients with, versus without, inducible VT. The results of this study support the hypothesis that TpTe reflects transmural dispersion of repolarization. However, further studies are needed for establishing cut-offs for patients at risk of SCD in the community.

Our results are similar to study of Markman TM et al[151] and Horacek JM et al[152] where anthracycline therapy has been shown to prolong the QTc interval in prior small studies in adult survivors of either pediatric or adult malignancies. A slightly larger pediatric study of Larsen RL et al[153] with 100 patients also showed QTc prolongation after anthracycline therapy.

In study of Horacek JM et al[154] decreases in QRS voltages have been associated with left ventricular dysfunction on echocardiogram both after anthracycline use and in patients with heart failure due to other causes. While the total anthracycline dose was shown to decrease the ΣQRS(6 L) and prolong the QTc interval in our study, the data suggest the magnitude of ECG changes due to development of cardiomyopathy were larger than changes due to anthracycline exposure alone. In addition, cardiotoxic radiation therapy did not alter the ΣQRS(6 L)or QTc interval, suggesting the ECG changes in patients exposed to anthracyclines should not be dismissed as secondary to therapeutic radiation exposure. A prospective long-term study should be considered to

reproduce our results using a systematic approach, and we established ΣQRS(6 L) and QTc as two appropriate outcome measures for evaluation.

The ECG score was calculated in all 193 patients, in which 40 patients achieved 0 points, points, 87 patients achieved 1 point, 46 patients achieved 2 points, 16 patients achieved 3 points and 4 achieved 4 points respectively. There was no significant increase in ECG score post-chemotherapy. We defined two groups concerning their risk of developing cardiotoxic side-effects: patients with an ECG score < 2 were assigned to the low-risk group and patients with an ECG score ≥ 2 were assigned to the high-risk group. The incidence of cardiotoxicity was 5.4% in the low-risk group and 57.1% in the high-risk group (n = 92/42, $p < 0.0001$). Our results are similar to study of Pohl et al[154] where ECG score was calculated in all 134 patients and 25 patients achieved 0 points, 67 patients achieved 1 point, 33 patients achieved 2 points, seven patients achieved and one achieved 4 or 5 points respectively.

The ECG test (TpTe) showed sensitivity of 88% and specificity of 80%.The area under the ROC curve for TpTe was 0.905 (95% CI, 0.69 to 0.77). While QTc showed sensitivity of 68.6% and specificity of 79.2%. The area under the ROC curve for TpTe was 0.79.

The results are similar to Pohl et al[154], where the sensitivity was 0.82 (95% CI 0.74–0.88) and the specificity was 0.82 (95% CI 0.64–0.92) with positive predictive value of 0.95 (95% CI 0.88–0.98) and a negative predictive value of 0.55 (95% CI 0.40–0.69) (Table 3). The ROC analysis revealed an area under the curve of 0.8432 (95% CI 0.77–0.92; $p < 0.0001$) for the prediction of cardiotoxicity.

Early identification of subclinical LV dysfunction is of utmost importance because previous studies have shown that such LV dysfunction may be reversible with

discontinuation of treatment. This patient subgroup requires periodic follow up with early initiation of cardio-protective agents. Treatment with an ACE-I, angiotensin receptor blocker (ARBs) before anthracycline, trastuzumab and radiotherapy have demonstrated to reverse he reduced LVEF, in the PRADA trial, while no such benefit was demonstrated with metoprolol (beta blocker)[155]. In contrast other studies have shown that use of beta blockers improved GLS in patients with subclinical LV dysfunction receiving anthracyclines, trastuzumab or both. Furthermore, Seicean et al[156] demonstrated in a study that use of Beta Blockers (either incidental or therapeutic) reduced incidence of new onset heart failure in patients treated with anthracyclines and trastuzumab.

Not only STE is a more sensitive marker than global LVEF in detecting silent myocardial dysfunction in chemotherapy patients, but declined GLS does not always lead to the development of left ventricular dysfunction and these changes may be reversible if treatment is initiated early. This was demonstrated in study by Donato et al[157] in breast cancer patients who received adjuvant chemotherapy with trastuzumab and taxanes after initial anthracycline therapy. Thus, reduced GLS helps to identify early cardiac dysfunction in asymptomatic HF cancer survivors who may benefit from early medical therapy in cases where conventional echocardiographic values are within normal limits.

LIMITATIONS

- Small sample size and brief study duration, which limited the power of the study. The sample size was too small to evaluate the impact of individual chemotherapeutic agents on myocardial function.
- The serial echocardiography was done by a single examiner. The echocardiographer was not blinded to the diagnosis of the patient. Dichotomization of the primary predictor variable (presence or absence of cardiomyopathy) can be a subjective process, especially when performed using only echocardiographic means without clinical correlation.
- The reproducibility of the estimates of systolic strain using the speckle-tracking method was not recorded. Thus, there could have been measurement bias.
- Other sensitive indices of LV function, such as strain rate or mitral annular systolic displacement may also be tested in further studies.
- When to obtain ECGs, a specific guideline is not currently available. This could potentially create bias in the study as patients with clinical concern many have more data points for analysis and could have extrinsic causes for ECG findings related to their complex oncologic care (i.e. electrolyte disturbance).
- Modern imaging modalities and techniques such as 3D echocardiography, and magnetic resonance imaging may be useful to detect early cardiotoxicity; however this data was also not consistently available for our review during the available study period.
- Incidence of cardiovascular events after chemotherapy is low; a study would require a much greater number of patients and a longer follow-up. Long-term, large-scale outcome studies with hard clinical endpoints will be required to determine the clinical significance of our findings.

CONCLUSION

Cardiac systolic performance declines in asymptomatic cancer patients after chemotherapy independent of gender, age and CV risk factors. The present study revealed that there was a significant worsening of LV systolic function as measured by the LVESV, LVEF and strain parameters (GLS and GCS) on STE in cancer patients on chemotherapy. STE may be a valuable tool in detecting early myocardial damage in cancer patients undergoing chemotherapy. LVEF, GLS and GCS were significantly reduced in dead patients as compared to alive. The detection of early myocardial dysfunction in cancer chemotherapy patients has potential therapeutic implications and may provide a rationale for the early implementation of anti-failure medication before the onset of irreversible functional LV changes.

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APPENDIX-1

ALL INDIA INSTITUTE OF MEDICAL SCIENCES, JODHPUR, RAJASTHAN

DEPARTMENT OF CARDIOLOGY

CONSENT FORM

Title of Thesis/Dissertation : Early detection of chemotherapy induced cardio toxicity in cancer patients by various non-invasive tools: a prospective observational study

Name of DM Student : Dr. Shubham Kumar Sharma; M. 8055045155

Patient/Volunteer Identification No.: _____

I, _____ S/o or D/o _____

R/o _____

give my full, free, voluntary consent to be a part of the "**Early detection of chemotherapy induced cardio toxicity in cancer patients by various non-invasive tools: a prospective observational study**", the procedure and nature of which has been explained to me in my own language to my full satisfaction.
I confirm that I have had the opportunity to ask questions.
I understand that my participation is voluntary and am aware of my right to opt out of the study at any time without giving any reason. I understand that the information collected about me and any of my medical records may be looked at by responsible individual from AIIMS Jodhpur or from regulatory authorities. I give permission for these individuals to have access to my records.

Date: _____ _____

Place: _____ Signature/Left thumb impression

This to certify that the above consent has been obtained in my presence.

Date: _____ _____

Place: _____ Signature of DM Student

Witness 1

Signature:

Name: _____

Address: _____

Witness 2

Signature:

Name: _____

Address: _____

अखिल भारतीय आयुर्विज्ञान संस्थान , जोधपुर, राजस्थान

हृदय रोग विभाग

सूचित सहमति प्रपत्र

थीसिस / निबंध का शीर्षक: Early detection of chemotherapy induced cardio toxicity in cancer patients by various non-invasive tools: a prospective observational study

डी एम छात्र का नाम: _शुभम कुमार शर्मा टेलिफोन नंबर _8055045155_
रोगी / स्वयंसेवक पहचान संख्या: _____

मैं, _____ पिता का नाम _____
निवासी _____
अध्ययन " **Early detection of chemotherapy induced cardio toxicity in cancer patients by various non-invasive tools: a prospective observational study"** का एक भाग बनने के लिए मेरी पूर्ण, स्वतंत्र, स्वैच्छिक सहमति दें, जिसकी प्रक्रिया और प्रकृति मुझे अपनी पूरी संतुष्टि के लिए अपनी भाषा में समझाई गई है। मैं पुष्टि करता हूं कि मुझे प्रश्न पूछने का अवसर मिला है।

मैं समझता हूं कि मेरी भागीदारी स्वैच्छिक है और मुझे किसी भी कारण दिए बिना किसी भी समय अध्ययन से बाहर निकलने के मेरे अधिकार की जानकारी है।

मैं समझता हूं कि मेरे और मेरे मेडिकल रिकॉर्ड के बारे में एकत्रित की गई जानकारी को _____ या विनियामक प्राधिकरणों से जिम्मेदार व्यक्ति द्वारा देखा जा सकता है। मैं इन लोगों के लिए मेरे रिकॉर्डों तक पहुंच की अनुमति देता हूं

तारीख : _____ _____
जगह: _____ हस्ताक्षर / बाएं अंगूठे का छाप

यह प्रमाणित करने के लिए कि मेरी उपस्थिति में उपरोक्त सहमति प्राप्त की गई है

तारीख : _____ _____
जगह: _____ पीजी छात्र के हस्ताक्षर

गवाह 1 **गवाह** 2

हस्ताक्षर हस्ताक्षर
नाम: _____ नाम: _____
पता _____ पता : _____

APPENDIX-2

ALL INDIA INSTITUTE OF MEDICAL SCIENCES, JODHPUR, RAJASTHAN

DEPARTMENT OF CARDIOLOGY

PATIENT INFORMATION SHEET

Title: Early detection of chemotherapy induced cardio toxicity in cancer patients by various non-invasive tools: a prospective observational study

Name of the patient: **Patient ID.:**

1. **Aim of the study:** To compare noninvasive tools for early detection of chemotherapy induced cardio toxicity in cancer patients: a prospective observational study.
2. **Study site:** Out Patient and in-patient services of Department of Cardiology & Radiation Oncology, All India Institute of Medical Sciences, Jodhpur, Rajasthan.
3. **Study procedure:** After informed consent, cancer patients will be subjected to blood investigations and ECG, detailed echocardiography pre, during and 1 month post chemotherapy.
4. **Likely benefit:** This will diagnose the asymptomatic cardiac dysfunction in chemotherapy treated patient.
5. **Confidentiality:** All the data collected from each study participant will be kept highly confidential.
6. **Risk:** Enrollment in above study poses no substantial risk to any of the study participant and if any point of time participant wants to withdraw himself/ herself, he/ she can do so voluntarily at any point of time during the study.

For further information, / questions, the following personnel can be contacted:

Dr. Shubham Kumar Sharma, Senior Resident, Department of Cardiology, All India Institute of Medical Sciences, Jodhpur, Rajasthan. Ph: 8055045155

<u>अखिल भारतीय आयुर्विज्ञान संस्थान , जोधपुर, राजस्थान</u>

<u>हृदय रोग विभाग</u>

<u>रोगी सूचना पत्र</u>

शीर्षक: **Early detection of chemotherapy induced cardio toxicity in cancer patients by various non-invasive tools: a prospective observational study**

रोगी का नाम: रोगी आईडी .:

1. अध्ययन का उद्देश्य: कैंसर के रोगियों में जल्दी कार्डियोटॉक्सिसिटी का पता लगाने के लिए
2. अध्ययन स्थल: कारडीयालजी विभाग तथा विकिरण कैंसर विज्ञान, ऑल इंडिया इंस्टीट्यूट ऑफ मैडिकल साईंसिस, जोधपुर, राजस्थान।
3. अध्ययन प्रक्रिया: सूचित सहमति के बाद, कैंसर रोगियों की इकोकार्डियोग्राफी तथा बायोमार्कर मॉनिटरिंग की जाएगी.
4. संभावित लाभ: कैंसर के रोगियों में जल्दी कार्डियोटॉक्सिसिटी के बारे में जानकारी मिलेगी ।
5. गोपनीयता: प्रत्येक अध्ययन प्रतिभागी से एकत्र किए गए सभी डेटा को अत्यधिक गोपनीय रखा जाएगा।
6. जोखिम: उपरोक्त अध्ययन में नामांकन किसी भी अभिलक्षक प्रतिभागी के लिए कोई महत्वपूर्ण जोखिम नहीं है और अगर किसी भी समय-प्रतिभागी खुद को अध्ययन से वापस लेना चाहता है, तो वह अध्ययन के दौरान किसी भी समय स्वेच्छा से ऐसा कर सकता है।

अधिक जानकारी के लिए, / प्रश्न, निम्नलिखित कर्मियों से संपर्क किया जा सकता है:

डॉ <u>शुभम कुमार शर्मा</u>, वरिष्ठ रेजिडेंट, कारडीयालजी विभाग, अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर, राजस्थान। फोन: 8055045155

APPENDIX-3

ALL INDIA INSTITUTE OF MEDICAL SCIENCES, JODHPUR, RAJASTHAN

DEPARTMENT OF CARDIOLOGY

Title: Early detection of chemotherapy induced cardio toxicity in cancer patients by various non-invasive tools: a prospective observational study

AIIMS ID: ..... Date.....
Baseline Characteristics
Name: ..... Age..... Gender- M / F
Phone No.: ..... Address: Urban / Rural.....
PAST CLINICAL and PERSONAL HISTORY:
Smoking Status: Never/ Former/ Current
Co-morbidities: DM Type2 / HTN / IHD / CKD / COPD /dyslipidemia/ PAD
Others.....
PRESENT CLINICAL HISTORY:
Presenting Complaints:
Drugs history: ACE-I/ARB, B-Blocker, MRA, Statin
CLINICAL EXAMINATION:
Height: Weight: BMI:
Pallor/Icterus/Clubbing/Cyanosis/Lymphadenopathy/Pedal Edema
JVP-raised/ not Raised
Pulse:
Blood Pressure:
CVS examination: S1-
S2-
Abnormal sounds……
Murmur……
Investigations
CBC: Hb . . . . . gm/dl, TLC . . . . ./µL PLT . . . . .
RBS:
Lipid Profile:
Electro-cardiography:
Herat Rate
PR interval . . . . . ms, QRS Duration . . . . . ms, QRS Duration . . . . .ms,
QT . . . . ms, QT Dispersion . . . . .
QRS Morphology . . . . . ST Morphology . . . . . .
Mean QRS amplitude of all 6 leads (ΣQRS(6 L))
Echocardiography :
LVESV(ml/m2) …… LVEDV(ml/m2) . . . . . SV . . . . . LVEF (%). . . . . .
Strain: GLS . . . . GCS . . . . GAS . . . . GRS . . . .
Mitral Inflow: E (m/s) . . . . A (m/s) . . . . E/A . . . .
Pulmonary Vein Flow
Tissue Doppler Velocity: E' velocity (m/s) . . . . E/e' . . . .
LV Diastolic Grade: Normal . . . Impaired . . . . Pseudo normal . . . .
Strain Rate: Esr . . . . E/Esr . . . .

ETHICAL CLEARNACE CERTIFICATE

अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर
All India Institute of Medical Sciences, Jodhpur
संस्थागत नैतिकता समिति
Institutional Ethics Committee

No. AIIMS/IEC/2021/3500 **Date: 12/03/2021**

ETHICAL CLEARANCE CERTIFICATE

Certificate Reference Number: **AIIMS/IEC/2021/3335**

Project title: **"Early detection of chemotherapy induced cardio toxicity in cancer patients by various non-invasive tools: A prospective observational study"**

Nature of Project:	**Research Project Submitted for Expedited Review**
Submitted as:	**D.M. Dissertation**
Student Name:	**Dr. Shubham Kumar Sharma**
Guide:	**Dr. Surender Deora**
Co-Guide:	**Dr. Rahul Choudhary, Dr. Atul Kaushik, Dr. Puneet Pareek & Dr. Kuldeep Singh, Dr. Poonam Elhence**

Institutional Ethics Committee after thorough consideration accorded its approval on above project.

The investigator may therefore commence the research from the date of this certificate, using the reference number indicated above.

Please note that the AIIMS IEC must be informed immediately of:

- Any material change in the conditions or undertakings mentioned in the document.
- Any material breaches of ethical undertakings or events that impact upon the ethical conduct of the research.

The Principal Investigator must report to the AIIMS IEC in the prescribed format, where applicable, bi-annually, and at the end of the project, in respect of ethical compliance.

AIIMS IEC retains the right to withdraw or amend this if:

- Any unethical principle or practices are revealed or suspected
- Relevant information has been withheld or misrepresented

AIIMS IEC shall have an access to any information or data at any time during the course or after completion of the project.

Please Note that this approval will be rectified whenever it is possible to hold a meeting in person of the Institutional Ethics Committee. It is possible that the PI may be asked to give more clarifications or the Institutional Ethics Committee may withhold the project. The Institutional Ethics Committee is adopting this procedure due to COVID-19 (Corona Virus) situation.

If the Institutional Ethics Committee does not get back to you, this means your project has been cleared by the IEC.

On behalf of Ethics Committee, I wish you success in your research.

Dr. Praveen Sharma
Member Secretary

Member secretary
Institutional Ethics Committee
AIIMS,Jodhpur

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