

The Role of Cardiovascular Imaging and Serum Biomarkers in Identifying Cardiotoxicity Related to Cancer Therapeutics

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ABSTRACT: Innovations and discoveries in cancer therapeutics have improved survival rates in patients with various types of malignancies. At the same time, physicians are identifying an increased number of patients with treatment-related cardiotoxicity. It is imperative that physicians recognize early treatment-related adverse effects to determine the safest therapeutic options for patients with cancer. This manuscript evaluates the role of cardiovascular imaging and biomarkers in identifying cardiotoxicity triggered by various chemotherapeutic agents and summarizes expert consensus statements regarding cardiotoxicity monitoring.

INTRODUCTION

New discoveries and innovation in cancer therapy have improved the survival of patients with many types of malignancies. However, these agents are not without the potential for adverse cardiovascular effects. For example, anthracyclines, anti-HER2 agents, and immune checkpoint inhibitors are effective for treating many malignancies but are also known to be cardiotoxic. It is essential that physicians be able to identify and monitor chemotherapy-related cardiotoxicity at the earliest onset to ensure patient safety and determine the safest therapeutic options. This manuscript discusses the role of various imaging techniques—including 2-dimensional transthoracic echocardiogram (2D TTE), 3-dimensional transthoracic echocardiogram (3D TTE), radionuclide angiography (MUGA), cardiac magnetic resonance (CMR), and cardiac biomarkers (eg, troponin, BNP)—to help diagnose and track therapy-related cardiotoxicity. We also highlight differences and similarities in expert consensus statements related to cardiotoxicity monitoring.

DEFINING CARDIOTOXICITY

In 2014, the American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI) described cardiotoxicity, or cancer therapeutics-related cardiac dysfunction (CTRCD), as a $\geq 10\%$ decrease from baseline left ventricular ejection fraction (LVEF) to a value $< 53\%$ as measured by 2D TTE.¹ CTRCD can be further defined based on the presence of symptoms (hypoxia, shortness of breath, lower extremity edema) and reversibility; it is considered reversible if LVEF returns to within 5% of baseline.

It is important to note that cardiotoxicity from anthracyclines is potentially reversible if detected early and managed appropriately,² whereas cardiotoxicity from trastuzumab is usually reversible only after cessation of chemotherapy.³ Resuming trastuzumab after the patient recovers LVEF is feasible because most patients do not demonstrate a subsequent reduction in LV systolic function when rechallenged while on heart failure medications.³

IMAGING MODALITIES

Echocardiography

I. Two-Dimensional Transthoracic Echocardiography

Its wide availability, portability, low cost, and lack of radiation exposure make 2D TTE a convenient method for monitoring the cardiotoxicity of chemotherapeutic agents and the ideal choice for imaging at baseline.⁴ Although there are multiple methods to estimate chamber sizes and LVEF, the ASE/EACVI recommend using the biplane method of disks (modified Simpson's rule).⁵ However, given the discrepancies between guidelines and consensus statements, we feel that a simplified recommendation of anthracycline- and trastuzumab-related cardiotoxicity monitoring is needed. Therefore, we suggest an easy algorithm to follow in asymptomatic patients (Figure 1).

Chemotherapeutic agents rarely cause valvular disease, yet many of these patients undergo concomitant radiation therapy that may lead to valvular disease.⁶ Marantic endocarditis also may cause valvular disease in some patients, such as those with solid tumor malignancies.⁷ In addition to assessing valve structure and function, 2D TTE may also be used to evaluate the pericardium because anthracyclines, other

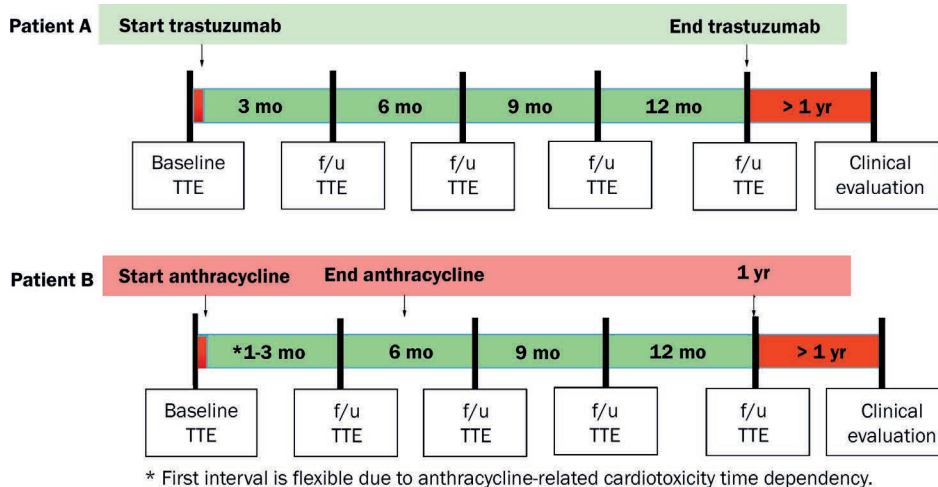


Figure 1.

Proposed timing of cardiotoxicity monitoring with transthoracic echocardiogram for anthracyclines and anti-HER2 therapies in patients with breast cancer without heart failure symptoms. TTE: transthoracic echocardiogram

chemotherapeutic agents, and immunotherapies have been associated with pericarditis and/or the development of pericardial effusions.^{8,9}

II. Three-Dimensional Transthoracic Echocardiography

Three-dimensional TTE offers distinct advantages over 2D TTE, such as more accurate assessment of LV volumes.¹⁰ Also, 3D TTE is more accurate than other echocardiographic techniques at detecting LVEF < 50% (using cardiac magnetic resonance as the gold standard) in survivors of childhood cancer, presumably because 3D TTE measurements are not skewed by geometric assumptions of LV shape.¹¹ Furthermore, LVEF measurements on 3D TTE demonstrate less variability at 1-year follow-up, and less inter- and intraobserver variability, compared to 2D TTE.¹² This is essential because serial echocardiographic measurements of LVEF may determine if a chemotherapeutic agent can be resumed or discontinued during treatment. Although preferable to 2D TTE, the use of 3D TTE is somewhat restricted by limited availability, increased cost, and the need for an experienced operator to obtain high-quality images.

III. Speckle-Tracking Global Longitudinal Strain

Although great emphasis is placed on monitoring the ejection fraction (EF) of cancer patients on chemotherapeutic agents, a decrease in EF may not be evident until substantial myocardial injury has taken place (Figure 2). Conversely, measurements of strain and strain rate may allow for earlier and more sensitive detection of myocardial injury among patients receiving chemotherapeutic agents, particularly anthracyclines.¹³

Based on one major study, patients with < 8% reduction in global longitudinal strain (GLS) are not likely to have meaningful cardiotoxicity, whereas those with a GLS reduction > 15% during chemotherapy may have clinically significant cardiotoxicity.¹⁴ Also, a GLS less negative than -17.5% may identify patients at higher risk of developing cardiotoxicity

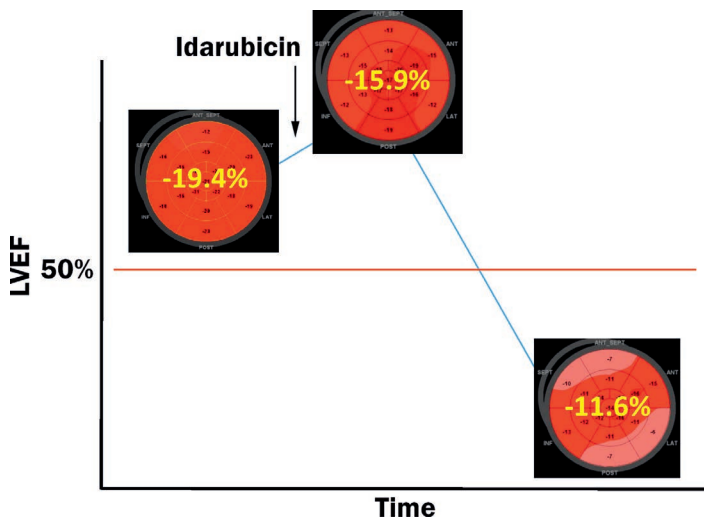


Figure 2.

An example of subclinical cardiotoxicity related to anthracycline detected by global longitudinal strain before a decrease in left ventricular ejection fraction (LVEF).

related to anthracyclines. (See the American College of Cardiology website for more information on GLS).¹⁵⁻¹⁷

As useful as they are, strain measurements do have limitations, such as variability in measurements between different ages, genders, and imaging vendors.^{16,18}

First-Pass or Radionuclide Multiple-Gated Acquisition Scan

First-pass or radionuclide multiple-gated acquisition (MUGA) scan was one of the initial tests used to identify anthracycline toxicity among cancer patients; in fact, some of the original guidelines for monitoring and potentially withholding anthracycline chemotherapy in the setting of reduced LVEF were based on this imaging modality.¹⁸ MUGA estimates of LVEF have been reported to be more accurate and reproducible than 2D TTE but not necessarily when compared to other imaging modalities.¹⁹ In a single-center study among 75 patients with different cancers, MUGA demonstrated a wide range in limits of agreement and less reproducibility, causing misclassification of LVEF in patients with cancer when compared to cardiac magnetic resonance (the gold standard for LVEF measurement).²⁰ Additionally, in a study with 50 breast cancer patients receiving trastuzumab, 3D TTE was as accurate and reproducible as MUGA for serial monitoring of LVEF.²¹

Although MUGA is widely available, one disadvantage is patient exposure to a minimal amount of radiation.

Cardiac Magnetic Resonance

Cardiac magnetic resonance (CMR) is the gold standard for obtaining accurate and reproducible measurements of LV volume and EF and is superior to echocardiography in this regard.^{22,23} CMR does not rely on geometric assumptions regarding LV shape; this is particularly important in patients who have undergone chemotherapy/radiation therapy, which may cause remodeling.

Accurately estimating EF is particularly important when patients reach thresholds that may predicate the cessation of chemotherapy. In one study, CMR was superior to 2D and 3D TTE at identifying patients with an EF < 50%.²⁴ Thus, CMR may be a robust alternative to echo when chemotherapy cessation is being considered (Figure 3). There is evidence of changes in myocardial T1 mapping in patients who have received anthracyclines in the past, as with childhood cancer survivors. These changes suggest fibrosis and seem to correlate well with impaired functional capacity by cardiopulmonary exercise testing.²⁵ In another study, increased cumulative anthracycline dose was associated with decreased LV mass on CMR, and both were associated with an increased risk of adverse cardiovascular events.²⁶

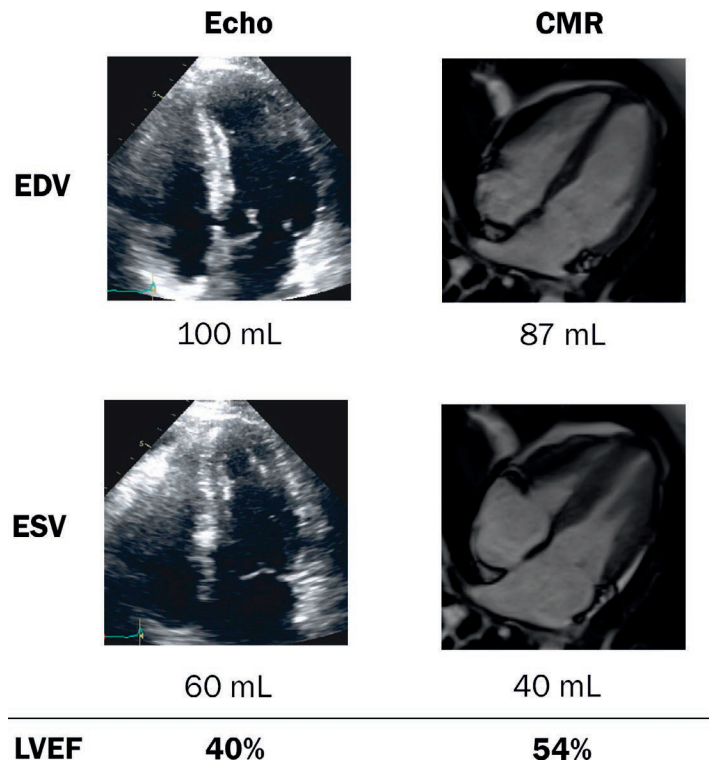


Figure 3.

Illustrative case of a 37-year-old woman with lymphoma undergoing chemotherapy. She had a decrease in left ventricular (LV) systolic function by echocardiogram (echo) biplane LV ejection fraction (LVEF) quantification, which was verified by cardiac magnetic resonance imaging, and LVEF > 50%. Treatment with anthracycline was resumed without any consequences in LV systolic function. CMR: cardiac magnetic resonance; EDV: end diastolic volume; ESV: end systolic volume

Immune Checkpoint Inhibitors (ICIs) are increasingly being used as an immunotherapy treatment for cancer, but they are known to potentially cause myocarditis. CMR has been used to help in noninvasively diagnosing ICI-associated myocarditis.²⁷

BIOMARKERS

Testing with cardiac biomarkers is a highly sensitive, widely available, and relatively cost-effective method of testing for myocardial injury among patients undergoing chemotherapy.²⁸ The following describes the biomarkers used to detect cardiotoxicity.

Troponin I

Cardinale et al. studied 703 cancer patients with aggressive malignancies who underwent high-dose chemotherapy and found no significant reductions in EF and only a 1% rate of

cardiac events in those with no troponin I elevation ≤ 1 month after chemotherapy. This suggests that a lack of troponin I elevation among patients undergoing chemotherapy has a high negative predictive value for cardiotoxicity. There was a higher rate of cardiac events among those with troponin I elevation soon after chemotherapy and an even higher rate of cardiac events among those with troponin I elevation both immediately and 1 month after chemotherapy.²⁸

Cardiotoxicity after trastuzumab chemotherapy is often reversible. However, in another study by Cardinale, patients with troponin I elevations during chemotherapy were more likely to undergo trastuzumab-associated cardiotoxicity and less likely to achieve LVEF recovery.²⁹ A more recent study showed that patients with a normal GLS and negative ultrasensitive troponin I measured at the end of anthracycline treatment are less likely to develop cardiotoxicity.³⁰ Elevations in ultrasensitive troponin I may identify breast cancer patients who will develop cardiotoxicity and heart failure if treated serially with anthracycline and trastuzumab.³¹

Troponin T

Among patients receiving trastuzumab, troponin T elevation was not shown to be a predictor of cardiotoxicity.³² On the other hand, among those treated with ICIs, a troponin T level of ≥ 1.5 ng/mL was associated with a 4-fold increase in the likelihood of a major adverse cardiac event.²⁷

High-Sensitivity Troponins

When compared with several biomarkers such as myeloperoxidase, PIGF, and GDF-15, elevations of high-sensitivity (hs) troponin I during treatment do not predict cardiotoxicity.³³ In a study by Pourier et al. of childhood cancer survivors, hs troponin T was not a sensitive marker for late-onset cardiotoxicity.³⁴ Of note, hs troponin T was elevated in 11% of cancer patients without a diagnosis of myocardial infarction who were receiving clinical care in our center.³⁵ This could be a limiting factor in establishing a diagnosis of CTRCD. Overall, hs troponin assays have limited value for identifying cardiotoxicity risk.

Brain Natriuretic Peptide (BNP) and NT-pro BNP

The role of natriuretic peptides in predicting cardiotoxicity is less clear. One small study demonstrated a rise in BNP after chemotherapy in patients who eventually developed anthracycline cardiotoxicity compared to those who did not.³⁶ However, other studies have shown no association between NT-pro BNP elevations and future systolic or diastolic dysfunction.³⁷ Although BNP levels may reflect filling pressures, the volume

status of a patient undergoing chemotherapy rapidly fluctuates (as a result of poor oral intake and/or vomiting), and this biomarker may not be as reliable.

Other Biomarkers

In addition to troponin, BNP, and NT-pro BNP, other biomarkers have been examined as potential predictors of cardiotoxicity. Galectin-3 is a biomarker associated with cardiac inflammation and fibrosis,³⁸ whereas biomarker ST2 is elevated in cardiac remodeling.³⁰ However, neither of these biomarkers have been shown to predict future cardiotoxicity among patients treated with cardiotoxic agents.^{30,39} Elevations in myeloperoxidase have been shown to predict cardiotoxicity.³⁹

Limitations of Biomarkers

Different biomarker assays used at different hospitals may make it difficult to standardize cutoffs that are deemed predictive of cardiotoxicity and may warrant cessation of chemotherapy. Also, other confounding factors—such as infection, arrhythmias, hypertensive events, pulmonary embolism—could cause an elevation in troponin assays. Lack of validation from large prospective trials is one of the main limitations when considering biomarkers. Table 1 outlines the utility of various biomarkers in detecting cardiotoxicity.^{28,30,32-34,36,37,39}

MONITORING DURING TREATMENT: EXPERT CONSENSUS

Early detection of cardiotoxicity is essential, not only because treatment may need to be held but also because the response to medical management for heart failure among those who have received anthracyclines is time sensitive.⁴⁰ Table 2 summarizes the most prominent consensus statements for the detection and monitoring of cardiotoxicity.^{1,18,41,42}

In the 1970s, MUGA was the primary method of detecting cardiotoxicity among those receiving anthracyclines. In 1987, Schwartz et al. proposed the following MUGA-based guidelines¹⁸:

1. Perform baseline MUGA for LVEF calculation. Subsequent studies should be performed at least 3 weeks after completing 100 mg/m² of doxorubicin and before the next dose.
2. Patients with normal baseline LVEF ($\geq 50\%$):
 - a. Perform the second study after 250 to 300 mg/m².
 - b. Repeat study after 400 mg/m² in patients with known heart disease, radiation exposure, abnormal electrocardiographic results, or cyclophosphamide therapy, or repeat after 450 mg/m² in the absence of any of these risk factors.

SERUM BIOMARKER	AUTHORS	SAMPLE SIZE (N)	RESULT
hs troponin I	Putt et al. ³³	78	Not predictive of cardiotoxicity
hs troponin T	Pourier et al. ³⁴	64	Not predictive of late cardiotoxicity in survivors
Troponin I	Cardinale et al. ²⁸	703	Predictive of adverse cardiac events
Troponin T	Fallah-Rad et al. ³²	42	Not predictive of cardiotoxicity
BNP	Okumura et al. ³⁶	13	May predict cardiotoxicity
NT-proBNP	Dodos et al. ³⁷	100	Not predictive of cardiotoxicity
ST-2	Sawaya et al. ³⁰	81	Not predictive of cardiotoxicity
Galectin-3	Ky et al. ³⁹	78	Not predictive of cardiotoxicity
MPO	Ky et al. ³⁹	78	May predict cardiotoxicity

hs: high sensitivity; NT-proBNP: N-terminal pro b-type natriuretic peptide; MPO: myeloperoxidase

Table 1.

Summary of studies assessing the role of biomarkers for predicting cardiotoxicity.^{28,30,32-34,36,37,39}

POSITION PAPER/GUIDELINE	BASELINE TTE (YES/NO)	FREQUENCY OF MONITORING (AC)	FREQUENCY OF MONITORING (T)	FOLLOW-UP AFTER TREATMENT
MUGA ¹⁸ (1987)	No, MUGA instead	At baseline, at the end of treatment, when cumulative dose reaches 250-500 mg/m ² , and at 450 mg/m ² (and each subsequent dose)	N/A	N/A
ASE/EACVI ¹ (2014)	Yes	At baseline, at the end of treatment, when cumulative dose reaches 240 mg/m ² , and each additional 50 mg/m ² dose thereafter	At baseline and every 3 months	6 months after completion of chemotherapy
ESC ⁴¹ (2016)	Yes	At baseline, at the end of treatment, when cumulative dose reaches 240 mg/m ²	At baseline and every 3 months	Long-term surveillance
ASCO ⁴² (2017)	Yes	N/A	N/A	6-12 months after completion

TTE: transthoracic echocardiography; MUGA: multiple-gated acquisition scan; AC: anthracycline; T: trastuzumab; N/A: not available or not commented; ASE: American Society of Echocardiography; EACVI: European Association of Cardiovascular Imaging; ESC: European Society of Cardiology; ASCO: American Society of Clinical Oncology

Table 2.

Summary of position papers/guidelines for the monitoring of cardiotoxicity.^{1,18,41,42}

- c. Perform sequential studies thereafter before each dose.
 - d. Discontinue doxorubicin therapy once functional criteria for cardiotoxicity develops (ie, absolute decrease in LVEF $\geq 10\%$ associated with a decline to $\leq 50\%$).
3. Patients with abnormal baseline LVEF ($< 50\%$):
 - a. Doxorubicin therapy should not be initiated with baseline LVEF $\leq 30\%$.
 - b. In patients with LVEF $> 30\%$ and $< 50\%$, sequential studies should be obtained before each dose.
 4. Discontinue doxorubicin with cardiotoxicity (absolute decrease in LVEF $\geq 10\%$ and/or final LVEF $\leq 30\%$).

The ASE/EACVI Expert Consensus Statement provides recommendations for cardiotoxicity monitoring. Prior to anthracycline administration, a baseline measurement of LVEF and GLS via echocardiogram in addition to troponin is recommended. These measurements should be repeated immediately and 6 months after anthracycline therapy. However, if a dose exceeds 240 mg/m² during treatment, then measurements at this point and before each additional 50 mg/m² dose are recommended. During trastuzumab therapy, measurements of LVEF, GLS, and troponin are recommended at baseline and every 3 months.¹

The European Society of Cardiology (ESC) position paper on cancer treatments and cardiovascular toxicity provides similar recommendations.⁴¹ Before anthracycline therapy, it also recommends assessing baseline cardiac function and considering an alternate chemotherapeutic agent if systolic dysfunction is noted. In addition, it recommends repeat assessment after anthracycline chemotherapy, or earlier assessment if a dose of 240 mg/m² is exceeded during therapy. Measuring at least one cardiac biomarker, in addition to high-sensitivity troponin I, is recommended with each cycle of anthracycline chemotherapy. For trastuzumab, the ESC recommends cardiac monitoring every 3 months during

chemotherapy and once after it is completed. It also recommends a repeat echocardiogram 3 weeks after an initial LVEF decrease in asymptomatic patients as well as measuring troponin with every cycle among patients with high baseline risk.⁴¹

The American Society of Clinical Oncology 2017 guidelines recommend performing a baseline TTE depending on the dose of anthracycline received, the number of cardiovascular risk factors, and whether or not the patient will receive sequential therapy (ie, lower-dose anthracycline followed by trastuzumab). They also recommend that a follow-up TTE be performed 6 to 12 months after completing chemotherapy in asymptomatic patients who are considered to have an increased cardiac risk.⁴²

Despite the frequency of monitoring during therapy, large trials for both anthracyclines and trastuzumab demonstrate that a vast majority of cardiotoxicity cases occur within 1 year of chemotherapy cessation.^{2,43} Thus, monitoring up to 1 year after treatment may be reasonable.

CONCLUSION

Advancements in cancer therapies have led to an improved prognosis for many patients. However, the potential for therapy-related cardiotoxicity still exists, most notably from anthracyclines and anti-HER2 agents. Recently, ICIs have been associated with myocarditis.²⁷ Table 3 summarizes the chemotherapeutic agents discussed in this manuscript, their associated cardiotoxicities, and possible treatments.⁴⁴

Imaging modalities such as echocardiography and CMR may result in earlier detection of cardiotoxicity, allowing physicians to promptly address common manifestations such as a decrease in LVEF. Early detection is essential for minimizing the risks of cardiotoxicity, since early initiation of heart failure therapy (including beta blockers and angiotensin-converting enzyme

CANCER THERAPY	TOXICITY	TREATMENT
Anthracyclines (doxorubicin, idarubicin)	Cardiomyopathy	Dexrazoxane, dose limitation, prolonged infusion, early initiation of guideline-directed medical therapy for heart failure
Anti-HER2 therapies (trastuzumab)	Cardiomyopathy	Guideline-directed medical therapy for heart failure, rechallenge (while on heart failure therapy) if ejection fraction recovers to $> 50\%$
Immune checkpoint inhibitors	Myocarditis	High-dose intravenous corticosteroids, plasmapheresis, immunoglobulins, other immunomodulators

Table 3.
Summary of cardiotoxicity from chemotherapeutic agents.

inhibitors) has been shown to increase the likelihood of reversing anthracycline-induced cardiotoxicity.⁴⁰ An integrated approach using both advanced cardiovascular imaging techniques and biomarkers may allow for the timely detection of cardiotoxicity.

KEY POINTS

- Cardiovascular imaging plays an essential role in monitoring for cardiotoxicity subsequent to cardiotoxic chemotherapeutic administration.
- Although serum biomarkers can aid in the diagnosis of cardiotoxicity, there is insufficient data to support their use as a sole diagnostic tool.
- An integrated approach using both cardiovascular imaging and serum biomarkers may be the best method to monitor for cardiotoxicity.

Conflict of Interest Disclosure:

All authors have completed and submitted the *Methodist DeBakey Cardiovascular Journal* Conflict of Interest Statement and none were reported.

Keywords:

cardiotoxicity, anthracyclines, immune checkpoint inhibitors, echocardiogram, cardiac magnetic resonance, CMR, biomarkers

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