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LEFT VENTRICULAR GLOBAL LONGITUDINAL STRAIN FOR EARLY DETECTION OF ANTHRACYCLINE-INDUCED CARDIOTOXICITY IN ADULT BREAST CANCER PATIENTS: A SYSTEMATIC REVIEW

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ABSTRACT

Introduction: Anthracycline-based chemotherapy remains an important component of breast cancer treatment, but its use is limited by the risk of cardiotoxicity, including subclinical left ventricular dysfunction and cancer therapy-related cardiac dysfunction. Conventional monitoring based on left ventricular ejection fraction may detect myocardial injury relatively late. Left ventricular global longitudinal strain (LV GLS), assessed by speckle-tracking echocardiography, has emerged as a more sensitive parameter for identifying early myocardial impairment. This systematic review summarizes current evidence on the role of LV GLS in the early detection of anthracycline-induced cardiotoxicity in adult breast cancer patients.
Methods: A systematic literature review was performed using PubMed/MEDLINE. The search strategy combined terms related to breast cancer, anthracyclines, global longitudinal strain, speckle-tracking echocardiography, and cardiotoxicity. Original English-language studies focused on adult breast cancer patients receiving anthracycline-based chemotherapy and undergoing strain echocardiographic assessment were considered eligible. After title, abstract, and full-text screening, seven studies were included in the qualitative synthesis.
Results: The included studies consistently suggested that LV GLS detects subclinical myocardial dysfunction earlier than conventional left ventricular ejection fraction assessment in breast cancer patients treated with anthracyclines. Several studies reported early impairment in myocardial deformation parameters during or shortly after chemotherapy, even in the presence of preserved ejection fraction. The reviewed evidence also indicated that changes in GLS may have diagnostic and prognostic relevance for subsequent cardiotoxicity and later decline in cardiac function. More recent studies additionally supported the value of integrating GLS with other echocardiographic parameters in the assessment of cancer therapy-related cardiac dysfunction.
Conclusions: LV GLS appears to be a sensitive and clinically useful echocardiographic marker for the early detection of anthracycline-induced cardiotoxicity in adult breast cancer patients. Its use may improve identification of subclinical cardiac dysfunction before a measurable decline in left ventricular ejection fraction occurs. Further studies are needed to clarify optimal cutoff values, monitoring intervals, and the role of GLS within standardized cardio-oncology surveillance protocols.

KEYWORDS

Breast Cancer; Anthracyclines; Cardio-Oncology; Left Ventricular Global Longitudinal Strain; Speckle-Tracking Echocardiography

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Introduction

Breast cancer remains the most frequently diagnosed malignancy in women worldwide and continues to represent a major clinical and public health challenge. Despite substantial progress in screening, surgical management, systemic therapy, and long-term survival, cardiovascular complications of anticancer treatment have emerged as an increasingly important component of survivorship care (Hwang et al., 2024; Lyon et al., 2022). Among systemic therapies used in breast cancer, anthracyclines retain a well-established role because of their antitumor efficacy, especially in selected early-stage and high-risk settings. However, their use is limited by the risk of cardiotoxicity, which may range from asymptomatic myocardial injury to overt heart failure and long-term impairment of left ventricular function (Camilli et al., 2024; Hwang et al., 2024; Lyon et al., 2022). As oncologic outcomes improve and more patients live long enough to experience delayed cardiovascular consequences of treatment, early identification of therapy-related cardiac dysfunction has become a central objective of modern cardio-oncology practice (Camilli et al., 2024; Lyon et al., 2022).

Anthracycline-induced cardiotoxicity is clinically important not only because of its immediate impact on cardiac function, but also because of its implications for treatment continuation, quality of life, and long-term prognosis (Camilli et al., 2024; Lyon et al., 2022). In breast cancer patients, interruption or de-escalation of effective oncologic therapy due to cardiac complications may adversely affect cancer outcomes, while delayed recognition of myocardial injury may reduce the opportunity for early cardioprotective intervention (Dobson et al., 2021; Lyon et al., 2022). This issue is particularly relevant in adult women receiving anthracycline-based regimens, in whom myocardial damage may initially remain subclinical despite progressive impairment at the tissue level (Dobson et al., 2021; Sławiński & Lewicka, 2023). Contemporary cardio-oncology guidance therefore emphasizes the need for structured cardiovascular surveillance before, during, and after potentially cardiotoxic cancer therapy, especially in patients exposed to anthracyclines and related regimens (Dobson et al., 2021; Lyon et al., 2022).

Traditionally, left ventricular ejection fraction (LVEF) has been the cornerstone of echocardiographic monitoring during cancer treatment. Although LVEF remains widely used and clinically familiar, it has important limitations in the early detection of anthracycline-related myocardial injury (Dobson et al., 2021; Lyon et al., 2022; Sławiński & Lewicka, 2023). A measurable decline in LVEF often occurs relatively late in the disease process, when more subtle abnormalities in myocardial mechanics may already be present (Lyon et al., 2022; Marwick, 2021; Sławiński & Lewicka, 2023). In addition, LVEF is influenced by loading conditions, image quality, and interobserver variability, which may reduce its sensitivity to minor but clinically relevant changes over time (Dobson et al., 2021; Lyon et al., 2022). For this reason, reliance on LVEF alone may underestimate early subclinical dysfunction and delay recognition of patients at risk of developing cancer therapy-related cardiac dysfunction (CTRCD) (Lyon et al., 2022; Marwick, 2021; Sławiński & Lewicka, 2023).

In recent years, speckle-tracking echocardiography (STE) and, in particular, left ventricular global longitudinal strain (LV GLS), have attracted growing attention as more sensitive tools for detecting early myocardial impairment in cardio-oncology (Dobson et al., 2021; Lyon et al., 2022; Marwick, 2021; Sławiński & Lewicka, 2023). GLS reflects longitudinal deformation of the left ventricular myocardium and is capable of identifying subtle reductions in systolic performance before conventional ejection fraction becomes abnormal (Marwick, 2021; Sławiński & Lewicka, 2023). Current clinical guidance and expert consensus increasingly recognize the value of GLS as an adjunctive parameter in surveillance protocols for patients receiving anthracyclines and/or trastuzumab (Dobson et al., 2021; Lyon et al., 2022). This is especially important in breast cancer populations, where repeated echocardiographic monitoring is frequently feasible and clinically

justified because of the established cardiovascular risk associated with anthracycline exposure (Dobson et al., 2021; Hwang et al., 2024; Lyon et al., 2022).

The growing role of GLS in cardio-oncology is supported by both conceptual and practical considerations. From a pathophysiological perspective, strain imaging may better reflect early anthracycline-related myocardial injury at a stage when structural and mechanical alterations precede overt decline in global ventricular pump function (Camilli et al., 2024; Marwick, 2021; Sławiński & Lewicka, 2023). From a clinical perspective, earlier detection of subclinical dysfunction may allow closer monitoring, timely cardiology referral, optimization of cardiovascular risk factors, and, in selected cases, initiation of cardioprotective treatment before irreversible deterioration occurs (Camilli et al., 2024; Dobson et al., 2021; Lyon et al., 2022). Nevertheless, despite increasing interest in GLS, important uncertainties remain regarding its optimal use in routine practice, including cutoff values, timing of repeated assessment, integration with conventional echocardiographic parameters, and the interpretation of strain changes in heterogeneous treatment settings (Dobson et al., 2021; Lyon et al., 2022; Marwick, 2021; Sławiński & Lewicka, 2023).

The available literature on GLS in anthracycline-treated breast cancer patients includes prospective observational studies, longitudinal echocardiographic monitoring studies, and more recent diagnostic investigations using combined imaging approaches (Cadeddu et al., 2017; Coutinho Cruz et al., 2020; Dogru et al., 2013; Esmaeilzadeh et al., 2022; Fei et al., 2016; Florescu et al., 2014; Portugal et al., 2017). These studies generally suggest that myocardial deformation abnormalities may appear during or shortly after anthracycline-based chemotherapy even when LVEF remains preserved (Cadeddu et al., 2017; Coutinho Cruz et al., 2020; Dogru et al., 2013; Florescu et al., 2014; Portugal et al., 2017). At the same time, the evidence base is relatively limited in scale and heterogeneous in design, with differences in patient selection, treatment regimens, timing of imaging, and definitions of cardiotoxicity (Cadeddu et al., 2017; Coutinho Cruz et al., 2020; Dogru et al., 2013; Esmaeilzadeh et al., 2022; Fei et al., 2016; Florescu et al., 2014; Portugal et al., 2017). Because of this heterogeneity, a focused synthesis of the literature is needed to clarify the practical role of LV GLS in the early identification of anthracycline-induced cardiotoxicity in adult breast cancer patients.

The aim of this systematic review was therefore to analyze currently available evidence on the role of left ventricular global longitudinal strain in the early detection of anthracycline-induced cardiotoxicity in adult breast cancer patients. Particular attention was given to studies assessing whether GLS detects subclinical myocardial dysfunction earlier than conventional LVEF-based monitoring and whether strain abnormalities may have diagnostic or prognostic relevance for subsequent CTRCD development (Cadeddu et al., 2017; Coutinho Cruz et al., 2020; Dogru et al., 2013; Esmaeilzadeh et al., 2022; Fei et al., 2016; Florescu et al., 2014; Portugal et al., 2017).

Material and Methods

This systematic review was conducted to evaluate the role of left ventricular global longitudinal strain (LV GLS) in the early detection of anthracycline-induced cardiotoxicity in adult breast cancer patients. The review was designed as a focused qualitative synthesis of original clinical studies addressing myocardial deformation assessment by echocardiography in this specific oncologic population.

The methodological approach was informed by contemporary cardio-oncology and echocardiographic surveillance principles described in current guidance documents and review literature (Dobson et al., 2021; Lyon et al., 2022; Sławiński & Lewicka, 2023). Particular attention was given to the clinical problem of subclinical myocardial dysfunction developing during anthracycline-based treatment despite preserved left ventricular ejection fraction (LVEF), as this issue represents the main rationale for integrating GLS into surveillance strategies (Camilli et al., 2024; Dobson et al., 2021; Lyon et al., 2022; Marwick, 2021; Sławiński & Lewicka, 2023).

Search strategy

A structured literature search was performed in PubMed/MEDLINE. The search strategy combined Medical Subject Headings and title/abstract keywords related to breast cancer, anthracycline therapy, global longitudinal strain, speckle-tracking echocardiography, and cardiotoxicity. The final search strategy was designed to maximize specificity for studies most relevant to the review question and focused on original studies in adult breast cancer patients receiving anthracycline-based chemotherapy.

The search was restricted to English-language publications. In addition to database screening, reference lists of selected articles were reviewed manually in order to identify additional studies potentially relevant to the topic.

Eligibility criteria

Studies were considered eligible if they met all of the following criteria:

Included adult patients with breast cancer; involved treatment with anthracycline-based chemotherapy; assessed left ventricular global longitudinal strain or closely related myocardial deformation parameters using speckle-tracking echocardiography; addressed early detection, screening, diagnosis, or prediction of cardiotoxicity, subclinical left ventricular dysfunction, or cancer therapy-related cardiac dysfunction; were original clinical studies, including prospective, longitudinal, observational, or diagnostic investigations.

Studies were excluded if they: were review articles, meta-analyses, editorials, letters, protocols, or design papers; focused primarily on cardioprotective interventions, exercise programs, rehabilitation, or dietary prevention rather than on the diagnostic role of GLS; included non-breast cancer populations without sufficiently relevant breast cancer data; focused mainly on non-anthracycline regimens without a clearly defined anthracycline-exposed population; evaluated primarily right ventricular strain or non-comparable imaging outcomes without clinically interpretable LV GLS-related findings.

Study selection

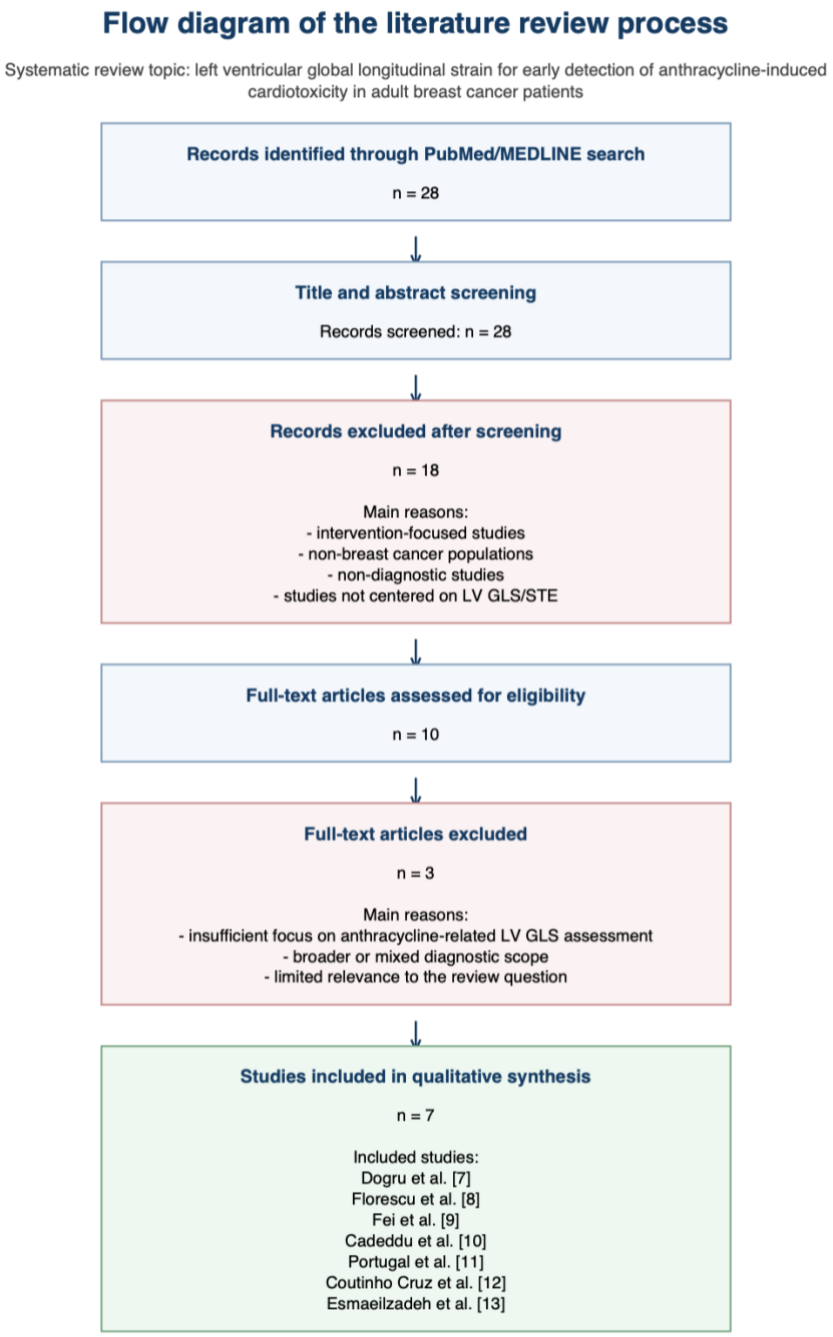
Titles and abstracts retrieved through the PubMed/MEDLINE search were screened for relevance to the predefined review question. During this stage, clearly irrelevant records were excluded, including non-breast cancer studies, studies centered on primary prevention interventions, and articles not focused on strain echocardiography.

Potentially eligible studies then underwent full-text assessment. Articles were retained only if they directly addressed adult breast cancer patients treated with anthracycline-based chemotherapy and evaluated LV GLS or closely related longitudinal deformation parameters in the context of early cardiotoxicity detection, diagnosis, or prediction.

After the full selection process, seven studies were included in the final qualitative synthesis (Cadeddu et al., 2017; Coutinho Cruz et al., 2020; Dogru et al., 2013; Esmaeilzadeh et al., 2022; Fei et al., 2016; Florescu et al., 2014; Portugal et al., 2017).

The included studies were:

- Dogru et al. [7]
- Florescu et al. [8]
- Fei et al. [9]
- Cadeddu et al. [10]
- Portugal et al. [11]
- Coutinho Cruz et al. [12]
- Esmaeilzadeh et al. [13]



Data extraction

For each included study, the following information was extracted and organized for qualitative comparison: first author and year of publication; study population and sample characteristics; breast cancer treatment exposure, with emphasis on anthracycline-containing regimens; echocardiographic method used, including 2D or 3D speckle-tracking echocardiography where applicable; role of LV GLS or other longitudinal deformation parameters in the study design; principal findings related to early myocardial dysfunction, cardiotoxicity, or CTRCD; overall relevance of the study to the review question.

Because of heterogeneity in study design, patient selection, treatment combinations, echocardiographic protocols, and cardiotoxicity definitions, the extracted material was synthesized narratively rather than quantitatively (Cadeddu et al., 2017; Coutinho Cruz et al., 2020; Dogru et al., 2013; Esmaeilzadeh et al., 2022; Fei et al., 2016; Florescu et al., 2014; Portugal et al., 2017).

Outcome of interest

The primary outcome of interest in this review was the usefulness of LV GLS in the early detection of anthracycline-induced cardiotoxicity in adult breast cancer patients. In practical terms, this included evidence that GLS:

- identified subclinical myocardial dysfunction before a decline in LVEF;
- detected deformation abnormalities during or shortly after anthracycline therapy; contributed to screening or diagnosis of CTRCD; had potential prognostic relevance for later left ventricular dysfunction.

Secondary considerations included whether studies used combined echocardiographic approaches, whether newer imaging techniques such as 3D speckle-tracking were applied, and whether GLS findings appeared clinically useful in structured cardio-oncology surveillance (Coutinho Cruz et al., 2020; Dobson et al., 2021; Esmaeilzadeh et al., 2022; Lyon et al., 2022; Marwick, 2021; Sławiński & Lewicka, 2023).

Quality and interpretive approach

This review was designed as a focused qualitative synthesis rather than a formal meta-analysis. Quantitative pooling was not performed because of heterogeneity across the included studies, including differences in imaging methods, follow-up schedules, treatment regimens, and endpoints (Cadeddu et al., 2017; Coutinho Cruz et al., 2020; Dogru et al., 2013; Esmaeilzadeh et al., 2022; Fei et al., 2016; Florescu et al., 2014; Portugal et al., 2017). Some studies emphasized early strain changes during treatment, whereas others focused more strongly on diagnostic classification or later clinical implications of myocardial deformation abnormalities.

To maintain interpretive consistency, all included studies were assessed in relation to the same core clinical question: whether LV GLS provides earlier or more sensitive information on anthracycline-related myocardial dysfunction than conventional echocardiographic assessment based primarily on LVEF (Dobson et al., 2021; Lyon et al., 2022; Marwick, 2021; Sławiński & Lewicka, 2023).

Ethical considerations

Because this article is a systematic review based exclusively on previously published studies, no direct patient recruitment or original patient-level data collection was performed. Therefore, separate ethical approval was not required for the present review.

Results

Characteristics of the included studies

The final qualitative synthesis included seven original studies evaluating the role of myocardial deformation imaging in the detection of anthracycline-related cardiac dysfunction in adult breast cancer patients (Cadeddu et al., 2017; Coutinho Cruz et al., 2020; Dogru et al., 2013; Esmaeilzadeh et al., 2022; Fei et al., 2016; Florescu et al., 2014; Portugal et al., 2017). The reviewed studies differed in design, imaging protocols, timing of follow-up, and cardiotoxicity definitions; however, they showed a consistent overall pattern. Across the available evidence, left ventricular global longitudinal strain (LV GLS) deteriorated earlier than left ventricular ejection fraction (LVEF) and appeared to identify subclinical myocardial dysfunction before the development of conventional echocardiographic criteria of cardiotoxicity (Cadeddu et al., 2017; Coutinho Cruz et al., 2020; Dogru et al., 2013; Esmaeilzadeh et al., 2022; Fei et al., 2016; Florescu et al., 2014; Portugal et al., 2017).

A recurrent finding across the included studies was that longitudinal deformation was affected during treatment even when LVEF remained within the normal range. This pattern was observed in early prospective studies, later observational studies, and more recent diagnostic work integrating GLS with additional echocardiographic parameters (Cadeddu et al., 2017; Coutinho Cruz et al., 2020; Esmaeilzadeh et al., 2022; Fei et al., 2016; Florescu et al., 2014; Portugal et al., 2017). Taken together, the evidence suggests that GLS is more sensitive than conventional LVEF for detecting early anthracycline-associated myocardial injury and may have both diagnostic and prognostic value in cardio-oncology surveillance (Cadeddu et al., 2017; Coutinho Cruz et al., 2020; Dogru et al., 2013; Esmaeilzadeh et al., 2022; Fei et al., 2016; Florescu et al., 2014; Portugal et al., 2017).

Early evidence supporting GLS as a marker of subclinical dysfunction

The earliest included study, by Dogru et al. (2013), supported the role of speckle-tracking echocardiography in identifying patients at risk of anthracycline-related cardiotoxicity and suggested that myocardial deformation abnormalities may be detected before clear deterioration in conventional systolic parameters becomes evident. Although this study provided less detail for extraction than several later reports, it remains relevant as an early signal that strain-derived parameters may reveal myocardial injury earlier than routine LVEF monitoring.

More detailed and clinically focused data were provided by Florescu et al. (2014), who prospectively studied 40 women with breast cancer treated with epirubicin. After the sixth cycle of therapy, 14 patients (35%) fulfilled the criteria for epirubicin-induced cardiotoxicity, defined as a reduction in EF of at least 10% to a value below 55%. Importantly, after the third cycle of treatment, the patients who later developed cardiotoxicity already had significantly lower longitudinal systolic indices, including longitudinal strain and longitudinal strain rate, whereas radial and circumferential deformation remained unchanged at that stage. The authors concluded that a decrease in longitudinal strain after the third cycle of epirubicin was the best independent and accurate predictor of cardiotoxicity after treatment completion. In the discussion, they further emphasized that a reduction in longitudinal strain of more than 9% after the third cycle represented the best predictor of later EF decline, directly supporting the superiority of longitudinal mechanics over conventional EF-based monitoring for early detection.

Studies showing GLS deterioration before overt LVEF decline

Portugal et al. (2017) provided one of the clearest demonstrations of the incremental value of GLS over LVEF in routine surveillance. In this prospective cohort of 158 breast cancer patients treated with anthracyclines with or without adjuvant trastuzumab, chemotherapy-induced cardiotoxicity (CIC) was defined as a decrease in LVEF to below 53%. During a mean follow-up of 5.4 months, the incidence of CIC was 18.9%. In the whole cohort, GLS worsened significantly from a baseline value of −20.1 ±3.5% to −18.7 ± 3.4% during follow-up ($p = 0.001$), while patients who eventually developed CIC had a more marked decrease, with GLS reaching −17.2 ±2.5%. Using the cutoff of −18%, the authors found impaired myocardial deformation in 97 patients (61.4%), and among these, 27 later developed CIC, whereas only 3 of 61 patients with preserved GLS developed CIC (27.8% vs. 4.9%, $p < 0.001$). Worsening GLS preceded overt cardiotoxicity by a mean of 101 days, and impaired GLS below the −18% threshold remained independently associated with CIC in multivariable analysis (OR 4.88; 95% CI 1.32–18.0; $p = 0.017$). This study is particularly important because it showed that strain deterioration occurred in many patients before LVEF crossed the conventional threshold for cardiotoxicity, making GLS clinically useful as an earlier warning parameter.

Similar conclusions emerged from Cadeddu et al. (2017), who prospectively examined 45 women with HER2-positive breast cancer treated sequentially with epirubicin followed by trastuzumab. Their analysis demonstrated that subendocardial function was already impaired after epirubicin treatment, as reflected by significant worsening of global longitudinal strain, while a compensatory increase in apical rotation was still present. After subsequent trastuzumab administration, further deterioration of myocardial mechanics was observed, and impairment of apical rotation appeared to be the earliest sign of more global LV dysfunction predicting later GLS reduction. Although this study also included additional deformation parameters beyond GLS, its results supported the concept that longitudinal mechanics reveal early myocardial injury before conventional systolic deterioration becomes fully apparent.

Prognostic implications of GLS values and changes over time

Fei et al. (2016) contributed a somewhat different but still clinically relevant perspective. In their cohort of 95 women with newly diagnosed breast cancer treated with anthracyclines followed by trastuzumab, 19 patients (20%) developed cardiotoxicity during follow-up. None of the baseline clinical or echocardiographic variables predicted later cardiotoxicity, but post-anthracycline measurements did. In multivariable Cox analysis, left ventricular end-diastolic volume index, LVEF, and GLS measured after anthracycline completion all independently identified patients who later developed cardiotoxicity; for GLS, the hazard ratio was 1.63 (95% CI 1.26–2.14; $p < 0.0001$). Importantly, GLS at the time of cardiotoxicity diagnosis also had prognostic value for reversibility. Patients with reversible cardiotoxicity had more preserved GLS at diagnosis than those with irreversible dysfunction, and a GLS value lower than −15.8% identified 12 of 13 patients with subsequent LVEF recovery, whereas values above this threshold were associated with poorer reversibility. Thus, in addition to earlier detection, GLS also appeared useful for risk stratification once cardiotoxicity had developed.

Quantitative strain findings from 3D echocardiography

Coutinho Cruz et al. (2020) expanded the available evidence by examining 3-dimensional speckle-tracking echocardiography in 105 women with breast cancer treated with anthracyclines. After a mean follow-up of 12.1 ±11.5 months, cancer therapy–related cardiac dysfunction was documented in 24 patients (22.9%). Standard echocardiographic assessment showed a significant decrease in 2D LVEF during treatment, but the most informative findings concerned strain parameters. Mean 3D global longitudinal strain worsened from −15.6 ±3.4% to −11.0 ±4.2% ($p < 0.001$), and 3D global circumferential strain worsened from −14.0 ±4.0% to −8.5 ±17.5% ($p < 0.001$). Variability of 3D GLS and 3D GCS was significantly associated with CTRCD, and both parameters showed predictive value; the authors reported area under the curve values of 0.69 for 3D GLS and 0.74 for 3D GCS for the prediction of CTRCD. Although this study also showed a reduction in LVEF, it reinforced the central message of the review: deformation imaging captured relevant myocardial deterioration during therapy and identified patients at risk before EF-based dysfunction became the only signal of injury.

Combined echocardiographic approaches: GLS beyond isolated LVEF measurement

The most diagnostically advanced study among those included was conducted by Esmaeilzadeh et al. (2022). In this prospective cohort, 136 women with HER2-positive early-stage breast cancer treated with sequential anthracyclines and trastuzumab underwent repeated imaging with echocardiography and cardiovascular magnetic resonance (CMR), which served as the reference standard for CTRCD diagnosis. CMR-identified CTRCD occurred in 37 patients (27%). By comparison, among analyzable studies, CTRCD was detected in 23% by 2D LVEF, 22% by 3D LVEF, 42% by GLS, and 50% by global circumferential strain. The authors found that GLS had greater sensitivity than either 2D or 3D LVEF for concurrent CMR-defined CTRCD. The most effective model was a sequential algorithm combining 3D LVEF, GLS, and GCS, which achieved an AUC of 0.893. When none of the 3D LVEF, GLS, or GCS criteria were met, the probability of CTRCD was only 1.0%; when 3D LVEF criteria were met, the probability rose to 76.9%. Even when 3D LVEF was replaced by 2D LVEF, the model still performed well in ruling out CTRCD. These findings indicate that GLS is not only more sensitive than isolated LVEF assessment but also becomes even more valuable when integrated into a multiparametric echocardiographic strategy.

Overall pattern across studies

Across the included studies, the evidence consistently favored GLS over LVEF as an earlier marker of anthracycline-related myocardial injury (Cadeddu et al., 2017; Coutinho Cruz et al., 2020; Dogru et al., 2013; Esmaeilzadeh et al., 2022; Fei et al., 2016; Florescu et al., 2014; Portugal et al., 2017). Conventional LVEF remained useful for confirming established cardiotoxicity, but strain-based parameters frequently worsened earlier and in a larger proportion of patients, often while EF was still preserved (Cadeddu et al., 2017; Coutinho Cruz et al., 2020; Esmaeilzadeh et al., 2022; Fei et al., 2016; Florescu et al., 2014; Portugal et al., 2017). The most clinically relevant thresholds repeatedly involved either a relative deterioration in GLS or absolute GLS values approaching or exceeding the range of approximately −18% to −15.8%, depending on study design and endpoint definition (Esmaeilzadeh et al., 2022; Fei et al., 2016; Portugal et al., 2017). In practical terms, these findings suggest that reliance on LVEF alone may delay recognition of cardiotoxicity, whereas serial assessment of GLS can reveal subclinical left ventricular dysfunction at a stage when closer monitoring and earlier cardioprotective intervention may still be possible (Cadeddu et al., 2017; Coutinho Cruz et al., 2020; Esmaeilzadeh et al., 2022; Fei et al., 2016; Florescu et al., 2014; Portugal et al., 2017).

Discussion

This systematic review analyzed the role of left ventricular global longitudinal strain (LV GLS) in the early detection of anthracycline-induced cardiotoxicity in adult breast cancer patients. The principal finding of the review is that the available evidence consistently supports GLS as a more sensitive marker of early myocardial injury than conventional left ventricular ejection fraction (LVEF) assessment (Cadeddu et al., 2017; Coutinho Cruz et al., 2020; Dogru et al., 2013; Esmaeilzadeh et al., 2022; Fei et al., 2016; Florescu et al., 2014; Portugal et al., 2017). Across the included studies, abnormalities in longitudinal deformation were repeatedly observed during or shortly after anthracycline-based therapy, often while LVEF remained within the normal range or had not yet reached the conventional diagnostic threshold for cardiotoxicity (Cadeddu et al., 2017; Coutinho Cruz et al., 2020; Esmaeilzadeh et al., 2022; Fei et al., 2016; Florescu et al., 2014; Portugal et al., 2017). In practical terms, this means that GLS appears to identify subclinical left ventricular dysfunction

at an earlier stage than standard EF-based monitoring, which is particularly relevant in breast cancer patients receiving potentially cardiotoxic systemic treatment (Camilli et al., 2024; Dobson et al., 2021; Lyon et al., 2022; Marwick, 2021; Sławiński & Lewicka, 2023).

This conclusion is well aligned with the current conceptual framework of cardio-oncology. Contemporary guidelines emphasize that anthracycline-induced myocardial injury may evolve gradually, with impairment in myocardial mechanics preceding overt reduction in pump function (Camilli et al., 2024; Dobson et al., 2021; Lyon et al., 2022). LVEF remains clinically important and is still central to many surveillance protocols, but it is relatively insensitive to small early changes and may decline only after more advanced myocardial injury has occurred (Dobson et al., 2021; Lyon et al., 2022; Marwick, 2021; Sławiński & Lewicka, 2023). By contrast, GLS directly reflects longitudinal myocardial deformation, which is strongly influenced by subendocardial fiber function, a compartment considered particularly vulnerable to anthracycline-related damage (Camilli et al., 2024; Marwick, 2021; Sławiński & Lewicka, 2023). The studies included in this review support this mechanistic interpretation, because the earliest detectable abnormalities were most often seen in longitudinal parameters rather than in conventional global systolic indices (Cadeddu et al., 2017; Coutinho Cruz et al., 2020; Florescu et al., 2014; Portugal et al., 2017).

Among the included studies, Florescu et al. (2014) provided particularly convincing evidence for the superiority of GLS over LVEF in early surveillance. In that study, a decrease in longitudinal strain after the third cycle of epirubicin predicted cardiotoxicity detected after completion of treatment, whereas radial and circumferential deformation remained unchanged at that earlier stage. After the sixth cycle, 14 of 40 patients had developed cardiotoxicity, but strain abnormalities had already emerged earlier in those who later experienced EF decline. This is clinically important because it suggests that GLS may identify a high-risk subgroup while anthracycline therapy is still ongoing, creating an opportunity for closer monitoring and potentially earlier cardioprotective management. In the context of routine practice, this is arguably the strongest clinical advantage of GLS: not merely confirming cardiac dysfunction once it is established, but signaling risk before conventional criteria are met.

Portugal et al. (2017) strengthened this interpretation by showing that worsening GLS was not only common during chemotherapy but also independently associated with subsequent chemotherapy-induced cardiotoxicity. In their study, GLS worsened from −20.1 ±3.5% at baseline to −18.7 ±3.4% during follow-up, while patients who developed cardiotoxicity showed more pronounced impairment, with GLS reaching −17.2 ±2.5%. Using the threshold of −18%, the authors identified a large subgroup with impaired myocardial deformation, and this abnormality preceded overt cardiotoxicity by approximately 101 days. From a clinical standpoint, this is a highly meaningful interval. A lead time of several weeks or months may allow intensified surveillance, modification of follow-up strategy, tighter control of cardiovascular risk factors, and—depending on the overall clinical scenario—consideration of cardioprotective therapy or collaboration with cardio-oncology services (Camilli et al., 2024; Dobson et al., 2021; Lyon et al., 2022). Therefore, the value of GLS does not lie only in statistical prediction, but also in its potential to alter the timing of clinical decision-making.

A similar message emerges from the more advanced imaging work of Coutinho Cruz et al. (2020). Although this study also demonstrated a reduction in LVEF during treatment, the most informative results concerned changes in 3-dimensional strain parameters. Mean 3D GLS worsened markedly, and variations in 3D GLS and 3D GCS were associated with CTRCD and showed predictive value for its development. This suggests that once myocardial deformation imaging is applied more comprehensively, functional deterioration becomes visible even before conventional EF thresholds alone fully capture the extent of injury. The study also highlights an important methodological point: while LVEF is a useful summary parameter, it may not reflect more subtle and regionally heterogeneous changes in myocardial performance. Strain imaging, especially when supported by 3D acquisition, may therefore provide a more nuanced description of treatment-related myocardial dysfunction.

The study by Esmaeilzadeh et al. (2022) further supports the idea that GLS is more sensitive than isolated LVEF measurement, but also shows that the optimal diagnostic strategy may not depend on GLS alone. In that cohort, CMR-defined CTRCD occurred in 27% of patients, whereas GLS identified abnormalities in a substantially larger proportion than either 2D or 3D LVEF. The strongest model was not a single strain measurement but a combined algorithm integrating 3D LVEF, GLS, and global circumferential strain, with excellent discriminatory performance and very low probability of CTRCD when all three criteria were negative. This finding is highly relevant to real-world surveillance. It suggests that the future of echocardiographic monitoring in cardio-oncology may not be a choice between GLS and LVEF, but rather a structured multiparametric approach in which GLS plays a central role because of its sensitivity, while LVEF

remains important for classification, confirmation, and longitudinal comparison (Dobson et al., 2021; Lyon et al., 2022; Marwick, 2021; Sławiński & Lewicka, 2023; Esmaeilzadeh et al., 2022).

Fei et al. (2016) add another clinically useful dimension to the discussion by showing that GLS may have prognostic value beyond early detection. In their study, post-anthracycline GLS was independently associated with later cardiotoxicity, and GLS at the time of cardiotoxicity diagnosis was associated with subsequent recovery of LVEF. The threshold of approximately −15.8% was particularly notable, because patients with more preserved GLS at the time of cardiotoxicity diagnosis were more likely to experience later recovery. This suggests that GLS may not only detect early dysfunction but may also help distinguish patients with more reversible forms of myocardial injury from those at risk of more persistent impairment. Such information could be useful when planning monitoring intensity, counseling patients, and determining the urgency of cardiology involvement.

Cadeddu et al. (2017) also provide support for the pathophysiological plausibility of GLS-based surveillance. Their study suggested that subendocardial dysfunction occurred after epirubicin exposure, while other compensatory mechanical changes were still present, and that further deterioration appeared after trastuzumab exposure. Although the study focused not only on GLS but also on additional deformation and rotational parameters, it reinforces the idea that myocardial mechanics are altered earlier than global EF. This is important because anthracycline-related toxicity is often not a binary event but a dynamic process. Detecting it at the stage of subtle mechanical abnormality is more clinically useful than waiting until a significant EF drop confirms established dysfunction.

Even the earliest included study, Dogru et al. (2013), supports the same overall direction of evidence. Although the full text was not available for detailed extraction in the present stage of manuscript preparation, the study fits the general pattern observed in the rest of the literature: speckle-tracking-derived longitudinal mechanics appeared useful in identifying anthracycline-treated patients at higher risk of cardiotoxicity before conventional deterioration became fully expressed. For that reason, it remains an important part of the review and helps situate later studies within an evolving evidence base.

One of the most important practical issues arising from this review concerns the interpretation of concrete GLS values. The included studies did not use a single universal threshold, but several values appeared repeatedly meaningful. In Portugal et al. (2017), a cutoff of −18% was used to define impaired myocardial deformation and was strongly associated with later cardiotoxicity. In Fei et al. (2016), a value around −15.8% helped distinguish patients with reversible and irreversible dysfunction. In Florescu et al. (2014), the key signal was not only the absolute value of strain but the early reduction after the third cycle, which predicted later EF decline. Taken together, these findings suggest that both absolute GLS thresholds and serial changes over time are clinically relevant. The most practical interpretation may therefore be that GLS should not be treated as a single isolated number, but rather as a serial surveillance marker whose baseline value, direction of change, and degree of worsening all matter.

This has direct implications for routine echocardiographic monitoring. If a patient begins treatment with a normal LVEF but demonstrates progressive worsening of GLS across serial examinations, especially toward values in the range of approximately −18% or less negative, this may indicate subclinical anthracycline-related injury even in the absence of overt CTRCD by EF criteria (Esmaeilzadeh et al., 2022; Florescu et al., 2014; Portugal et al., 2017). Conversely, waiting for LVEF to decline by 10 percentage points or fall below the conventional lower limit may delay recognition of relevant myocardial dysfunction (Dobson et al., 2021; Lyon et al., 2022; Marwick, 2021; Sławiński & Lewicka, 2023). Therefore, the evidence synthesized in this review supports the growing clinical practice of integrating GLS into structured cardio-oncology surveillance rather than reserving it for selected or uncertain cases only (Dobson et al., 2021; Lyon et al., 2022).

At the same time, the review also highlights several limitations of the evidence base. First, the included studies were heterogeneous in design, sample size, treatment regimen, follow-up schedule, and cardiotoxicity definition (Cadeddu et al., 2017; Coutinho Cruz et al., 2020; Dogru et al., 2013; Esmaeilzadeh et al., 2022; Fei et al., 2016; Florescu et al., 2014; Portugal et al., 2017). Some focused on anthracycline therapy alone, while others included sequential trastuzumab exposure, which may influence both the pattern and timing of cardiac dysfunction (Cadeddu et al., 2017; Esmaeilzadeh et al., 2022; Fei et al., 2016; Portugal et al., 2017). Second, not all studies used the same imaging protocol. Some relied mainly on 2D GLS, whereas others incorporated 3D strain or combined models including GCS and 3D LVEF (Coutinho Cruz et al., 2020; Esmaeilzadeh et al., 2022). Third, the thresholds used to define abnormal strain or clinically relevant change were not uniform, which limits direct numerical comparison across studies. As a result, although the direction of findings is remarkably consistent, exact cutoffs should be interpreted cautiously and in the context of imaging technique,

vendor, follow-up schedule, and overall clinical setting (Dobson et al., 2021; Lyon et al., 2022; Marwick, 2021; Sławiński & Lewicka, 2023).

Another limitation is that not all included studies were designed primarily to test GLS against hard clinical outcomes such as symptomatic heart failure or long-term cardiovascular mortality (Cadeddu et al., 2017; Coutinho Cruz et al., 2020; Dogru et al., 2013; Esmaeilzadeh et al., 2022; Fei et al., 2016; Florescu et al., 2014; Portugal et al., 2017). Most focused on subclinical dysfunction and imaging-defined cardiotoxicity. This is not a weakness of the concept itself, because subclinical injury is precisely the stage at which surveillance is intended to operate, but it does mean that the downstream clinical consequences of early GLS-guided intervention remain less clearly defined. In other words, the current evidence strongly supports GLS as an earlier marker, but the extent to which earlier detection consistently translates into improved long-term patient outcomes still requires additional study.

Despite these limitations, the overall clinical message of the review is coherent. In adult breast cancer patients treated with anthracyclines, GLS appears to detect myocardial injury earlier than LVEF, provides more sensitive information on subclinical dysfunction, and may contribute to risk stratification once dysfunction has developed (Cadeddu et al., 2017; Coutinho Cruz et al., 2020; Dogru et al., 2013; Esmaeilzadeh et al., 2022; Fei et al., 2016; Florescu et al., 2014; Portugal et al., 2017). The strongest studies suggest that values around −18% may be important for identifying impaired deformation, while more pronounced abnormalities, including values around −15.8%, may carry additional prognostic meaning (Fei et al., 2016; Portugal et al., 2017). This evidence supports the view that GLS should be considered a core component of modern echocardiographic surveillance in breast cancer patients exposed to anthracyclines, especially when the goal is to recognize myocardial dysfunction before irreversible EF deterioration occurs (Camilli et al., 2024; Dobson et al., 2021; Lyon et al., 2022; Marwick, 2021; Sławiński & Lewicka, 2023).

Conclusions

Anthracycline-induced cardiotoxicity remains a major challenge in breast cancer treatment, particularly because subclinical myocardial dysfunction may develop before a measurable decline in left ventricular ejection fraction becomes apparent (Camilli et al., 2024; Hwang et al., 2024; Lyon et al., 2022). The evidence reviewed in this study indicates that left ventricular global longitudinal strain is a more sensitive marker of early myocardial injury than conventional LVEF assessment and may identify patients at increased risk of cardiotoxicity at an earlier stage of treatment (Cadeddu et al., 2017; Coutinho Cruz et al., 2020; Dogru et al., 2013; Esmaeilzadeh et al., 2022; Fei et al., 2016; Florescu et al., 2014; Portugal et al., 2017).

From a practical cardio-oncology perspective, the most important implication of these findings is that GLS can be incorporated into routine echocardiographic examination as an additional surveillance parameter rather than as a separate or highly specialized test (Dobson et al., 2021; Lyon et al., 2022; Marwick, 2021; Sławiński & Lewicka, 2023). Because GLS is obtained during standard transthoracic echocardiography using speckle-tracking analysis, its inclusion in serial monitoring protocols may improve the detection of subclinical dysfunction without fundamentally changing the overall structure of cardiovascular assessment. In this sense, GLS should be viewed not as a replacement for LVEF, but as an important extension of conventional echocardiography that increases the sensitivity of routine follow-up in patients exposed to anthracyclines (Dobson et al., 2021; Esmaeilzadeh et al., 2022; Lyon et al., 2022; Marwick, 2021; Sławiński & Lewicka, 2023).

The reviewed studies suggest that serial deterioration in GLS, especially toward values around −18% or less negative, may provide an early warning signal of myocardial injury, while more pronounced abnormalities may have additional prognostic significance (Fei et al., 2016; Portugal et al., 2017). Therefore, the combination of conventional echocardiographic assessment and GLS-based deformation analysis appears to offer a more complete approach to surveillance than LVEF measurement alone (Coutinho Cruz et al., 2020; Dobson et al., 2021; Esmaeilzadeh et al., 2022; Lyon et al., 2022; Marwick, 2021; Portugal et al., 2017; Sławiński & Lewicka, 2023). This is particularly relevant in cardio-oncology, where the clinical objective is not only to diagnose established cardiac dysfunction, but also to recognize myocardial injury early enough to allow closer monitoring, earlier intervention, and more individualized management.

In conclusion, LV GLS appears to be a clinically useful parameter that can be realistically integrated into routine echocardiographic monitoring in adult breast cancer patients receiving anthracycline-based chemotherapy. Its broader incorporation into cardio-oncology practice may improve early detection of therapy-related myocardial dysfunction and strengthen the diagnostic value of echocardiography in this population. Further prospective studies are needed to define the most appropriate cutoff values, optimal monitoring intervals, and the best way to combine GLS with LVEF and other echocardiographic markers in standardized surveillance protocols (Dobson et al., 2021; Esmaeilzadeh et al., 2022; Lyon et al., 2022; Marwick, 2021; Sławiński & Lewicka, 2023).

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