

## Review Article

# Prognostic value of absolute global longitudinal strain for chemotherapy-related cardiac dysfunction in breast cancer patients: a systematic review and meta-analysis

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**Abstract:** Objective: To determine the general predictive effect of absolute global longitudinal strain (GLS) in predicting chemotherapy-induced cardiotoxicity (CTRCD) for breast cancer patients. Methods: A systematic literature search was conducted on the PubMed, Embase, Cochrane Library, Web of Science, Scopus, China National Knowledge Infrastructure (CNKI), Wanfang and VIP databases to identify cohort studies published up to May 31, 2026, on the application of GLS for predicting CTRCD in breast cancer patients undergoing chemotherapy. Two researchers independently carried out the article filtering, data collection and quality assessment. RevMan 5.4 and Stata 18.0 software were used for meta-analysis; the size of the general effect was presented as an odds ratio (OR), and a hierarchical summary receiver operating characteristic (HSROC) curve was constructed to assess diagnostic accuracy. Subgroup analysis and meta-regression were used to identify the sources of heterogeneity; sensitivity analysis was conducted by a stepwise exclusion strategy; and a funnel plot was employed to examine publication bias. Result: 12 papers included data from 955 breast cancer patients. A meta-analysis indicated that the odds of being affected by CTRCD were significantly higher in the low-GLS group (absolute drop in GLS) compared with the high-GLS group (OR = 11.88, 95% CI: 7.88-17.92,  $P < 0.00001$ ), and there was low heterogeneity across trials ( $I^2 = 18\%$ ,  $P = 0.26$ ). The area under the HSROC curve (AUC) was 0.86 (95% CI: 0.82-0.89), and the combined sensitivity and combined specificity were 83.0% and 73.0% (95% CI: 75.4%-88.6%, 95% CI: 65.1%-79.6%), respectively. Subgroup analysis and meta-regression showed that research type, breast cancer subtype and the CTRCD definition were not significant sources of heterogeneity (all  $P > 0.05$ ). Exclusion of one study at a time in sensitivity analysis did not change the combined results. The funnel plot was symmetrical, and therefore publication bias is likely not present. Conclusion: the absolute GLS value can be used as a good prognostic index for chemotherapy-induced CTRCD in breast cancer patients, and a lower absolute GLS is associated with a significantly increased risk of CTRCD. An index has been developed to determine the risk of damage to the heart muscle after chemotherapy in breast cancer at a specific time, and scientific support will be provided for treatment decisions.

**Keywords:** Breast cancer, chemotherapy-induced cardiotoxicity, global longitudinal strain, meta-analysis, prognostic value

## Introduction

Breast cancer is a major health burden among women worldwide. The application of adjuvant chemotherapy and targeted therapies has substantially improved survival outcomes [1]. Cancer therapy-related cardiac dysfunction (CTRCD) remains an important clinical concern. Patients receiving anthracycline-based chemotherapy regimens and trastuzumab ther-

apy are at increased risk of CTRCD [2]. This condition may progress to severe cardiovascular complications, including cardiac failure, arrhythmias, and even death [3]. Therefore, continuous cardiac surveillance during oncological treatment is essential for early identification of patients at risk of cardiac dysfunction and timely implementation of preventive strategies to reduce cardiovascular morbidity and mortality [4].

Currently, left ventricular ejection fraction (LVEF), primarily assessed by 2D echocardiography, is the most commonly used parameter for cardiac function assessment. Contemporary studies have characterized CTRCD as a symptomatic decline in LVEF by  $\geq 5\%$  to  $< 55\%$ , or an asymptomatic reduction in LVEF of  $\geq 10\%$  to  $< 55\%$  [5]. However, LVEF is relatively insensitive to early myocardial injury due to its limited ability to detect subtle changes in myocardial mechanics and its susceptibility to physiological variability and loading conditions. Significant reductions in LVEF generally indicate advanced myocardial damage and are associated with unfavorable clinical outcomes [6]. Notably, LVEF decline typically occurs at a relatively late stage of CTRCD, and cardiac dysfunction may not be fully reversible after intervention in some patients. Therefore, increasing attention has been directed toward myocardial strain assessment using speckle-tracking methods as an early warning of cardiotoxicity.

Global longitudinal strain (GLS) is a left ventricular functional parameter derived from speckle-tracking echocardiography that quantifies myocardial deformation along the longitudinal axis of the left ventricular myocardium [7]. By tracking the spatial displacement of acoustic markers within the myocardium throughout the cardiac cycle, GLS enables detection of subtle abnormalities in myocardial contractile function [7]. GLS can identify subtle myocardial dysfunction before a measurable decline in LVEF occurs [8, 9]. Previous studies have demonstrated associations between GLS values or relative changes in GLS during breast cancer treatment and the development of cardiac dysfunction; however, considerable variability remains regarding the optimal predictive thresholds [10]. The joint guideline published by the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) suggests that a relative GLS reduction of more than 15% after anthracycline treatment may represent an early indicator of CTRCD, whereas a reduction of  $< 8\%$  is generally considered non-diagnostic [11]. Nevertheless, the clinical practice guidelines from the American Society of Clinical Oncology (ASCO) do not provide specific recommendations regarding GLS thresholds [12]. Therefore, despite existing evidence supporting the role of GLS in detecting chemotherapy-induced sub-

clinical cardiotoxicity, the optimal predictive criteria remain unclear.

Previous studies have also explored the combined use of GLS and cardiac biomarkers, including high-sensitivity cardiac troponin and natriuretic peptides, for early detection of CTRCD [13, 14]. However, the predictive value of these combined methods has not yet been systematically evaluated. Furthermore, the relationship between reduced GLS values and subclinical myocardial injury remains insufficiently investigated.

Therefore, this systematic review and meta-analysis aimed to comprehensively evaluate the prognostic value of quantitative GLS parameters obtained by speckle-tracking echocardiography for predicting CTRCD in patients with breast cancer undergoing chemotherapy.

### Methods

#### *Selection criteria*

Inclusion criteria: (1) Subjects: Adults aged  $\geq 18$  years with a confirmed diagnosis of breast cancer who received systemic chemotherapy; (2) Outcome definition: Studies that applied established clinical benchmarks for the diagnosis of CTRCD, with no striction on the specific definition used; (3) Predictive assessment: Studies that evaluated the predictive performance of GLS for CTRCD development; (4) Assessment method: GLS measured using speckle-tracking echocardiography before or during breast cancer treatment, with subsequent follow-up assessments based on LVEF changes for CTRCD surveillance; (5) Diagnostic performance data: Studies that provided sufficient data to construct or calculate a  $2 \times 2$  contingency table, including true positives, false positives, false negatives, and true negatives, or data that could be transformed into these parameters; (6) Study design: Prospective or retrospective cohort studies; (7) Language: English or Chinese; (8) Publication period: Studies published from database inception to May 31, 2026.

Exclusion criteria: (1) Case reports, reviews, editorials, comments, conference abstracts, or animal experiments; (2) Studies with a sample size of fewer than 30 participants; (3) Studies lacking sufficient original data for extraction or

quantitative analysis; (4) Duplicate publications.

## Search strategy

This systematic review and meta-analysis were conducted in accordance with the PRISMA guidelines [15]. The study was structured according to the PICO framework, including Population, Intervention, Comparison, and Outcome. The review protocol was registered in the INPLASY database (registration No.: INPLASY202670094). A comprehensive literature search was performed in the following databases: PubMed, Embase, Cochrane Library, Web of Science, Scopus, China National Knowledge Infrastructure (CNKI), Wanfang Data Knowledge Service System (WANFANG), and VIP database. The search strategy included combinations of Medical Subject Headings (MeSH) terms and free-text keywords related to breast cancer, cardiotoxicity, chemotherapy, and myocardial strain. The main search terms included: 'breast neoplasms', 'cardiotoxicity', 'heart failure', 'chemotherapy', 'anthracycline', 'trastuzumab', 'doxorubicin', 'daunorubicin', 'echocardiography', 'deformation', 'strain', 'breast cancer', 'cardiotoxicity' and 'strain', together with their related synonyms. Additionally, the reference lists of relevant reviews and previously published systematic reviews were manually screened to identify potentially eligible studies. The final database search was completed on May 31, 2026.

## Data extraction

The following information was extracted: author information, publication years, sample size, baseline demographic and clinical data (including age, baseline LVEF and GLS values, chemotherapy protocols, an tumor characteristics), study design, duration of GLS monitoring and follow-up periods, CTRCD diagnostic criteria, GLS thresholds, echocardiographic equipment and analysis software, as well as predictive performance indicators, including sensitivity, specificity, area under the curve (AUC), odds ratios (ORs), hazard ratios (HRs), and corresponding 95% confidence intervals (CIs). Two independent investigators collected data extraction from all included studies to minimize potential errors and bias. Any disagreements were resolved through discussion and consensus.

## Quality assurance

Newcastle-Ottawa (NOS) scale was used to assess the methodological quality of the included cohort studies. The NOS evaluates study quality based on three domains: participant selection, comparability between groups, and outcome assessment. Each item was assigned one point, except for the comparability domain, in which up to two points could be awarded. The total score ranged from 0 to 9, with scores  $\geq 6$  considered indicative good procedural soundness.

## Data analysis

Because GLS values are typically expressed as negative percentages, absolute GLS values were used to enhance clinical interpretability. Given the heterogeneity in GLS reporting methods among included studies, GLS was analyzed either as a categorical variable (reporting GLS thresholds for risk stratification) or a continuous variable.

Considering that the association between GLS and CTRCD risk may not follow a simple linear pattern and that the reported GLS thresholds varied across studies, participants were divided into low-GLS and high-GLS groups according to the cut-off values defined in each individual study. The number of CTRCD events and total participants in each group were subsequently extracted for pooled analysis.

Meta-analyses were performed using RevMan 5.4 and Stata 18.0. Odds ratios (OR) were used as the primary effect measure to estimate the association between GLS levels and CTRCD risk. An  $OR > 1$  with a  $P < 0.05$  indicated that patients with lower GLS values had a significantly higher risk of CTRCD compared with those with higher GLS values.

Statistical heterogeneity was assessed using the  $I^2$  statistic, with  $I^2$  values  $> 50\%$  indicating substantial heterogeneity. Subgroup analyses and meta-regression analyses were performed to explore potential sources of heterogeneity. A random-effects model based on the DerSimonian-Laird method was employed to account for heterogeneity among the included studies. The predictive performance of GLS for CTRCD was further evaluated using hierarchical summary receiver operating characteristic (HSROC) analysis.

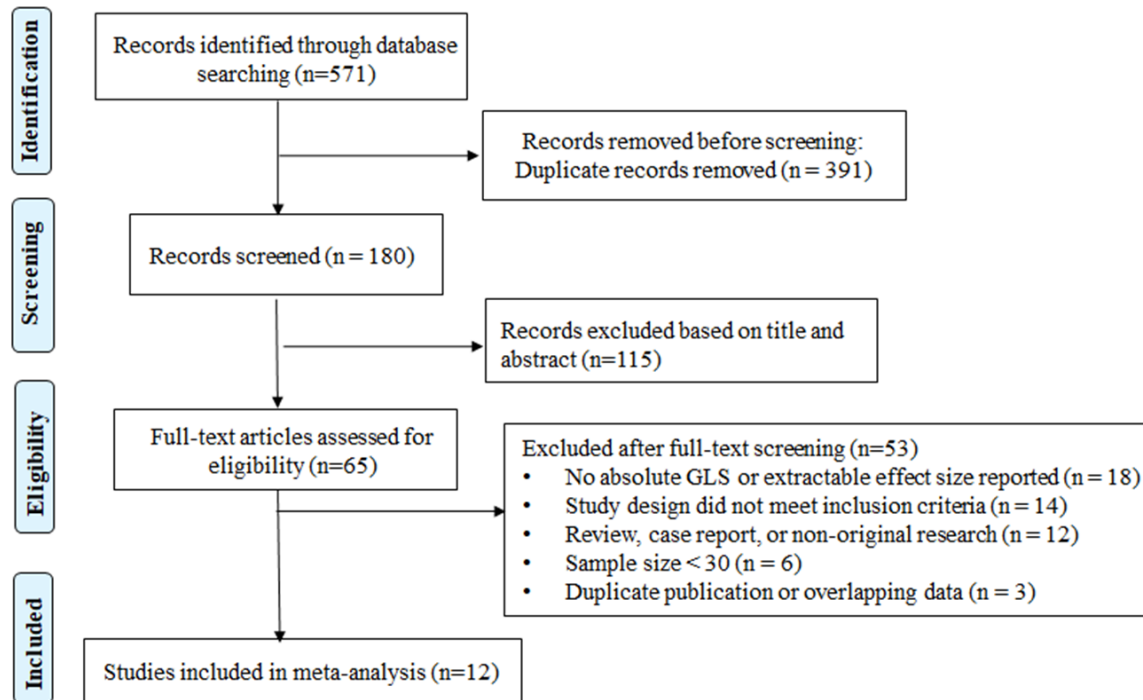


**Figure 1.** PRISMA flowchart for literature screening. Notes: GLS: global longitudinal strain.

Sensitivity analyses were conducted using a step-wise exclusion strategy, and after removing each individual study, the size of the total effect was recalculated to determine whether it remained consistent. Potential publication bias was assessed using funnel plots. A  $P$  value  $<0.05$  in the corresponding statistical test was considered indicative of significant publication bias. Publication bias was assessed using funnel plots and formally tested with Begg's rank correlation test and Egger's linear regression test. A  $P$  value  $<0.05$  was considered indicative of significant publication bias.

## Results

### Literature search and study selection

A total of 571 publications were identified through database searches. After removal of duplicates, 180 studies remained for title and abstract screening, leaving 65 articles for full-text analysis. After full-text assessment, 53 articles were excluded due to failure to meet the predefined inclusion criteria. Finally, 12 studies [3, 16-26] involving 955 patients with breast cancer were included this meta-analysis. The detailed study selection process is presented in the PRISMA flowchart (Figure 1).

### General characteristics of the included studies

Among the included studies, six studies specifically enrolled patients with HER2-positive breast cancer, whereas the remaining studies did not report HER2 status. All included patients received anthracycline-based chemotherapy, and patients with HER2-positive disease frequently received additional trastuzumab therapy. Nine studies were prospective cohort studies, and three were retrospective cohort studies.

Various definitions of CTRCD were applied across the included studies. According to the diagnostic criteria used, CTRCD definitions were categorized into four groups: (1) definitions based on the ESC Guidelines for Cardiac-Oncology; (2) definitions based on specific LVEF threshold, including a symptomatic decrease in LVEF of  $\geq 5\%$  to  $<55\%$ , or an asymptomatic decline in LVEF of  $\geq 10\%$  to  $<55\%$ ; (3) definitions based on an LVEF reduction of  $\geq 10\%$  from baseline levels; and (4) combined definition integrating LVEF and GLS change, including an LVEF reduction of  $>10\%$  with an absolute LVEF value  $\geq 50\%$  or a relative GLS decline of  $>15\%$ . Detailed baseline characteristics and extracted data are provided in Tables 1-4.

## Absolute GLS and CTRCD in breast cancer: a meta-analysis

**Table 1.** Features of included studies

| Author/Year           | Cancer phenotype | Chemotherapy regimen                    | Study type    | Follow-up Period (months) | CTRCD incidence (%) | Baseline LVEF (%) | Baseline GLS (%) | Ultrasound device model | Definition of CTRCD                                        |
|-----------------------|------------------|-----------------------------------------|---------------|---------------------------|---------------------|-------------------|------------------|-------------------------|------------------------------------------------------------|
| Fawzy 2024 [3]        | -                | Anthracyclines ± trastuzumab            | Prospective   | 6                         | 25.5                | 62.1±4.1          | 18.9±1.6         | Vivid 7 (GE)            | 2022 ESC Guidelines [27]                                   |
| Calle 2018 [16]       | -                | Anthracyclines or trastuzumab or both   | Retrospective | 5.44 (4.61-6.47)          | 20                  | 65.2±4.4          | 19.9±2.8         | Vivid 7 (GE)            | Absolute decrease in LVEF of ≥10% from baseline [28]       |
| El-Sherbeny 2019 [17] | Her-2            | Anthracyclines + taxanes + trastuzumab  | Prospective   | 12                        | 29.5                | 60±3              | 20.3±1.3         | Vivid E9 (GE)           | General Standard*                                          |
| Gripp 2018 [18]       | Her-2            | Anthracyclines ± trastuzumab            | Prospective   | 12±1.0                    | 10.2                | 68                | 20.4             | Vivid E9 (GE)           | General Standard*                                          |
| Guerra 2016 [19]      | -                | Anthracyclines ± Taxanes + Trastuzumab  | Outlook       | 12                        | 27.5                | 64                | 19.8             | Vivid 7 Pro (GE)        | General Standard*                                          |
| Jia XH 2023 [20]      | Her-2            | Anthracyclines                          | Review        | 6                         | 13.33               | 64.01±3.61        | 20.79±2.58       | GE Vivid E95            | LVEF reduced by >10% and ≥50%, or GLS reduced by >15% [29] |
| Kridis 2020 [21]      | Her-2            | Anthracyclines ± taxanes + trastuzumab  | Prospective   | 15                        | 14                  | 62.4±2.7          | 20.7±2.3         | Vivid 7 (GE)            | 2016 ESC Guidelines [30]                                   |
| Milks 2018 [22]       | -                | Anthracyclines ± trastuzumab            | Review        | -                         | 18                  | 59                | 22.4             | Several                 | 2016 ESC Guidelines                                        |
| Negishi 2013 [23]     | Her-2            | Anthracyclines or taxanes + trastuzumab | Prospective   | 12                        | 29.63               | 62±4              | 20±2             | Vivid 7/E9 (GE)         | Decrease in LVEF of ≥10%                                   |
| Sawaya 2012 [24]      | Her-2            | Anthracyclines or taxanes + trastuzumab | Prospective   | 15                        | 32.1                | 64±5              | 21±2             | Vivid 7/E9 (GE)         | General standard*                                          |
| Wen XL 2023 [25]      | -                | Anthracyclines                          | Outlook       | 12                        | 8.1                 | 66.1±6.3          | 20.7±3.2         | GE Vivid E95            | General standard*                                          |
| Zhou YC 2025 [26]     | -                | Anthracyclines + Trastuzumab            | Prospective   | 6                         | 14.3                | 67.35±5.32        | 21.95±3.26       | Vivid E9 (GE)           | Decrease in LVEF of ≥10%                                   |

Notes: Her-2: human epidermal growth factor receptor 2; CTRCD: cancer treatment-related cardiac dysfunction; LVEF: left ventricular ejection fraction; GLS: global longitudinal strain; ESC: European Society of Cardiology; GE: General Electric; baseline GLS values are expressed as negative percentages (%-); a higher absolute value (more negative) indicates better longitudinal strain.\*: LVEF ≥5% to <55% with symptoms, or ≥10% to <55% without symptoms.

**Table 2.** Clinical characteristics of breast cancer patients

| Author/Year           | Sample size | Mean age (years) | Radiotherapy (%) | Diabetes (%) | Hypertension (%) | Hyperlipidaemia (%) | History of smoking (%) | ACEI/ARB (%) | Beta-blockers (%) | Statins (%) |
|-----------------------|-------------|------------------|------------------|--------------|------------------|---------------------|------------------------|--------------|-------------------|-------------|
| Fawzy 2024 [3]        | 101         | 48.84±10.17      | -                | 34           | 28.7             | -                   | -                      | -            | -                 | -           |
| Calle 2018 [16]       | 66          | 52±9             | 76               | 5            | 20               | 18                  | 20                     | -            | -                 | -           |
| El-Sherbeny 2019 [17] | 61          | 47.4±9.1         | 90               | 11           | 36               | 24.6                | 8                      | -            | -                 | -           |
| Gripp 2018 [18]       | 49          | 50               | 53.1             | 4.1          | 32.7             | -                   | -                      | -            | -                 | 6.1         |
| Guerra 2016 [19]      | 69          | 56±13            | -                | 6            | 42               | 19                  | 16                     | 26           | 20                | 10          |
| Jia XH 2023 [20]      | 30          | 47.94±8.46       | -                | -            | -                | -                   | -                      | -            | -                 | -           |
| Kridis 2020 [21]      | 50          | 49.64±8.52       | 86               | 16           | 22               | 12                  | 0                      | -            | -                 | -           |
| Milks 2018 [22]       | 183         | 51±11            | 63.9             | 8.2          | 31.7             | 18.6                | 27.9                   | 21.3         | 14.2              | 12.6        |
| Negishi 2013 [23]     | 81          | 50±11            | 62               | 7            | 21               | 16                  | 15                     | -            | 0                 | -           |
| Sawaya 2012 [24]      | 81          | 50±18            | 60               | 1            | 32               | 22                  | 7                      | 17           | 11                | -           |
| Wen XL 2023 [25]      | 86          | 46.5±8.2         | -                | -            | -                | -                   | -                      | -            | -                 | -           |
| Zhou YC 2025 [26]     | 98          | 47.45±7.72       | -                | -            | -                | -                   | -                      | -            | -                 | -           |

Notes: ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker.

## Absolute GLS and CTRCD in breast cancer: a meta-analysis

**Table 3.** Prognostic value of absolute GLS scores for CTRCD in breast cancer patients

| Author/Year           | Univariate AUC (95% CI) | Unadjusted OR/HR (95% CI) | Adjusted OR/HR (95% CI) | Covariates (if adjusted models)                                                                     |
|-----------------------|-------------------------|---------------------------|-------------------------|-----------------------------------------------------------------------------------------------------|
| Fawzy 2024 [3]        | 0.938                   | OR 9.333 (2.516-34.214)   | -                       | -                                                                                                   |
| Calle 2018 [16]       | 0.85                    | OR 1.47 (1.13-2.04)       | -                       | -                                                                                                   |
| El-Sherbeny 2019 [17] | 0.98                    | -                         | -                       | -                                                                                                   |
| Gripp 2018 [18]       | 0.95 (0.87-1.00)        | HR 2.77 (1.39-5.54)       | HR 4.10 (1.07-15.72)    | Left ventricular ejection fraction (LVEF)                                                           |
| Guerra 2016 [19]      | 0.93                    | -                         | -                       | -                                                                                                   |
| Jia XH 2023 [20]      | 0.752                   | -                         | -                       | -                                                                                                   |
| Kridis 2020 [21]      | -                       | -                         | HR 2.4 (1.2-6.03)       | LVEF                                                                                                |
| Milks 2018 [22]       | -                       | -                         | OR 1.71 (1.26-2.33)     | Renal failure, beta-blocker use, trastuzumab treatment, age, anthracycline dose, post-treatment GLS |
| Negishi 2013 [23]     | 0.67                    | -                         | -                       | -                                                                                                   |
| Sawaya 2012 [24]      | -                       | -                         | -                       | -                                                                                                   |
| Wen XL 2023 [25]      | 0.85 (0.76-0.88)        | -                         | -                       | -                                                                                                   |
| Zhou YC 2025 [26]     | 0.657 (0.511-0.802)     | -                         | -                       | -                                                                                                   |

Notes: AUC: area under the curve; OR: odds ratio; HR: hazard ratio; CTRCD: cancer treatment-related cardiac dysfunction; GLS: global longitudinal strain; CI: confidence interval; LVEF: left ventricular ejection fraction.

**Table 4.** Sensitivity and specificity of absolute GLS values for predicting CTRCD

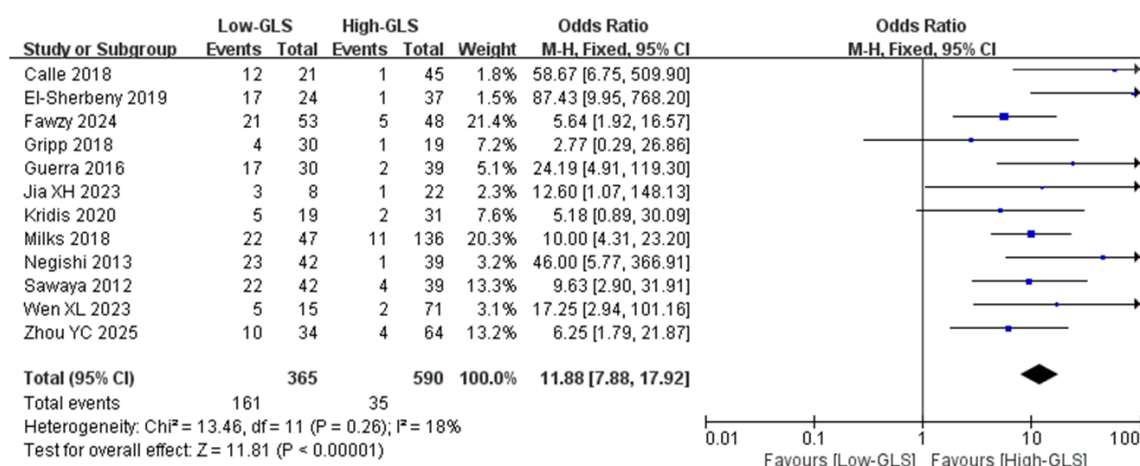
| Author/Year           | Low GLS group    |                      |             | High GLS group   |                      |             | Cutoff value (%) | Sensitivity (95% CI) | Specificity (95% CI) |
|-----------------------|------------------|----------------------|-------------|------------------|----------------------|-------------|------------------|----------------------|----------------------|
|                       | Number of events | Number of non-events | Sample size | Number of events | Number of non-events | Sample size |                  |                      |                      |
| Fawzy 2024 [3]        | 21               | 32                   | 53          | 5                | 43                   | 48          | -18              | 0.815                | 0.5714               |
| Calle 2018 [16]       | 12               | 9                    | 21          | 1                | 44                   | 45          | -14.06           | 0.92 (0.64-1.00)     | 0.83 (0.70-0.92)     |
| El-Sherbeny 2019 [17] | 17               | 7                    | 24          | 1                | 36                   | 37          | -18              | 0.94 (0.73-1.00)     | 0.84 (0.69-0.93)     |
| Gripp 2018 [18]       | 4                | 26                   | 30          | 1                | 18                   | 19          | -16.6            | 0.80 (0.28-0.99)     | 0.95 (0.85-0.99)     |
| Guerra 2016 [19]      | 17               | 13                   | 30          | 2                | 37                   | 39          | -18              | 0.89 (0.67-0.99)     | 0.74 (0.60-0.85)     |
| Jia XH 2023 [20]      | 3                | 5                    | 8           | 1                | 21                   | 22          |                  | 0.706                | 0.821                |
| Kridis 2020 [21]      | 5                | 14                   | 19          | 2                | 29                   | 31          | -19.4            | 0.71 (0.29-0.96)     | 0.68 (0.49-0.83)     |
| Milks 2018 [22]       | 22               | 25                   | 47          | 11               | 125                  | 136         | -19              | 0.66 (0.47-0.81)     | 0.83 (0.76-0.89)     |
| Negishi 2013 [23]     | 23               | 19                   | 42          | 1                | 38                   | 39          | -21              | 0.96 (0.79-1.00)     | 0.67 (0.53-0.79)     |
| Sawaya 2012 [24]      | 22               | 20                   | 42          | 4                | 35                   | 39          | -19              | 0.74 (0.52-0.90)     | 0.73 (0.59-0.84)     |
| Wen XL 2023 [25]      | 5                | 10                   | 15          | 2                | 69                   | 71          | -15              | 0.753                | 0.876                |
| Zhou YC 2025 [26]     | 10               | 24                   | 34          | 4                | 60                   | 64          | -20.35           | 0.68                 | 0.717                |

Notes: GLS: global longitudinal strain; CTRCD: cancer treatment-related cardiac dysfunction; CI: confidence interval.

**Table 5.** Quality assessment of included studies (NOS scale)

| Author/Year           | Study Population |    |    |    | Comparability between groups | Outcome Assessment |    |    | Total score |
|-----------------------|------------------|----|----|----|------------------------------|--------------------|----|----|-------------|
|                       | Q1               | Q2 | Q3 | Q4 |                              | Q6                 | Q7 | Q8 |             |
| Fawzy 2024 [3]        | 1                | 1  | 1  | 1  | 0                            | 1                  | 1  | 1  | 7           |
| Calle 2018 [16]       | 1                | 1  | 0  | 1  | 1                            | 1                  | 1  | 1  | 7           |
| El-Sherbeny 2019 [17] | 1                | 1  | 0  | 1  | 1                            | 1                  | 1  | 1  | 7           |
| Gripp 2018 [18]       | 1                | 1  | 1  | 1  | 1                            | 1                  | 1  | 1  | 8           |
| Guerra 2016 [19]      | 1                | 1  | 1  | 1  | 1                            | 0                  | 0  | 1  | 6           |
| Jia XH 2023 [20]      | 1                | 0  | 1  | 1  | 1                            | 1                  | 0  | 1  | 6           |
| Kridis 2020 [21]      | 1                | 1  | 1  | 0  | 1                            | 1                  | 0  | 1  | 6           |
| Milks 2018 [22]       | 1                | 1  | 1  | 1  | 1                            | 1                  | 0  | 1  | 7           |
| Negishi 2013 [23]     | 1                | 1  | 1  | 1  | 1                            | 1                  | 1  | 1  | 8           |
| Sawaya 2012 [24]      | 1                | 0  | 1  | 1  | 1                            | 1                  | 1  | 1  | 7           |
| Wen XL 2023 [25]      | 1                | 1  | 1  | 1  | 1                            | 1                  | 1  | 1  | 8           |
| Zhou YC 2025 [26]     | 1                | 1  | 1  | 1  | 1                            | 1                  | 0  | 1  | 7           |

Notes: Q1-Q8: Items on the NOS scale, where Q1: representativeness of the exposed group; Q2: selection of the unexposed group; Q3: identification of the exposure factor; Q4: absence of the outcome at the start of the study; Q5: comparability between groups; Q6: assessment of the outcome; Q7: sufficient duration of follow-up; Q8: completeness of follow-up; NOS: Newcastle-Ottawa Scale.

**Figure 2.** Forest plot of absolute GLS for predicting CTRCD in breast cancer patients. Notes: GLS: global longitudinal strain; CTRCD: cancer treatment-related cardiac dysfunction; CI: confidence interval; M-H: Mantel-Haenszel method.

### Quality assessment of included studies

According to the NOS assessment scores, three studies were scored 8 points, six scored 7 points, and three scored 6 points. All included studies achieved an NOS score  $\geq 6$ , indicating relatively high methodological quality and suitability for quantitative synthesis (Table 5).

### Meta-analysis of absolute GLS values for predicting CTRD

Compared with patients in the higher absolute GLS group, patients with reduced absolute GLS

values showed a significantly higher incidence of CTRCD. The pooled odds ratio (OR) was 11.88 (95% CI: 7.88-17.92), indicating a significantly increased risk of CTRCD among patients with lower absolute GLS values ( $Z = 11.81$ ,  $P < 0.00001$ ) (Figure 2).

Low heterogeneity was observed among studies ( $I^2 = 18\%$ ,  $P = 0.26$ ), suggesting good consistency across the included cohorts. Sensitivity analysis was performed by sequentially excluding individual studies, and the pooled effect estimate remained largely unchanged, supporting the robustness of the primary findings (Table 6).

**Table 6.** Sensitivity analysis for the predictive value of absolute GLS for CTRCD in breast cancer patients

| Study excluded        | Heterogeneity test       |         | Meta-analysis results |         |
|-----------------------|--------------------------|---------|-----------------------|---------|
|                       | I <sup>2</sup> value (%) | P-value | OR (95% CI)           | P-value |
| Fawzy 2024 [3]        | 15                       | 0.30    | 13.58 (8.70-21.21)    | <0.001  |
| Calle 2018 [16]       | 9                        | 0.36    | 11.01 (7.22-16.77)    | <0.001  |
| El-Sherbeny 2019 [17] | 0                        | 0.47    | 10.69 (7.01-16.32)    | <0.001  |
| Gripp 2018 [18]       | 17                       | 0.28    | 12.59 (8.30-19.09)    | <0.001  |
| Guerra 2016 [19]      | 19                       | 0.26    | 11.22 (7.33-17.18)    | <0.001  |
| Jia XH 2023 [20]      | 26                       | 0.20    | 11.87 (7.83-18.00)    | <0.001  |
| Kridis 2020 [21]      | 21                       | 0.24    | 12.43 (8.14-19.00)    | <0.001  |
| Milks 2018 [22]       | 25                       | 0.20    | 12.36 (7.74-19.76)    | <0.001  |
| Negishi 2013 [23]     | 12                       | 0.33    | 10.77 (7.06-16.41)    | <0.001  |
| Sawaya 2012 [24]      | 26                       | 0.20    | 12.23 (7.90-18.95)    | <0.001  |
| Wen XL 2023 [25]      | 24                       | 0.21    | 11.74 (7.69-17.84)    | <0.001  |
| Zhou YC 2025 [26]     | 21                       | 0.25    | 12.74 (8.23-19.73)    | <0.001  |

Notes: GLS: global longitudinal strain; CTRCD: cancer treatment-related cardiac dysfunction; OR: odds ratio; CI: confidence interval.

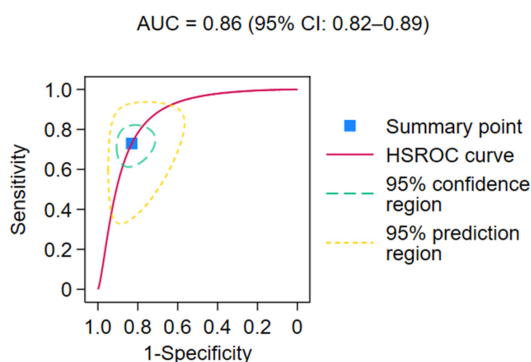


**Figure 3.** HSROC curve analysis of absolute GLS for predicting CTRCD in breast cancer patients. Notes: HSROC: hierarchical summary receiver operating characteristic; GLS: global longitudinal strain; CTRCD: cancer treatment-related cardiac dysfunction.

#### HSROC curve analysis

The overall diagnostic performance of absolute GLS values for predicting chemotherapy-induced CTRCD in breast cancer patients was evaluated using a HSROC curve. The HSROC curve showed that the study estimates were consistently distributed within the ROC space, suggesting that absolute GLS values exhibited stable discriminative ability for CTRCD prediction.

The pooled sensitivity of absolute GLS values in predicting CTRCD was 83.0% (95% CI: 75.4%-88.6%), and the pooled specificity reached

73.0% (95% CI: 65.1%-79.6%). The corresponding diagnostic odds ratio (DOR) was 13.20 (95% CI: 7.67-22.72). The pooled positive likelihood ratio (LR+) was 3.07 (95% CI: 2.35-4.01), and the pooled negative likelihood ratio (LR-) was 0.23 (95% CI: 0.16-0.34). The AUC was 0.86 (95% CI: 0.82-0.89), indicating that absolute GLS values demonstrated moderate-to-good diagnostic performance for predicting CTRCD (Figure 3).

The goodness-of-fit assessment of the HSROC model showed a shape parameter ( $\beta$ ) of 0.36 ( $P = 0.623$ ). In the HSROC framework,  $\beta$  reflects the asymmetry of the SROC curve and may indicate variations in the relationship between sensitivity and specificity across various GLS diagnostic thresholds. A  $\beta$  value close to 0 indicates that the curve is more symmetrical, and thus the threshold effect on model calibration is reduced. In the present analysis,  $\beta$  was not significantly different from zero ( $\beta = 0.36$  and  $P = 0.623 > 0.05$ ), indicating no significant asymmetry or substantial considerable threshold-related effect among the included studies. Furthermore, the relatively narrow 95% confidence interval and prediction interval supported the robustness of absolute GLS values in predicting CTRCD.

#### Meta-regression analysis

To explore the possible sources of heterogeneity among the included studies, univariate

**Table 7.** Univariate meta-regression analysis of absolute GLS in predicting CTRCD

| Covariates        | $\beta$ | (95% CI)        | P-value |
|-------------------|---------|-----------------|---------|
| GLS cut-off value | -0.135  | -0.501 to 0.231 | 0.426   |
| Sample size       | -0.003  | -0.015 to 0.010 | 0.629   |
| Average age       | 0.087   | -0.154 to 0.328 | 0.44    |
| Baseline LVEF     | -0.053  | -0.259 to 0.152 | 0.577   |
| Baseline GLS      | -0.105  | -0.619 to 0.409 | 0.658   |

Notes: GLS: global longitudinal strain; CTRCD: cancer treatment-related cardiac dysfunction; LVEF: left ventricular ejection fraction;  $\beta$ : regression coefficient; CI: confidence interval.

meta-regression analyses were performed using the pooled log OR as the dependent variable. GLS threshold, sample size, mean age, baseline LVEF, and baseline GLS were used as independent variables. The results showed that none of the evaluated variables significantly influenced the pooled effect size. Specifically, GLS threshold ( $\beta = -0.135$ ,  $P = 0.426$ ), sample size ( $\beta = -0.003$ ,  $P = 0.629$ ), mean age ( $\beta = 0.087$ ,  $P = 0.440$ ), baseline LVEF ( $\beta = -0.053$ ,  $P = 0.577$ ), and baseline GLS ( $\beta = -0.105$ ,  $P = 0.658$ ) were not significantly associated with the overall effect estimate (all  $P > 0.05$ ) (**Table 7**).

#### Subgroup analysis

**Subgroup analysis by study design:** The included studies were categorized according to study design into prospective studies ( $n = 9$ ) and retrospective studies ( $n = 3$ ). The pooled OR for prospective studies was 11.23 (95% CI: 6.86-18.37), with low heterogeneity ( $I^2 = 27\%$ ,  $P = 0.20$ ). The pooled OR for retrospective studies was 13.92 (95% CI: 6.75-28.70), and heterogeneity remained low ( $I^2 = 13\%$ ,  $P = 0.32$ ). No statistically significant difference was observed between the two subgroups ( $P = 0.63$ ), suggesting that study design was not a significant source of variation in the predictive value of GLS for CTRCD (**Figure 4**).

**Subgroup analysis by breast cancer phenotype:** According to breast cancer phenotypes, the included studies were divided into HER2-positive breast cancer ( $n = 6$ ) and unspecified HER2 status ( $n = 6$ ). The pooled OR was 14.18 (95% CI: 6.98-28.82) in the HER2-positive subgroup and 10.64 (95% CI: 6.42-17.63) in the unspecified phenotype subgroup. Both subgroups demonstrated low heterogeneity. No

statistically significant difference was observed between the two subgroups ( $P = 0.52$ ), indicating that breast cancer subtype did not significantly influence the predictive performance of GLS for CTRCD (**Figure 5**).

**Subgroup analysis by CTRCD definitions:** Based on the diagnostic criteria used for CTRCD, the included studies were classified into four subgroups: ESC guideline-based criteria ( $n = 3$ ), expanded criteria ( $n = 5$ ), criteria based on an absolute LVEF reduction  $\geq 10\%$  ( $n = 3$ ), and combined LVEF/GLS-based criteria ( $n = 1$ ). The pooled ORs were 7.37 (95% CI: 3.93-13.82), 15.22 (95% CI: 7.29-31.81), 18.45 (95% CI: 7.48-45.50), and 12.60 (95% CI: 1.07-148.13), respectively. No significant differences were identified among the subgroups ( $P = 0.32$ ), suggesting that variations in CTRCD diagnostic criteria were not the major source of heterogeneity (**Figure 6**).

#### Publication bias

Potential publication bias was assessed using funnel plot analysis. The funnel plot for the association between absolute GLS values and CTRCD risk, based on the 12 included studies, showed a relatively symmetrical distribution of study estimates around the pooled effect size. To formally evaluate publication bias, Begg's rank correlation test and Egger's linear regression test were performed. Begg's test ( $P = 0.582$ ) and Egger's test ( $P = 0.371$ ) showed no evidence of significant publication bias, consistent with the symmetrical funnel plot. These findings suggested no obvious evidence of publication bias (**Figure 7**).

#### Discussion

This systematic review and meta-analysis investigated the prognostic value of absolute GLS values in predicting CTRCD in breast cancer patients undergoing chemotherapy. A total of 12 cohort studies cohort studies 955 breast cancer patients were included. The pooled analysis demonstrated that lower absolute GLS values were associated with an 11.88-fold increased risk of CTRCD compared with higher absolute GLS values (OR = 11.88, 95% CI: 7.88-17.92,  $P < 0.00001$ ), with low between-study heterogeneity ( $I^2 = 18\%$ ). Furthermore, HSROC analysis demonstrated favorable predictive performance, with an AUC of 0.86 (95%

# Absolute GLS and CTRCD in breast cancer: a meta-analysis

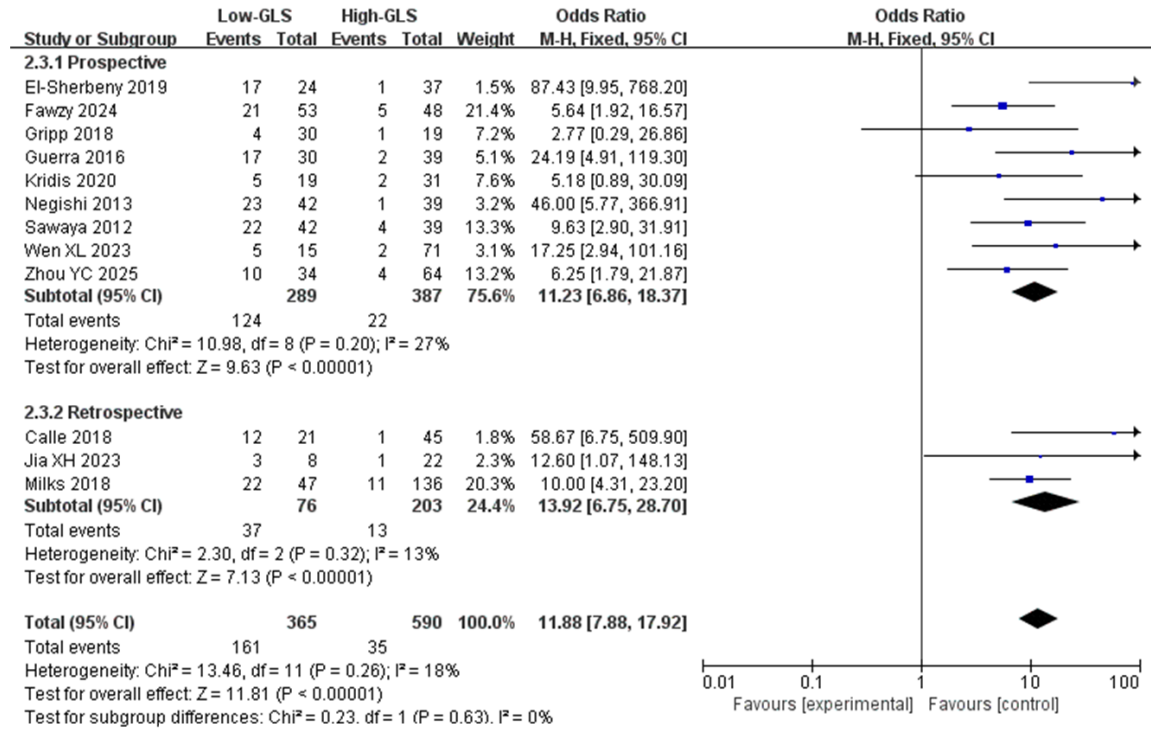


**Figure 4.** Forest plot of subgroup analysis stratified by study type. Notes: GLS: global longitudinal strain; CI: confidence interval; M-H: Mantel-Haenszel method.

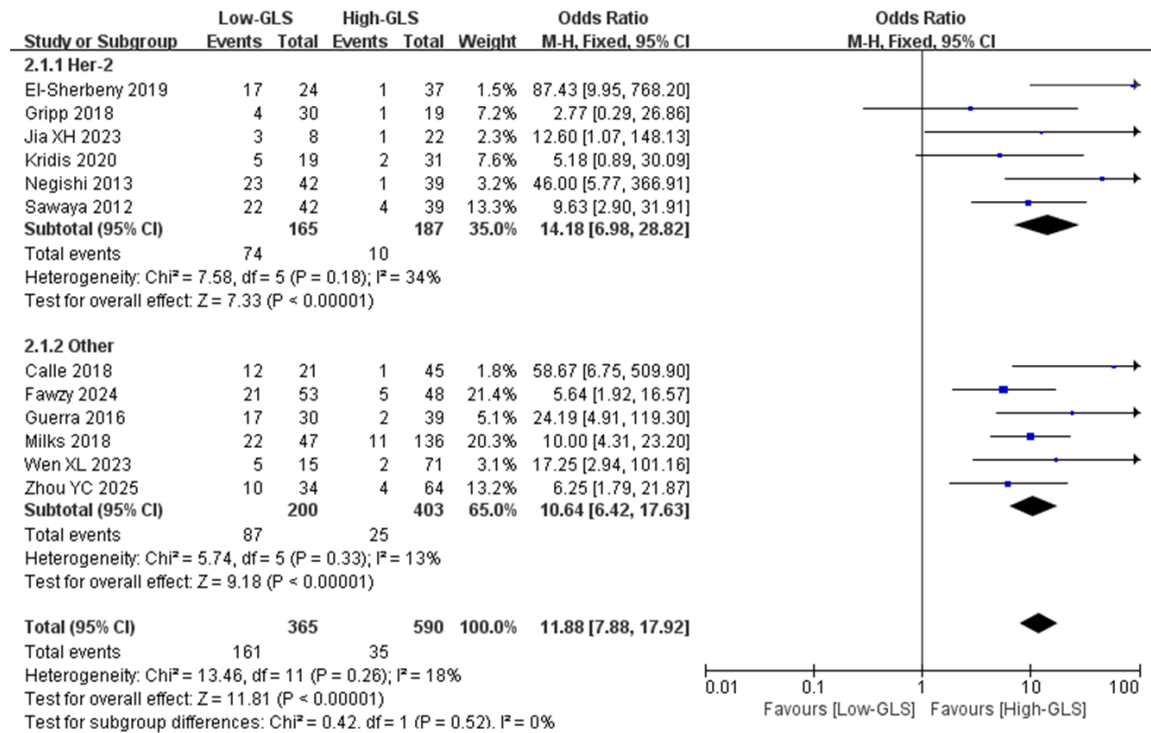


**Figure 5.** Forest plot of subgroup analysis stratified by breast cancer phenotype. Notes: GLS: global longitudinal strain; CI: confidence interval; M-H: Mantel-Haenszel method.

## Absolute GLS and CTRCD in breast cancer: a meta-analysis

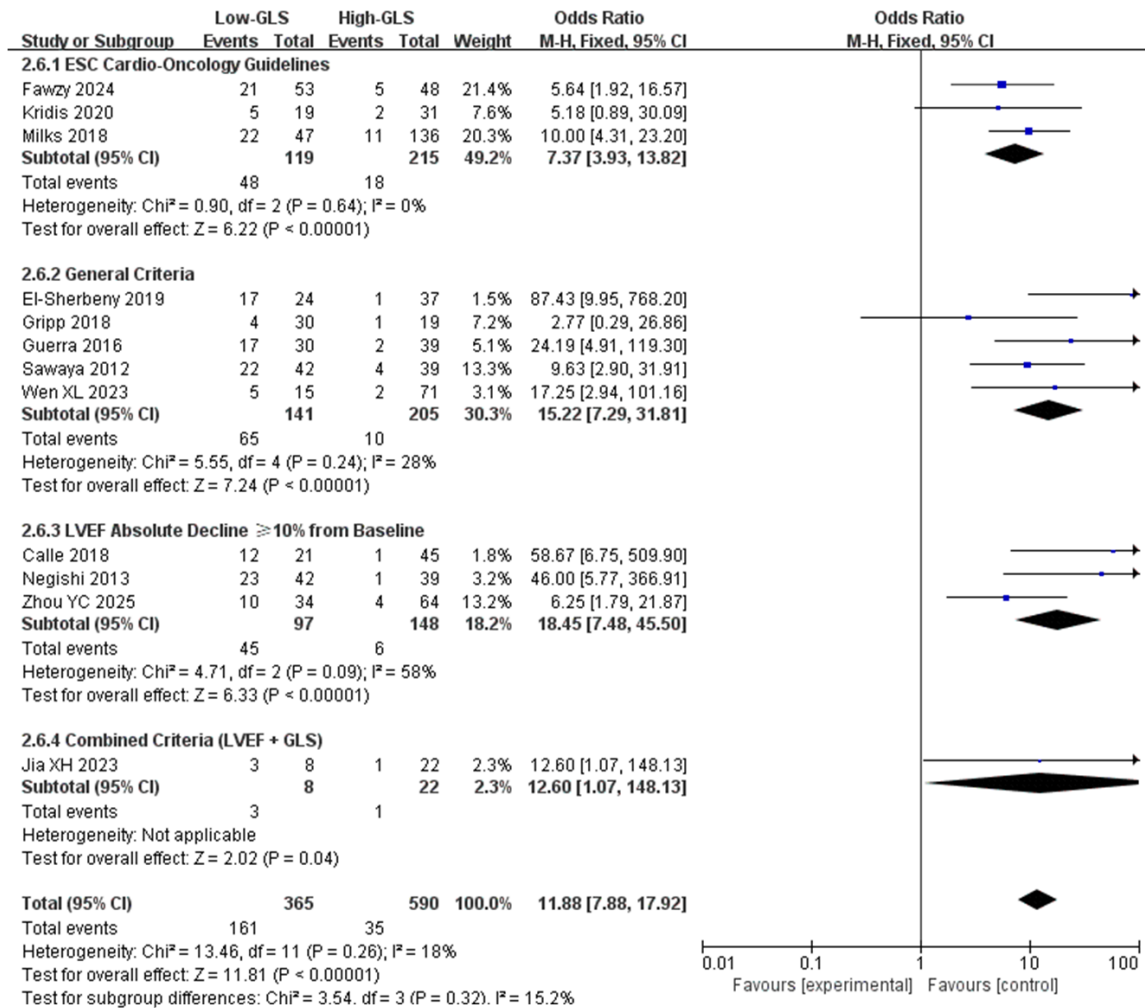


**Figure 6.** Forest plot of subgroup analysis stratified by CTRCD definition. Notes: GLS: global longitudinal strain; CI: confidence interval; CTRCD: cancer treatment-related cardiac dysfunction; M-H: Mantel-Haenszel method.

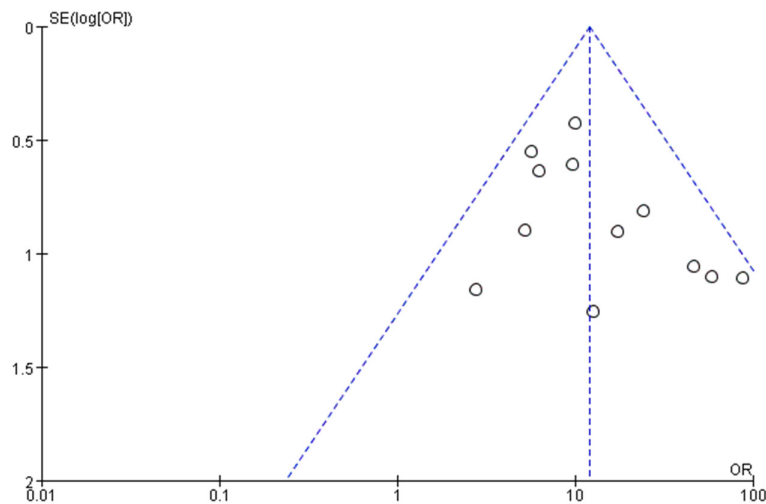


**Figure 7.** Funnel plot for the assessment of publication bias. Notes: SE[log(OR)]: standard error of the logarithm of the odds ratio; OR: odds ratio.

CI: 0.82-0.89), pooled sensitivity of 83.0%, and pooled specificity of 73.0%. These findings indicate that absolute GLS values may serve as a reliable predictor for identifying patients at increased risk of CTRCD.

The findings of this study are consistent with previous meta-analyses. For instance, Li et al. [8] systematically analyzed 13 studies involving more than 1,000 breast cancer patients and reported that GLS had a pooled sensitivity of 84%, specificity of 77%, and HSROC-AUC of 0.88 in

predicting CTRCD. Similarly, Oikonomou et al. [31] conducted a meta-analysis of 21 studies involving 1,782 oncology patients and demonstrated that GLS was a reliable surrogate marker for chemotherapy-induced cardiotoxicity, with an HSROC-AUC of 0.86. In this study, the pooled sensitivity (83.0%) was close to that reported by Li et al., whereas the specificity (73.0%) was slightly lower. This discrepancy may be attributed to variations in CTRCD definitions, GLS thresholds, and follow-up durations across studies [32]. Overall, our findings reinforce previous evidence that reductions in absolute GLS values are significantly associated with an increased risk of CTRCD, thus supporting the clinical utility of GLS as a prognostic marker in cardio-oncology surveillance.

This study specifically evaluated the prognostic value of absolute GLS values, while previous research has predominantly used a relative reduction in GLS of >15% from baseline as a criterion for predicting CTRCD [33]. However, the intrinsic predictive value of baseline or absolute GLS measurements has received comparatively less attention. By incorporating studies reporting precise GLS values, the present analysis demonstrated that patients with lower absolute GLS values remained at significantly higher risk of CTRCD, even without adjustment for individual baseline GLS changes. These findings extend the potential application of GLS in CTRCD risk stratification, suggesting that absolute GLS values may provide clinically meaningful information even when baseline follow-up measurements are unavailable.

GLS provides additional information beyond LVEF by detecting subclinical myocardial injury at an earlier stage. Sartorio et al. [34] demonstrated that substantial myocardial injury may occur despite preserved LVEF, highlighting GLS as an earlier indicator of cardiotoxicity before overt ventricular dysfunction develops. A recent systematic review and meta-analysis further confirmed that GLS is more sensitive than conventional parameters for detecting early myocardial function impairment after chemotherapy and provides a valuable window for initiating cardioprotective treatment [35]. In this study, baseline LVEF among included cohorts were generally within the normal range (59%-68%); however, absolute GLS values successfully discriminated between patients who subsequently

developed CTRCD and those who did not. These findings are consistent with previous reports. For example, Dong et al. [36] conducted a network meta-analysis involving 33 studies and 4,613 participants and demonstrated that both anthracycline-based chemotherapy and radiotherapy were associated with reductions in GLS. Collectively, absolute GLS values not only reflect early myocardial impairment after heart anticancer therapy but may also serve as an independent predictor of CTRCD risk, providing prognostic information beyond conventional LVEF assessment.

This study highlights the clinical importance of absolute GLS values in predicting CTRCD. According to the ASE/EACVI guidelines, a relative reduction in GLS of >15% from baseline is considered an early indicator of CTRCD. Terluk et al. provided further evidence supporting the complementary role of absolute GLS values [32]. In their prospective longitudinal study of 114 patients with HER2-negative breast cancer receiving anthracycline-based chemotherapy, 43 patients (38%) exhibited a relative GLS reduction of  $\geq 10\%$  after 12 months; however, only 20 patients (47%) in this subgroup demonstrated an absolute GLS value below 16%. Among patients with a baseline GLS  $\geq 20.5\%$ , the ability to maintain a normal absolute GLS value ( $\geq 16\%$ ) at 1 year showed a sensitivity of 79% and a specificity of 87%. These findings indicate an important clinical consideration: patients with relatively preserved baseline GLS may remain within the normal absolute GLS range despite a substantial relative decline and may therefore have a lower risk of CTRCD. Conversely, patients with an already impaired baseline absolute GLS value may enter a higher-risk category even after a relatively small proportional reduction. Therefore, absolute GLS values and relative GLS changes should be considered complementary rather than mutually exclusive parameters in clinical practice. Consistent with this meta-analysis, Terluk et al. [32] demonstrated that incorporating baseline absolute GLS value alongside relative GLS changes improved the accuracy of risk stratification for CTRCD.

In addition to absolute GLS measurements, integrating GLS with additional echocardiographic parameters and circulating biomarkers may further improve CTRCD risk prediction. Di Lisi et al. [37] proposed GAVS (the combined

index of GLS and left atrial peak longitudinal strain [PALS]), a new atrioventricular strain index, and demonstrated superior predictive performance compared with GLS alone. Similarly, Shaaban et al. [38] reported that combining relative GLS reduction with elevated NT-proBNP levels improved the identification of subclinical CTRCD in patients receiving anthracycline-based chemotherapy. Subgroup analyses in this study showed no significant differences in the predictive value of absolute GLS according to CTRCD definitions, breast cancer subtypes, or study design, suggesting that the predictive performance of absolute GLS remained relatively consistent across various clinical settings. However, the specificity of GLS alone (73.0%) was moderate. Future studies should therefore investigate multimodal prediction models combining GLS with other imaging indicators (such as left atrial strain and right ventricular strain) or circulating biomarkers (e.g., high-sensitivity troponin and NT-proBNP) to establish more accurate CTRCD risk classification strategies [39].

This study also has some limitations. First, considerable variability existed among the 12 included studies (from -14.06% to -21%), CTRCD diagnostic criteria, and observation periods; although subgroup analysis and meta-regression analyses failed to identify these factors as significant sources of heterogeneity, these variations may still have influenced the precision generalizability of the pooled estimates. Second, some included studies did not specify the type of echocardiographic equipment or the specific software platforms used for GLS analysis, limiting the assessment of potential technical heterogeneity related to image acquisition and strain analysis. Third, only studies published in English and Chinese were included, which may have introduced language bias. Fourth, several studies reported only relative GLS changes rather than absolute GLS values and were therefore excluded due to insufficient data compatibility. Finally, some included studies had relatively small sample sizes (e.g., 30 participants in Jia XH 2023), which may have reduced statistical power and affected the stability of individual study estimates.

Based on our findings, absolute GLS values may serve as a valuable predictor of chemotherapy-related cardiotoxicity in breast cancer patients. Routine assessment of absolute GLS

before and during anthracycline- or trastuzumab-based therapy may facilitate early identification of patients at increased risk of CTRCD. Patients with reduced absolute GLS values may benefit from intensified cardiac surveillance and timely implementation of preventive cardioprotective strategies. Future studies should focus on: (1) establishing standardized reference ranges for absolute GLS values to improve CTRCD risk stratification across diverse populations; (2) conducting large-scale, multi-center, prospective studies to validate integrated prediction models combining absolute GLS values with circulating biomarkers and other imaging parameters; and (3) exploring whether GLS-guided cardioprotective interventions can enhance long-term cardiovascular outcomes among breast cancer survivors.

### Conclusions

Absolute GLS values are reliable predictors of chemotherapy-induced cardiotoxicity in patients with breast cancer. Absolute GLS values may provide additional risk stratification information beyond conventional LVEF assessment and may help identify patients at risk of CTRCD before overt cardiac dysfunction develops. Therefore, routine evaluation of absolute GLS before and during anthracycline- and/or trastuzumab-based therapy may improve early cardiac surveillance. Patients with reduced absolute GLS values may require closer cardiac monitoring and consideration of preventive cardioprotective strategies. Future large-scale prospective trials are warranted to establish standardized clinical thresholds for absolute GLS values and to determine their role in individualized CTRCD prevention and management strategies.

### Disclosure of conflict of interest

None.

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