Supplementary Online Content

Oikonomou EK, Kokkinidis DG, Kampaktsis PN, et al. Assessment of prognostic value of left ventricular global longitudinal strain for early prediction of chemotherapy-induced cardiotoxicity: a systematic review and meta-analysis. *JAMA Cardiol*. Published online August 21, 2019. doi:10.1001/jamacardio.2019.2952

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Database search algorithms

The search algorithms used in this study are presented below. All databases were searched from their inception until June 1st 2018. The number of retrieved items is presented next to each database.

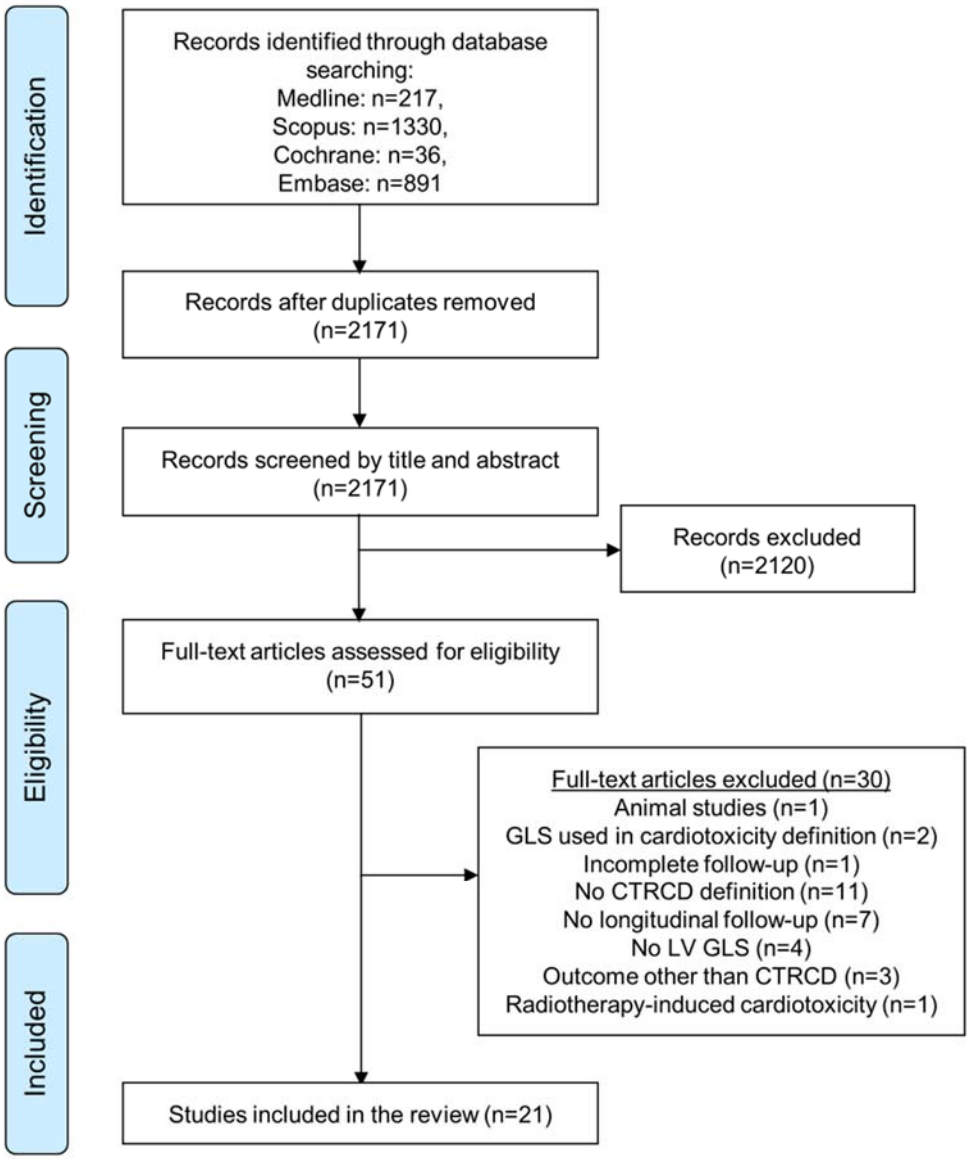
Search for PubMed (n=217):
(cardiotoxicity[mh] OR cardiotox*[tw] OR "heart failure"[mh] OR "heart failure"[tw] OR "ventricular dysfunction"[tw]) AND (chemotherapy[mh] OR chemotherap*[tw] OR trastuzumab[tw] OR anthracycline[tw] OR doxorubicin[tw] OR adriamycin[tw] OR idarubicin[tw] OR epirubicin[tw] OR daunorubicin[tw] OR mitoxantrone[tw] OR 5-fluorouracil[tw] OR paclitaxel[tw] OR cyclophosphamide[tw]) AND (echocardiography[mh] OR echocardiogr*[tw] OR ultrasound[tw]) AND (deformation[tw] OR strain[tw])
NOT ("case reports"[Publication Type] OR "comment"[Publication Type] OR "editorial"[Publication Type])

Search for Embase (n=891→864 non-duplicates):
('cardiotoxicity'/de OR cardiotox* OR 'heart failure'/de OR 'heart failure' OR 'ventricular dysfunction') AND ('chemotherapy'/de OR chemotherap* OR trastuzumab OR anthracycline OR doxorubicin OR adriamycin OR idarubicin OR epirubicin OR daunorubicin OR mitoxantrone OR 5-fluorouracil OR paclitaxel OR cyclophosphamide) AND ('echocardiography'/de OR echocardiogr* OR ultrasound) AND (deformation OR strain)
limit 2 to (article or article in press or conference paper or letter)

Search for Cochrane library (n=36)
(cardiotoxicity OR cardiotox* OR "heart failure" OR "ventricular dysfunction")
AND (chemotherap* OR trastuzumab OR anthracycline OR doxorubicin OR adriamycin OR idarubicin OR epirubicin OR daunorubicin OR mitoxantrone OR fluorouracil OR paclitaxel OR cyclophosphamide)
AND (echo* OR ultrasound)
AND (deformation OR strain)

SCOPUS library (n=1330) – search in all fields
(ALL (cardiotoxicity OR cardiotox* OR "heart failure" OR "ventricular dysfunction") AND ALL (chemotherap* OR trastuzumab OR anthracycline OR doxorubicin OR adriamycin OR idarubicin OR epirubicin OR daunorubicin OR mitoxantrone OR fluorouracil OR paclitaxel OR cyclophosphamide) AND ALL (echo* OR ultrasound) AND ALL (deformation OR strain)) AND (LIMIT-TO (DOCTYPE , "ar") OR LIMIT-TO (DOCTYPE , "le") OR LIMIT-TO (DOCTYPE , "cp") OR LIMIT-TO (DOCTYPE , "ip"))

eFigure. PRISMA flowchart



CTRCD: cancer therapy related cardiac dysfunction; **(**LV) GLS: (left ventricular) global longitudinal strain.

eTable 1. Exclusion criteria for studies at the full manuscript review stage

Serial number	Publication title	Reason for exclusion
1	Ali MT, et al. Myocardial Strain Is Associated with Adverse Clinical Cardiac Events in Patients Treated with Anthracyclines. J Am Soc Echocardiogr. 2016;29(6):522-527.e523.	Outcome other than CTRCD
2	Cardinale D, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. Circulation. 2015;131(22):1981-1988.	No LV GLS
3	Chang WT, et al. The Early Predictive Value of Right Ventricular Strain in Epirubicin-Induced Cardiotoxicity in Patients with Breast Cancer. Acta Cardiol Sin. 2016;32(5):550-559.	No LV GLS
4	Christiansen JR, et al. Utility of Global Longitudinal Strain by Echocardiography to Detect Left Ventricular Dysfunction in Long-Term Adult Survivors of Childhood Lymphoma and Acute Lymphoblastic Leukemia. Am J Cardiol. 2016;118(3):446-452.	No longitudinal follow-up
5	de Almeida AL, et al. Subclinical ventricular dysfunction detected by speckle tracking two years after use of anthracycline. Arq Bras Cardiol. 2015;104(4):274-283.	No longitudinal follow-up
6	Hare JL, et al. Use of myocardial deformation imaging to detect preclinical myocardial dysfunction before conventional measures in patients undergoing breast cancer treatment with trastuzumab. Am Heart J. 2009;158(2):294-301.	Incomplete follow-up
7	Ho E, et al. Subclinical anthracycline- and trastuzumab-induced cardiotoxicity in the long-term follow-up of asymptomatic breast cancer survivors: A speckle tracking echocardiographic study. Heart. 2010;96(9):701-707.	No CTRCD definition
8	Jassal DS, et al. Utility of Tissue Doppler and Strain Rate Imaging in the Early Detection of Trastuzumab and Anthracycline Mediated Cardiomyopathy. J Am Soc Echocardiogr. 2009;22(4):418-424.	Animal study
9	Jurcut R, et al. Strain rate imaging detects early cardiac effects of pegylated liposomal Doxorubicin as adjuvant therapy in elderly patients with breast cancer. J Am Soc Echocardiogr. 2008;21(12):1283-1289.	No CTRCD definition
10	Kang Y, et al. Early detection of anthracycline-induced cardiotoxicity using two-dimensional speckle tracking echocardiography. Cardiol J. 2013;20(6):592-599.	No CTRCD definition

11	Kang Y, et al. Subclinical anthracycline-induced cardiotoxicity in the long- term follow-up of lymphoma survivors: A multi-layer speckle tracking analysis. Arq Bras Cardiol. 2018;110(3):219-228.	No longitudinal follow-up
12	Lorenzini C, et al. Reliability of Left Ventricular Ejection Fraction from Three-Dimensional Echocardiography for Cardiotoxicity Onset Detection in Patients with Breast Cancer. J Am Soc Echocardiogr. 2017;30(11):1103-1110.	No longitudinal follow-up
13	Mavinkurve-Groothuis AM, et al. Myocardial 2D strain echocardiography and cardiac biomarkers in children during and shortly after anthracycline therapy for acute lymphoblastic leukaemia (ALL): a prospective study. Eur Heart J Cardiovasc Imaging. 2013;14(6):562-569.	No CTRCD definition
14	Mirzaee F, et al. Speckle tracking echocardiography for detection of early myocardial changes in patients treated with anthracyclines. Int Cardiovasc Res J. 2017;11(2):55-59.	No CTRCD definition
15	Mousavi N, et al. Echocardiographic parameters of left ventricular size and function as predictors of symptomatic heart failure in patients with a left ventricular ejection fraction of 50-59% treated with anthracyclines. Eur Heart J Cardiovasc Imaging. 2015;16(9):977-984.	Outcome other than CTRCD
16	Murbraech K, et al. Impaired Right Ventricular Function in Long-Term Lymphoma Survivors. J Am Soc Echocardiogr. 2016;29(6):528-536.	No LV GLS
17	Narayan HK, et al. Detailed Echocardiographic Phenotyping in Breast Cancer Patients: Associations with Ejection Fraction Decline, Recovery, and Heart Failure Symptoms over 3 Years of Follow-Up. Circulation. 2017;135(15):1397-1412.	No CTRCD definition
18	Narayan V, et al. Prospective evaluation of sunitinib-induced cardiotoxicity in patients with metastatic renal cell carcinoma. Clin Cancer Res. 2017;23(14):3601-3609.	No LV GLS
19	Negishi K, et al. Use of speckle strain to assess left ventricular responses to cardiotoxic chemotherapy and cardioprotection. Eur Heart J Cardiovasc Imaging. 2014;15(3):324-331.	No CTRCD definition
20	Poterucha JT, et al. Changes in left ventricular longitudinal strain with anthracycline chemotherapy in adolescents precede subsequent decreased left ventricular ejection fraction. J Am Soc Echocardiogr. 2012;25(7):733-740.	No CTRCD definition
21	Rhea IB, et al. Incremental prognostic value of echocardiographic strain and its association with mortality in cancer patients. J Am Soc Echocardiogr. 2015;28(6):667-673.	Outcome other than CTRCD

22	Santoro C, et al. 2D and 3D strain for detection of subclinical anthracycline cardiotoxicity in breast cancer patients: A balance with feasibility. Eur Heart J Cardiovasc Imaging. 2017;18(8):930-936.	No CTRCD definition
23	Stoodley PW, et al. Left ventricular systolic function in HER2/neu negative breast cancer patients treated with anthracycline chemotherapy: a comparative analysis of left ventricular ejection fraction and myocardial strain imaging over 12 months. Eur J Cancer. 2013;49(16):3396-3403.	No CTRCD definition
24	Stoodley PW, et al. Two-dimensional myocardial strain imaging detects changes in left ventricular systolic function immediately after anthracycline chemotherapy. Eur J Echocardiogr. 2011;12(12):945-952.	No longitudinal follow-up
25	Thavendiranathan P, et al. Single Versus Standard Multiview Assessment of Global Longitudinal Strain for the Diagnosis of Cardiotoxicity During Cancer Therapy. JACC Cardiovasc Imaging. 2018.	GLS used to define cardiotoxicity
26	Toro-Salazar OH, et al. Feasibility of Echocardiographic Techniques to Detect Subclinical Cancer Therapeutics-Related Cardiac Dysfunction among High-Dose Patients When Compared with Cardiac Magnetic Resonance Imaging. J Am Soc Echocardiogr. 2016;29(2):119-131.	No longitudinal follow-up
27	Toufan M, et al. Two-dimensional strain echocardiography for detection of cardiotoxicity in breast cancer patients undergoing chemotherapy. J Cardiovasc Thorac Res. 2017;9(1):29-34.	GLS used to define cardiotoxicity
28	Tuohinen SS, et al. Detection of early radiotherapy-induced changes in intrinsic myocardial contractility by ultrasound tissue characterization in patients with early-stage breast cancer. Echocardiography. 2017;34(2):191-198.	Radiotoxicity
29	Ylänen K, et al. Three-dimensional echocardiography and cardiac magnetic resonance imaging in the screening of long-term survivors of childhood cancer after cardiotoxic therapy. Am J Cardiol. 2014;113(11):1886-1892.	No longitudinal follow-up
30	Zhang KW, et al. Abnormalities in 3-Dimensional Left Ventricular Mechanics With Anthracycline Chemotherapy Are Associated With Systolic and Diastolic Dysfunction. JACC Cardiovasc Imaging. 2018.	No CTRCD definition
CTRCD: cancer therapy-related cardiac dysfunction; LV GLS: left ventricular global longitudinal strain		

eTable 2. Summary clinical characteristics of the included study populations

Study ID #	Author (year)	Study size (n)	Age (years)	Female sex (%)	Radiotherapy (%)	Diabetes mellitus (%)	Hypertension (%)	Dyslipidemia (%)	Tobacco use (%)	ACEI/ARB (%)	Beta-blockers (%)	Statins (%)
Studies examining the value of absolute or relative GLS cut-offs												
1	Baratta et al. (2013)[1]	36	47 (mean)	41.7	16.7	5.6	25	19.4	41.7	19.4	-	-
2	Charbonnel et al. (2017)[2]	86	48 [30-64]	36	15	2	15	9	23	8	7	6
3	Gripp et al. (2018)[3]	49	50 (mean)	100	53.1	4.1	32.7	-	-	-	-	6.1
4	Fallah-Rad et al. (2011)[4]	42	47±9	100	98	14	12	36	17	-	-	-
5	Florescu et al. (2014)[5]	40	51±8	100	-	0	0	14	28	-	-	-
6	Guerra et al. (2016)[6]	69	56±13	96	-	6	42	19	16	26	20	10
7	Kang et al. (2013)[7]	75	54±14	45.3	-	4	13.3	-	29.3	9.3	10.7	-
8	Milks et al. (2018)[8]	183	51±11	100	63.9	8.2	31.7	18.6	27.9	21.3	14.2	12.6
9	Mornos et al. (2013)[9]	74	51±11	58.1	-	4	14.8	10.8	20.2	-	0	-
10	Mornos et al. (2014)[10]	59	51±10	59.3	-	1.6	11.8	6.7	16.9	-	0	-
11	Negishi et al. (2013)[11]	81	50±11	10	62	7	21	16	15	-	0	-
12	Paraskevaidis et al. (2017)[12]	80	45±11	45	-	-	15	10	20	15	10	9
13	Portugal et al. (2017)[13]	158	55±13	100	16.5	-	-	-	-	-	-	-
14	Sawaya et al. (2012)[14]	81	50±18	100	60	1	32	22	7	17	11	-
15	Sawaya et al. (2011)[15]	43	49 (mean)	100	11.6	2.3	27.9	18.6	14	9.3	7	-
16	Tang et al. (2016)[16]	86	49±8	100	19	6	13	19	9	-	0	-
Studies with no GLS cut-offs identified or examined												
17	Fei et al. (2016)[17]	95	47±11	100	81	0	16	12	5	3	5	5
18	Lorenzini et al. (2013)[18]	65	53±11	-	-	-	-	-	-	-	-	-
19	Narayan et al. (2016)[19]	135	48 [41-57]	100	67	8	27	17	43	8	7	6
20	Narayan et al. (2017)[20]	165	53±13	77	0.6	11	32	20	42	14	23	18
21	Shaikh et al. (2016)[21]	80	62	45	-	26	53	44	-	29	31	30

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin-II-receptor blocker. Data presented as percentages for categorical variables and either mean ± standard deviation or median [interquartile range] for continuous variables (i.e. age).

eTable 3. Prognostic and discriminatory value of continuous GLS for chemotherapy-induced cardiotoxicity

Study	Univariate AUC (95% CI)	Unadjusted OR/HR (95% CI)	Adjusted OR/HR (95% CI)	Covariates (if adjusted models)
A) Absolute pre-treatment GLS				
Narayan et al. (2016)[19]	-	-	OR 1.25 (0.89-1.75)	age, race, heart rate, DM, HTN, HLD, ACEi/ARB/BB use, regimen, echo timepoint
Narayan et al. (2017)[20]	-	-	OR 1.09 (0.86-1.38)	age and sex
Milks et al. (2018)[8]	-	-	OR 1.48 (1.15-1.89)	renal failure, BB use, trastuzumab therapy, age, ANT dose, post-treatment GLS
Charbonnel et al. (2017)[2]	0.76 (0.58-0.88)	-	-	-
B) Absolute on-treatment GLS				
Milks et al. (2018)[8]	-	-	OR 1.71 (1.26-2.33)	renal failure, BB use, trastuzumab therapy, age, ANT dose, post-treatment GLS
Gripp et al. (2018)[3]	0.95 (0.87-1.00)	HR 2.77 (1.39-5.54)	HR 4.10 (1.07-15.72)	LAVi, LVEF
Fei et al. (2016)[17]	-	OR 1.75 (1.36-2.29)	OR 1.63 (1.26-2.14)	LVEF, LVEDVI
Lorenzini et al. (2013)[18]	-	-	OR 1.33 (1.13-1.57)	LVEF
Charbonnel et al. (2017)[2]	0.82 (0.52-0.997)	-	-	-
Guerra et al. (2016)[6]	0.93 (N/A)	-	-	-
Negishi et al. (2013)[11]	0.67 (N/A)	-	-	-
Paraskevaidis et al. (2017)[12]	0.86 (0.76-0.96)	-	-	-
Tang et al. (2016)[16]	0.90 (N/A)	-	-	-
C) ΔGLS (absolute difference in %)				
Mornos et al. (2013)[9]	0.84 (0.84-0.94)	OR 3.98 (1.68-9.40)	-	-
Narayan et al. (2016)[19]	0.61 (0.45-0.70)[a]	-	OR 1.25 (1.01-1.53)	age, race, heart rate, DM, HTN, HLD, ACEi/ARB/BB use, regimen, echo timepoint
Narayan et al. (2017)[20]	-	-	OR 1.18 (0.95-1.47)	age & sex
Shaikh et al. (2016)[21]	-	OR 0.94 (0.84-1.05)[a]	OR 0.94 (0.84-1.05)[a]	age
Charbonnel et al. (2017)[2]	0.72 (0.45-0.92)	-	-	-
D) Relative change in GLS (% change)				
Negishi et al. (2013)[11]	0.84 (N/A)	-	OR 1.11 (1.03–1.19)	age, HTN, DM, HLD, smoking, LVEF
Sawaya et al. (2011)[15]	-	OR 1.06 (1.02-1.12)	-	-
Kang et al. (2013)[7]	0.82 (N/A)	OR 1.22 (1.07–1.32)	-	-
Mornos et al. (2014)[10]	0.90 (0.81-0.99)	OR 1.65 (1.13-2.40)	-	-
Charbonnel et al. (2017)[2]	0.74 (0.48-0.94)	-	-	-
Gripp et al. (2018)[3]	0.97 (0.91-1.00)	-	-	-
Florescu et al. (2014)[5]	0.85 (0.73–0.97)	-	-	-

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin-II-receptor blocker; ANT: anthracycline; BB: beta-blockers; CTRCD: cancer treatment-related cardiac dysfunction; GLS: left ventricular global longitudinal strain; HLD: hyperlipidemia; HR: hazard ratio; HTN: hypertension; LAVi: left atrial volume index; LVEDVI: left ventricular end-diastolic volume index; LVEF: left ventricular ejection fraction; MACE: major adverse cardiac events; N/A: not available (not reported or cannot be calculated); OR: odds ratio.

[a]95% CI derived from ratios and P values based on the method proposed by Altman DG. BMJ 2011;343:d2090.[22]

eTable 4. Meta-regression analysis of prognostic odds ratios for threshold GLS changes

	Absolute on-treatment GLS as a predictor of cardiotoxicity (n=9) Beta (95% CI)	**Relative % change in GLS as a predictor of cardiotoxicity (n=9) Beta (95% CI)**
Study size (n)	-0.01 (-0.02 – 0.00), P=0.13	**-0.02 (-0.03 – -0.01), P=0.003**
Average age (years)	-0.03 (-0.24 – 0.17), P=0.71	-0.08 (-0.63 – 0.48), P=0.76
Cardiotoxicity (%)	-0.01 (-0.10 – 0.07), P=0.71	0.06 (-0.08 – 0.20), P=0.32
Cutoff used (%)	0.17 (-0.20 – 0.53), P=0.32	-0.04 (0.32 – 0.23), P=0.73
Average EF at baseline (%)	0.13 (-0.09 – 0.35), P=0.22	0.16 (-0.24 – 0.56), P=0.37
Average GLS at baseline (%)	0.29 (-0.13 – 0.70), P=0.15	0.37 (-0.32 – 1.05), P=0.25
Cancer type (breast vs other)	-0.17 (-1.92-1.57), P=0.82	-0.27 (-2.50-1.95), P=0.78
ASE definition (versus other)	-0.45 (-1.68 – 0.79), P=0.42	**-2.25 (-3.49 - -1.01), P=0.004**

ASE: American Society of Echocardiography; CI: confidence interval; EF: ejection fraction; GLS: global longitudinal strain.

eTable 5. Quality in Prognostic Studies (QUIPS) risk of bias tool

Study Name	1. Study participation	2. Study attrition	3. Prognostic factor (GLS) measurement	4. Outcome (CTRCD) assessment	5. Study confounding	6. Statistical analysis and reporting	7. Overall risk of bias
Studies examining the value of absolute or relative GLS cut-offs							
Baratta et al. (2013)[1]	moderate	moderate	moderate	moderate	high	moderate	moderate
Charbonnel et al. (2017)[2]	moderate	moderate	low	moderate	high	high	moderate
Gripp et al. (2018)[3]	moderate	moderate	low	moderate	high	high	high
Fallah-Rad et al. (2011)[4]	moderate	moderate	low	moderate	high	moderate	moderate
Florescu et al. (2014)[5]	moderate	moderate	moderate	moderate	high	high	moderate
Guerra et al. (2016)[6]	moderate	high	low	moderate	high	high	high
Kang et al. (2013)[7]	moderate	moderate	low	moderate	high	low	moderate
Milks et al. (2018)[8]	high	moderate	moderate	high	low	low	moderate
Mornos et al. (2013)[9]	moderate	high	moderate	moderate	high	high	high
Mornos et al. (2014)[10]	moderate	high	moderate	moderate	high	high	high
Negishi et al. (2013)[11]	low	moderate	low	moderate	moderate	low	moderate
Paraskevaidis et al. (2017)[12]	moderate	moderate	low	low	moderate	low	moderate
Portugal et al. (2017)[13]	moderate	moderate	low	moderate	high	high	moderate
Sawaya et al. (2012)[14]	moderate	moderate	moderate	moderate	high	high	moderate
Sawaya et al. (2011)[15]	moderate	moderate	moderate	moderate	high	high	moderate
Tang et al. (2016)[16]	high	moderate	moderate	moderate	high	high	high
Studies with no GLS cut-offs identified or examined							
Fei et al. (2016)[17]	high	moderate	low	moderate	high	moderate	moderate
Lorenzini et al. (2013)[18]	moderate	high	moderate	moderate	high	moderate	moderate
Narayan et al. (2016)[19]	low	moderate	low	moderate	low	low	low
Narayan et al. (2017)[20]	low	moderate	low	moderate	moderate	low	moderate
Shaikh et al. (2016)[21]	high	moderate	low	moderate	moderate	low	moderate

CTRCD: cancer therapeutics-related cardiac dysfunction; GLS: global longitudinal strain.

eReferences.

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