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Prognostic value of myocardial strain by magnetic resonance imaging in nonischemic dilated cardiomyopathy: a systematic review and meta-analysis

Aim	This study was aimed at performing a systematic review and meta-analysis to investigate the prognostic role of left ventricular (LV) myocardial strain variables as determined by magnetic-resonance imaging in non-ischemic dilated cardiomyopathy.
Material and methods	A search was performed in PubMed (MEDLINE), Google Scholar, and EMBASE databases for studies on the prognostic role of LV myocardial strain based on MR feature-tracking in non-ischemic dilated cardiomyopathy. Uncorrected odds ratio (OR) values reported by the studies where similar evaluation criteria of myocardial strain were available, were combined for a meta-analysis.
Results	Nine studies were selected from 351 publications for this systematic review and meta-analysis. The analysis included a totality of 2139 patients (mean age, 52.3 years; mean follow-up duration, 42.5 months). The meta-analysis showed that the worsening of the LV global longitudinal strain (GLS), global circumferential strain (GCS), and global radial strain (GRS) was associated with increased risk of major adverse cardiovascular events (MACE): OR, 1.13 per each % of GLS; 95% CI: 1.050–1.225; p=0.001; OR, 1.16 per each % of GCS; 95% CI: 1.107–1.213; p<0.0001; OR, 0.95 per each % of GRS; 95% CI: 0.92–0.97; p<0.0001.
Conclusion	The LV GLS, GCS, and GRS variables by MR feature-tracking data are powerful predictors for the development of MACE. Evaluation of myocardial strain can be used as an effective instrument for risk stratification in patients with non-ischemic dilated cardiomyopathy.

Keywords	Non-ischemic dilated cardiomyopathy; cardiac magnetic-resonance imaging; myocardial strain; prognostic value; prediction
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Introduction

Nonischemic dilated cardiomyopathy (DCM) is one of the leading causes of systolic heart failure and is associated with adverse outcomes [1]. Global left ventricular (LV) systolic function, most commonly assessed during echocardiography by evaluating left ventricular ejection fraction (LVEF), is still used as the main indicator for identifying patients at high risk of adverse events, including the risk of sudden cardiac death (SCD) [2]. Speckle tracking echocardiography (STE) allows identifying the earliest prognostically significant changes in cardiac function when the standard echocardiographic methods are nondiagnostic. The obtained data make is possible to quantify both systolic and diastolic functions of the heart chambers [3]. Even despite the fact that STE is the most commonly used method for assessing myocardial strain, this technique does have certain limitations, these are mainly a strong dependence on image quality and a lower signal-to-noise ratio compared to magnetic resonance imaging (MRI) [4]. Due to the excellent spatial resolution and high reproducibility, MRI is the gold standard for noninvasive assessment of the structure and function of the heart including in various forms of heart failure (HF) [5, 6].

The so-called MR feature-tracking (MR-FT) has been recently developed, which is a tool for assessing myocardial strain based on MR images [7]. Reference values are already available for this technique, and its applicability has been shown in various forms of cardiomyopathy [8, 9]. An assessment of LV long axis strain (LAS) based on MRI data has been proposed as a reliable and quickly evaluated

parameter of the global longitudinal LV function without the need to use any additional software for strain analysis [10]. The studies investigating the prognostic role of measuring LV myocardial strain by MR-FT produce limited data and show inconsistent results. Moreover, most of these studies were single-center with small samples and few events.

In view of these shortcomings, we conducted a systematic review and meta-analysis of studies evaluating LV myocardial strain based on MRI data to predict adverse events in patients with nonischemic DCM.

Material and Methods

Search for publications and selection of studies. The information search algorithm was developed following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [11] in the PubMed (MEDLINE), Google Scholar, and EMBASE databases. The latest search of data to be included in the analysis was performed on January 16, 2022. The search for information in the PubMed (MEDLINE) and EMBASE databases was carried out using the following query: ((dilated cardiomyopathy) OR (nonischemic dilated cardiomyopathy) OR (idiopathic dilated cardiomyopathy) AND ((CMR) OR (cardiac magnetic resonance imaging)) AND ((Feature-Tracking Global Longitudinal Strain) OR (Strain) OR (circumferential strain) OR (Feature-Tracking) OR (Myocardial strain)) AND ((risk assessment) OR (predictive value) OR (prognostic value)). The following query was used to search the Google Scholar database: Feature-Tracking Global Longitudinal Strain, Nonischemic Dilated Cardiomyopathy, prognostic value, hazard ratio cox regression. Two authors examined independently whether abstracts and full-text reports meet inclusion and exclusion criteria to select eligible studies for this systematic review and meta-analysis.

Inclusion/exclusion criteria

The criteria for including primary studies in the systematic review with subsequent meta-analysis were the availability of full texts; subjects of 18 years and older; studies with adequately presented baseline data mainly the results of LV myocardial strain assessment based on MRI data. Another prerequisite for including publications in the meta-analysis was the presentation of data on clinical outcomes and the results of the univariate Cox regression analysis with hazard ratios (HR). The lower threshold for the duration of follow-up was 12 months (mean follow-up period). Articles in languages other than English, case reports, nonclinical studies, reviews, and expert opinions were excluded from the meta-analysis.

Assessment of methodological quality

The quality of the studies was determined using the Newcastle-Ottawa Quality Assessment Scale for cohort studies [12]. The studies were assessed based on the following main criteria: selection of study groups, comparability of groups, and determination of an outcome of interest. All inconsistencies were eliminated by the discussion between the authors.

Statistical analysis

Statistical processing of data was performed in Comprehensive Meta-Analysis 3.0 (Biostat, NJ). The meta-analysis was conducted using a random effects model and the inverse-variance approach. The main results are presented as a forest plot. Statistical heterogeneity was assessed using the Pearson's chi-square test and the heterogeneity index I^2. Statistical heterogeneity was interpreted based on the I^2 index according to the Cochrane Handbook: $I^2 = 0–40\%$ corresponds to insignificant heterogeneity; 30–60 % – moderate heterogeneity; 50–90 % – significant heterogeneity; 75–100% – high heterogeneity. The values of unadjusted hazard ratio (HR) for a univariate model determined for a 1 % change in the LV myocardial strain were used for the meta-analysis as the baseline values of the survival indicators. Publication bias was assessed by visual inspection of funnel plots and the Egger test.

Results

Literature search results

Keyword search in the PubMed (MEDLINE), Google Scholar, and EMBASE databases produced a total of 351 publications. When duplicates were excluded, the number of publications decreased to 344. After analyzing the headlines and abstracts, 25 eligible publications were left. The most frequent reasons for excluding articles were inconsistency with the object and the lack of specified data; reviews, discussions, abstracts, and reports were also excluded. Full-text screening of 13 publications was performed, and two publications were excluded due to the lack of data of the univariate Cox regression analysis [13, 14], and three studies included mixed patient populations [15–17]. However, in the study by Romano et al. [17] that included patients with nonischemic and ischemic forms of cardiomyopathy, the results of the regression analysis were presented separately for each group, which is why this study was included in our analysis. Thus, 9 studies were included in the review. The process of selecting relevant studies is shown in Figure 2, which is presented among supplementary materials in the journal website.

General characteristics of studies

A total of 2,139 patients with DCM subjected to the evaluation of the prognostic role of LV myocardial strain based on MRI findings were included in this analysis. The mean age was 52.3 years. The mean follow-up period was

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42.5 months. Study design, endpoints, and patient baseline characteristics are summarized in Table 1 and Table 2.

Endpoints and adverse outcomes

The prognostic role of GLS was reported in 7 studies [17, 18, 21–25], GCS in 6 studies [18, 21–25], and GRS in 5 studies [18, 21–23, 25]. Data on the prognostic role of LAS were presented in only 2 studies [19, 20]. The main endpoints in the studies that evaluated the prognostic role of MRI indicators of myocardial strain were all-cause death (2 studies) and a composite endpoint including cardiac mortality, ventricular arrhythmias, SCD, adequate pacing, cardiac arrest, heart transplant, and hospitalization for decompensated HF. When major adverse cardiovascular events (MACE) were reported, the definition of this endpoint was the same as in the original literature. In studies that did not report the rates of MACE, it was calculated as the sum of cardiac mortality, ventricular arrhythmias, SCD, adequate pacing, cardiac arrest, heart transplant, and hospitalization for decompensated HF. Table 5 (see supplementary materials in the journal site) presents the hazard ratios for the onset of respective endpoints calculated in the univariate Cox regression analysis, in which various MRI indicators of myocardial strain were included as a predictor. Studies with similar evaluation criteria (a 1% change in the corresponding myocardial strain indicator) were later combined for a meta-analysis depending on the endpoint.

Left ventricular global longitudinal strain

Univariate analysis of changes in MACE risks for continuous estimates of LV GLS was presented in 5 studies [18, 22–25] (Table 5 in the supplementary materials). In these studies, a similar evaluation criterion was available (a 1% change in GLS), which allowed us to combine them in the meta-analysis. In these studies, the MACE endpoint was achieved by 201 patients (23.3 %, n=861). The mean follow-up period was 35 months. Given the analysis results, a decrease in LV GLS was associated with a statistically significant increase in the weighted mean risk of MACE (HR 1.13 per 1 % of GLS worsening; 95 % CI: 1.050 – 1.225; p=0.001) (Figure 1A). The assessment the study

Table 1. General characteristics of studies included in the systematic review

Title (first author)	Year	Patients (n)	Study design	Follow-up period, months	Endpoints	Events, n (%)
Buss [18]	2015	210	Prospective, single-center	63.6	Primary endpoint: Cardiac death, heart transplant, aborted CVD, adequate pacing	39 (18,6)
Riffel [19]	2016	146	Prospective, single-center	51.6	Primary endpoint: Cardiac death, heart transplant, aborted SCD, adequate pacing. Secondary endpoint: cardiac events and hospitalization for HF	34 (23.3)
Arenja [20]	2017	453	Prospective, single-center	57.6	Cardiac death, heart transplant, aborted SCD, adequate pacing, hospitalization for HF	97 (21.4)
Romano (nonischemic DCM) [17]	2018	1012 (507)	Prospective, multicenter	52.8	All-cause death	133 (13.1)
Pi [21]	2018	172	Prospective, single-center	45.6	Primary endpoint: All-cause death and heart transplantation. Secondary endpoint: hospitalization for HF	43 (25.0)
Chen [22]	2019	46	Retrospective, single-center	13	Cardiac death, heart transplant, hospitalization for cardiac events	9 (19.6)
Fu [23]	2021	126	Retrospective, single-center	31	MACE: Cardiac death, heart transplant, repeated hospitalization	44 (34.9)
Ochs [24]	2021	350	Retrospective, single-center	50.4	Cardiac death, heart transplant, aborted SCD, adequate pacing	59 (16.8)
Shu [25]	2021	129	Prospective, single-center	17	Cardiac death, aborted SCD, adequate pacing	50 (38.7)

SCD, sudden cardiac death; HF, heart failure; MACE, major adverse cardiovascular events.

Table 2. General characteristics of patients included in the systematic review

Study	Age, years	Male, %	BMI, kg/m²	Arterial hypertension	Diabetes mellitus	NYHA FC III, n (%)	ACE inhibitors/ ARBs, n (%)	β-blockers	MRAs
Buss, 2015[18]	52 + 15	159 (76)	25.6 + 3.9	81 (39)	22 (10)	NR	196 (93)	184 (88)	84 (40)
Riffel, 2016 [19]	53±14	116 (80)	25.7±3.9	64 (44)	20 (14)	56 (38)	143 (98)	141 (97)	79 (54)
Arenja, 2017 [20]	53.6±15.1	341 (75.3)	26.1±4.2	230 (50.8)	52 (11.5)	127 (28)	442 (97.5)	392 (86.5)	186 (41.1)
Romano, 2018[17]	59.8±15.7	661 (65.3)	28.9±8.6	675 (66.7)	310 (30.6)	NR	670 (66.2)	502 (49.6)	NR
Pi, 2018 [21]	56.4±14.3	116 (67.4)	24.0±4.5	58 (33.7)	36 (20.9)	NR	134 (77.9)	120 (69.8)	101 (58.7)
Chen, 2019 [22]	46.7±12.9	33 (72 %)	23.8 (21.7, 27.0)	8 (17)	7 (15)	20 (43)	39 (84.7) – ACE inhibitors; 11 (23.9) – ARBs	45 (98)	41 (89)
Fu, 2021 [23]	49.9±15.8	88 (69.8 %)	23.4±4.3	28 (22.2)	19 (15.1)	NR	104 (82.5)	105 (83.3)	112 (88.9)
Ochs, 2021 [24]	52.2±15.2	259 (73.9)	25.8±4.3	154 (44.0)	42 (12.0)	108 (30.9)	346 (98.9)	300 (85.7)	145 (41.4)
Shu, 2021 [25]	47.0 (34.0, 57.0)	84 (65.1)	23.7 (21.0, 26.3)	23 (17.8)	17 (13.2)	80 (69.7)	42 (32.6)	95 (73.6)	84 (65.1)

BMI, body mass index; NYHA, New York Heart Association; FC, functional class;
ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; MRA, mineralocorticoid receptor antagonist.

homogeneity produced a statistically significant result (Q-value=12.58; df(Q)=4; p=0.01) and a heterogeneity index $I^2 = 68.2\%$, which suggests a moderate general inconsistency for all studies and indicates the need for cautious interpretation of the combined value of HR for all studies.

Left ventricular global circumferential strain

A univariate analysis of changes in MACE risks among patients with nonischemic cardiomyopathy was presented for continuous estimates of LV GCS in the same studies as for LV GLS [18, 22–25] (Table 5). Given the analysis results, a decrease in LV GCS was associated with a statistically significant increase in the weighted mean risk of major adverse cardiovascular events (HR 1.16 per 1 % of GCS worsening; 95 % CI: 1.107 – 1.213; p < 0.0001) (Figure 1B). The assessment of the study homogeneity produced a statistically insignificant result (Q-value=5.23; df(Q)=4; p=0.264) and a heterogeneity index $I^2 = 23.5\%$, which suggests a low heterogeneity of all studies included in this analysis.

Left ventricular global radial strain

Univariate analysis of changes in MACE risks for continuous estimates of LV GRS was presented in 4 studies [18, 22, 23, 25] (Table 5). In these studies, a similar evaluation criteria was also available (a 1% change in GRS), which allowed us to combine them in the meta-analysis.

In these studies, the MACE endpoint was achieved by 192 patients (23.5 %, n=815). The mean follow-up period was 40.5 months. Given the analysis results, a 1 % increase in LV GRS was associated with a statistically significant decrease in the weighted mean risk of MACE (HR 0.95; 95 % CI: 0.92±0.97; p < 0.0001) (Figure 1C). In other words, as GRS decreases by 1 %, the risk of MACE increases by 5.26 %. Noteworthy, the assessment of the study homogeneity produced a statistically insignificant result (Q-value=4.94; df(Q)=3; p=0.176) and a heterogeneity index $I^2 = 39.3\%$, which suggests a low heterogeneity of all studies included in this analysis.

Evaluation of publication bias

Funnel plots were constructed to qualitatively assess the presence of bias in a meta-analysis including five or more studies. Visual evaluation of the GLS and GCS funnel plots did not detect significant asymmetry (Figure 3 in supplementary materials in the journal website). These findings were confirmed by quantitative results of the Egger test: t=2.07; p=0.13 and t=1.99; p=0.14 for GLS and GCS, respectively. The estimation of the Egger test for GRS also produced a statistically insignificant result: t=0.71; p=0.55.

Discussion

The variability of phenotypic and clinical manifestations of nonischemic DCM is the reason modern strategies do not allow clearly identifying patients at high risk of adverse events. There remains a clinical need for identifying new markers that would help in risk stratification.

MRI is a non-invasive multiparameter technique that visualize myocardial structures, evaluate tissue characteristics

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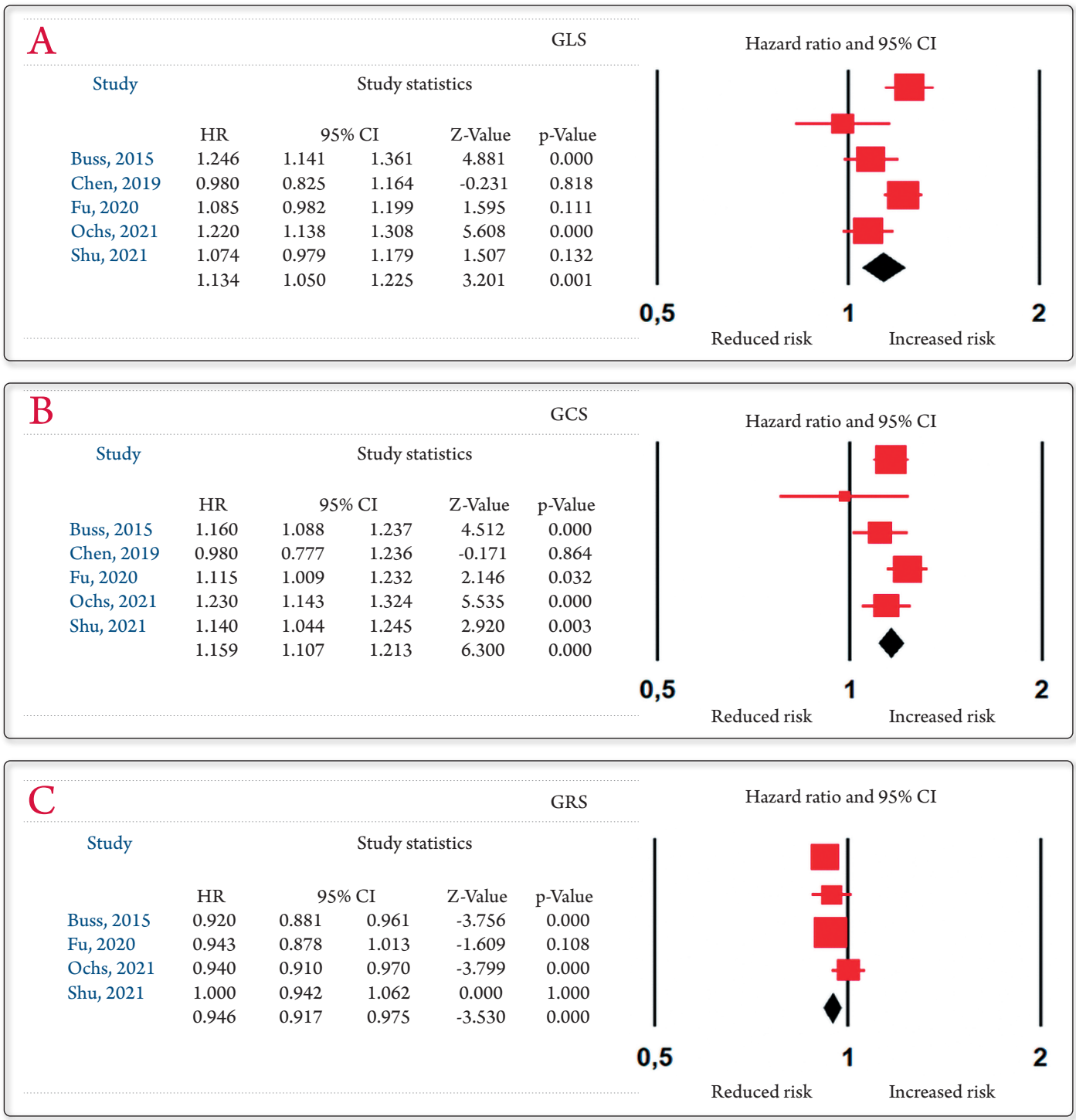
Figure 1. Results of the meta-analysis of MACE HR:
(A) a 1 % worsening of GLS; (B) a 1 % worsening of GCS; (C) a 1 % worsening of GRS



The red squares show the weighted effect size for each specific study (the size of red square corresponds to the study weight), the red segments are 95% CI, the black diamond corresponds to the weighted mean HR.
GLS, global longitudinal strain; GCS, global circumferential strain; GRS, global radial strain; CI, confidence interval, HR, hazard ratio.

(e.g., edema and fibrosis). The number of studies examining the prognostic value of measuring myocardial strain based on MRI data, including in patients with nonischemic DCM, has increased in the past few years [7]. Such MRI techniques as late gadolinium enhancement (LGE) and T1 mapping are the most promising for the prediction of adverse cardiac events in patients with nonischemic DCM [6]. However, there is limited data on the prognostic role of myocardial strain assessed with MRI in patients with nonischemic cardiomyopathy. As new MRI myocardial evaluation techniques become available, additional studies are necessary to determine which combination of parameters is optimal

for the risk stratification in this heterogeneous patient population compared to traditional MRI markers.

This is the first systematic review and meta-analysis aimed at evaluating the prognostic role of myocardial strain imaging with MRI. According to our findings, a 1 % worsening of GLS and GCS is accompanied by a statistically significant increase in the weighted mean risk of MACE by 13 % and 16 %, respectively. According to the meta-analysis, the risk of MACE also increased by 5.3 % when GRS decreased by 1 %.

Limitations

Firstly, the systematic review and meta-analysis included only few studies. Secondly, the analysis included only the HR data obtained for the myocardial strain index according to the univariate Cox regression analysis, and we did not study the multivariate HR (adjusted) because various variables (age, sex, LVEF, presence of late gadolinium enhancement (LGE) zones, etc.) were included in the multivariate analysis as well as the LV myocardial strain index in different studies. Finally, despite the availability of a similar assessment criterion (a 1 % change in strain), which allowed combining them in the meta-analysis depending on an endpoint of the study, different software was used to assess the strain during post-processing. Moreover, MACE that we used as the primary endpoint for the pooled analysis was not presented in all studies, and it was calculated as the sum of cardiac mortality, ventricular arrhythmias, SCD, adequate pacing, cardiac arrest, heart transplant, and hospitalization for decompensated HF in the studies where MACE was not reported.

Conclusion

The systematic review and meta-analysis showed that the MRI indicators of LV myocardial strain (GLS, GCS, and GRS) were statistically significantly associated with adverse cardiovascular events and thus can be used as additional prognostic markers for risk stratification in patients with DCM. These data require further verification in larger specific populations during a longer follow-up period.

No conflict of interest is reported.

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