ECHOCARDIOGRAPHIC PARAMETERS OF CARDIAC STRUCTURE AND FUNCTION IN THE DIAGNOSIS OF ACUTE MYOCARDITIS IN ADULT PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Background: Transthoracic echocardiography (TTE) plays a key role in the initial work-up of myocarditis where the identification of pathologic structural and functional changes may assist in its diagnosis and management. The aim of this systematic review was to appraise the evidence for the utility of echocardiographic parameters of cardiac structure and function in the diagnosis of acute myocarditis in the adult population. **Methods:** A systematic literature search of medical databases was performed using PRISMA principles to identify all relevant studies assessing TTE parameters in adult patients with myocarditis (1995-2020; English only; PROSPERO registration CRD42021243598). Data for a range of structural and functional TTE parameters were individually extracted and those with low heterogeneity were then meta-analysed using a random-effects model for overall effect size, and assessed through standardized mean difference (SMD). **Results:** Available data from up to six included studies revealed that myocarditis can be reliably differentiated from healthy controls using echocardiographic measures of left ventricular (LV) size and systolic function, in particular LV end-diastolic diameter, LV ejection fraction (LVEF) and LV global longitudinal strain (LV-GLS) (p[?]0.01 for all). LV-GLS demonstrated the highest overall effect size, followed by LVEF and LVEDD (SMD: |0.46-1.98|). Two studies also demonstrated that impairment in LV-GLS was associated with adverse cardiovascular outcomes in this population, irrespective of LVEF. **Conclusions:** LV-GLS demonstrated the greatest overall effect size and therefore ability to differentiate myocarditis populations from healthy controls. GLS was also shown to be a predictor of adverse cardiovascular outcomes, in this population.

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Running Title: Echocardiography in Myocarditis: A Systematic Review and Meta-Analysis

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Abbreviations

CMR: cardiac magnetic resonance; TTE: Transthoracic echocardiography; LV-GLS: left ventricular global longitudinal strain; STE: speckle tracking echocardiography; 2D: two-dimensional; 3D: three-dimensional; CI: confidence interval; SMD: standardized mean difference; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; 3D: Three Dimensional; ICI: immune checkpoint inhibitor.

HIGHTLIGHTS

What is already known on this subject?

Myocarditis is a disease process that is often a diagnosis of exclusion, as it frequently mimics other acute cardiac pathologies.

Transthoracic echocardiography is traditionally the initial imaging modality used for non-invasive structural assessment in populations with myocarditis.

What might this study add?

This study demonstrates that left ventricular global longitudinal strain, left ventricular ejection fraction and left ventricular end-diastolic diameter can differentiate between myocarditis patients and healthy controls.

LV-GLS demonstrated the greatest overall effect size when comparing these two populations, in comparison to the other measures.

How might this impact on clinical practice?

This study demonstrates that assessment of myocardial deformation indices allows for sensitive discrimination between myocarditis patients from healthy controls.

Routine assessment of LV-GLS may serve as an important diagnostic tool in the acute care setting.

Structured Abstract (Word Count: 245)

Background: Transthoracic echocardiography (TTE) plays a key role in the initial work-up of myocarditis where the identification of pathologic structural and functional changes may assist in its diagnosis and management. The aim of this systematic review was to appraise the evidence for the utility of echocardiographic parameters of cardiac structure and function in the diagnosis of acute myocarditis in the adult population.

Methods: A systematic literature search of medical databases was performed using PRISMA principles to identify all relevant studies assessing TTE parameters in adult patients with myocarditis (1995-2020; English only; PROSPERO registration CRD42021243598). Data for a range of structural and functional TTE parameters were individually extracted and those with low heterogeneity were then meta-analysed using a random-effects model for overall effect size, and assessed through standardized mean difference (SMD).

Results: Available data from up to six included studies revealed that myocarditis can be reliably differentiated from healthy controls using echocardiographic measures of left ventricular (LV) size and systolic function, in particular LV end-diastolic diameter, LV ejection fraction (LVEF) and LV global longitudinal strain (LV-GLS) (p[?]0.01 for all). LV-GLS demonstrated the highest overall effect size, followed by LVEF and LVEDD (SMD: |0.46-1.98|). Two studies also demonstrated that impairment in LV-GLS was associated with adverse cardiovascular outcomes in this population, irrespective of LVEF.

Conclusions: LV-GLS demonstrated the greatest overall effect size and therefore ability to differentiate myocarditis populations from healthy controls. GLS was also shown to be a predictor of adverse cardiovascular outcomes, in this population.

INTRODUCTION

Myocarditis has been historically defined as an acute disease process which results in myocardial inflammation and necrosis**(1).** The often-resultant impairment in myocardial function increases the predisposition to the development of a non-ischemic cardiomyopathy, which has been shown to result in poor prognostic outcomes such as chronic congestive failure, cardiac arrhythmias and sudden cardiac death**(1).** Whilst the gold-standard investigation is cardiac magnetic resonance (CMR), the initial non-invasive assessment typically utilised is transthoracic echocardiography (TTE), as it is widely available, easily accessible, and cost-effective within most healthcare settings

(2).

The traditional TTE parameters assessed in myocarditis include left ventricular (LV) regional or global dysfunction, presence of LV dilatation, LV hypertrophy, right ventricular (RV) dysfunction, bi-ventricular thrombi, pericardial effusions and diastolic dysfunction**(2).** These findings however typically represent more clinically significant disease with more substantial myocardial injury**(1).** Early and subclinical myocardial dysfunction is usually not often recognised by standard two-dimensional TTE, particularly in the setting of normal LV systolic function as assessed through traditional measures such as LV ejection fraction (LVEF). The emergence of advanced echocardiographic imaging techniques such as two-dimensional and three-dimensional myocardial strain, have allowed for identification of subclinical myocardial dysfunction, and have been shown to increase sensitivity of echocardiography in the diagnosis and prognosis of the disease

(3).

The aim of this systematic review and meta-analysis was to identify key echocardiographic parameters of LV structure and function based on available published evidence which may allow for discrimination of adult patients with myocarditis from healthy controls.

METHODS

Search Strategy and Selection (move structure)

The methods and results of this review have been done in accordance to the Meta-analysis Of Observational Studies in Epidemiology and Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement **(4, 5).** The review protocol is previously registered on the International Prospective Register of Systematic Reviews (PROSPERO) with Centre of Reviews and Dissemination (CRD) report number of CRD42021243598. A number of medical databases were searched including PubMed, Ovid Medline, EMBASE, Web of Science, Cochrane Central Register of Controlled Trials (2005-2020), Scopus, Proquest, Science Direct and grey literature using both free-text terms and Medical Subject Heading (MeSH) terms for studies with English language and adult human studies that reported standardized TTE indices. The search terms and key search strategies are listed in **Supplementary Materials 1.** A grey literature search identified additional studies that were not identified in the initial search of the afore-mentioned medical databases. All diagnostic cohort and case-control studies that measured and compared echocardiographic parameters between myocarditis and adult control populations were included. Studies which were not able to provide sufficient data, those with pediatric populations or those that did not compare the study populations involved in the analysis hypothesis were excluded.

Inclusion Criteria

Studies that (a) compared myocarditis and healthy control adult patients (age of [?] 18 years) (b) included patients who had a comprehensive TTE (c) reported their results with means and standard deviations to allow measurement of standardized mean difference (SMD) were included.

Exclusion Criteria

Studies were excluded if they were (a) only in abstract form, (b) did not compare myocarditis patients to controls, (c) reported medians and interquartile ranges, or (d) had missing data.

Data Extraction

Two investigators (S.K and A.A) independently screened records retrieved from the search by title and abstract. Details such as first author, year of publication, study design, participant characteristics, age, sample size, sample stratification, outcome measures, results and author's conclusion were collated and examined. Selected records were further screened for eligibility in full text by the same investigators (S.K and A.A). Data collection was performed independently by two investigators (S.K and C.L) using the same pre-determined template. Discrepancies at any stage of selection were arbitrated by the senior author (T.C.T) if discussion between all three reviewers failed to achieve a consensus (S.K, A.A, and C.L).

Quality Appraisal of the selected studies for the review

The quality of included studies and risk of bias was assessed by two investigators (S.K and A.A) using the Joanna Briggs Institute Critical Appraisal tools for use in Analytical Cross-Sectional Studies (JBI tool)**(6).** See **Supplementary Table 3.** This process afforded increased methodological rigor and evaluated potential bias and threats to validity. Publication bias was assessed by visual analysis of funnel plots and using Egger methods**(7, 8).** Both reviewers were trained in the use of the appraisal tool prior to this process. In brief, the quality assessments of the checklist included eight questions to assess the methodological quality of a study and to determine the extent to which a study has addressed the possibility of bias in its design, conduct and analysis. This criterion is available in **Supplementary Materials 3.**

Statistical analysis

For individual TTE measures of interest, a meta-analysis was only performed if studies reported continuous variable indices as means and standard deviations. All indices were meta-analyzed with random-effects modeling for overall effect size through SMD. The observational design of the selected studies was considered, and the methodological differences potentially responsible for a significant component of the variance within the measures of interest. Pooled estimates were obtained through a random-effect model. Articles were required to report on a quantitative estimation including mean, confidential interval (CI), and standard deviation. 95% confidence intervals (CIs) were calculated for all indices. Lack of heterogeneity (magnitude of inconsistency) within the pooled studies was tested using the I^2 statistic and deemed significant if [?]50%. Potential publication bias was assessed visually from funnel plots (supplementary materials). All statistical analysis was performed using the Metan package included in the STATA version 16.1 statistical software. A p value <0.05 was considered statistically significant for all analyses.

RESULTS

Search Results

The initial literature search yielded 1276 studies from various literature sources, including grey literature. After removing duplicates, 1058 records were screened by title and abstract of which 558 studies were initially excluded, as they included non-myocarditis populations or were in supplementary format. The remaining 500 records were reviewed by title and abstract screening by two reviewers (SK and AA). A total of 110 peer-reviewed studies were assessed by full text for eligibility of which 14 studies were shortlisted for inclusion in this study. Studies that did not have a direct comparison between myocarditis patients and controls, those that included pediatric populations and those that did not report results as means and standard deviations were excluded (n=8). Data from 6 studies with publication dates ranging from Jan 2010–Jan2020 was extracted and meta-analyzed, and is shown in**Table 1.** A detailed flow diagram with the study selection process and various reasons for exclusion is shown in **Figure 2.**

Study Quality and Characteristics

Four of the six included studies were assessed to be of fair quality and two of good quality using the JBI Tool, indicating a good selection of studies. **See Supplementary Materials 3.** Four of the included studies were retrospective analyses and the other two were prospective studies. There was a pooled total of 269 myocarditis patients and 240 control patients included in this meta-analysis.

Diagnosis of Myocarditis

The diagnosis of myocarditis as per the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases, requires fulfillment of [?]1 clinical presentation and [?]1 diagnostic criteria. These criteria have to be fulfilled in the absence of coronary artery disease as detected by coronary angiography, and absence of pre-existing cardiovascular disorder that can otherwise explain the presentation**(9).** All studies included in the meta-analysis made a clinical diagnosis of myocarditis that fulfilled international criteria as per European Society of Working Group on Myocardial and Pericardial diseases. Whilst the majority of studies used CMR diagnostic criteria (non-ischemic late gadolinium enhancement and/or Lake Louise Criteria) **(10)** , others used echocardiography and/or endo-myocardial biopsy for diagnosis.

Diagnostic Discrimination of Parameters Assessed

Data on a range of echocardiographic parameters was assessed, although only indices which were reported in [?]4 studies were meta-analyzed in this study. Three echocardiographic parameters i.e. LV end diastolic diameter (LVEDD), LVEF and LV global longitudinal strain (LV-GLS) were meta-analyzed from available data from 6 included studies. All TTE measurements were able to discriminate between adult myocarditis and control populations (p[?]0.01), but with variable effect sizes. See**Figures 3-5.** None of the included studies, as visually assessed by Funnel Plots, demonstrated to be high risk for publication bias. See**Supplementary Material 4.** Meta- Analysis Forest plots for LVEDD, LVEF and LV-GLS are demonstrated in **Figures 3-5.** A summary of the meta-analysis results is displayed in **Table 2.**

Measurement of Left Ventricular Indices

In terms of the methodology for echocardiographic imaging, the majority of studies followed recommendations from the American Society of Echocardiography **(11),** with two studies following recommendations from the European Association of Cardiovascular Imaging **(12),** for two-dimensional echocardiographic measurements including LVEDD and LVEF. LV-GLS was measured using software from different vendors including TomTec Imaging systems, GE Echopac workstation, X-Strain and Syngo Vector Imaging which increased the variability of absolute strain values. All studies had reported mean LV-GLS values derived from offline measurements made in the standard three apical views by at least two operators. Despite different software used, all algorithms for strain assessment appeared to utilise similar approaches where the endocardial borders were manually traced throughout the cardiac cycle. Longitudinal strain was assessed in all 17 longitudinal LV segments, and the segmental values were averaged to give the mean LV-GLS.

Parameters of left ventricular size

Two-dimensional Left Ventricular End-Diastolic Diameter

LVEDD had the lowest overall effect size with a standard mean difference of 0.47 (95%CI; 0.11-0.81, p[?]0.01), with no significant heterogeneity (54%). Fifty percent of the studies individually demonstrated statistically significant differences in LVEDD between myocarditis populations and controls, whilst the other half did not. Importantly the two studies that demonstrated this difference, also showed a significant difference in LVEF **(13, 14).**

Two dimensional Left Ventricular Volumes

Only three out of the six included studies reported standard two-dimensional LV end-systolic and end-diastolic volumes, hence a meta-analysis was not performed. All volumes were calculated using Simpson's Biplane method from the standard three apical views. Only one study indexed two-dimensional volumes to body surface area**(15).** In this study, indexed LV-EDV (ml/m^2) was significantly higher in myocarditis patients when compared to controls (59±13 vs 57±14, p=0.03). Overall, there was no significant differences between non-indexed volumes in each of the other individual studies.

Three-Dimensional Left Ventricular mass and volume

Only one published study evaluated three-dimensional left ventricular structure and function, hence a meta-analysis was not performed to assess these parameters. In this study, echocardiography images were obtained using a Vivid S9 Ultrasound Machine and analysis was done offline using EchoPAC v113 software. Only three-dimensional LV end-diastolic volume (3D LVEDV, ml/m^2) and three-dimensional LV mass indexed (g/m^2) were reported. Interestingly, 3D LVEDV (60.3±13.5 vs 57±10, p=0.219) and 3D LV mass (66.7±6.9 vs 67.8±9.1, p=0.54) were not significantly different between myocarditis populations and controls.

Wall Motion Index Score

The wall motion score index was calculated by sum of all segment scores divided by the number of segments assessed. 16 segments were assessed with scores as followed: 1 = normal, 2 = hypokinesis, 3 = akinesis, 4 = dyskinesis and 5 = aneurysmal **(11).** Two of the three studies that assessed for wall motion score index demonstrated normal values in myocarditis and control populations, particularly as they only included patients with a normal left ventricular ejection fraction. One study showed that the myocarditis population had a higher wall motion score index compared to controls (1.6±0.7 vs 1, p<0.01)

(13).

Parameters of left ventricular systolic function

In our study, functional parameters such as LVEF and LV-GLS proved to have a higher overall effect size between myocarditis and control populations.

2D Left Ventricular Ejection Fraction

LVEF had a higher overall effect size compared to LVEDD, with a standard mean difference of |0.77| (95% CI: |0.26| - |1.28|, p[?]0.01), with a higher degree of heterogeneity at 86%. Four out of the six studies demonstrated a statistically significant difference in LVEF between those with acute myocarditis when compared to controls. Importantly, Hsaio et al. demonstrated a significantly lower LVEF in myocarditis patients compared to controls (LVEF (%): 49+-12 vs 64+-4, p<0.01), with a large proportion with impaired systolic function and significantly higher wall motion index score**(13).** Furthermore, a subgroup analysis in this study for myocarditis patients with preserved LV function, also demonstrated significant difference in comparison to control populations (LVEF (%): 59+-6 vs. 64+-4; p=0.002)**(13).** Three other studies also demonstrated similar findings with statistically significant differences in LVEF, despite normal-range values**(14-16).** Two studies (Di Bella et al. 2018 and Caspar et al. 2017) demonstrated no significant differences in LVEF between myocarditis and control populations (61+-4 vs 62+-3, p=0.78 and 62.1+-3.7 vs 63.5+-3.8, p=0.099, respectively). Importantly, these studies did show significantly different LV-GLS values between these populations

(15, 17).

2D Left Ventricular Global Longitudinal Strain

LV-GLS had the highest overall effect size compared to LVEDD and LVEF with a SMD of |1.98| (95% CI: |1.51| - |2.45|, p<0.01), with no significant heterogeneity (76%). All six studies demonstrated statistically significant differences in LV-GLS between myocarditis populations and controls, irrespective of baseline LVEF. Interestingly, Caspar et al. demonstrated that two-dimensional LV-GLS was impaired in patients with myocarditis (-17.8% vs -22.1%, p<0.01) as were 2D layer-specific sub-epicardial GLS (-15.4% vs -19.7%, p<0.01) and sub-endocardial GLS (-20.7% vs -25.1%, p<0.0001), even two years after the initial myocarditis event **(17).** Di Bella et al. demonstrated that longitudinal strain was significantly lower in areas of late gadolinium enhancement (p=0.04), and that GLS was shown to have a moderate predictive value of distinguishing the two groups with an AUC of 0.73 (95% CI: 0.66-0.79)

(13).

Three-Dimensional Measure of Left Ventricular Function

Unfortunately, there were no studies which compared 3D LVEF between patients with myocarditis and controls. Only one published study assessed 3D strain (3D STE) hence a meta-analysis was not performed to assess this parameter. In this study, 3D-STE was measured using the Vivid E9 (GE-healthcare) echocardiographic system **(17).** Acquisitions were performed with the highest possible frame rate and then analysed offline using EchoPAC v113 for 3D STE LV myocardial deformation. 3D LV-GLS, global area strain (GAS) and global radial strain (GRS) was calculated using average of 17 myocardial segments. 3D LV-GLS, GCS, GAS and GRS were lower in magnitude in the myocarditis group compared to controls (-11.80% vs -14.98%, p<0.0001; -12.57% vs -15.12%, p<0.001; -22.28% vs -25.87%, p<0.001; and 31.47% vs 38.06 %, p<0.0001, respectively). ROC curve analysis identified diagnostic values of 3D GLS, GCS, GAS and GRS for the diagnosis of myocarditis with AUC values of 0.78, 0.71, 0.73 and 0.70 respectively.

Parameters of right ventricular size and systolic function

Only one published study was identified to have assessed parameters of RV size and systolic function in patients with acute myocarditis compared to controls and therefore none of the RV parameters of size and systolic function were meta-analysed **(17).** This study by Caspar and colleagues assessed standard measures of RV size and systolic function in the apical four-chamber view with an average of the six segments (including the RV free wall and septum). The right ventricular parameters assessed included RVS' (13.2+-2 vs 14.2+-2.1, p=0.028), RV global strain (-20.6+-3.5 vs -22.9+-3.3, p=0.003) and RV free wall strain (-24.6+-5.4 vs -27.2+-4.3, p=0.023), were all significantly lower in the myocarditis population when compared to healthy controls.

DISCUSSION

This study seeks to examine the evidence for the utility of 2D and 3D echocardiographic parameters of cardiac chamber size and systolic function in differentiating between adult patients with acute myocarditis and controls. Our study identified three echocardiographic parameters (LVEDD, LVEF and LV-GLS) to be useful in the differentiation between myocarditis and control populations, but with different overall effect sizes. This study also highlights the application and value of echocardiography as first line imaging in the clinical setting for differentiation of patients with acute- and sub-acute phases of myocarditis. As this disease entity manifests in a heterogeneous manner, with a known preponderance to LV impairment (due to greater quantity of myocardium), assessment of the LV systolic function may provide greater sensitivity to clinical and subclinical changes to the myocardium. Patients presenting with myocarditis, both acute and recurrent, typically undergo echocardiography for an initial assessment of ventricular size and function, along with assessment of regional wall-motion abnormalities **(18).**More sensitive measures of LV systolic function such as LV-GLS have been found to be useful in several cardiac pathologies, both for diagnosis and prognostication. Similarly, these measures have also demonstrated the greatest ability to identify earlier phenotypes of myocarditis, especially those where baseline LV systolic function is preserved

(19).

2D Parameters of Left Ventricular Size

This meta-analysis demonstrated that half of the studies featured quantifiable changes in LV end-diastolic diameter, a marker of structural myocardial remodeling, thus potentially useful as a discriminator between myocarditis and control populations although not strong. Measurement of LV diameter was demonstrated to have the lowest overall effect size when compared to the parameters of LV function which was consistent with the notion that measures of LV function being more sensitive for the detection of underlying myocardial pathology compared to measures of LV structural change**(20).** Identification of increased LV diameter may also be reflective of the chronicity of disease hence effective in distinguishing more chronic or fulminant myocarditis, which would also be more likely to have other echocardiographic abnormalities such as regional wall motion abnormalities and impaired LV systolic function, as demonstrated in two of the included studies **(13, 14).**

Only four out of the six studies included in this systematic review reported LV volumes with only one study reporting significant differences in indexed volumes. The heterogeneity in the methodology for the assessment of LV volumes did not allow for meta-analysis of this parameter although it is postulated that LV volume changes would provide a more accurate reflection of LV structural change compared to linear measurements of LV size changes. Moreover, current guidelines do not recommend use of LVEDD for routine quantification of LV size but indexed volumes instead. Whilst LV dilatation has been hypothesized to be associated with an increased risk of heart failure, LV volumes have been shown to more accurately reflect LV remodeling, in comparison to single dimensional assessment **(21, 22).** One study did demonstrate that indexed left ventricular end-diastolic volumes were greater in their cohort of myocarditis patients compared to controls consistent with expectations. However, the remaining studies reporting non-indexed LV volumes did not demonstrate any significant differences between myocarditis populations and controls. This finding is largely thought to be attributed to the non-indexation of LV volumes, limiting its precision and accuracy.

Left Ventricular Systolic Function

The importance of a baseline echocardiogram during the acute-phase of myocarditis is important as it allows for appropriate classification between severe and non-severe myocarditis, based on preservation of LVEF. This is important as these populations exhibit different pathologic changes, disease states and clinical outcomes**(23).** Impairment in LV systolic function in patients with myocarditis is attributed to a greater percentage of myocardial involvement secondary to an inflammatory myopathic process, which is consistent with the immune checkpoint inhibitor (ICI) myocarditis**(24).** As a result, there is development of regional and/or global systolic dysfunction, which is typically seen in more severe forms of myocarditis, such as immune-mediated myocarditis. Two of the included studies in this meta-analysis demonstrated no significant differences in LVEF between myocarditis and control populations, both in the initial phase**(17),** and on a follow-up at a mean period of 22 months, highlighting the heterogeneous nature of this disease process **(15).**Interestingly, the majority of patients with myocarditis in this systematic review had a normal LVEF. Only one study demonstrated an impaired mean LVEF in the myocarditis population. This study focused on patients with ICI myocarditis secondary to checkpoint inhibition chemotherapy **(13).**

This study also reinforces the value of LV-GLS in differentiating cases of both severe and non-severe myocarditis in both the acute- and sub-acute disease states. All included studies clearly demonstrated significantly lower LV-GLS values in myocarditis populations, compared to controls suggesting that LV-GLS may be a more sensitive marker of LV systolic function compared to LVEF. LV-GLS was shown to be directly associated with degree of myocardial inflammation, and diagnostic of regional myocardial fibrosis, when correlated with CMR**(16).** In some longitudinal studies, LV-GLS was shown also shown to remain impaired on follow-up**(17)** , which highlights the value of LV-GLS as a potential marker for monitoring and diagnosing chronic myocarditis or response to treatment.

The main advantages of LV-GLS compared to standard echocardiographic parameters in assessment of myocarditis, are the signal-to-noise ratio, angle independence and ability to differentiate between active and passive myocardial segmental motion**(25).** LV-GLS has recently emerged as a measure of cardiac function which is sensitive in detecting subclinical cardiac injury relative to LVEF and has been shown to have prognostic value in multiple pathologies

(14, 26).

Additionally, the sub-endocardial layers of the myocardium with a predominance of longitudinal myocardial fibers are typically impacted in myocarditis. Hence the longitudinal left ventricular contractile function is expected to be most impaired in acute myocarditis (27, 28). These are consistent with results from the study which demonstrated the endo-GLS to be more impaired compared to mid- and epicardial-GLS**(29).** The distribution of LV-GLS impairment in studies examining regional systolic dysfunction which match areas of inflammatory response further strengthens the value of measuring LV-GLS in the clinical setting.

Whilst the majority of the included studies included patients with acute inflammatory myocarditis, one study included patients with immune checkpoint inhibitor (ICI) myocarditis**(14),** an entity that is more complex and multi-faceted than inflammatory myocarditis, despite similar diagnostic criteria **(30).**Patients with ICI myocarditis may possibly have a greater impairment in LV-GLS and LV systolic function compared to other subtypes, particularly with the presence of confounding factors such as para-neoplastic cytokines, and other mechanisms of treatment mediated toxicity

(31).

Three dimensional Parameters of Cardiac Structure and Function

Current guidelines recommend the use of 3D volumes in the quantification of LV size. This is due to several advantages of 3D over 2D imaging including minimal foreshortening and more accurate volumetric quantification **(32).** Of the included studies, only one study assessed 3D LVEDV and 3D LV mass, showing no significant difference between myocarditis populations and controls **(17).** The proposed reason for this negative finding is again likely due to the absence of chronicity and the acute pathogenesis of myocarditis and its effect on the myocardium **(1).** The other reason could relate to the inclusion of only populations with preserved LV systolic function, highlighting a non-severe myocarditis process in this cohort. Unfortunately, none of the included studies compared 3D left ventricular ejection fraction in myocarditis populations vs controls. The lack of any studies examining changes in 3D LVEF is not surprising since 3D echocardiography has only been studied in a handful of cardiac pathologies to date largely due to inter-vendor differences, lack of standardization and unclear feasibility or added clinical value

(33).

Three-dimensional speckle tracking echocardiography is an advanced echo imaging technique that is postulated to provide a comprehensive assessment of LV function with additional advantaged over 2D imaging**(34),** i.e. simultaneous speckle tracking in more than one direction allowing for assessment of longitudinal, circumferential and radial strain simultaneously, and requirement for a single apical acquisition, which in turn, may make assessment of LV strain more time efficient and thus more applicable in a busy clinical setting **(34).**The utility of 3D-LVS has been demonstrated in several pathologies including ischemic heart disease, cardio-oncology, valvular heart disease, left ventricular hypertrophy hence certainly applicable for myocarditis. Furthermore, 3D-LVS has successfully been used to identify subclinical LV dysfunction **(35),**and shown to be non-inferior to 2D STE in patients with aortic stenosis**(36).** Of the included studies, one study did demonstrate that patients with acute myocarditis in comparison to controls had lower 3D LV-GLS values. This study also highlighted that there was a good correlation between 2D- and 3D- GLS measurements in this study ($r=0.84$, $p<0.01$). These findings are also in keeping with pooled results on 2D LV-GLS from the meta-analysis in our study. Nonetheless, 3D-STE is still currently used primarily in the research settings and not in routine clinical practice given its high image and operator dependency. Some of the disadvantages of 3D STE which may still serve as barriers for application in routine clinical use, include the requirements for a stable regular heart rhythm during image acquisition and analysis, optimal LV images and with good temporal resolution and a high frame rate. Nonetheless, 3D-LVS may still have a useful role in the diagnostic work-up in myocarditis

(35).

Right Ventricular Systolic Function

Whilst there have been several case reports on isolated RV involvement in myocarditis, there is only one published study that fulfilled our search criteria assessed RV systolic functional parameters in a cohort of patients with myocarditis**(17).** This study demonstrated that both traditional echocardiographic measures of RV size and systolic function including RV strain parameters are both impaired in patients with myocarditis. The prognostic significance of RV impairment has been established in several cardiac pathologies, particularly non-ischemic dilated cardiomyopathy, a known complication of myocarditis**(37).** RV systolic dysfunction is a known independent predictor of transplant-free survival and adverse heart failure outcomes in dilated cardiomyopathy**(37).** Therefore, the there is definitely some value in assessing RV size and function in patients with myocarditis, as these parameters may not only assist in the diagnostic process, but may also provide prognostic information

Clinical Outcomes

Two of the studies included in this systematic review assessed primary and secondary longitudinal cardiovascular events in these populations**(13, 14).** In patients with myocarditis, every 1% decline in longitudinal strain increased hazard ratios by 1.26 (95% CI: 1.10–1.47) for primary cardiovascular MACE events**(13).** Similarly, in patients with ICI myocarditis, after adjustment for LVEF, each 1% reduction in GLS was associated with a 1.5-fold increase in cardiovascular MACE among patients with impaired systolic function (HR: 1.5; 95% CI: 1.2-1.8) and a 4.4-fold increase with a preserved systolic function (HR: 4.4; 95% CI: 2.4-7.8) **(14).** These results highlight the value of LV-GLS in the diagnosis and prognostication of patients with acute inflammatory and ICI myocarditis, independent of two-dimensional LVEF.

Study Limitations

There were some limitations identified in this systematic review and meta-analysis. Firstly, the severity of the disease in the patients included from the included studies were variable which may potentially impact test performances. Secondly, strain assessment reported in the included studies were all acquired using four different vendor-specific software, which may potentially also impact the external validity of 2D LV-GLS across different settings. Thirdly, different aetiologias of myocarditis were included which can also bias the overall results. Lastly, the included studies were all single-centre studies, which are typically limited by greater inherent bias due to the greater variation and generalisability between diagnostic work-up and protocols between different centres in different studies. However, we did assess for potential small-study effects on the individual parameters studied using Egger's tests which did not demonstrate any evidence of small study effects confounding the results.

CONCLUSIONS

This systematic review and meta-analysis demonstrated the discriminatory value of a range of echocardiographic parameters, particularly with LV-GLS, in discriminating acute myocarditis from normal controls and highlights the potential value of early TTE in suspected cases of myocarditis. However, there is also clearly a need for further large multi-centre studies or randomized controlled trials to further characterize the sensitivity and specificity of each of the individual parameters assessed. Nonetheless, these results support the importance of echocardiography as an initial non-invasive diagnostic tool for the work-up of such populations.

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Figure 1: Graphical Abstract

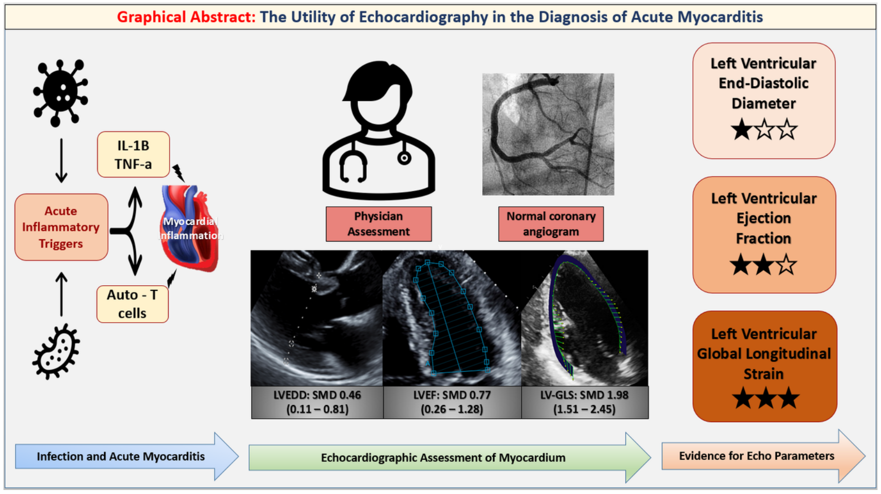

Figure 1: Graphical Abstract showing the utility of Echocardiography in the Diagnosis of Acute Myocarditis. Left ventricular global longitudinal strain (three stars) showed the largest overall effect size, followed by left ventricular ejection fraction (two stars) and left ventricular end-diastolic diameter (one star).

Figure 2: PRISMA Flow Diagram

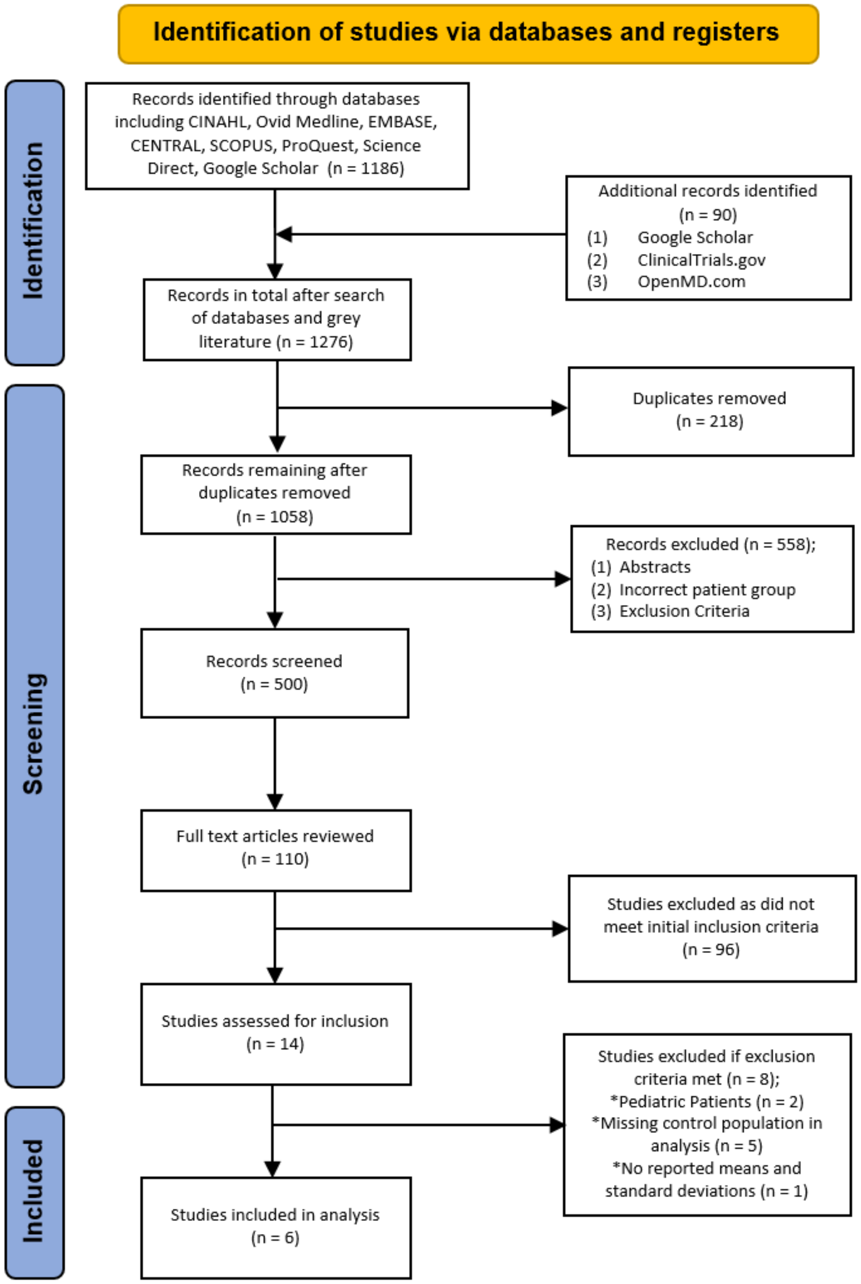

Figure 2: PRISMA flow diagram showing screening, identification and inclusion of studies in the meta-analysis.

Table 1: Study Summary

First Author	Year Published	Study Design	Myocarditis Subjects (n)	Control Subjects (n)	Parameters Assessed by Study
Di Bella et al **(38)**	2010	Retrospective	13	13	LVEDD, LVEF, LV-GLS

First Author	Year Published	Study Design	Myocarditis Subjects (n)	Control Subjects (n)	Parameters Assessed by Study
Hsaio et al **(13)**	2013	Retrospective	45	83	LVEDD, LVEF, LV-GLS
Caspar et al **(17)**	2017	Retrospective	50	50	LVEF, LV-GLS
Kostakou et al **(16)**	2018	Prospective	25	19	LVEDD, LVEF, LV-GLS
Di Bella et al **(15)**	2018	Prospective	35	25	LVEF, LV-GLS
Awadalla et al **(14)**	2020	Retrospective	101	50	LVEDD, LVEF, LV-GLS

Table 1: Summary of Studies. LVEDD: Left Ventricular End-Diastolic Diameter; LVEF: Left Ventricular Ejection Fraction; LV-GLS: Left Ventricular Global Longitudinal Strain

Table 2: Echocardiographic Indices Summary

Echo indices	Number of Studies	Number of Myocarditis Patients	Number of Control Patients	Overal
LVEDD	**4**	**184**	**165**	**0.46**
LVEF	**6**	**269**	**240**	**-0.77**
LV-GLS	**6**	**269**	**240**	**-1.98**

Table 2: Summary of Meta-Analysis results. LVEDD: Left Ventricular End-Diastolic Diameter; LVEF: Left Ventricular Ejection Fraction; LV-GLS: Left Ventricular Global Longitudinal Strain; SMD: Standardized Mean Difference; I^2 assess degree of heterogeneity; z reflects Egger's values

Figure 3: Meta-Analysis of Studies with LVEDD

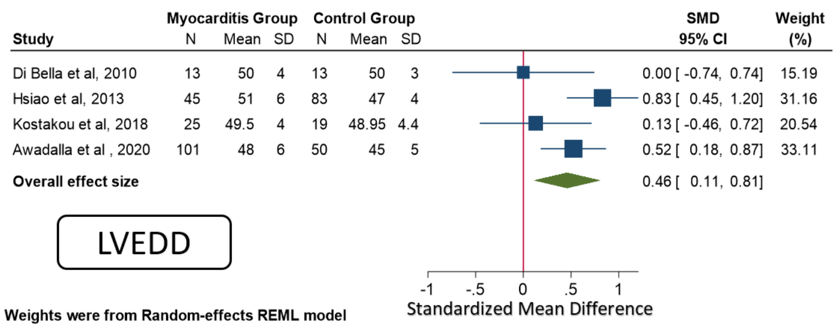

Figure 3: Forest Plot for LVEDD. LVEDD: Left Ventricular End-Diastolic Diameter

Figure 4: Meta-Analysis of Studies with LVEF

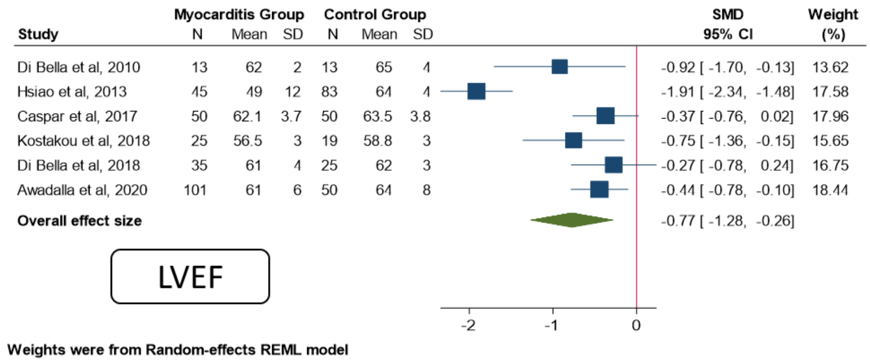

Figure 4: Forest plot for LVEF. LVEF: Left Ventricular Ejection Fraction

Figure 5: Meta-Analysis of Studies with LV-GLS

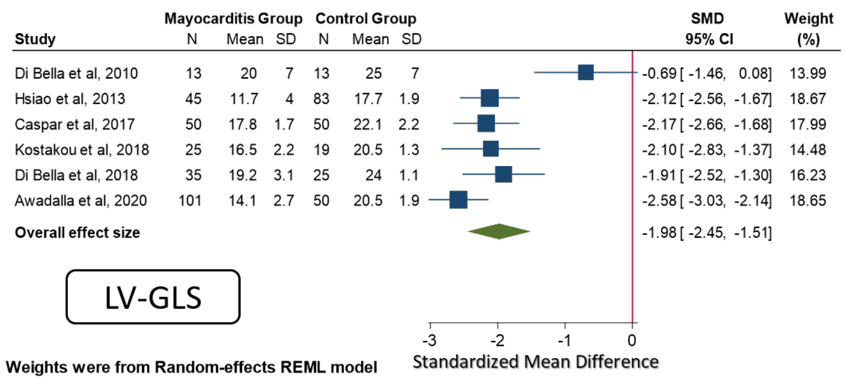

Figure 5: Forest Plot for LV-GLS. LV-GLS: Left Ventricular Global Longitudinal Strain