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Myocardial Performance Index to assess cardiac function in autoimmune connective tissue disease: a systematic review and meta-analysis

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ABSTRACT

Objectives This study aimed to evaluate cardiac function using Myocardial Performance Index (MPI) in autoimmune connective tissue disease (ACTD) patients without cardiovascular abnormalities.

Methods A systematic search of databases including Medline, Google Scholar, ProQuest, Scopus and Cochrane Library was conducted to identify relevant studies on ACTD and MPI from 1995 to 2023. ACTD included in the search were rheumatoid arthritis (RA), systemic sclerosis (SSc), systemic lupus erythematosus (SLE), Sjögren syndrome (SjD), polymyositis and dermatomyositis. Quality assessment was performed using the Newcastle-Ottawa Scale, followed by meta-analysis computation of mean differences (MDs) of MPI using Review Manager V.5.4.

Results A total of 22 studies for qualitative and 19 for quantitative synthesis were included. We found six studies on RA, eight studies on SSc, five studies on SLE, two studies on SjD and one on mixed connective tissue disorder. Conventional echocardiography and tissue Doppler imaging (TDI) were used to assess the MPI. Both conventional MPI and tissue Doppler MPI values were elevated compared with healthy control (MD=0.11, 95% CI 0.08 to 0.14, p value<0.00001 and MD=0.06, 95% CI 0.03 to 0.10, p value=0.00001, respectively).

Conclusions We found elevated MPI values in patients with ACTD compared with healthy controls. MPI assessment has the potential for early detection and management of cardiac dysfunction in patients with ACTD, but further studies are required to corroborate these findings.

PROSPERO registration number CRD42023490643.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Cardiovascular disease (CVD) has become a leading cause of death in patients with autoimmune connective tissue disease (ACTD).

WHAT THIS STUDY ADDS

⇒ This study examines the utility of Myocardial Performance Index (MPI) to assess CVD in patient with ACTD as a simple, non-invasive and widely available in clinical practice.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ MPI has the potential for early detection and management of cardiac dysfunction in ACTD.

INTRODUCTION

Connective tissue disease (CTD) is a broad and heterogeneous group of diseases, characterised by an inflammatory process, resulting in tissue damage and abnormal repair disorders. This condition affects certain target organs both locally and systemically, leading to diminished function due to degeneration and fibrosis.[1] The underlying causes are multifactorial, influenced by the environment, genetics and idiopathic mechanisms. Within this group, a distinct subgroup emerged, characterised by inflammation mediated by autoimmune processes, known as autoimmune connective tissue disease (ACTD), which further classified into systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (SSc), myositis ((dermatomyositis (DM) and polymyositis (PM)) and Sjögren syndrome (SjD).[2]

Emerging evidence has shown that patients with ACTD have an increased risk of cardiovascular disease (CVD) and become one of the leading causes of mortality in ACTD, with a mortality relative risk: 2.2 in SLE, 1.5 in RA, 1.48 in SjD, 2.24 in myositis and 3.1 in SSc.[3] The involvement of CVD in ACTD primarily results from the inflammatory process, impacting the initiation of atherosclerosis, vasculitis, myocarditis, pericarditis and even heart failure.[4] Risk factors that may influence this include those coincidentally present in patients, specific pathophysiology of the disease, as well as long-term side effects of

treatments such as nonsteroidal anti-inflammatory drug (NSAID) and steroid use.[5] The most commonly encountered general risk factors are hypertension, diabetes and hypercholesterolemia, while specific factors in ACTD may include chronic inflammation, endothelial dysfunction, lipid disturbances and platelet activation.[5 6] In 2022, European League Against Rheumatism has suggested that all rheumatic and musculoskeletal diseases including SLE and antiphospholipid syndrome patients should be assessed for early cardiovascular risk management.[3]

Ejection fraction (EF) has traditionally been the primary and most used echocardiography parameter to assess myocardial function. Nonetheless, it is important to note that left ventricular ejection fraction (LVEF) only describes systolic function, while both systolic and diastolic dysfunction often coexist. Myocardial Performance Index (MPI) or usually known as 'Tei index' was developed by Tei *et al* in 1995.[7] This echocardiography parameter has been well validated and acknowledged for its use to evaluate the myocardium's global function, which is an index of both systolic and diastolic function, generated by the sum of isovolumic relaxation times (IVRT) divided by the ejection time. Although this index is not frequently used in current clinical practice, MPI has been proven useful for assessing cardiac function in various non-autoimmune clinical conditions, including heart failure, cardiomyopathy, congenital heart disease and acute myocardial infarction.[8] MPI has also been identified as an independent predictor of heart failure, arrhythmias, cardiogenic shock and cardiac death during hospitalisation. Unlike EF, MPI is a simple, non-invasive, easily obtained and reproducible parameter, with its independence to preload and afterload changes. Therefore, this index has been suggested as an alternative to the EF.[9]

Due to increasing interest in using MPI in evaluating cardiac function in ACTD and lack of a thorough systematic review or meta-analysis, this systematic review and meta-analysis was embarked to assess the MPI in patients with ACTD.

METHODS

This systematic review and meta-analysis was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis 2020 statement standard and methodology. This systematic review and meta-analysis was registered at the International Prospective Register of Systematic Reviews (PROSPERO) on 31 December 2023 with registration number CRD42023490643.

Variable of interest

The aim of this study was to investigate MPI value in patients with ACTD without pre-existing cardiovascular abnormalities.

Search strategy

A comprehensive literature search was initiated on 1 January 2024, to identify relevant studies. This search encompassed multiple electronic databases including MEDLINE, EBSCOhost, ScienceDirect, ProQuest and Google Scholar. To ensure consistency and minimise bias, three independent investigators conducted the search using predefined keywords and participant, exposure, comparator, outcomes, time, setting, study design criteria. These criteria are detailed in online supplemental file.

Eligibility criteria

Type of studies

This review employed a rigorous approach to study selection, encompassing all observational studies published in English between 1995 (coinciding with the introduction of the MPI) and 2023. The included studies adopted either a cross-sectional, case–control or cohort design. We excluded in vitro, in silico, interventional researches as well as reviews, case reports, case series, conference abstracts, book chapters and commentaries/editorials publications.

Participants

This study recruited adult patients (aged≥18 years) diagnosed with a spectrum of ACTD, including RA, SLE, SSc, SjD, DM and PM. To minimise confounding variables related to pre-existing cardiovascular conditions, patients with a history of myocardial infarction, stroke, severe valvular disease, atrial fibrillation, hypertrophic cardiomyopathy, congenital heart defects or prior cardiac interventions (angioplasty, revascularisation, valve replacement) were excluded, together with pregnant or breastfeeding individuals.

Outcome of interest

This study primarily investigated MPI values in patients with ACTD. Secondary outcomes assessed systolic and diastolic function qualitatively.

Study selection

A systematic screening process ensured the selection of relevant studies. Following deduplication using Mendeley software, titles and abstracts were independently screened by three authors using Rayyan software. Studies deemed irrelevant based on these initial evaluations were excluded. Subsequently, the remaining full-text articles were assessed against pre-established eligibility criteria. Reasons for exclusion at this stage were documented within the chosen software. Finally, reference lists of included studies were manually screened for potentially eligible articles to ensure comprehensive coverage, by achieving majority agreement among the reviewers.

Data collection process

A standardised data extraction process was employed. Two independent reviewers extracted the following information from each included study: author name, country of origin, study design, sample size, participant demographics (age and gender), disease duration and activity, echocardiography methodology and outcome of interest.

Summary measures

Data on MPI, systolic and diastolic function were assessed in both the patients with ACTD and in the control groups and are reported as mean differences (MDs). MDs were determined as the most appropriate effect size measure to evaluate group differences.

Assessment of risk of bias/quality assessment

Two independent reviewers evaluated each study using the Newcastle-Ottawa Scale (NOS) adapted for observational designs (cross-sectional, case–control and cohort studies). This tool assesses methodological quality across three key domains: selection, comparability and outcome. Based on the potential for bias identified, the overall quality of each study was categorised into three groups based on the total NOS Score: very high risk of bias (0–3 points), high risk of bias (4–6 points) and low risk of bias (7–9 points), with higher scores indicating a stronger methodology. Any discrepancies in quality assessment were resolved through discussion among the entire review team until consensus was reached.

Confidence in cumulative evidence

The confidence in the cumulative body of evidence was assessed using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach.[10] This framework involves a systematic evaluation of the quality of evidence for each outcome of interest. The GRADE system considers factors such as the risk of bias within individual studies (methodological quality), the directness of the evidence to the research question, the level of heterogeneity (variation) in study findings, the precision of effect estimates, and the potential for publication bias. Based on these factors, the overall certainty of the evidence was categorised as high, moderate, low or very low quality.

Synthesis of results and statistical analysis

Review Manager V.5.4 (Cochrane Collaboration) software was employed to synthesise pooled data, assess heterogeneity and evaluate the power of each study. Forest plots were used to visually represent the synthesised data. Due to potential variations in outcome evaluation methods across studies, a random effects model was used for meta-analyses. Heterogeneity was assessed using the I^2 statistic, with values categorised as low (<25%), moderate (25%–50%), high (51%–75%) and very high (>75%). Sensitivity analyses were planned to explore potential sources of heterogeneity if detected. Statistical significance was set at $p<0.05$.

RESULT

Study selection

The study selection process and the obtained results were depicted in a flowchart as shown in figure 1. A comprehensive search strategy identified a total of 2239 relevant studies. Following duplicate removal, 1694 studies remained and 41 studies were extracted after the title and abstract screening according to the selection criteria. Four studies were not retrieved and a total of 37 studies were further screened for full-text screening. 15 studies did not meet the criteria, with 13 did not assess MPI and two studies assessed only right ventricular MPI. Finally, 22 studies were included in the systematic review, and 19 eligible for data extraction were used in meta-analysis.

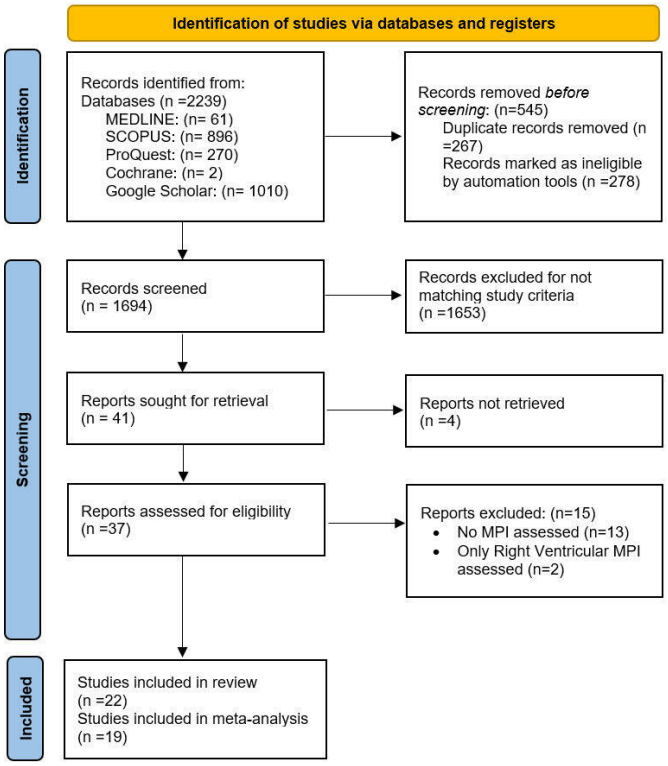

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analysis 2020 flow diagram of literature search. MPI, Myocardial Performance Index.

Quality assessment

A total of 20 case–control studies, including six RA studies,[11–16] eight SSc studies,[17–24] five SLE studies,[25–29] two SjD studies[30 31] and one mixed connective tissue disorder (MCTD) study,[32] were evaluated based on the findings of the NOS quality assessment (see online supplemental file). Overall, there were four studies of fair quality, one study of poor quality and 17 studies of good quality.

Confidence in cumulative evidence

According to the NOS assessment, there were a majority of fair to good quality studies in the included studies, meaning that conceivable bias was unlikely to have major impact on the outcomes. In all conventional MPI (cMPI) outcomes for RA, SLE and SSc, some studies favouring control and others favouring CTD groups, therefore the results depicted inconsistent findings. The literature search yielded no evidence of unpublished studies, potentially reducing publication bias in the overall effect estimate. However, all outcomes demonstrated imprecision due to small sample sizes. Following these assessments, the GRADE approach was used to develop an evidence

profile, ultimately determining a moderate quality of evidence, as presented in online supplemental file.

Characteristics of the included studies

Out of the 22 included studies on ACTD, there were six studies focused on RA, eight on SSc, five on SLE, two on SjD and one on MCTD. The study designs consisted of one cross-sectional, one cohort and 20 case–control studies. Eleven studies were conducted in Turkey, six in Europe (Germany, Greece, Serbia, Italy and two in Poland) and five in Asia (two in India, two in Egypt and Taiwan). Transthoracic echocardiographywas consistently used across all studies, incorporating conventional echocardiography or tissue Doppler imaging (TDI) to assess the left ventricular systolic–diastolic function and MPI. The total number of case group participants was 1051 while the control group consisted of 724 participants. Further details of data characteristics are summarised in table 1.

Final results

A total of 19 included studies in the quantitative synthesis showed various results in between group comparisons. Significant heterogeneity was indicated between studies. We therefore pooled the MPI values from all the included studies with random effects model. Table 2 shows the pooled MPI values from cMPI between ACTD and healthy control groups. Meanwhile, table 3 demonstrated pooled MPI values from tissue Doppler MPI (tdMPI) between ACTD and healthy control groups.

Meta-analysis results

The quantitative synthesis results of cMPI between group comparison were shown in figure 2, whereas the results for tdMPI were displayed in figure 3. Based on the results, the mean value of cMPI and tdMPI in patients with ACTD were highly significant than healthy control (p value of 0.0001 and <0.00001, respectively). In subgroup analyses, the MDs of cMPI in RA and SSc were statistically significant (p=0.003and p=0.02) compared with healthy control, only SLE patients showed no significant MDs (p=0.11). While in subgroup analyses of tdMPI, all of the groups (RA, SLE and SSc) demonstrated significant MDs when compared with healthy control (p=0.003, p<0.0001 and p<0.00001, respectively). However, the overall heterogeneity of MPI in both conventional echocardiography and TDI demonstrated a high heterogeneity when (I^2=89% and 77%, respectively).

DISCUSSION

The precise mechanism of cardiac dysfunction in patients with ACTD remains unclear. The decrease of LV systolic or diastolic function (LVDD) in SLE patients was thought to be related to myocarditis or coronary artery disease associated with immune complexes mediated inflammatory state.[33] Extensive fibrous degeneration, microcirculation changes and autonomic dysfunction in SSc patients may result in general impairment of the cardiac function.[18 22] In RA, the presence of circulating inflammatory substances and autoantibodies plays a key role, whereas in SjD, the main factors are chronic inflammation, autoimmune dysfunction and dyslipidaemia. Endothelial dysfunction may be accelerated by systemic inflammation, which contributes to the development of CVD. Chronic inflammation is identified as a critical factor in the pathogenesis of myocardial disease and atherosclerosis in ACTD. To mitigate cardiovascular risk factors and optimise outcomes, this highlights the significance of comprehensive cardiovascular assessment and management in CTD patients.[32]

It is hypothesised that a combined assessment of LV chamber performance to be more reflective of global cardiac dysfunction since systolic and diastolic dysfunction typically coexist, compared with solely focusing on systolic or diastolic measurements.[7] Developed by Tei *et al* in 1995, MPI has the capability to evaluate both LV systolic and diastolic performance and predict heart disease.[7] MPI are also independent with age, blood pressure and heart rate.[34] MPI can be measured quickly and non-invasively with minimal training requirements. Its simplicity and durability in helping identify the myocardial dysfunction severity in a variety of illnesses, make it a clinical mainstay. It is important to remember that MPI serves as only one of several measures used to evaluate cardiac function and should be interpreted alongside other clinical and imaging findings.[34]

A decrease in LVEF in the study group compared with the control group were reported in three studies.[18 20 28] It may be suggested that the LVEF findings do not depict cardiovascular disturbances in asymptomatic patients within the ACTD population. While no significant differences were found in LVEF between the study and control groups, notable differences were observed in MPI measurements (reported in three out of six studies on RA, three out of five on SLE, four out of eight on SSc and two out of two on SjD).[12 15–17 21–23 25 27 29–31] Unlike LVEF, which focuses primarily on systolic function, MPI captures abnormalities in both contraction and relaxation phases of the cardiac cycle. These broader assessment makes MPI more sensitive to early myocardial dysfunction compared with LVEF and less influenced by variations in ventricular geometry or loading conditions. Additionally, MPI has demonstrated superior prognostic value compared with LVEF, particularly in patient cohorts with heart failure or acute coronary syndrome.[35] Rahman *et al*, study showed MPI had more sensitivity (86% vs 65%), specificity (82% vs 50%) and accuracy (83% vs 58%) compared with LVEF, becoming a better predictor of major adverse outcome predicting cardiac complications.[36] In 2018, Abuomara *et al*, also revealed that MPI>0.73 was more sensitive (78.3% vs 56.5%) and equal specificity (94.6%) compared with LVEF≤33 for heart failure prediction.[37]

LVDD in patients with ACTD was clinically important, as patients with LVDD had higher MPI values, which were correlated with haemodynamic measures describing LV relaxation. RA patients frequently develop diastolic

Table 1 Study characteristics

No	Author, publication year	Country	Type of study	Echocardiography technique	Participant N Case	Participant N Control	Age (years) Case	Age (years) Control	Disease duration (years)	Disease activity	Outcome of interest
RA											
1	Ilter *et al*, 2016[12]	Turkey	Cross-sectional	TTE	35 **Female**: 30 (85.7%) **Male**: 5 (14.3%)	25 **Female**: 17 (68%) **Male**: 8 (32%)	47.1±6.3	46.8±6.9	7.5±5.6	DAS-28: 3.9±1.7	**Conventional Echocardiography** **LV systolic indices**: ► EF in RA (65.6±4.4) vs control (66.7±5.4) were similar (p=0.72). **LV Diastolic indices**: ► E/A in RA (1.1±0.3) vs control (1.2±0.3) were not significant (p=0.22). ► E/Em in RA (6.9±2.8) vs control (6.5±2.2) were not significant (p=0.47).
2	Caglayan *et al*, 2018[13]	Turkey	Case- control study	TTE	48 **Female**: 35 (72.9%) **Male**: 13 (27.1%)	22 **Female**: 11 (50%) **Male**: 11 (50%)	52.0±9.4	47.1±6.1	7.11±5.97	DAS-28: N/A	**Conventional Echocardiography** **LV Systolic indices**: ► EF in RA (63.21±9.40%) vs control (64.00±2.00%) were similar (p=0.698). **LV Diastolic indices**: ► N/A **Tissue Doppler Imaging** **LV Diastolic indices**: ► E/Ea in RA (0.72±0.18) vs control (1.20±0.26) were significant (p=0.000).
3	Alpaslan *et al*, 2003[14]	Turkey	Case- control study	TTE	32 **Female**: 20 **Male**: 9	32 **Female**: 22 **Male**: 7	52±11	50±10	9±8	N/A	**Conventional Echocardiography** **LV systolic indices**: ► MPI in RA (0.44±0.11) vs control (0.35±0.11) were significant (p<0.05). **LV Diastolic indices**: ► E/A in RA (0.9±0.3) vs control (1.2±0.3) were significantly (p<0.05).
4	Rexhepaj *et al*, 2006[15]	Germany	Case- control study	TTE	81 **Female**: 61 (75%) **Male**: 20 (25%)	40 **Female**: 29 (72%) **Male**: 11 (28%)	48.6±11.9	48.05±12.4	6.3±4.4	N/A	**Conventional Echocardiography** **LV systolic indices**: ► EF in RA (66.1±8.4) vs control (65.5±7.1%) were similar (p=NS). **LV diastolic indices**: ► E/A ratio in RA (0.97±0.3) vs control (1.32±0.37) was lower significantly (p<0.001).
5	Levendoglu *et al*, 2004[16]	Turkey	Case- control study	TTE	40 **Female**: 32 (80%) **Male**: 8 (20%)	44 **Female**: 35 (80%) **Male**: 9 (20%)	48.5±11.8	46.1±12.7	10.00±6.70	N/A	**Conventional Echocardiography** **LV systolic indices**: ► EF in RA (69.1±4.2) vs control (69.1±4.6) were similar (p>0.05). **LV Diastolic indices**: ► E/a in RA (0.90+0.2) vs control (1.3+0.31) was lower significantly (p<0.05).

Continued

Table 1 Continued

No	Author, publication year	Country	Type of study	Echocardiography technique	Participant N Case	Participant N Control	Age (years) Case	Age (years) Control	Disease duration (years)	Disease activity	Outcome of interest
6	Akgol *et al*, 2023[11]	Turkey	Case- control study	TTE	50 **Female**: 39 (78%) **Male**: 11 (22%)	50 **Female**: 32 (64%) **Male**: 18 (36%)	46.54±9.31	43.42±12.02	10.77±8.52	DAS-28: 2.98±0.36	**Conventional Echocardiography** **LV Diastolic indices**: ► E/A in RA (0.92+0.24) vs controls (1.21+0.35) was lower significantly (p=0.000). **Tissue Doppler Imaging** **LV Diastolic indices**: ► E/e' in RA (8.21±2.52) vs control (7.21±2.11) was higher significantly (p=0.034). **Other outcome**: ► MPI with DAS-28 (r=0.173, p=0.228). ► MPI with disease duration (r=−0.071, p=0.622).
SSc											
1	Ciurzynski *et al*, 2008[17]	Poland	Case- control study	TTE	51 **Female**: 47 (92.2%) **Male**: 4 (7.8%)	31 **Female**: 28 (90.3%) **Male**: 3 (9.7%)	53.3±15.2	52.6±12.1	9±12.4	N/A	**Conventional Echocardiography** **LV Systolic indices**: ► EF in SSc (65±5.1%) vs control (65.1±3.2%) were similar (p=NS). **LV Diastolic indices**: ► E/A ratios in the SSc group (1.0±0.3) vs control (1.2±0.3) was lower significantly (p=0.04).
2	Ciurzyński *et al*, 2014[18]	Poland	Cohort study	TTE	111 **Female**: 101 (91%) **Male**: 10 (9%)	21 **Female**: 18 (86%) **Male**: 3 (14%)	54.2±13.8	49.3±10.5	9.4±11.4	N/A	**Conventional Echocardiography** **LV Systolic indices**: ► EF in SSc (65.05±5.1) vs control group (67.57±2.52) was lower significantly (p=0.01). **LV Diastolic indices**: ► E/A ratio in SSc (0.98±0.3) vs controls (1.21±0.28) was lower significantly (p=0.002). **Tissue Doppler Imaging** **LV Diastolic indices**: ► E/E' lateral in SSc (7.55±2.85) vs controls (6.87±2.30) were similar (p=NS). ► E/E' septal in SSc (9.69±3.05) vs controls (8.46±2.59) were similar (p=NS).
3	Dimitroulas *et al*, 2010[19]	Greece	Case- control study	TTE	52 **Female**: 51 (98%) **Male**: 1 (2%)	25 (sex matched-control)	55.7±10.1	Age-match control	11 (0.7–27)	N/A	**Conventional Echocardiography** **LV Systolic indices**: ► EF in SSc (71.2±7.9%) vs control (68.6±5.8%) were similar (p=NS). **LV Diastolic indices**: ► E/A ratios in SSc (1.01±0.16) vs control (1.52±0.17) was lower significantly (p<0.0001).

Continued

Table 1 Continued

No	Author, publication year	Country	Type of study	Echocardiography technique	Participant				Disease duration (years)	Disease activity	Outcome of interest
					N		Age (years)				
					Case	Control	Case	Control			
4	Karna *et al*, 2015[20]	India	Case- control study	TTE	30 **Female**: 23 (76%) **Male**: 7 (24%)	30 **Female**: 23 (76%) **Male**: 7 (24%)	38.87±10.41	39.23±10.31	48 (21–84) (months)	N/A	**Conventional Echocardiography** **LV Systolic indices**: ► EF in SSc (63±9.5%) vs control (69.4±7.4%) was lower significantly (p=0.006). **LV Diastolic indices**: ► E/A ratios in SSc (1.17±0.29) vs control (1.32±0.17) was lower significantly (p=0.021).
5	Gerede *et al*, 2015[21]	Turkey	Case- control study	TTE	31 **Female**: 29 (80%) **Male**: 2 (20%)	21 **Female**: 18 (85.7%) **Male**: 3 (14.3%)	50±9	47±6	N/A	N/A	**Conventional Echocardiography** **LV Systolic indices**: ► EF in SSc (61±4) vs control (60±5) was found NS (p=0.28) **LV Diastolic indices**: ► E/A ratio in SSc (0.9±0.3) vs control (1.3±0.3) was lower significantly (p<0.0001). **Tissue Doppler Imaging** **LV Diastolic indices**: ► E′/A′ ratio in SSc (1.0±0.5) vs control (1.7±0.7) was lower significantly (p<0.0001).
6	Ivanovic *et al*, 2012[22]	Serbia	Case- control study	TTE	50 **Female**: 45 (90%) **Male**: 5 (10%)	48 **Female**: 44 (92%) **Male**: 4 (8%)	55+9	54+8	9 (2–23)	N/A	**Conventional Echocardiography** **LV Systolic indices**: ► EF in SSc (59±5) vs control (60±5) was found NS. **LV Diastolic indices**: ► E/A ratio in SSc (1.08±0.18) vs control (1.24±0.21) was lower significantly (p<0.001). **Tissue Doppler Imaging** **LV Diastolic indices**: ► E′/A′ ratio for lateral mitral annulus in SSc (1.07±0.43) vs control (1.28±0.45) was statistically significant (p=0.020). ► E′/A′ ratio for septal mitral annulus in SSc (1.17±0.37) vs control (1.24±0.41) was found NS.
7	Yilmaztepe *et al*, 2018[23]	Turkey	Case–control study	TTE	24 **Female**: 22 (92%) **Male**: 2 (8%)	24 **Female**: 22 (92%) **Male**: 2 (8%)	46.8±12.3	44.3±8.0	6.5±4.8	N/A	**Conventional Echocardiography** **LV Systolic indices**: ► EF in SSc (64.0 (56–74)) vs control (65.5 (58–77)) was NS (p=0.305). **Tissue Doppler Imaging** **LV Diastolic indices**: ► E/E′ in SSc (6.0 (4–16)) vs control (5.4 (3–9)) was NS (p=0.056).

Continued

Table 1 Continued

No	Author, publication year	Country	Type of study	Echocardiography technique	Participant N Case	Participant N Control	Age (years) Case	Age (years) Control	Disease duration (years)	Disease activity	Outcome of interest
8	Gullulu *et al*, 2005[24]	Turkey	Case–control study	TTE	22 **Female**: 20 (91%) **Male**: 2 (9%)	22 **Female**: 20 (91%) **Male**: 2 (9%)	50.2+4.8	45.4+13.4	N/A	N/A	**Conventional Echocardiography** **LV Systolic indices**: ► Mitral E/A in SSc (1.02+0.38) vs control (1.18+0.23) (p=0.047). **Tissue Doppler Imaging** **LV Diastolic indices**: ► Mitral annular E/Ea in SSc (1.38+0.77) vs control (1.29+0.27) were similar (p=NS).
SLE											
1	Gin *et al*, 2006[25]	Taiwan	Case–control study	TTE	40 **Female**: 39 (97.5%) **Male**: 1 (2.5%)	45 **Female**: 43 (95.5%) **Male**: 2 (4.5%)	38±11.2	42.7±16	5.1±3.8 (with PH) 2.9±2.0 (without PH), p<0.01	N/A	**Conventional Echocardiography** **LV Systolic indices**: ► EF in SLE (58.1±10.3) and control (62.5±7.9) were similar (p=0.072).
2	Barutcu *et al*, 2015[26]	Turkey	Case–control study	TTE	50 **Female**: 46 (92%) **Male**: 4 (8%)	30 **Female**: 28 (93%) **Male**: 2 (7%)	38.6±10	35.9±8	Disease duration (n): ≥5 years=21; <5 years =29	SLEDAI≥6 = 15 patients; SLEDAI<6=35 patients	**Tissue Doppler Imaging** **LV Systolic indices** ► EF in SLE (69.1±2.5) vs control (68.7±3.8) were found NS (p=0.624). LV Diastolic indices ► E/A in SLE (1.39±0.19) vs control (1.29±0.31) were found NS (p=0.096). ► E/E′ in SLE (5.6±0.7) vs control (4.6±1.2) was higher significantly (p<0.001). Other outcomes: ► No significant correlation between SLEDAI and MPI (r=−0.145, p=0.315). ► There was no significant correlation between MPI and disease period (r=−0.127, p=0.850). ► No significant differences of MPI between disease duration<5 years (0.43±0.06) and>5 years (0.44±0.06). ► No significant differences of MPI between SLEDAI<6 (0.45±0.05) and SLEDAI≥6 (0.42±0.07).
3	Allam *et al*, 2013[27]	Egypt	Case–control study	TTE	50 **Female**: 50 (100%) **Male**: 0 (0%)	20 **Female**: 20 (100%) **Male**: 0 (0%)	26.82±6.96 (18–50)	27.5±8.57 (17–52)	9.2±4.91 (1–15)	SLEDAI>10 = 30 patients; SLEDAI<10 = 20 patients	**Conventional Echocardiography** **LV Systolic indices**: ► EF in SLE (70±7.7%) vs control (71.7±3.31%) was found NS (p=0.084). **LV Diastolic indices**: ► E/A ratio in SLE (1.16±0.28) vs control (1.27±0.78) was found NS (p=0.896). **Other outcomes**: ► Significant positive correlation was found between the MPI at the lateral annulus and the septum and each of the following; disease duration (p=0.01, 0.001 respectively) and SLEDAI (p=0.002, 0.019 respectively).

Continued

Table 1 Continued

No	Author, publication year	Country	Type of study	Echocardiography technique	Participant N		Age (years)		Disease duration (years)	Disease activity	Outcome of interest
					Case	Control	Case	Control			
4	Bakhoum *et al*, 2015[28]	Egypt	Case- control study	TTE	50 **Female**: 47 (94%) **Male**: 3 (6%)	25 **Female**: 23 (92%) **Male**: 2 (8%)	28.5+8.5	30.2+10.2	4.5 (2–7.25) years	SLEDAI 5.9+5.75 (range: 0–20)	**Conventional Echocardiography** **LV Systolic indices**: ► EF in SLE (64.0±6.7%) vs control (68.8±7.7%) was found significant (p=0.007). **LV Diastolic indices**: ► E/A in SLE (1.3+0.4) vs controls (1.4+0.4) was found NS (p=0.2). **Tissue Doppler Imaging** **LV Diastolic indices**: ► E/E′ in SLE (11.1±5) vs controls (7.6±2.2) was higher significantly (p=0.002).
5	Cacciapuoti *et al*, 2005[29]	Italy	Case–control study	TTE	44 **Female**: 37 (84%) **Male**: 7 (16%)	41 **Female**: 33 (80%), **Male**: 8 (20%)	43±2	41±7	N/A	N/A	**Conventional Echocardiography** **LV systolic indices**: ► EF in SLE (62±3) vs control (64±2) were similar (p=NS).
SjD											
1	Akyel *et al*, 2012[30]	Turkey	Case–control study	TTE	40 **Female**: 36 (90%) **Male**: 4 (10%)	25 **Female**: 21 (84%) **Male**: 4 (16%)	47.5±9.8	47.1±9.6	N/A	ESSDAI=1.2±0.9	**Conventional Echocardiography** **LV Systolic indices**: ► EF in SS (64.3±1.8) vs control (65.0±1.9) were similar (p=NS). **LV Diastolic indices**: ► E/A ratios in the SS group (0.9±0.2) vs control (1.3±0.3) were lower significantly (p<0.01).
2	Bayram *et al*, 2013[31]	Turkey	Case–control study	TTE	50 **Female**: 47 (94%) **Male**: 3 (6%)	48 **Female**: 42 (88%) **Male**: 6 (12%)	42.8±8.3	39.9±8.1	N/A	N/A	**Conventional Echocardiography** **LV Systolic Indices**: ► EF in SS (65.2±2.8) vs control (65.4±3.9) were similar (p=0.731). **LV Diastolic indices**: ► E/A ratio (1.1±0.3) vs control (1.2±0.2) were similar (p=0.163). **Tissue Doppler Imaging** ► Em/Am ratio (1.1±0.4) in SS vs control (1.4±0.4) was lower significantly (p=0.001).
MCTD											

Continued

Table 1 Continued

No	Author, publication year	Country	Type of study	Echocardiography technique	Participant N		Age (years)		Disease duration (years)	Disease activity	Outcome of interest
					Case	Control	Case	Control			
1	Thakur *et al*, 2020[32]	India	Case–control study	TTE	35 **Female**: 33 (94%) **Male**: 2 (6%)	35 **Female**: 33 (94%) **Male**: 2 (6%)	36.9±12.5	33. 7±11.9	SLE: 1.5 (0.5–4) SSc: 8 (2–11.5) MCTD: 5.5 (5-6) Overlap:21DM: 1	SLE: SLEDAISLE & SSc: Modified Rodnan Skin Care	**Conventional Echocardiography** **LV Systolic indices**: ▲ EF in CTD (64.2±6.3%) vs control (66.3±4.9%) were similar (p=0.31). **LV Diastolic indices**: ▲ E/A ratios in the CTD group (1.4±0.4) vs control (1.3±0.3) were similar (p=0.56). **Tissue Doppler Imaging** ▲ Med E/E′ in CTD (8.5±2.3) vs control (9.1±2.7) were similar (p=0.27). ▲ Lat E/E′ in CTD (6.3±2.1) vs control (7.1±3.1) were similar (p=0.00.8). ▲ Average E/E′ in CTD (7.4±1.9) vs control (8±1.9) were similar (p=0.19).

A′, tissue Doppler A wave velocity; A, peak late diastolic myocardial velocity; Am, late diastolic myocardial wave; CTD, connective tissue disorder; DAS-28, Disease Activity Score-28; E′, tissue Doppler E wave velocity; E, peak early diastolic myocardial velocity; EF, ejection fraction; Em, early diastolic myocardial wave; ESSDAI, The European League Against Rheumatism Sjögren's syndrome (SS) disease activity index; MCTD, mixed connective tissue disorder; MPI, myocardial performance index; RA, rheumatoid arthritis; SjD, Sjögren syndrome; SLE, systemic lupus erythematosus; SLEDAI, SLE Disease Activity Index; SSc, systemic sclerosis; TTE, transthoracic echocardiography.

dysfunction, with a prevalence reported around 57%.[38] RA patients with diastolic dysfunction frequently exhibit prolonged IVRT as the most prominent abnormality.[39] In SLE, a meta-analysis conducted by Chen *et al*, also found that E/e′ were significantly higher, and a significantly lower E/A ratio was detected.[33] Consistent with existing literature, which identifies female gender and older age as risk factors for diastolic dysfunction in SSc, our findings predominantly involved older women (76%–98%).[20 40] Notably, abnormal diastolic dysfunction is a prevalent finding in SSc (approximately 15%–21%).[41] LVDD was documented by Ye *et al* in 13.7% of patients with SjD, whereas Manganelli *et al* identified irregularities in the E/A wave ratio in 50% of SjD patients, indicating a significant prevalence of LVDD in this demographic.[31 42 43] Significantly, Lee *et al*[44] postulated a correlation between the state of inflammation and LVDD, implicating tumour necrosis factor-alpha (TNF-α) as a possible exacerbating element. Thakur *et al*[32] study found LVDD in 11.4% of cases, which was comparable to the 12% reported by Kini *et al*.[45] In Thakur *et al* study, patients diagnosed with SLE and SjD comprised the majority of the ACTD group, which underscores the significance of diastolic dysfunction in relation to different subtypes of ACTD.[32]

In this review, a significant difference was shown in cMPI between ACTD groups compared with healthy control (MD=0.06, 95% CI 0.03 to 0.10, p=0.0001). In contrast, non-significant findings were observed in the SLE group compared with the control (MD=0.07, 95% CI −0.02 to 0.15, p=0.11). These findings suggest that cMPI may be involved in detecting early asymptomatic cardiac involvement in ACTD groups. Both conventional echocardiography and TDI can be used to calculate MPI; however, there are several limitations associated with using conventional echocardiography. Conventional echocardiography relies on patterns of mitral inflow, which are highly sensitive to preload and can change dramatically as diastolic dysfunction progresses.[46] TDI is relatively less load dependent, not affected by preload and afterload changes.[47] TDI is also less influenced by left atrial pressure, myocardial relaxation velocity, and volume status.[48] Therefore, TDI can be used for early diagnosis of LVDD, especially in conditions where conventional echocardiography is insufficient. It allows measurement of both relaxation and contraction velocities simultaneously within one cardiac cycle compared with conventional echocardiography.[47] Instead of measuring the movement of blood flow as a result of the myocardial wall's motion, TDI measures the myocardial wall's systolic and diastolic movements directly.[29] Our quantitative analysis reveals a significant difference in tdMPI between ACTD groups and healthy control (MD=0.11, 95% CI 0.08, 0.14, p<0.00001). All subgroup analyses consistently demonstrate a tendency toward higher tdMPI values in patients with ACTD. The findings of impaired tdMPI in patients with ACTD without cardiac symptoms may suggest that tdMPI has a potential in early detection of subclinical cardiac involvement.

Table 2 Results of Conventional Myocardial Performance Index (cMPI) in Autoimmune Connective Tissue Disease (ACTD) compared to healthy control

		Conventional Myocardial Performance Index (cMPI)						
		ACTD			Control			
No	Author, Year	Mean	SD	Participants	Mean	SD	Participants	P value
RA								
1	Alpaslan *et al*, 2003[14]	0.44	0.11	32	0.35	0.11	32	0.0017
2	Levendoglu *et al*, 2004[16]	0.52	0.12	40	0.43	0.06	44	0
3	Rexhepaj *et al*, 2006[15]	0.51	0.1	81	0.52	0.2	40	0.7139
4	Caglayan *et al*, 2018[13]	0.55	0.18	48	0.49	0.05	22	0.1304
SLE								
1	Gin *et al*, 2006[25]	0.5	0.07	40	0.41	0.06	45	0
2	Bakhoum *et al*, 2015[28]	0.62	0.12	50	0.49	0.05	25	0
3	Barutcu *et al*, 2015[26]	0.39	0.03	50	0.4	0.06	30	0.3241
SSc								
1	Gullulu *et al*, 2005[24]	0.49	0.12	22	0.42	0.07	22	0.0228
2	Ciurzynski *et al*, 2008[17]	0.44	0.08	51	0.38	0.05	31	0.0003
3	Dimitroulas *et al*, 2010[19]	0.31	0.06	52	0.31	0.04	25	1
4	Gerede *et al*, 2015[21]	0.67	0.2	31	0.41	0.17	21	0
5	Karna *et al*, 2015[20]	0.42	0.15	30	0.4	0.07	30	0.5107

RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

Out of all types of ACTD included, only RA and SLE studies evaluate MPI with either disease activity or disease duration. In RA, Akgol *et al*, reported no significant correlation of MPI values with disease duration and Disease Activity Score-28.[11] These findings were relevant with Midtbø *et al*, where disease duration in RA patients did not appear to differ significantly in risk of CVD during the first 10 years compared after 10 years of disease duration (p=0,82); however, for disease activity, RA patients with higher disease activity were associated with lower LV systolic myocardial function.[49] In SLE patients, Barutcu *et al* study showed no significant differences of MPI values with disease duration<5 years compared with >5 years (p=0.85).[26] Similar results were found for patients with SLE Disease Activity Index (SLEDAI)<6 compared with SLEDAI≥6 (p=0.68). In contrast, Allam *et al*, study showed

Table 3 Results of Tissue Doppler Myocardial Performance Index (tdMPI) in Autoimmune Connective Tissue Disease (ACTD) compared to healthy control

		Tissue doppler myocardial performance index (tdMPI)						
		ACTD			Control			
No	Author, Year	Mean	SD	Participants	Mean	SD	Participants	P value
RA								
1	Ilter *et al*, 2016[12]	0.46	0.12	35	0.36	0.07	25	0.0004
2	Caglayan *et al*, 2018[13]	0.55	0.18	48	0.49	0.05	22	0.1304
3	Akgol *et al*, 2023[11]	0.67	0.18	50	0.47	0.05	50	0.0000
SLE								
1	Cacciapuoti *et al*, 2005[29]	0.58	0.05	44	0.48	0.1	41	0.0000
2	Allam *et al*, 2013[27]	0.53	0.17	50	0.37	0.04	20	0.0001
SSc								
1	Yilmaztepe *et al*, 2018[23]	0.42	0.04	24	0.34	0.04	24	0.0000
2	Ivanovic *et al*, 2012[22]	0.45	0.12	50	0.38	0.1	48	0.0023
3	Gerede *et al*, 2015[21]	0.81	0.3	31	0.53	0.24	21	0.0008
4	Ciurzynski *et al*, 2014[18]	0.46	0.09	111	0.39	0.06	21	0.0008

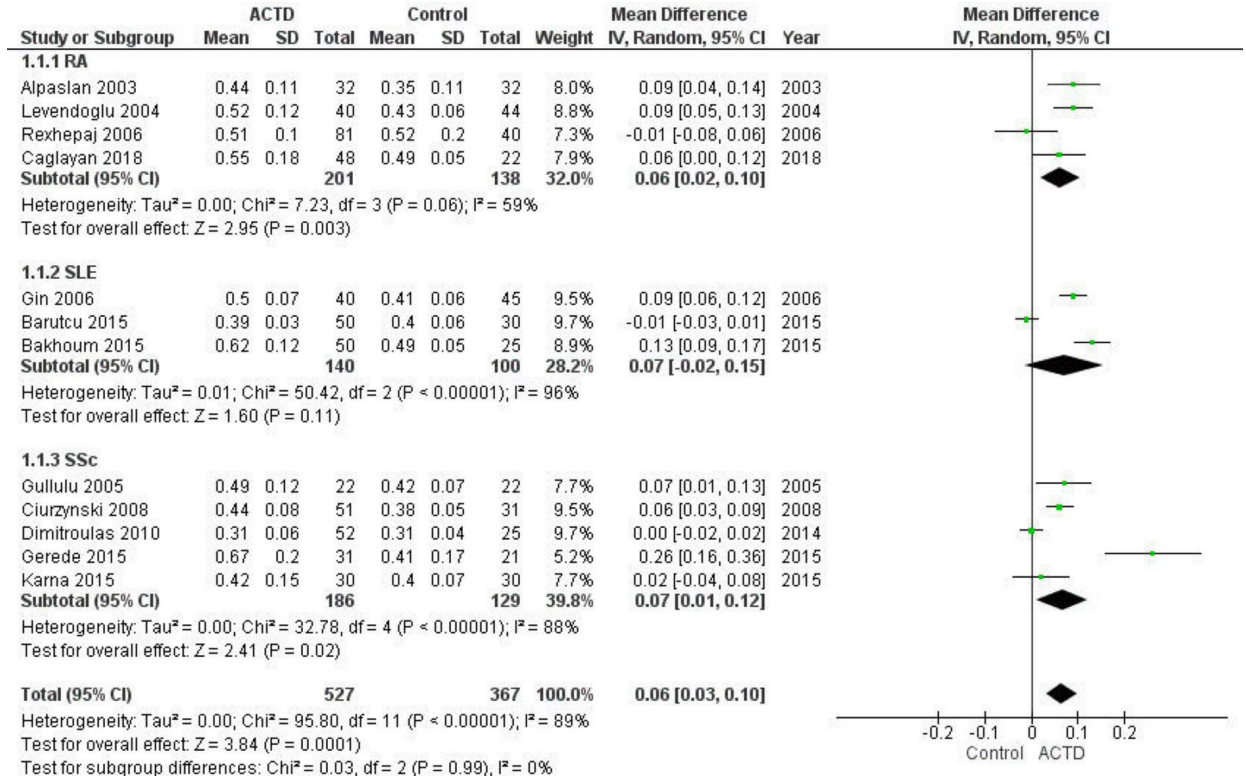

Figure 2 Meta-analysis results (forest plot) for Conventional Myocardial Performance Index (cMPI) in autoimmune connective tissue disease (ACTD) compared with healthy control. RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

significant correlation between MPI at septum (p=0.001) and lateral mitral annulus (p=0.01) with disease duration.[27] Significant correlation between MPI at septum (p=0.019) and lateral mitral annulus (p=0.002) with SLEDAI were found. Higher septum and lateral mitral annulus tdMPI values in SLE patients with SLEDAI>10

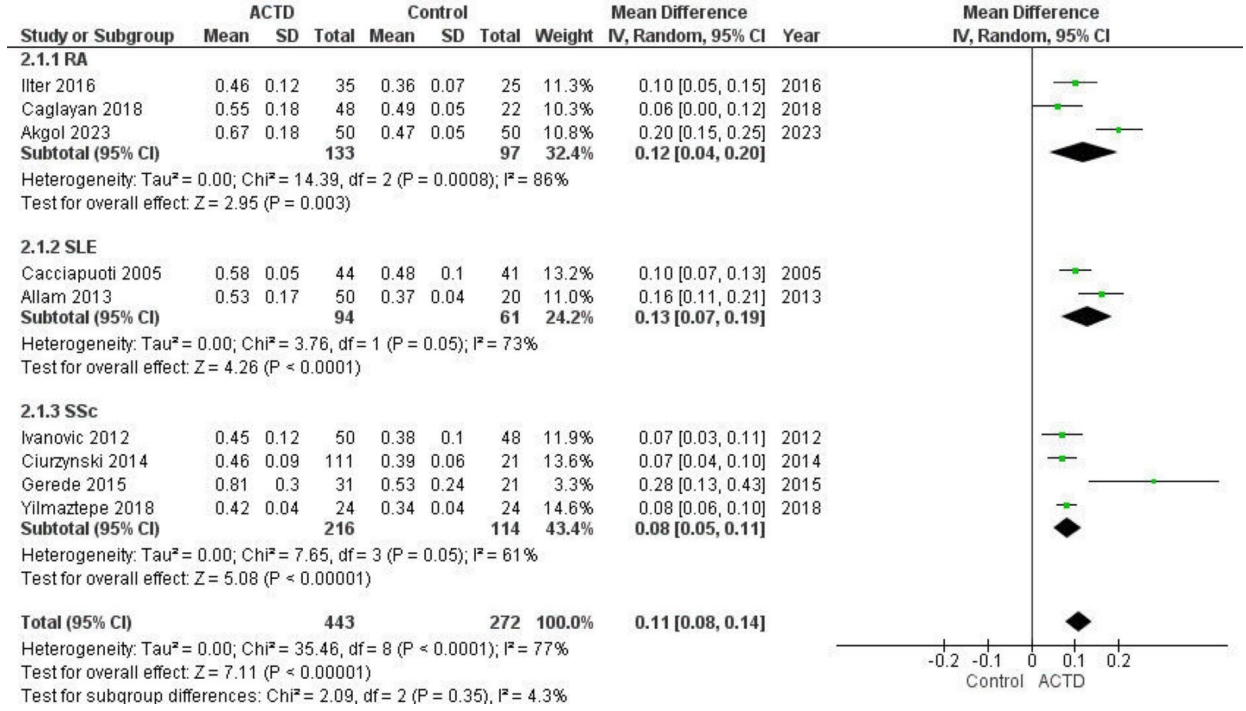

Figure 3 Meta-analysis results (forest plot) for Tissue Doppler Myocardial Performance Index in autoimmune connective tissue disease (ACTD) compared with healthy control. RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

compared with SLEDAI<10 (p=0.001, p=0.002, respectively) were also reported. These findings were relevant with Chen *et al*, study, as the most changes echocardiographic in SLE patients such as the cardiac structure and function abnormalities including a decrease in both systolic and diastolic function related with the longer of disease duration (especially more than 10 years) and with high disease activity score using SLEDAI or Systemic Lupus International Collaborating Clinic (SLICC).[33] Leone *et al*, also suggests a possible association between active SLE and LVDD.[50]

Heterogeneity and publication bias analysis

Evaluation of heterogeneity using the I^2 statistic revealed moderate to high variability in ACTD subgroups compared with controls. cMPI yielded I^2 values of 59% (p=0.06) for RA, 96% (p<0.00001) for SLE and 88% (p<0.00001) for SSc, with a cumulative value of 89% (p<0.00001). Similarly, tdMPI displayed substantial heterogeneity across all outcomes, with I^2 values of 86% (p=0.0008), 73% (p=0.05) and 61% (p=0.05), respectively. This observed variability might stem from clinical characteristics of the patients, methodological differences between studies or statistical considerations.

Potential sources of heterogeneity in this study include variations in sample size across participant groups. The case and control groups ranged from 210 to 283 individuals for RA, 222 to 371 for SSc, 161 to 234 for SLE and 73 to 163 for SjD. Additionally, the age distribution and disease duration within each ACTD group exhibited significant disparity. This is crucial as disease progression demonstrably correlates with both age and disease duration with in some ACTD, the early age at onset emerges as a strong negative prognostic factor.[51]

CONCLUSION

Our findings reveal a significant difference in pooled MPI values among patients with ACTD compared with healthy controls, indicating cardiac dysfunction across these conditions. The comprehensive evaluation of both systolic and diastolic function using MPI underscores the clinical importance of detecting diastolic dysfunction in patients with ACTD early on. These findings emphasise the significance of identifying and monitoring cardiac involvement to mitigate cardiovascular complications in ACTD populations. MPI assessment has the potential for early detection and management of cardiac dysfunction in patients with ACTD. Further studies are required to validate these findings.

STRENGTHS AND LIMITATIONS

This study represents the first meta-analysis study to review the utility of MPI in ACTD as a sensitive marker for cardiac dysfunction. The analysis encompassed studies with various spectra of ACTD and included both conventional and tdMPI measurement. However, limitations are evident, including heterogeneity among the included studies and disease types, a limited sample size and potential publication bias. Some studies also could not be retrieved or the full articles were not accessible. Furthermore, the retrospective nature of our analysis may limit causal inference.

FUTURE DIRECTION

Future directions in research could explore the potential of MPI as a predictive tool for cardiovascular outcomes and mortality in patients with ACTD, further elucidating its clinical utility. Additionally, investigating the role of novel imaging modalities, such as cardiac MRI, in conjunction with MPI could provide deeper insights into cardiac pathophysiology in these conditions. While MPI calculation for both LV and RV provides valuable insights, future studies could explore the clinical implications of elevated RV MPI, which is associated with either pulmonary hypertension or cardiac dysfunction.

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