Echocardiographic Prevalence and Risk Predictors of Ventricular Dysfunction in Connective Tissue Disorders: Tertiary Care Hospital-Based Prospective Case-Control Study

Saru Thakur¹, Geeta Ram Tegta¹, Prakash Chand Negi², Kunal Mahajan², Ghanshyam Verma¹, Mudita Gupta¹, Ajeet Negi¹, Reena Sharma¹, and Kuldeep Verma¹

Abstract

**Background:** There is a paucity of contemporary Indian data about the prevalence of cardiac abnormalities in patients of connective tissue disorders (CTD) and their risk determinants.

**Methods:** We prospectively recorded data from 35 consecutive CTD patients who presented to our out-patient department and had no significant cardiovascular risk factors at baseline. We also recorded data from their age- and sex-matched controls. All cases and controls were subjected to 12 lead electrocardiogram and echocardiography after routine investigations.

**Results:** The CTD group comprised 19 (54.3%) patients of systemic lupus erythematosus, 12 (34.3%) patients of systemic sclerosis, 2 (5.7%) patients of mixed CTD, and 1 (2.9%) patient each of overlap syndrome and dermatomyositis. Cardiovascular involvement on echocardiography was documented in 71.4% of CTD patients despite majority of them having no cardiac symptom. Overt left ventricular (LV) systolic dysfunction was observed in 3 (8.6%) CTD patients, while subclinical LV systolic dysfunction was recorded in 13 (37.1%) patients. LV diastolic dysfunction was observed in 11.4% (n = 4) patients. RV systolic dysfunction was prevalent in 20% (n = 7) patients. Pulmonary hypertension was observed in 40% (n = 14) of CTD patients.

**Conclusion:** The present study evaluated subclinical LV systolic dysfunction and pulmonary hypertension in about one third of CTD patients. It is imperative to screen for these abnormalities in CTD to ensure timely diagnosis and treatment.

Keywords

Connective tissue disorder, cardiovascular complications, echocardiography, case-control study

Background

Connective tissue disorders (CTDs) represent a spectrum of systemic autoimmune diseases characterized by circulating autoantibodies and significant autoimmune-mediated organ damage. This heterogeneous group includes systemic lupus erythematosus (SLE), systemic sclerosis (SSc), Sjögren’s syndrome, mixed connective tissue disorder (MCTD), overlap syndrome, and inflammatory muscle diseases such as dermatomyositis (DM) and polymyositis (PM).¹ Specific or multiple organ systems targeted by the antibodies include pulmonary, renal, musculoskeletal, gastrointestinal, nervous, and hematological. One of the major causes of morbidity and mortality in patients of CTDs is the involvement of cardiovascular system.²

Cardiac involvement in CTDs may be directed to all the components of the heart: pericardium, conduction system,
myocardium, valves, and coronary arteries.\textsuperscript{3} Libman-Sacks endocarditis is the most characteristic cardiac abnormality in SLE, seen in up to 50\% of patients at necropsy in the past.\textsuperscript{4} Pericarditis is a common cardiac manifestation of CTDs, seen in up to 39\% of cases of SLE\textsuperscript{5} and up to 43\% cases in MCTD.\textsuperscript{6} In the past, cardiac manifestations were severe at the time of diagnosis, often leading to death and frequently found in postmortem examinations.\textsuperscript{4} But nowadays, because of diagnostic advancement, cardiac manifestations are often mild and asymptomatic as they can be recognized early by echocardiography and other noninvasive tests at initial stages of CTDs.\textsuperscript{7} However, there is a paucity of contemporary Indian data about prevalence of structural and functional abnormalities of heart in patients of CTD and their risk determinants.

\section*{Methods}

\subsection*{Study Design}

This study was conducted as a case-control study in the department of dermatology and cardiology of our institute, which is a tertiary care hospital in a hilly northern Indian state.

\subsection*{Patient Selection}

All consecutive patients of CTD diagnosed by using standard criteria reporting in the department of dermatology of our institute over one year with effect from 1 July 2018 to 30 June 2019 were screened for enrollment, and those willing were included. The patient’s attendants, relatives, friends, and the patients attending dermatology out-patient department for minor skin ailments such as fungal infections, common warts, acne patients, etc. constituted the control population and were screened to be enrolled as age- and sex-matched controls. Exclusion criteria consisted patients with congenital heart diseases, prior history of coronary artery disease, associated malignancies, chronic obstructive pulmonary diseases, pulmonary fibrosis secondary to infections, patients aged <10 years and >60 years, and patients having poor echo window and not willing to participate. Patients with other confounding factors such as diabetes, hypertension, and smoking were also excluded.

\subsection*{Data Collection}

Self-reported data related to demographic characteristics and medical history were recorded as per the structured data recording format. This was followed by anthropometric and blood pressure measurement using validated tools and following standard guidelines. Body mass index (BMI) was calculated as a ratio of weight in kilograms divided by height in meters squared (kg/m\textsuperscript{2}). The mucocutaneous examination was done as per the structured data format. Disease severity was assessed using Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and modified Rodnan skin score for SLE and SSc, respectively. Around 10 cc of blood was withdrawn in fasting state and collected in separate container vials with appropriate reagents for biochemistry and hemogram. The Cockcroft-Gault equation was used to estimate creatinine clearance. Pulmonary status was also evaluated by using pulmonary function tests.

\subsection*{Cardiovascular Evaluation}

All subjects underwent 12 lead “electrocardiogram” (ECG) to analyze the heart rate, rhythm, features of ventricular hypertrophy, old myocardial infarction, and conduction abnormalities. “Echocardiography” was done using I33 echo machine with 2 to 5 broad band phased array probe of Philips medical system with simultaneous ECG recording in the left lateral decubitus position to record different parameters. The same cardiologist conducted echocardiography in all the patients. For left ventricular (LV) systolic function, LV ejection fraction (LVEF) was calculated by measuring LV internal diameter at the end of diastole and end-systole using Teicholtz formula.\textsuperscript{8} LV global longitudinal and circumferential strains were measured in apical 4-chamber and parasternal short-axis view at 55 MHz frequency using speckle tracking method (QLAB software, version 10.2 was used for analysis). 3 apical and 3 parasternal image planes were recorded and the average was taken as the represented value. Early diastolic inflow velocity (E wave) and late diastolic flow velocity (A wave) and E wave deceleration time were measured as the indices of “LV diastolic function”\textsuperscript{9}; the ratio of E wave velocity and tissue Doppler-derived E’ were also calculated for the assessment of diastolic function. 3 readings for each index were recorded and average was taken as the representative value. “RV systolic function”\textsuperscript{10} was estimated by measuring the following 3 indices: (a) TAPSE, measured as an index of axial shortening of RV, was recorded with M mode tracing recorded at lateral TV annulus in modified 4 chamber view. A mean of 3 values was recorded. (b) Ratio of RV ejection period/RV preejection period; the RV preejection period was measured from the peak of R wave to the onset of spectral pulse Doppler envelope at right ventricular outflow tract (RVOT). RVET was measured using a pulse Doppler spectral envelop recorded at RVOT as an interval between onset to end of Doppler flow signal. (c) Myocardial performance index (MPI) was calculated as follows: the ratio of summation of isovolumetric contraction time and isovolumetric relaxation time to RV ejection time (ICT+IRT)/ET.\textsuperscript{8} The data were obtained by recording pulse wave Doppler spectral at RVOT and tricuspid valve closure to opening using pulse wave Doppler across tricuspid valve annulus. “Mean pulmonary arterial pressure” (MPAP) was
measured by recording the “pulmonary flow acceleration time” (PFAT); pulmonary flow velocity Doppler spectral envelope was recorded in RVOT with pulse Doppler. PFAT was measured as the interval between the onset point to the peak of the spectral envelope. 3 consecutive spectral envelopes were analyzed and the average was taken as the representative pulmonary flow acceleration time. Mean PAP was calculated using Mahan’s formula. The equation used differed for PFAT less than 120 ms (MPAP = 90 – [0.62 × acceleration time of pulmonary flow trace] if PFAT < 120) and PFAT above 120 ms (MPAP = 79 – [0.45 × acceleration time of pulmonary flow trace] if PFAT > 120).

Definitions

CTD was defined as the presence of any one of the disorders such as SLE, SSc, MCTD, undifferentiated connective tissue disorders (UCTD), DM, and PM diagnosed by the standard criteria. Controls were age- and sex-matched healthy asymptomatic individuals free of skin and systemic lesions suggestive of CTDs. “LV systolic dysfunction” (LVSD) was defined as the presence of any one of the following parameters: (a) LVEF <54% (females) and <52% (males), (b) peak global strain in longitudinal plane > –20% (ie, <20% in absolute value), (c) peak global strain in circumferential plane > –20% (ie, <20% in absolute value). “LV diastolic dysfunction” (LVDD) was defined if more than 2 of the available variables met the following abnormal cut off values: (a) Septal e’ velocity < 7 cm/s, (b) lateral e’ < 10 cm/s, (c) average E/e’ ratio > 14. RV systolic dysfunction (RVSD) was defined as any of the following: (a) TAPSE < 17 mm, (b) MPI > 0.43. “Pulmonary hypertension” was defined as MPAP > 25 mm Hg. Deranged lipid profile was defined as any of the following: S. cholesterol > 240 mg/dL , S. triglycerides > 150 mg/dL, S. LDL > 130 mg/dL, or S. HDL < 50 mg/dL. “Deranged LFT” was defined as values above the reference range in our institute’s pathology laboratory.

Ethical Clearance

The institutional review board approved the study protocol. The study was conducted with the patient’s understanding and consent.

Statistical Analysis

Categorical variables and continuous variable were reported as absolute frequency, relative frequency, and mean ± SD (standard deviation), respectively, and/or median and interquartile range for not normally distributed continuous variables. The difference between case and control groups of continuous variables and categorical variables was analyzed using unpaired t-test and chi-square test, respectively. Variables found to have significant association with outcomes in univariate analysis were modeled in multivariable logistic regression to determine the independent association of the clinical characteristics. Data were analyzed using Epi-info software, version 3.4.3. A P value of <.05 was taken as statistically significant.

Results

Patient Characteristics

A total of 46 consecutive CTD patients were considered for enrollment in this study, out of which 11 met the exclusion criteria leaving 35 CTD patients for final analysis. Equal number (n = 35) of age- and sex-matched controls were also included in the study. There were 19 (54.3%) patients of SLE, 12 (34.3%) patients of SSc, 2 (5.7%) patients of MCTD, and 1 (2.9%) patient each of overlap syndrome and DM (Figure 1).

Demographic Characteristics

The mean age of CTD patients and control group was 36.9 ± 12.5 years and 33.7 ± 11.9 years, respectively (Table 1). The subjects were predominantly females, 33(94.3%).

![Figure 1. Details of Enrolled Patient](image-url)
Table 1. Characteristics of the Patient and Control Group

| Characteristics          | Total n = 70 | CTD Group n = 35 | Control Group n = 35 | P Value |
|--------------------------|-------------|------------------|----------------------|--------|
| Age                      | 35.3 ± 12.2 | 36.9 ± 12.5      | 33.7 ± 11.9          | .27    |
| Female                   | 66 (94.3%)  | 33 (94.3%)       | 33 (94.3%)           | .69    |
| History                  | 11 (15.7%)  | 11 (31.4%)       | 0                    | .001*  |
| Breathlessness           | 1 (1.4%)    | 1 (2.8%)         | 0                    | .50    |
| Chest pain               | 11 (15.7%)  | 11 (31.4%)       | 0                    | .001*  |
| Palpitation              | 4 (5.7%)    | 4 (11.4%)        | 0                    | .06    |
| BMI                      | 20.4 ± 3.0  | 20.1 ± 3.0       | 20.7 ± 3.0           | .46    |
| Systolic BP              | 111.6 ± 11  | 111.2 ± 13.9     | 112.1 ± 9.9          | .76    |
| Diastolic BP             | 73 ± 7.2    | 72.3 ± 7.6       | 73.7 ± 6.8           | .44    |
| Hemoglobin               | 11.8 ± 1.6  | 11.5 ± 1.7       | 12.1 ± 1.4           | .10    |
| ESR                      | 10 (5-25)   | 25 (8-42)        | 7 (5-10)             | .0001* |
| RBS                      | 84.6 ± 12.6 | 85.9 ± 14.6      | 83.4 ± 10.4          | .41    |
| S. cholesterol           | 159.7 ± 32  | 160.7 ± 36.9     | 158.7 ± 28.8         | .80    |
| S. triglyceride          | 111.3 ± 42  | 130.7 ± 49.3     | 97.6 ± 18.5          | .003*  |
| S. HDL                   | 45.4 ± 9.4  | 42.4 ± 10.4      | 45.4 ± 31.9          | .21    |
| S. LDL                   | 85.9 ± 22.2 | 85.6 ± 24.8      | 86.1 ± 19.8          | .92    |
| S. albumin               | 4 ± 0.4     | 4 ± 0.5          | 4.1 ± 0.2            | .45    |
| S. uric acid             | 4.4 ± 0.4   | 4.2 ± 0.8        | 4.5 ± 0.6            | .09    |
| Deranged LFT             | 15 (21.4%)  | 14 (40%)         | 1 (2.9%)             | .001*  |
| S. creatinine            | 0.7 ± 0.03  | 0.7 ± 0.03       | 0.7 ± 0.04           | .9     |
| Restrictive lung disease | 25 (39.05%) | 25 (78.1%)       | 0                    | .0001  |
| Thrombotic events        |             |                  |                      |        |
| ECG finding              |             |                  |                      |        |
| HR                       | 84.3 ± 7.4  | 85 ± 9.2         | 83.7 ± 5.1           | .47    |
| AF                       | 0           | 0                | 0                    |        |
| LVH                      | 1 (1.4%)    | 1 (2.9%)         | 0                    | .5     |
| ECHO findings            |             |                  |                      |        |
| LV systolic dysfunction  | 18 (25.7%)  | 16 (45.7%)       | 2 (5.7%)             | .0001* |
| Overt                    | 3 (4.2%)    | 3 (8.6%)         | 0                    |        |
| Subclinical              | 15 (21.4%)  | 13 (37.1%)       | 2 (5.7%)             |        |
| RV systolic dysfunction  | 7 (10%)     | 7 (20%)          | 0                    | .006*  |
| LV diastolic dysfunction | 4 (5.7%)    | 4 (11.4%)        | 0                    | .05*   |
| PAH                      | 17 (24.3%)  | 14 (40%)         | 3 (8.6%)             | .002*  |

Note: *Significant P value.

Abbreviations: AF, atrial fibrillation; BMI, body mass index; BP, blood pressure; CTD, connective tissue disorder; ESR, erythrocyte sedimentation ratio; HDL, high density lipoprotein; HR, heart rate; LFT, liver function tests; LV, left ventricle; LVH, left ventricular hypertrophy; PAH, pulmonary arterial hypertension; RBS, random blood sugar; RV, right ventricle.

Medical History

Dyspnea and palpitations, the commonest cardiovascular complaints, each were seen in 11 (31.4%) CTD patients, which was statistically significant compared to the control group (P = .0001). History of chest pain and thrombotic events was recorded in 1 (2.8%) and 4 (11.4%) patients, respectively. All the controls were asymptomatic. Cutaneous involvement at the time of cardiac evaluation was seen in all the CTD patients (Table 2). The details of cutaneous involvement and other relevant signs and symptoms have been enlisted in detail in Table 2.

Table 2. Characteristics of Patient Population With CTD

|          | SLE n = 19 | SSc n = 12 | MCTD n = 2 | Overlap n = 1 | DM n = 1 | P Value |
|----------|------------|------------|------------|---------------|----------|---------|
| Age      | 33.05 ± 12.1 | 43.8 ± 12.3 | 34.5 ± 6.4 | 40 ± 30 | 30 ± 0 | .2      |
| Female gender | 18 (94.7%) | 11 (91.7%) | 2 (100%) | 1 (100%) | 1 (100%) | 1 (100%) |
| BMI      | 20 ± 19.8 | 20.4 ± 21.7 | 23.8 ± 20.7 | 3.6 | 2.3 | 3 ± 0.0 |
| Duration of disease (years) | 1.5 (0.5-4.5) | 8 (2-11.5) | 1.5 | 5.5 | 21 | 1 (0.5-6) |
| Cutaneous involvement | 18 (94.7%) | 4 (33.3%) | 2 (100%) | 0 (100%) | 0 (100%) | 0 (100%) |
| Photosensitivity | 2 | 0 | 0 | 1 (100%) | 0 | 0 |
| Oral ulcers | 10 (5%) | 0 | 1 | 0 | 0 | 0 |
| Malar rash | 8 | 0 | 50% | 1 | 0 | 0 |
| Discooid rash | 42.1% | 12 | 0 | 1 (100%) | 0 | 0 |
| Raynaud's | 10 | 0 | 100% | 2 | 0 | 1 (100%) |
| Sclerodactyly | 52.6% | 12 | 100% | 1 (100%) | 1 | 0 (100%) |
| Pigmentation | 6 | 1 (100%) | 0 | 1 (100%) | 1 | 0 |
| Deformities | 31.6% | 3 (25%) | 0 | 1 (100%) | 0 | 0 |
| Calcinosus cutis | 0 | 1 (100%) | 0 | 1 (100%) | 0 | 0 |
| Alopecia | 10.5% | 2 (50%) | 0 | 0 | 0 | 0 |
| Lupus hair | 4 (16.7%) | 0 | 1 (100%) | 0 | 0 | 0 |
| Proteinuria > 500 mg/24 h | 5 | 1 (8.3%) | 0 | 1 (100%) | 0 | 0 |
| GFR | 88.3 ± 25.6 | 81.3 ± 25.7 | 98.5 ± 44.5 | 55 | 143 | .26 |
| Deranged PFTs | 13 (72.2%) | 10 | 1 | 0 | 1 | 0 |
| Hypothyroidism | 6 | 50% | 1 (100%) | 0 | 0 | 0 |
| ECG | 84.3 ± 9.7 | 83.2 ± 13.4 | 97.5 ± 0 | 96 | 84 | .3 |
| HR | 8.1 | 9.7 | 13.4 | 0 | 0 | 0 |
| Sinus arrythmia | 1 (5.3%) | 2 | 0 | 0 | 0 | 0 |
| LVH | 0 | 16.7% | 0 | 0 | 0 | 0 |

(Table 2 Continued)
Pulmonary involvement was assessed by pulmonary function testing which revealed restrictive pattern in 25 (78.1%) patients (Table 1). Laboratory parameters were comparable between CTD group and the control group except for acute phase reactant like erythrocyte sedimentation ratio (ESR), which was significantly higher in the CTD group ($P = .0001$). The lipid profile was comparable in both the groups except serum triglyceride level, which was observed to be higher in the CTD group as compared to controls ($P = .003$). Deranged LFTs were more commonly observed in the CTD group (40% vs 2.9%, $P < .0001$).

**Cardiac Abnormalities**

Cardiac involvement was seen in 25 (71.4%) patients in one or the other form (Figure 2).

**ECG Abnormalities**

12 lead ECG was found to be normal in almost all the patients. The heart rate was observed to be more in the CTD group with a mean (+standard deviation) of 85 ± 9.2 as compared to 83.7 ± 5.1 in the control group ($P = .47$). LV hypertrophy was observed in only 1 patient.

**Echocardiographic Abnormalities**

Echocardiographic evaluation revealed abnormalities in overall 25 (71.4%) patients and 5 (14.2%) controls ($P = .0001$).

**Left Ventricular Systolic Dysfunction**

The assessment of the LV systolic function by recording LVEF did not reveal any significant difference in the LVEF between the CTD group and the controls (64.2 ± 6.3 vs 66.3 ± 4.9, $P = .31$) (Table 3). On strain imaging, the absolute value of global longitudinal was lower in CTD patients when compared with controls ($-20.1 ± 2.5$ vs $-22.5 ± 1.4$, $P < .0001$). No significant difference was seen in absolute values of global circumferential strain ($-21.5 ± 3.9$ vs $-22.8 ± 2.4$) in both the groups ($P = .1$). LVEF was found to be abnormal in 3 (8.6%) patients, who were considered to have overt LV systolic dysfunction. Further, global strain imaging in longitudinal plane and circumferential planes revealed systolic dysfunction in 9 (28.1%) and 7 (25.9%) patients, respectively. Hence, a prevalence of 45.7% ($n = 16$) was recorded for LV systolic dysfunction in the present study. Among subsets of CTD, LVSD was seen in 45.7% SLE patients ($n = 9$), and 33.3% patients of SSc ($n = 4$; Table 2).

| Echocardiographic Parameters | Study Group | Control Group |
|-----------------------------|-------------|---------------|
|                            | n = 35      | n = 35        | $P$ Value |
| Cardiac chamber dimensions  |             |               |           |
| Left atrial diameter        | 42.4 ± 4.4  | 40.6 ± 3.4    | 0.06      |
| LV end diastolic diameter   | 27.8 ± 4.1  | 26.1 ± 2.4    | 0.08      |
| LV end systolic diameter    |             |               |           |
| LV systolic function        |             |               |           |
| LVEF                        | 64.2 ± 6.3  | 66.3 ± 4.9    | .31       |
| Fractional shortening       | 34.7 ± 4.6  | 36.8 ± 4.7    | 0.06      |
| LV global longitudinal strain| $-20.1 ± 2.5$| $-22.5 ± 1.4$| $< .001^{*}$|
| LV global circumferential strain| $-21.5 ± 3.9$| $-22.8 ± 2.4$| .1        |

*Significant $P$ value.

**Note:**

**Abbreviations:** BMI, body mass index; ECG, electrocardiogram; DM, dermatomyositis; GFR, glomerular filtration rate; HR, heart rate; LV, left ventricle; LVH, left ventricular hypertrophy; MCTD, mixed connective tissue disorder; PFT, pulmonary function tests; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.
(Table 3 Continued)

|                        | Study Group n = 35 | Control Group n = 35 | P Value |
|------------------------|--------------------|----------------------|---------|
| RV systolic function   |                    |                      |         |
| TAPSE                  | 20.5 ± 3.8         | 22.8 ± 3.2           | .003*   |
| RV PEP/ET (prejection period/ejection time) | 5.2 ± 1.3         | 4.7 ± 0.8            | .23     |
| Myocardial performance index | 0.2 (0.09-0.31) | 0.13 (0.08-0.26) | .18     |
| LV diastolic function  |                    |                      |         |
| E/A                    | 1.4 ± 0.4          | 1.3 ± 0.3            | .56     |
| E wave deceleration    | 160.1 ± 33.3       | 168.6 ± 26.02        | .24     |
| time                   | 9.5 ± 2.5          | 9.7 ± 2.6            | .68     |
| Med E'                 | 8.5 ± 2.3          | 9.1 ± 2.7            | .27     |
| Med E/E'               | 12.1 ± 3.7         | 12.2 ± 3.6           | .92     |
| Lat E'                 | 6.3 ± 2.1          | 7.1 ± 3.1            | .08     |
| Lat E/E'               | 7.4 ± 1.9          | 8 ± 1.9              | .19     |
| Average E/E'           |                    |                      |         |
| Pulmonary hemodynamics |                    |                      |         |
| PFAT                   | 109.8 ± 25.5       | 126.68 ± 21.6        | .001*   |
| MPAP                   | 25.8 ± 11.8        | 18.06 ± 7.6          | .02*    |
| Valvular incompetence  |                    |                      |         |
| TR                     | 9 (25.7%)          | 3 (8.6%)             | .05     |
| MR (mild)              | 2 (5.7%)           | 0                    | .24     |
| Pericardial effusion   | 3 (8.6%)           | 0                    | .24     |
| Constrictive pericarditis | 0                 | 0                    | –       |

Note: *Significant P value.

Abbreviations: LV, left ventricle; LV/E, left ventricle ejection fraction; MPAP, mean pulmonary artery pressure; MR, mitral regurgitation; PFAT, pulmonary flow acceleration time; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

There was no significant association of age, BMI, ESR, uric acid, lipid profile, hematological parameters, and systemic involvement with LVSD (Table 4). Among cutaneous involvement in both groups, patients with LVSD had photosensitivity in 15 (93.8%) patients as compared to 11 (57.9%) patients without LVSD (P = .018). When adjusted for age, BMI, discoid rash, and ESR, photosensitivity was found to be an independent factor with odds ratio (95% CI) of 17.4 [3.1, 98.4] and with a P value of .0012. Hence, photosensitivity was observed as a significant finding associated with LVSD in CTD patients. Also, discoid rash was more commonly seen in these patients (43.8% vs 15.8%), but it was not statistically significant (P = .07). However, on logistic regression, when adjusted for age and BMI, the value for discoid rash was significant with odds 9.98 [2.1, 45.7], P = .003. 15 (93.8%) patients with LV systolic dysfunction were observed to be on therapy with steroids at the time of enrollment, as compared to 57.8% patients in the other group without LV systolic dysfunction. An odd of developing LV systolic dysfunction, while being on treatment with steroids was observed to be 10.2, with a significant P value of .018.

On adjusting for age, BMI, duration of disease by multivariate analysis, being on treatment at the time of enrollment still remained a significant factor with odds ratio (95% CI) of 16.1 [3.35, 76.8], P = .0005 (Table 4).

### Table 4. Risk Determinants of LV Systolic Dysfunction

|                        | CTD With LV Systolic Dysfunction n = 16 | CTD Without LV Systolic Dysfunction n = 19 | Odds Ratio (95% Confidence Interval) | P Value |
|------------------------|----------------------------------------|------------------------------------------|--------------------------------------|---------|
| Age                    | 35.5 ± 14.4                            | 38.6 ± 9.9                               | –                                    | .48     |
| Disease duration >4.5 years | 6 (37.5%)                             | 8 (42.1%)                               | 0.8 (0.2, 4)                          | .5      |
| History                | 4 (25%)                                | 3 (15.8%)                               | 1.7 (0.2, 4)                          | .4      |
| Dyspnea                | 0                                      | 1 (5.3%)                                | 14.2 (1.4, 107.7)                     | .5      |
| Chest pain             | –                                      | –                                       | –                                    | .7      |
| ESR                    | 22.5 (10-38)                           | 25 (8-43)                               | –                                    | .018*   |
| Hypertriglyceridemia   | 6 (37.5%)                              | 5 (26.3%)                               | 1.6 (0.3, 9)                          | .4      |
| Deranged LFT           | 6 (37.5%)                              | 8 (42.1%)                               | 0.8 (0.2, 4)                          | .5      |
| ANA > 640              | 4 (25%)                                | 14 (73.6%)                              | 1.3 (0.2, 107.7)                      | .5      |
| Photosensitivity        | 15 (93.8%)                             | 11 (57.9%)                              | 10.2 (1, 515)                         | .018*   |
| Discoid rash           | 7 (43.8%)                              | 3 (15.8%)                               | 4 (0.7, 30)                           | .07     |
| Oral mucosal ulcers    | 1 (6.3%)                               | 1 (5.3%)                                | 1.2 (0.01, 99.3)                      | .7      |
| Sclerodactyly          | 8 (50%)                                | 8 (42.1%)                               | 1.4 (0.3, 64.4)                       | .4      |
| Hematology abnormalities | 6 (37.5%)                         | 4 (21.1%)                               | 2.2 (0.4, 13.6)                       | .2      |
| GFR                    | 90.3 ± 26.7                            | 84.4 ± 28.8                             | –                                    | .5      |
| Deranged PFT           | 11 (78.6%)                             | 14 (77.8%)                              | 0.1 (0.1, 8.7)                        | .6      |
| Parenchymal lung changes on CXR | 4 (25%)          | 1 (5.3%)                                | 5.7 (0.5, 311)                        | .1      |
| ILD on HRCT            | 6 (37.5%)                              | 3 (15.8%)                               | 3 (0.5, 236)                          | .1      |
| GIT involvement        | 2 (12.5%)                              | 4 (21.1%)                               | 0.5 (0.04, 4.5)                       | .4      |
| Arthritis              | 5 (31.3%)                              | 4 (21.1%)                               | 1.7 (0.3, 106.4)                      | .4      |
| On treatment at enrolment | 15 (93.8%)                           | 11 (57.9%)                              | 10.2 (1.1, 515)                       | .02*    |
| Type of CTD-SSc/ SLE   | 4 (25%)                                | 12 (75%)                                | 0.5 (0.08, 2.4)                       | .2      |

Note: *Significant P value.

Abbreviations: ANA, anticytoplasmic nuclear antibody; CTD, connective tissue disorder; CXR, chest x-ray; ESR, erythrocyte sedimentation rate; GFR, glomerular filtration rate; GIT, gastrointestinal, HRCT, high resolution computed tomography; ILD, interstitial lung disease; LFT, liver function tests; LV, left ventricle; PFT, pulmonary function tests; SSc, systemic sclerosis; SLE, systemic lupus erythematosus.
Left Ventricular Diastolic Dysfunction

The mean value of medial E’ was 9.5 ± 2.5 in CTD patients and 9.7 ± 2.6 in control group (P = .68). Abnormal values of medial E’ were seen in 6 (17.1%) patients. Lateral E’ had a mean of 12.1 ± 3.7 in patients and 12.2 ± 3.6 in controls (P = .9). Abnormal lateral E’ values were seen in 7 (20%) patients. Average E/E’ ratio had a mean of 7.4 ± 1.9 in CTD patients and 8 ± 1.9 in controls (P = .2). The prevalence of LVDD was estimated to be 11.4% (n = 4) in the present study as per the standard guidelines followed. These included 3 patients of SSc and 1 patient of SLE, but because of the small sample size, risk determinants were not assessed.

Right Ventricular Systolic Dysfunction

The abnormal values for TAPSE and MPI were seen in 5 (14.3%) and 2 (5.7%) patients respectively. Presence of any of the above constituted RVSD. Hence, a prevalence of 20% (n = 7) was observed in the present study. The mean values of TAPSE were lower in CTD patients (mean of 20.5 ± 3.8) as compared to controls (60 ± 11.5 vs 66.2 ± 9.1, P = .0079). RV PEP was also observed to be significantly lower in cases as compared to controls as a mean of 25.8 ± 11.76 mm Hg as compared to controls with a P value of .015. Pulmonary flow acceleration time also showed statistically significant lower values than controls with a P value of .0038 (Table 3). Valvular abnormalities were seen in 11 (31.4%) patients. Quantifying, 8 of them had trivial tricuspid regurgitation (TR) and 1 had mild TR. Even 3 controls manifested trivial TR and difference was not found to be statistically significant with a P value of .05. 2 (5.7%) patients had mild mitral regurgitation. There was no aortic valve involvement or Libman-Sacks vegetations. Pericardial effusion was found in 3 (8.6%) patients, but it was mild. All patients were asymptomatic with no evidence of chest pain, hemodynamic compromise, and pericarditis or cardiac tamponade.

Discussion

The structural damage of myocardium, pericardium, and valves can be mediated by immunoinflammatory injury as an autoimmune response. Therefore, patients with CTD with...
evidence of systemic inflammatory state are likely to have involvement of the cardiovascular system.13,14 However, there are no case control prospective studies from an Indian population demonstrating the same.

In the present study involving 35 CTD patients and their age- and sex-matched controls, we have investigated the cardiac involvement in patients with CTDs primarily constituted by SLE and SSc patients who presented mainly with cutaneous manifestations. In the present study population of CTD, there were no patients of RhA, Sjögren’s syndrome, and PM. In brief, overall 25 (71.4%) patients had cardiac involvement in the form of structural and functional abnormalities. The systolic dysfunction (overt and/or subclinical) of LV and RV was observed in 16 (45.7%) and 7 (20%) patients, respectively, and diastolic dysfunction of left ventricle in 4 (11.4%) patients. The valvular incompetence of tricuspid and mitral valves was recorded in 9 (25.7%) and 2 (5.7%) patients, respectively.

Overall, both traditional and nontraditional risk factors for cardiovascular involvement have been associated with CTD. Traditional risk factors include hypertension, diabetes mellitus, dyslipidemia, male gender, metabolic syndrome, obesity, smoking, advanced age, menopausal status, family history of cardiovascular disease, hormone replacement therapy, and hyperhomocysteinemia.15 Nontraditional factors include polyautoimmunity, increased ESR and C-reactive protein, higher disease activity, organ damage, longer duration of disease, medication, long-term steroid therapy, and renal involvement.15 In the present study, we had excluded all patients who were smokers, had hypertension and diabetes, and who were aged >60 years, and we had predominantly female patients (94.6%), so as to evaluate the unerring prevalence of cardiac involvement among CTD patients.

Among different subsets of CTD population, we observed higher prevalence of ventricular dysfunction among patients of SLE, but this association of CTD subtype with ventricular involvement has not been established statistically. Wang et al2 reported LV systolic dysfunction in a retrospective case control study of 436 patients of CTD and 436 controls, in 42.4% of patients. However, the criteria used for defining myocardial function limitation were based on the presence of ventricular dilatation, regional wall motion abnormalities and depressed LVEF. Strain imaging was not used. Similarly many other investigators16,17 have evaluated LVSD in heterogeneous population of CTD and reported depressed systolic function compared to healthy controls. However, they have not reported the prevalent clinical and subclinical systolic dysfunctions. In the present study, overt LV systolic dysfunction was observed in only 3 (8.6%) CTD patients, while subclinical LV systolic dysfunction was recorded in 13 (37.1%) patients by strain imaging. Previously, Spethmann et al18 also detected subclinical LV systolic dysfunction using strain imaging in a case-control study of 22 patients of SSc and reported a prevalence of 40.9%. Our data demonstrate the utility of strain imaging in early detection of LV dysfunction (before it is clinically evident) in patients with CTD.

In the present study, we found statistically significant association of photosensitivity and treatment status, ie, high dose of long duration steroid therapy at the time of enrollment with LVSD. Discoid rash was also significant on univariate analysis. Previous studies have observed disease duration as a determinant for LVSD,14 but none of the previous studies have reported photosensitivity and discoid rash as significant determinants of cardiac involvement in CTD. This generates curiosity but there is need for further larger studies to validate and find the possible explanation behind this association.

Systolic functions of the right ventricle are also affected in CTD patients. Karna et al19 have reported significantly raised MPI values in the patient group in comparison to controls (0.54 ± 0.26 vs 0.35 ± 0.07, P < .001), suggesting overall diminished right ventricular performance in the patient group. The present study also recorded higher values of MPI among patients of CTD. Buss et al20 reported significantly lower values of TAPSE among CTD population similar to our study. RVSD was prevalent in 20% (n = 7) of the CTD patients in the present study, but no statistically significant determinant of RVSD was recorded, possibly because of the small sample size of CTD patients with RV dysfunction.

Thus, future studies with large sample size are required to evaluate the risk determinants.

Various case-control studies have observed deranged diastolic functions in patients with CTD as compared to controls.2,14,16 hence, diastolic dysfunction is a known cardiac manifestation of CTD. LV diastolic dysfunction was observed in 11.4% cases in the present study, which was comparable to the prevalence of 12% reported by Kini et al.20 However, methods for evaluating dysfunction were not described, and hence, the data of these 2 studies cannot be compared. Previous studies have reported association of aging and disease duration with type 1 and type 2 diastolic dysfunction, respectively,2,7 whereas in the present study, because of very small sample of patients (n = 4) with LVDD, determinants were not assessed.

Pericardial disorders occurring in CTDs are not uncommon and may present as pericarditis with or without effusion. Cardiac tamponade and constrictive pericarditis are possible but rare complications. Pericardial effusion was documented in only 3 (8.6%) patients in the present study, but was of mild nature. Wang et al2 reported 12.5% prevalence in a large heterogeneous sample of CTD population whereas many other investigators4,5,20 have reported higher prevalence of pericardial effusion ranging from 18.5% to 39%. However, all these studies included exclusively SLE patients with larger sample size and active disease.

Limitations

Because of the single center setting, potential center-specific bias cannot be ruled out. However, our center is a tertiary care
unit and caters to patients referred from different parts of the state. The overall CTD group and in particular MCTD, DM, and overlap subgroups are small. There were no patients of RA, primary Sjogren’s syndrome, and PM, and hence, our results cannot be extrapolated to whole CTD population. We enrolled all patients coming to the dermatology department with primarily cutaneous involvement; hence, patients with severe systemic features presenting to medical out-patient department may have been missed leading to an inherent selection bias. The small sample size of study population is the major limitation of this study; however, the results can be helpful in generating new hypothesis and can pave way for future studies with larger sample size and longer follow-up duration. Another important limitation of the present study was the use of a cut-off value of ≤–20% for global longitudinal strain (GLS), although the current practice is to take a cut-off value of ≤–20% for global longitudinal strain (GLS), although the current practice is to take a cut-off value of <–15%.

The normal values for GLS depend on the definition of the measurement position in the myocardium, the vendor, and the version of the analysis software, resulting in considerable heterogeneity in the published literature. Various authors have previously suggested that the expected value of LV GLS in a healthy individual is around –20% and any value of LV GLS less negative than –20% could be considered pathological.

**Conclusion**

Cardiovascular involvement occurs in a substantial number of CTD patients (71.4%), most of them being asymptomatic. The subclinical LV systolic dysfunction was the commonest manifestation, which was detected using strain imaging. Patients with photosensitivity and long duration of steroid therapy had higher prevalence of LV systolic dysfunction. Pulmonary hypertension was found in nearly one-third of patients of CTD. Significant cardiac involvement in the form of overt LV systolic dysfunction and mild valvular incompetence was documented in very few CTD patients. Furthermore, long-term studies enrolling higher number of CTD patients are needed to validate these findings. Such data are needed to device screening strategies against cardiovascular complications in CTD patients.

**Declaration of Conflicting Interests**

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Funding**

The authors received no financial support for the research, authorship, and/or publication of this article.

**References**

1. Mayr A, Kitterer D, Latus J, et al. Evaluation of myocardial involvement in patients with connective tissue disorders: a multi-parametric cardiovascular magnetic resonance study. *J Cardiovasc Magn Reson*. 2016;18:67-76.

2. Wang X, Lou M, Li Y, et al. Cardiovascular Involvement in connective tissue disease: the role of interstitial lung disease. *PLoS One*. March 16, 2015;10(3):e0121976.

3. Wozniacka A, Cygankiewicz I, Chudzik M, Drzejowska AS, Wranicz JK. The cardiac safety of chloroquine phosphate treatment in patients with systemic lupus erythematosus: the influence on arrhythmia, heart rate variability and repolarization parameters. *Lupus*. 2006;15:521-525.

4. Cervera R, Font J, Pare C, et al. Cardiac disease in systemic lupus erythematosus: prospective study of 70 patients. *Ann Rheum Dis*. 1992;51:156-159.

5. Badui E, Garcia-Rubi D, Robles E, et al. Cardiovascular manifestations in systemic lupus erythematosus. *Angiology*. 1985;36:431-441.

6. Ungprasert P, Wannarong T, Panichsillapakit T, et al. Cardiac involvement in mixed connective tissue disease: a systemic review. *Int J Cardiol*. 2014;171:326-330.

7. Tincani A, Rebaoli CB, Taglietti M, Shoenfeld Y. Heart involvement in systemic lupus erythematosus, antiphospholipid syndrome and neonatal lupus. *Rheumatology*. 2006;45:8-13.

8. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American society of echocardiography and the European association of cardiovascular imaging. *J Am Soc Echocardiogr*. 2015;28:1-39.

9. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American society of echocardiography and the European association of cardiovascular imaging. *J Am Soc Echocardiogr*. 2016;29:277-314.

10. Galié N, Humbert M, Vachier JY, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2016;37:67-119.

11. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American heart association task force on practice guideline. *J Am Coll Cardiol*. 2014;63:2889-2934.

12. Bossone E, D’Andrea A, D’Alto M, Citro R, Argiento P, Ferrara F. Echocardiography in pulmonary arterial hypertension: from diagnosis to prognosis. *J Am Soc Echocardiogr*. 2013;26:1-14.

13. Kalko S, Balakrishanan C, Mangat G, Mittal G, Kumar N, Joshi VR. Echocardiography in systemic lupus erythematosus. *Lupus*. 1998;7:540-544.

14. Buss SJ, Wolf D, Korosoglu G, et al. Myocardial left ventricular dysfunction in patients with systemic lupus
erythematosus: new insights from tissue doppler and strain imaging. *J Rheumatol.* 2010;37:79-86.

15. Amaya-Amaya J, Montoya-Sánchez L, Rojas-Villarraga A. Cardiovascular involvement in autoimmune diseases. *Biomed Res Int.* 2014;367359:1-32.

16. Wislowska M, Derej D, Kochmajski M, Sypuia S, Rozbicka J. Systolic and diastolic heart function in SLE patients. *Rheumatol Int.* 2009;29:1469-1476.

17. Meune C, Avouac J, Wahbi K, et al. Cardiac involvement in systemic sclerosis assessed by tissue-Doppler echocardiography during routine care. *Arthritis Rheum.* 2008;58:1803-1809.

18. Spethmann S, Dreger H, Schattke S, et al. Two-dimensional speckle tracking of the left ventricle in patients with systemic sclerosis for an early detection of myocardial involvement. *Eur Heart J Cardiovas Imaging.* 2012;13:863-1870.

19. Karna SK, Rohit MK, Wanchu A. Right ventricular thickness as predictor of global myocardial performance in systemic sclerosis: a Doppler tissue imaging study. *Indian Heart J.* 2015;67:521-528.

20. Kini S, Vekhande C, Londhey V. A cross-sectional study of cardiovascular involvement in systemic lupus erythematosus in an urban Indian tertiary care centre with emphasis on 2-D echocardiography. *J Assoc Physicians India.* 2017;65:59-64.

21. Roque MCF, Sampaio-Barros PD, Arruda AL, et al. Evaluation of left ventricular diastolic function by echocardiography with tissue Doppler in systemic sclerosis. *Arq Bras Cardiol.* 2017;109(5):410-415.

22. Vijayaraghavan G, Sivasankaran S. Global longitudinal strain: a practical step-by-step approach to longitudinal strain imaging. *J Indian Acad Echocardiogr Cardiovas Imaging.* 2020;4:22-28.

23. Tops LF, Delgado V, Marsan NA, Bax JJ. Myocardial strain to detect subtle left ventricular systolic dysfunction. *Eur J Heart Fail.* 2017;19(3):307-313.