Section: Medicine

Original Research Article

ASSESSMENT OF LEFT VENTRICULAR DYSFUNCTION IN RHEUMATOID ARTHRITIS PATIENTS

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Abstract

Background: The current investigation is aimed to determine the prevalence of Left Ventricular (LV) dysfunction in Rheumatoid Arthritis (RA) patients and whether there is a relationship between LV dysfunction and the severity or duration of the disease. Patients with established cardiovascular illness or risk factors were excluded from the study in an effort to establish a direct link between RA and LV Dysfunction. **Materials and Methods:** Participants were recruited for the study between January 2021 to June 2022, from the Department of Medicine at the Darbhanga Medical College and Hospital, Laheriasarai. Each patient's DAS-28 score was determined based on their subjective rating of impairment, the number of swollen/tender joints, and their ESR. All patients underwent baseline examinations, which included liver and renal function tests (LFT / RFT), acute phase reactants (ESR and CRP), and haemoglobin (Hb). Left Ventricular End Diastolic Diameter (LVEDD) and Left Ventricular End-Systolic Diameter was measured by performing a 2D Echocardiography and was used to evaluate the LV systolic function (LVESD) by M-mode Quinone's approach. The stroke volume (SV) was computed, and the LV ejection fraction was expressed in percentage. Participants' demographic characteristics and echocardiography characteristics were summarized using descriptive statistics.**Result:**80 RA patients in all were enrolled for this trial. DAS -28 scores were directly proportional to the prevalence of LV dysfunction. 78.75% of patients with LV dysfunction identified through screening are typically asymptomatic, and only 15% of subjects had clinical indications of HF. People with LV systolic dysfunction made up 25% of the entire study population, whereas 43.75% reported LV diastolic dysfunction and 52.5% complained of both LVSD and LVDD. **Conclusion:** The study suggests a high index of suspicion for LV dysfunction should be present in evaluating and managing patients of RA even in the absence of other cardiovascular risk factors or symptoms of HF, particularly in those who present with a longer duration of the disease and higher DAS-28 score.

INTRODUCTION

A chronic, systemic, inflammatory disease with an uncertain etiology, rheumatoid arthritis (RA) primarily affects synovial joints and 1-3% of the population. RA patients have a roughly two-fold greater incidence of heart failure than those without RA.[1] However, other, more conventional risk factors do not adequately explain the increased probabilities of cardiac failure. It is possible that amyloidosis, inflammatory mediators, anti-rheumatic medication therapy, ischemic heart disease, and inflammatory mediators are the enteropathogenic pathways causing an upraise of heart failure in RA patients.[2] Systolic pump failure can result from pancarditis and small vessel vasculitis, whereas right ventricular failure can be brought on by pulmonary fibrosis. Diastolic heart failure can develop from restrictive cardiomyopathy brought on by amyloid, although overall, as in the general population, the atherosclerotic disease is more likely to cause heart failure in RA. Myocardial dysfunction symptoms, such as dyspnea, are uncommon in RA, probably as a result of decreased physical activity, whereas symptoms are non-specific. The above listed pathogenic circumstances, many of which may be aided by the RA disease process, can give rise to the CHF phenotype.

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However, very few studies have made an effort to analyze this intricate problem. Recent research has demonstrated the role that cytokine-mediated tissue inflammation, especially which of the myocardium, plays in RA symptoms, including cardiac involvements. The most recent research on this topic suggests more research be done to examine heart failure in RA patients.[3] Due to the small number of research, there is little information available on the frequency of HF in patients of Indian origin with RA. The fact that any patient with RA who is screened for heart failure by assessing Left Ventricular Function (systolic as well as diastolic) provides an excellent tool for early diagnosis of subclinical cardiac dysfunction, which assumes importance in the setting where patients are presented very late with symptoms of heart failure. Therefore, periodic cardiac function testing at regular intervals aids in minimizing RA patients' mortality and morbidity by identifying patients with LV dysfunction early and implementing early therapies and management.[4] Also, medication for RA occasionally quickens the evolution of LV dysfunction, and early identification of LV dysfunction could lead to preventable morbidity and mortality.

As reported by previous research, heart failure is one of the significant causes of death and morbidity in RA patients. Although there have been numerous studies in the past, the results have not been consistent, and prior researchers have underlined the need for more research in this area. Many of these studies evaluated an independent connection between RA and HF while not excluding conventional cardiovascular risk variables. HF in a RA patient has significant clinical and prognosis repercussions. Due to these individuals' limited mobility and potential for negative outcomes, a delayed diagnosis could result in a quiet worsening of the ailment. More information is needed about the relationship between the length and severity of RA and HF because there is currently a paucity of literature on the subject. The prevalence of RA is 0.75 percent in India, which, if applied to the entire population, would result in a total of seven million sufferers. RA and its correlations with HF were adopted as part of fewer studies on Indian patients, and data on the condition's prevalence is also inadequate. Investigations on this topic are urgently needed since they will significantly impact how RA patients are treated and monitored.

MATERIALSANDMETHODS

Study Design

After the hospital ethics committee approved the protocol, the current study was carried out in the Department of Medicine at Darbhanga Medical College and Hospital, Laheriasarai, Bihar, India. This research was cross-sectional, conducted over a period of one and a half years on consecutive rheumatoid arthritis patients who will attend medicine OPD and/or those who will be admitted to medicine IPD at Darbhanga Medical College and Hospital, Laheriasarai.

Study Samples

Regardless of the length of the illness or its severity, all individuals diagnosed with RA based on the 2010 revisions to the 1987 ACR Classification criteria and within the age range of 18 to 65 years were chosen for the study. Participants who have any of the following conditions were disqualified: cardiovascular history, particularly CAD, diabetic nephropathy, high blood pressure, endocrine conditions like Cushing's syndrome and hypothyroidism, blood Hb <10 g/dl, people with renal or hepatic impairment.

Based on the length of the sickness, participants were roughly divided into three groups:

Group A: duration < 5yrs,
Group B: duration 5-10 yrs
Group C: duration > 10 yrs

Interventions

The medical histories of the patients were carefully documented, including the length and severity of the RA, the existence of any co-morbidities, and, if any, indications of cardiovascular disease. Each patient's DAS-28 score was determined based on their subjective rating of impairment, the number of swollen/tender joints, along with their ESR. To check for any signs of heart disease, a clinical assessment was done; such as the previously stated LV S3/S4 etc., high JVP, pulmonary basal crackles, pedal edema, etc.

All patients underwent baseline examinations, which included liver and renal function tests (LFT / RFT), acute phase reactants (ESR and CRP), and haemoglobin (Hb). Patients with Hb <10 g/dl and disturbed LFT/RFT were not allowed to participate in the trial. Electrocardiogram and a chest radiograph of selected patients was acquired, and was looked for any signs of heart failure.

Following that, a 2D Echocardiography was performed on each patient by a single cardiologist who was unaware of the patient’s illness state. A Phillips iE 33 xMatrix Echocardiography equipment was used for this. Each patient's cardiac structure and function had a thorough evaluation, and the results were put into the performa.

By measuring the LV End Diastolic Diameter (LVEDD) and LV End Systolic Diameter, the M-mode Quinone's approach was used to evaluate the LV systolic function (LVESD). The LV ejection fraction (LVEF) was calculated as (LVEDD) 2 - (LVESD)2 / (LVEDD)2, and reported in percentage. The stroke volume (SV) was estimated as the difference between LVEDV and LVESV. As shown in tab. 1 (5), LVEF was further subcategorized.

Using TDI and Doppler echocardiography, transmitral flow data from the apical four-chamber/two chamber views were used to evaluate the LV diastolic function. To measure transmitral flow, the sample volume was placed at the mitral

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valve's leaflet tips. As indicators of left ventricular filling, the peak of early diastolic (E) and late (or atrial) diastolic (A) flow velocity, the E/A ratio, the deceleration time (DT), e/e', and IVRT were examined. Further evaluation of LV diastolic dysfunction is depicted in fig. 1 and tab. 2 below.

Statistical Analysis

The subjects' demographic characteristics and echo-cardiographic characteristics were summarized using descriptive statistics. Data were tallied and quantitative and qualitative demographic variables were summarized. Results are shown graphically and in tabular form. The median (with a range of the 25th to 75th percentiles) and percentage were used to express the data. For all the measurable variables, the means of the two groups were compared using the Chi-square test and Student's t-tests. For all measurable data, analysis of variance was used to compare the means of more than two groups, followed by multiple comparisons and post hoc testing. Using Pearson's coefficient of correlation, the degrees of relationship between various observable variables were computed. We used Fisher's exact test or the Chi-square test, depending on which was more appropriate, to determine the relationship between one category and the other for all the categorical/classified data. At a p-value of 0.05, differences between the groups were deemed statistically significant.

RESULTS

Baseline demographics and clinical characteristics

Participants were recruited for the study from the Department of Medicine at the Darbhanga Medical College and Hospital, Laheriasarai, over the course of an entire year and a half.

80 RA patients in all were enrolled for this trial. In the study population, there were more women (60) than men (20). The participants' average age was 42.94 years. Participants' RA lasted somewhere from 27 and 80 years [Table1]. They were divided into groups based on their length and frequency [Figure 1].

It has been found that the development of the illness and the presence of a malfunctioning LV are strongly correlated. The prevalence of LV dysfunction was found to be significantly positively correlated with the DAS-28 score by analysis utilizing the Student's t-test (p 0.0001). It is known that patients with higher DAS-28 scores are more likely to get LV dysfunction [Table2]. The relative distribution is depicted in [Figure 2]. Dyspnea was the most common sign of heart failure, which was also present in 21.25% of patients [Figure 3], along with weariness, edema, and/or abdominal distension. However, only 15% of subjects had clinical indications of HF. [Figure 4]

Additionally, it was noted that patients with LV dysfunction identified through screening are typically asymptomatic rather than symptomatic, and only a smaller proportion of patients have clinical indicators of HF.

Echocardiographic findings

Results from 2D echocardiography based on M-mode Twenty subjects were found to have LV systolic dysfunction according to Quinone's approach, with five having grade 1 LVSD with LVEF 45–54% and eleven having grade 2 LVSD having 30-44% of LVEF and four had grade-3 LVSD with 30% of LVEF [Figure 5]. 25% of the total population involved in the study was people who had LV systolic dysfunction. 20.0% was the lowest LVEF ever observed. The Chi-Square Test result in this inquiry indicated a value of 14.3617 to 3.841 with a p value0.001 which is significant when compared to the standard data set of LV Systolic Dysfunction in the general population (6%).[6]

LV diastolic dysfunction was found in 45 patients according to 2D echocardiography assessments of diastolic function, color Doppler investigations, and TDI. Fourteen patients, each of grade 1 and grade 2 LVDD, two of grade 3, and five of grade 4 LVDD [Figure 6]. 43.75% of the entire population under study was patients who had LV systolic dysfunction in some way. The Chi-Square Test produced a statistically significant value of 19.553 to 3.841 with a p-value of 0.001 based on the analysis conducted in this research of the standard data on LV Diastolic Dysfunction on the broader population (27.3%) (6) [Figure 7].

Together, the two numbers show that 42 patients (52.5%), of whom 13 had both LVSD and LVDD, i.e. LV dysfunction (figure 8). Among other findings, 08 patients exhibited mitral regurgitation (MR), 08 had concentric LVH, three had a little pericardial effusion, and one had a mild global hypokinesia of the LV.

Disease Associations

The Student's t-test was used to analyze the relationship between the participant's age and the occurrence of LV dysfunction. It was discovered that there was no correlation between age and the presence of LV dysfunction (p = 0.186). In this study, girls were more likely than males to develop the condition [Figure 9]. Additionally, as shown in figure 10, females had a substantially higher prevalence of LV dysfunction than did males (45% versus 40%). However, statistical analysis reveals that regardless of sex, the incidence of RA is about the same (45% for both), as shown in [Figure 10].

Table 1: Relationship between the duration of the disease and presence of LV dysfunction

Duration	LVDD Present	LVDD Absent	P-value
<5	5	23	0.639
5>10	15	18	
5>10	15	4	

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Table 2: Relationship between DAS-28 score and LV Function in RA Patients

DAS-28	Normal LV Function	LV Dysfunction	P- value
<3.2	9	3	0.7082
3.2>5.1	16	15	
>5.1	19	19	

Table 3: Percentage of symptomatic and asymptomatic patients with LV dysfunction in RA

Type of LV dysfunction	Symptomatic	Asymptomatic
Percentage	21.25%	78.75%

Table 4: Percentage of patients with clinical signs of HF with LV dysfunction in RA

Clinical Signs	Signs Present	Signs Absent
Percentage	15.00%	85.00%

Table 5: Frequency and classification of LVSD

Classification	Normal	LVDD Grade 1	LVDD Grade 2	LVDD Grade 3	LVDD Grade 4
Frequency	45	14	14	2	5

Table 6: Prevalence of diastolic dysfunction

Normal	LVSD Grade 1	LVSD Grade 2	LVSD Grade 3
60	5	11	4

Table 7: Frequency of LVDD

Grade	0	1	2	3	4
Frequency	45	14	14	2	5

Table 8: Presence of LV dysfunction

Type of Dysfunction	Normal	LVSD	LVDD	LVSD+LVDD
Percentage	46.25%	25%	43.75%	52.50%

Table 9: Sex distribution in RA patients

Sex	Male	Female
Distribution	45%	45%

Table 10: Prevalence of Sex distribution in RA patients with LV Dysfunction

Sex	Male	Female
Prevalence with LV Dysfunction	40%	45%

Table 11: Grading of LVEF

LVEF	Interpretation	Grade
> 55%	Normal	0
45 – 54%	Mild	1
30 – 44%	Moderate	2
< 30 %	Severe	3

Table 12: LVDD Grading

Grade	LVDD	Interpretation
0	Normal	Normaldiastolic function
1	Mild	Impairedrelaxation
2	Moderate	Pseudonormal
3	Severe	Reversiblerestrictive
4	Severe	Fixedrestrictive

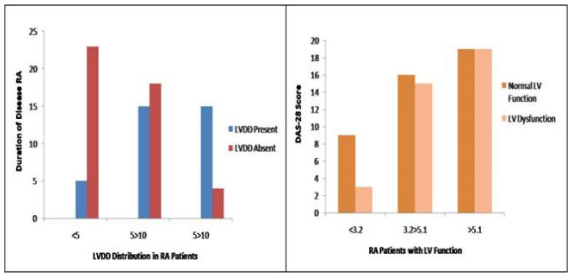

Figure 1: (a) Relationship between the duration of the disease and presence of LV dysfunction, 1(b) Correlation between DAS-28 score and LV Function in RA Patients

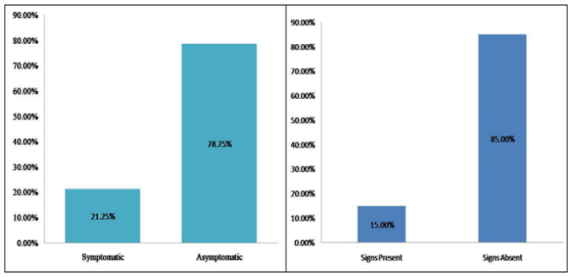

Figure 2: (a) Percentage of symptomatic and asymptomatic patients with LV dysfunction in RA, 2(b) Percentage of patients with clinical signs of HF with LV dysfunction in RA

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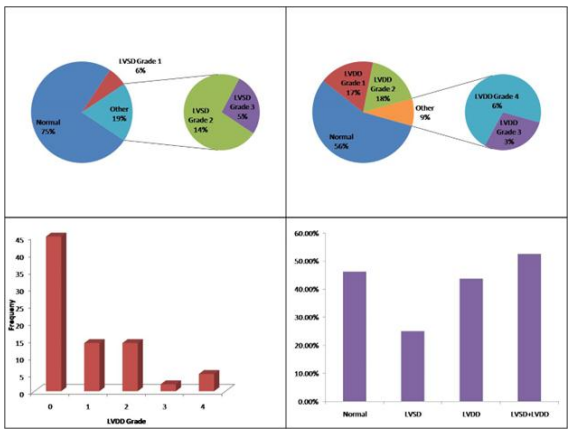

Figure 3: (a) Frequency and classification of LVSD, 3(b) Prevalence of diastolic dysfunction, 3(c) Frequency of LVDD, 3(d) Presence of LV dysfunction

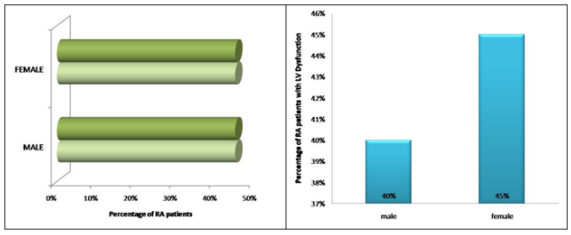

Figure 4: (a) Sex distribution in RA patients, 4(b) Prevalence of Sex distribution in RA patients with LV Dysfunction

DISCUSSION

The purpose of the current investigation was to determine the prevalence of LV Systolic dysfunction in RA patients and to determine whether there was a relationship between LV dysfunction and the severity or duration of the disease. Patients with established cardiovascular illness or risk factors were excluded from the study in an effort to establish a direct link between RA and LV dysfunction. The Anti CCP test was used to locate and confirm the RA patients. This examination searches the blood for antibodies to the CCP (cyclic citrullinated peptide). Auto-antibodies, commonly known as CCP antibodies or anti-CCP antibodies, are a class of antibody. The immune system produces proteins called antibodies and auto-antibodies. Antibodies to cyclic citrullinated proteins (anti-CCP +) are very sensitive and specific for RA diagnosis in people who have RA symptoms, although there is mounting evidence that anti-CCP+ vs. anti-CCP RA differs. Anti-CCP+RA has been linked to increased disease activity, the shared HLA-DR epitope, significantly greater cytokine levels, especially for anti-CCP+/RF+,[7] and increased mortality was reported by others including us.[8] Additionally, anti-CCP+ or RF+ are suggested by current CVD guidance as signs of increased CVD risk in RA.[9] Uncertainty persists regarding the association between anti-CCP+ and RF+ with a variety of CHD and CVD morbidity and death outcomes.

Women with RA had higher age-adjusted risks of coronary heart disease (CHD), stroke, CVD, fatal CVD, and overall mortality than women without RA, with multivariable-adjusted HR (95% CI) for CHD and fatal CVD of 1.46 (1.17, 1.83) and 2.55 (1.86, 3.51), respectively, according to a study conducted by Mackey et al. in 2015.[10] Anti-CCP+ and RF+ were not statistically associated with a higher risk of any outcomes within RA, despite a marginally elevated risk of fatal CVD and death for anti-CCP+ RA compared to anti-CCP RA. The severity of joint pain and CVD risk factors were substantially correlated with CVD risk, even in women without RA. Nearly all risk factor levels, with the exception of modest levels of joint pain or inflammation, showed an increase in CVD incidence for RA vs. no RA. Inflammation was more strongly related to total mortality and fatal CVD in RA than CHD or CVD.

Participants' profiles included a clinical assessment, baseline investigations, a chest radiograph, and an ECG. To evaluate LV function, 2D ECHO and colour Doppler investigations (with TDI) were used. In total, 80 RA patients were included in this trial. The study's participant population had 60 more women than men (20 men). The participants were 42.94 years old on average. The duration of the participants' RA ranged between 27 and 80 years. In groups, they were separated based on frequency and duration. Disease activity score (DAS) (DAS28) a total index that assesses rheumatoid arthritis patients' disease activity (RA). It has received considerable validation for use in clinical trials in conjunction with the response criteria of the European League against Rheumatism (EULAR). Participants DAS -28 scores ranged from 2.2 – 7.1. When a patient's DAS28 score is less than 2.6, they are considered to be in remission; when it is larger than 2.6 but less than 3.1, it indicates low activity; when it is greater than 3.1 but more than 5.1, it suggests moderate activity; and when it is 5.1 or more, it indicates high activity. There was a strong correlation between the existence of LV dysfunction with the duration of RA and a positive correlation with the severity of disease as measured by DAS-28 score.

According to the current study, 25% of the overall population included in the study showed LV systolic dysfunction, proving that RA patients actually have significantly higher rates of both LVSD and LVDD than the general population. LVSD typically affects 6% of the general population, but LVDD affects up to 27.3% of the population.[11] In contrast, LV dysfunction is clearly more frequent in RA patients. This discrepancy may seem significant in the context of LVSD, but it is more significant in LVDD.

Numerous early investigations have found that RA patients have a higher incidence of LVSD. According to local population forecasts, Bhatia et al,[12] compared the results of 226 RA patients with echocardiography. Systolic dysfunction (LVEF

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50%) was more common in RA patients (10.2% vs. 5.3%), however, the occurrence may have been influenced by the patients' older age relative to the general population and the lack of conventional cardiovascular risk factors. A sample of 100 RA patients and 100 matched controls revealed lower LV ejection%, according to Wislowska and colleagues.[13] Their RA sample had much more valvular heart disease than the controls (39% versus 19%), which may be related to the fact that they excluded individuals with hypertension, myocardial infarction, rheumatic fever, or a history of diabetes.

Recent research has explained and demonstrated that people with rheumatoid arthritis (RA) have a significantly increased risk for cardiovascular illness due to a chronic inflammatory state, accelerated atherosclerosis, and alterations in the left ventricular (LV) structure. People are susceptible to LV systolic dysfunction (LVSD) as a result of specific circumstances. Since there is a strong correlation between LVSD and RA, Cioffi G. and Viapiana O [14] have demonstrated in their research that over fifty percent of asymptomatic RA patients without previous signs of cardiac disease have subclinical LVSD that may be easily detected by echocardiography and TDI.

In spite of identified risk factors, the Rebecca et al.,[15] study discovered that RA patients have raised LV mass. Compared to patients with fewer symptoms and lower disease activity in the beginning phases of RA illness,[16] patients with high disease activity and elevated anti-CCP titers had worsened left ventricular dysfunction. Gloria Arminio Berlinski, MS echocardiographic data showed that RA patients had lower LV diameters and volumes, higher relative wall thickness and mass, and more concentric remodeling and hypertrophy than matched control patients. After stress reduction, they also experienced decreased mid-wall shortening. RA patients had significantly higher rates of aberrant stress-corrected mid-wall shortening than comparable control patients (56% versus 15%; P=0.001). A higher incidence of LVSD is seen in RA patients compared to the general population, as seen by the incidence of impaired LV ejection fraction, which is considered low if it is below 50%. This prevalence was equal in study patients (3%) and control patients (1%). Multiple logistic regression analyses revealed a link between RA and LVSD. According to past analyses, there is conflicting evidence tying RA and LVDD together. Diastolic dysfunction was found to be more common in RA individuals than in the general population in a study by Kimberly P. Liang et al,[17] with a prevalence of 31% as compared to 26% (age and sex adjusted) in non-RA subjects. Additionally, they found that the duration of the RA and the interleukin 6 (IL-6) levels persisted even after adjusting for cardiovascular risk factors. Furthermore, they found that the severity of the RA and the interleukin 6 (IL-6) levels continued to be independently correlated with diastolic dysfunction in RA even after correcting for cardiovascular risk factors.

According to studies parallel to us, pancarditis and vasculitis are primarily to blame for the increased prevalence of LVSD in RA patients, which ultimately increases mortality and morbidity. Additionally, the presence of isolated or diastolic dysfunction with preserved EF has been linked to a significant rise in mortality in the general population.[18,19] Diastolic dysfunctions in RA could result from a number of reasons. In individuals with collagen diseases, including RA, fibrous heart muscle scarring, myocardial infarcts, localised inflammation, and vasculitis have been observed.[20] There have also been reports of other lesions in RA patients, including nodular granulomatous lesions,[21] myocarditis,[22] and arteritis.[23] Another potential contributing element to the pathophysiology of the disease's diastolic dysfunction is amyloidosis.[24] In addition to systolic dysfunction, all of these factors may have a role in the impairment of left ventricular diastolic function in RA patients.

According to current guidelines and standard practice for RA patients, echocardiography is only used to check for evidence of LV dysfunction in RA patients when they exhibit symptoms or signs of HF or other cardiac co-morbidities. In RA patients who are asymptomatic or subclinical, our study unequivocally demonstrates a significant frequency and prevalence of LV systolic dysfunction as well as diastolic dysfunction, with a higher degree of suspicion for those who have a longer course of the disease or higher DAS-28 scores. Therefore, developing a methodology for early and routine checking for LV dysfunction using 2D ECHO, Color Doppler, and TDI tests will lead to an early, rapid diagnosis and the right kind of HF treatment, greatly reducing mortality and morbidity.

CONCLUSION

In the current investigation, it was discovered that 25% of RA patients had LV Systolic Dysfunction. A prevalence of LVDD was discovered in 43.75% of patients, and a total of 52.5% of patients had LV dysfunction. In the current study, the lowest LVEF ever recorded was 20.0%. The investigation that was conducted revealed that the prevalence of LVSD (25%) is about four times greater than the general population's (6%). RA patients have a considerably greater prevalence of LVDD (43.75%) than the overall population (27.3%). Because patients with a history of cardiovascular disease were not included in the trial, this connection is unrelated to other established cardiovascular risk factors. Most LV dysfunction cases in RA are asymptomatic (78.75%) and those without signs (85%). LV dysfunction is prevalent in RA patients regardless of age or gender (45% in both males and females). There is a significantly substantial correlation between the

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length of RA and the existence of LV dysfunction. There is also a strong correlation between LV dysfunction and the severity of RA.

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