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ORIGINAL ARTICLE

Evaluation, Comparison and Correlation of the Disease Activity and Damage Index among Patients of SLE with Healthy Controls through Echocardiography

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ABSTRACT

OBJECTIVE: To assess and compare echocardiographic findings in SLE patients with healthy controls and their correlation with disease activity and damage index.
METHODOLOGY: This cross-sectional study was undertaken in the Department of Medicine, Civil Hospital Karachi, an affiliated Dow University of Health Sciences (DUHS) Karachi, Pakistan, from January to July 2023. Forty-one patients with SLE and Thirty-nine healthy controls were enrolled, undergoing echocardiographic analysis for cardiovascular complications with the clinical and biochemical profile. Statistical differences among groups were assessed using the Chi-square test for qualitative variables and the independent sample *t*-test for quantitative variables. The correlation between disease severity and cardiovascular events was determined by Pearson correlation. $P \leq 0.05$ was measured as statistically significant.
RESULTS: The most joint valvular abnormality was mitral regurgitation (48.7%), then tricuspid regurgitation (21.9%), aortic regurgitation (17.7%), mitral stenosis (2.4%) and mitral valve prolapse (4.8%) in SLE, Left ventricular internal diameter end diastole [p 0.001], Intraventricular septal wall thickness, and end-diastolic left ventricular internal diameter end-systole [p 0.002] were found statistically significant among the groups. Left ventricular posterior wall end-diastole [$p < 0.00001$] and pulmonary artery systolic pressure [$p < 0.00001$] were also substantial among groups. Lupus nephritis positively correlated to ejection fraction (r=0.00013, p 0.56).
CONCLUSION: Cardiovascular complications and valvular and structural echocardiographic findings are frequently reported in SLE. SLE severity is related to echocardiographic changes, and SLE with secondary Antiphospholipid syndrome (APS) significantly affects renal, haematological, and echocardiographic parameters.
Keywords: SLE, Echocardiography, Valvular heart diseases, lupus nephritis, Antiphospholipid syndrome, Systemic lupus erythematosus

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease typified by multisystem inflammation[1]. In addition to affecting several organ systems, cardiovascular involvement in SLE causes significant morbidity and a higher chance of mortality[2]. These cardiovascular complications happen even more frequently later in the illness without active SLE[3]. Cardiovascular events affect SLE patients more regularly than the age and gender-matched general population[4]. Earlier data have shown race disparity, with a 19-fold more significant burden of cardiovascular disease among White lupus patients when compared with Black lupus patients[5].

There are various cardiovascular complications like pericarditis, heart failure, myocarditis, valvular heart diseases, cerebrovascular accidents, pulmonary embolism, Libman-Sacks endocarditis, etc, have been described in patients with SLE. Coronary vasculitis, Ischemic coronary disease and pulmonary Hypertension resulting in angina pectoris or myocardial infarction can manifest slowly as atypical anginal counterparts[6,7]. Even after modifying the classic Framingham cardiovascular risk variables, SLE remains one of the most vital known risk factors for cardiovascular events despite improvements in the diagnosis and therapy of SLE[8]. The 15,000 incident SLE patients in the **Li et al.** [9] **s**tudy showed a higher risk of all-cause death and cardiovascular events when compared between mild and severe SLE (HR of 3.11 (95% CI: 2.49, 3.89 for mortality). Transthoracic echocardiography has shown its usefulness in detecting acute cardiovascular manifestations related to SLE[10]. Furthermore, echocardiography has the extra benefits of being non-invasive and without radiation, as well as being practical and convenient.

Although exact epidemiological data on SLE is scarce in Pakistan, a recent study highlighting the epidemiology of SLE in Asia has shown a high incidence (30-50 per 10,0000) of SLE in Pakistan, Iran, and China[12]. Considering the rising incidence of SLE in Pakistan and reported high mortality due to cardiovascular complications of SLE the world over, early detection of cardiovascular events in SLE through transthoracic echocardiography would be of paramount importance. The study aimed to assess and compare echocardiographic findings in patients with SLE with those with healthy controls and correlate the findings with disease activity and damage index of SLE.

METHODOLOGY

It was a cross-sectional study undertaken in the Department of Medicine, Civil Hospital Karachi, an affiliated hospital of Dow University of Health Sciences (DUHS) Karachi, Pakistan, from January – July 2023, after seeking permission from the institution's review board for the ethics. For the consecutive, systematic sampling technique, we used OpenEpi version 3.01 and the sample size calculation for cohort, cross-sectional, and randomized control trials to determine the sample size for this investigation while maintaining CI at 95%, power at 80%, and an equal group ratio. The number of samples found was 38. These results assume that the population proportion under the null hypothesis (P0) is 0.5.

Forty-one Patients with a confirmed diagnosis of SLE and Thirty-nine healthy controls were enrolled and underwent echocardiographic analysis. Patients of SLE having potential cardiovascular symptoms (breathlessness, syncope, palpitations and chest pain); clinical suspicion for endocarditis and valvular heart disease) and in case of a history of recent stroke for the assessment of the cardiac source of embolism will be assessed for echocardiography. Patients with prior cardiac surgery, valvular heart disease, pericarditis, endocarditis, symptomatic heart failure, acute coronary symptoms determined by initial echocardiography and symptoms related to acute coronary events were excluded.

SLE was diagnosed following the classification criteria put by the 2012 American College of Rheumatology (ACR)/Systemic Lupus International Collaborating Clinics (SLICC)[13].

The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) was used to measure the disease activity of SLE; a score of > 6 indicated active illness. The SLICC damage index (SLICC DI) was utilized to evaluate the extent of illness damage[14].

Echocardiography was executed in all enrolled patients using 2D-transthoracic echocardiography (TTE), where the left ventricular dimensions, left atrial volumes and dimensions, LV dimensions, and ejection fraction (EF), the pulmonary artery systolic pressure, abnormalities of the resting wall motion, the presence and severity of valvular regurgitation, along with diastolic function and pericardial effusion were looked for. The above parameters were carried out following the published guidelines given by the American society of echocardiography[15].

All clinical information related to SLE, like duration, systemic manifestations, coexisting morbidities and cardiovascular-related risk factors like diabetes mellitus, obesity, Hypertension, hyperlipidaemia, and smoking, as well as a family history of early coronary artery disease, was sought. Demographic information like gender, age, weight, height, pulse, and systolic and diastolic blood pressures were essentially pursued. Haematological indices (Complete blood count (CBC), erythrocyte sedimentation rate (ESR), inflammatory marker (CRP concentrations (>6 mg/l are labelled positive), serum complement 3 (C3) and 4 (C4), immunological assay (antinuclear antibody (ANA) and anti-ds DNA, urinalysis), and 24-hour urinary proteins were all done. X-ray chest PA view and an ECG were performed whenever needed.

The SPSS software program version 22.0 (IBM, Chicago, IL, USA) was employed for the statistical analyses. Continuous variables across patients and healthy controls were compared using the T-test for normally distributed data and the Mann-Whitney test for skewed data. Mean and standard deviation were used for normally distributed continuous variables, whereas the median and interquartile range were calculated for continuous variables that are non-normally distributed. The Pearson chi-square test was employed to compare counts and percentages of categorical data. The correlation between disease severity and cardiovascular events was determined by Pearson correlation.

RESULTS

The SLE patients had a mean age of 30.4±4.6 years, whereas controls were 32.1±5.2 years. The BMI in SLE patients and controls were calculated as 21.4±0.4 and 21.0±0.5 Kg/m^2, respectively. The statistical variance was not found when patients with SLE and healthy controls were compared. The heart rates of SLE patients and healthy controls were 82± 12 and 86±14 beats/minute, respectively, with no statistical difference (p = 0.927). Both systolic as well as diastolic blood pressures of patients with SLE were 126.6±12.72 and76±5 whereas healthy controls had 117.1±11.9 and 73±6 mm of Hg with statistical significance on comparison (p=0.007 and 0.003) [**Table I**].

Table I: Baseline characteristics of the study population

Variables	SLE (N=41)	Healthy controls (n= 38)	P value
Demographic			
Age	30.4±4.6	32.1±5.2	0.295
Female	41 (100)	38 (100)	NA
BMI Kg/m^2	21.4±0.4	21.0±0.5	NS
Cardiovascular			
Systolic BP, mmHg	126.6±12.72	117.1±11.9	.0007
Diastolic BP, mmHg	76±5	73±6	0.003
Harte Rate, bmp	82±12	86±14	0.927

The most common clinical manifestations in patients with SLE were arthritis (26%) followed by photosensitivity (25%), renal (23%), oral ulcers (22%) and dyspnoea (20%) [**Table II**].

Table II: Baseline clinical characteristics of patients with SLE

Variable - n (%) or mean ± SD (range)	SLE patients (n=41)
Clinical characteristics	
Photosensitivity	25(62%)
Malar rash	21 (59%)
Discoid rash	02(4.8%)
Oral ulcers	22(54%)
Arthritis	26(63.4%)
Haematological	05(12.1%)
Neurological	04(9.7%)
Renal	23(29.9%)
Palpitation	05(12.1%)
Dyspnoea	20(49%)
Fever	11(26.8%)
Alopecia	08(19.5%)
Myositis	07(18%)
Serositis	08(19.5%)
SLE related Cardiovascular factors	
Hypertension	4 (10.0%)
Diabetes mellitus	7 (17.0%)
H/O of DVT	13(31.7%)
H/o prior IE	02 (4.8%)
SLE related Autoantibodies	
Positive antinuclear antibody (%)	39(95%)
Positive anti-double-stranded DNA (%)	23(56%)
Positive anti-Smith antibody (%)	12 (29.2%)
Positive U1-small nuclear ribonucleoprotein (%)	08(19.5%)
Positive antiphospholipid antibodies (%)	
Laboratory investigations	
Haemoglobin (g/dl)	10.5± 1.9
TLC	6.2±3.2
Platelets	194±82
ESR (mm/1st h)	71±31
CRP (mg/L)	27.4±13.2
Creatinine clearance(ml/min)	59±16
SLE Severity index	
SLEDAI Score	14.1±8.3
SLICC DI	0.9± 0.7

Other clinical manifestations such as fever. Alopecia, serositis, myositis, and palpitations beheld even lesser presentations. Hypertension (10%), diabetes (17%), hypercholesterolemia (32.5%), prior history of infective endocarditis (4.8%) and deep venous thrombosis (31%) were the cardiovascular-related comorbidities in patients with SLE. SLE related autoimmune markers that

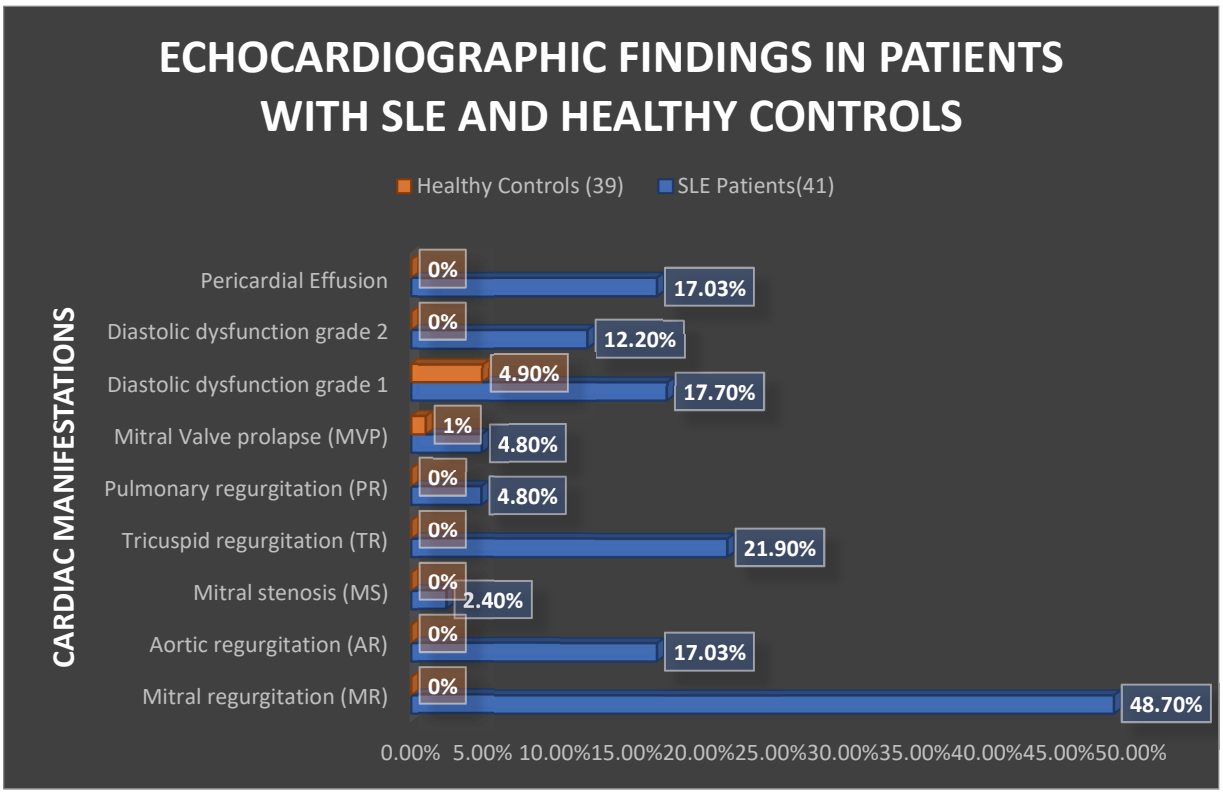
are various antibodies such as antinuclear antibody was positive in 91%, anti- double-stranded DNA antibody 56%, anti-Smith antibody 29.1 %, U1-small nuclear ribonucleoprotein (23.5%) and antiphospholipid antibodies in (19.5%) of the patients. Laboratory parameters upon investigation are shown in **Table II**. SLE severity assessment scores like SLEDAI and SLICC DI were found (0.9± 0.7) and (14.1±8.3), respectively, in patients with SLE.

Among patients with SLE, the most common valvular abnormality was mitral regurgitation (48.7%), followed by tricuspid regurgitation (21.9%), aortic regurgitation (17.7%), mitral stenosis (2.4%) and mitral valve prolapse (4.8%) [**Figure 1**]

Patients with SLE had 17.7% grade 1 and 12.19 % grade 2 diastolic dysfunctions. Whereas only two healthy controls had grade 1 diastolic dysfunction [**Figure 1**]

Pericardial effusion was present in only 17% of patients with SLE [**Figure 1**].

Figure I:



LVIDD Left ventricular internal diameter end diastole, LVISD Left ventricular internal diameter end-systole, EF Ejection fraction, IVSTD intraventricular septal wall thickness; end-diastolic, LVPWd Left ventricular posterior wall end diastole, E-wave mitral peak velocity of early filling, A-wave mitral peak velocity of late filling, PASP Pulmonary artery systolic pressure.

Various echocardiographic parameters were compared among patients with SLE and healthy controls [**Table III**]

Table III: Echocardiographic parameters among patients with SLE and healthy control

Variables	SLE group (n = 41)	Healthy controls (n = 38)	P-value
LVIDD	43.5±4.1	41.1±3.7	0.001
LVISD	24.4±3.2	23.6±2.5	.732
EF	60.1±2.5	60.5±2.0	.097
IVSTd	8.6±1.1	7.5±1.3	.002
LVPWd	7.2±0.9	6.1± 1	< .00001
E wave velocity m/s	0.75±0.2	0.66±0.14	.0128
A-wave m/s	0.69±0.21	0.51±0.13	.0005
E/A	1.22±0.42	1.42±0.66	.0941
PASP/RVSP mm Hg	32.5±4.2	22.5±2.8	< .00001

Table IV: Correlation of valvular and Echocardiographic parameters with clinical features and severity of SLE

Parameters	Valvular lesions			Ejection fraction, chamber dimensions and pressure			Pericardial involvement
	MR	TR	AR	LVDD	PASP	EF %	PE
SLE clinical parameters							
Oral ulcers	0.29 (-0.167)	0.95 (0.011)	0.08 (0.275)	0.71(0.06)	0.23(0.19)	0.06(-0.28)	0.54(-0.098)
Malar rash	0.21 (-0.198)	0.80 (0.040)	0.052 (0.31)	0.93(-0.02)	0.15(0.23)	0.29(-0.16)	0.64(-0.075)
Discoid rash	0.52 (-0.103)	0.46 (0.118)	0.52 (0.103)	0.37(-0.15)	0.94(0.01)	0.72(0.05)	0.53(-0.102)
Photosensitivity	0.64 (-0.075)	0.84 (0.033)	0.25 (0.185)	0.64(0.075)	0.67(0.07)	0.22(-0.19)	0.29(-0.168)
Lupus nephritis	0.39 (-0.137)	0.45 (0.314)	0.62 (-0.08)	0.86(0.029)	0.54(0.09)	0.00(0.56)	0.11(-0.251)
SLE Severity and damage							
SLEADI	0.93(0.013)	0.27(-0.177)	0.44(0.123)	0.77(-0.05)	0.95(-0.01)	0.43(0.128)	< .00001(0.64)
SLICC DI	0.08(0.272)	0.45(0.120)	0.21(0.198)	< .00001(0.7)	0.73(0.06)	0.46(0.119)	0.51(0.107)

MR Mitral regurgitation, TR Tricuspid regurgitation, AR Aortic regurgitation, LVDD Left ventricular diameter end diastole, PSAP Pulmonary artery systolic pressure, EF Ejection fraction, PE Pericardial effusion.

Left ventricular internal diameter end diastole (LVIDD) was 43.5±4.1 and 41.1±3.7 mm in SLE patients and healthy controls, respectively, and when compared, was found statistically significant (p 0.001). However, left ventricular internal diameter end-systole (LVISD) was 24.4± 3.2 and 23.6±2.5 mm in patients having SLE along with healthy controls, respectively and remained insignificant statistically when compared (p .732). Intraventricular septal wall thickness; end-diastolic left ventricular internal diameter end-systole (LVISD) was 8.6±1.1 and 7.5±1.3 mm in patients having SLE along with healthy controls, respectively and remained statistically significant when compared (p 0.002) [**Table IV**]. Left ventricular posterior wall end diastole (LVPWd) was 7.2±0.9 and 6.1±1 mm in patients having SLE along with healthy controls, respectively and remained statistically significant when compared (p < .00001) [**Table III**]. Ejection fraction was 60.1±2.5 and 60.5±2.0% in patients having SLE along with healthy controls, respectively and remained insignificant statistically when compared (p .097). E (wave mitral peak velocity of early filling), A-wave mitral peak velocity of late filling ratio E/A was 1.22±0.42 and 1.42±0.66 in patients having SLE along with healthy controls, respectively and remained statistically significant when compared (p .0941) [**Table III**]

Pulmonary artery systolic pressure (PASP) was 32.5±4.2 and 22.5±2.8 in patients having SLE along with healthy controls, respectively, and remained statistically significant when compared among groups (< .00001) [**Table III**].

Various clinical parameters of SLE were correlated with cardiac manifestations (valvular lesions, EF and pericardial) in [**Table IV**]. Among clinical parameters, only lupus nephritis was positively correlated to EF (r=0.00013, p 0.56). At the same time, SLE severity and damage score SLICC DI were positively correlated with LVDD (r=.00001, p 0.77) [**Table IV**].

DISCUSSION

Systemic lupus erythematosus is one of the most noteworthy autoimmune diseases with varying incidence, prevalence and disease activity[16]. The current study has no significant hypertension in patients with SLE when drawn compared with the healthy controls. While **Zhang et al.**[17] showed significantly higher diastolic and systolic blood pressure in patients with SLE compares to healthy controls. Patients with SLE in the current study had various comorbidities like Hypertension, diabetes, hypercholesterolemia, prior history of infective endocarditis and deep venous thrombosis. **Zhang et al.** [17] have also shown similar cardiovascular-related comorbidities in their study. The current study had autoimmune markers like antinuclear antibody (91%), anti-double-stranded DNA antibody (56%), anti-Smith antibody (29.1%), U1-small nuclear ribonucleoprotein (23.5%) among patients with SLE. Earlier studies[17,18] have shown ANA (100%, 80.0%), anti-ds DNA (42%, 56.0%), anti-Smith antibody (38.9%, 50%), U1-small nuclear ribonucleoprotein (23.5, 48%) respectively in patients with SLE.

A current study has shown 19.5 % antiphospholipid syndrome (APS) in patients with SLE, whereas an earlier study[19] has shown 30-40% APS in patients with SLE. **Zhang et al**[17] have also demonstrated 17.3% APLA positivity in their patients of SLE. Among patients with SLE, the most common valvular abnormality was mitral regurgitation (48.7%), followed by tricuspid regurgitation (21.9%), aortic regurgitation (17.7%), mitral stenosis (2.4%) and mitral valve prolapse (4.8%).

Mohammed AG et al. [20] showed MR of (32%), pericardial effusion (32%), AR (10%) and TR (20%), whereas 22% of patients with SLE had LVH and 8% of these patients had left ventricular diastolic dysfunction. **Shazzad MN et al.**[21] have shown in their patients with SLE, MR (8%), AR (12%) and pericardial effusion (20%). **Bourré-Tessier J et al**.[22] have shown MR (26%), AR (3.7%) and pericardial effusion (4.6%) in SLE patients. Various earlier studies have also shown similar patterns of valvular lesions and pericardial effusion among the patients of SLE[23,24]. Earlier studies[20,25] have also demonstrated the pre-dilection of MR and TR in patients with SLE, which is similar to the current research. However, **M. Hojnik et al.** [26] and **P. Leszczyński et al.**[27] contrasted our research where the aortic valve was most affected after MR.

Among various echocardiographic parameters in the current study, LVIDD, IVSTd, LVPWd and PASP/RVSP were found statistically significant when compared between SLE patients and healthy controls (p 0.001, 0.002, < 0.0001 & < 0.001 correspondingly). **Zhang et al**. [17] have shown similar results to the current study where on comparison among SLE patients with healthy controls IVSTd, LVPWd and PASP were found significant over statistical analysis ($p < 0.001$, < 0.001, and < 0.001 respectively**). P. Leszczyński et al.** [27] have also shown similar results to the current study where on comparison of SLE patients with healthy controls IVSTd, LVPWd and PASP were statistically observed significant ($p < 0.05$, < 0.01, and < 0.001 respectively). However, **P. Leszczyński et al**. [27] have also shown posterior wall end-systolic thickness (mm) and E/E' ratio statistically significant when compared between SLE patients and controls. Similarly, **Zhang et al.** [17] showed LVISD and EF statistically significant when compared between SLE patients and controls.

This study has shown positive correlation of lupus nephritis to EF and SLE severity damage score (SLICC DI) to LVDD, similar to an earlier study[28]. **Maha et al.**[28] have also shown a positive correlation with LVDD.

The renal parameters among patients with SLE with and without APS were to be significant in this study. **Maha et al.** [28] have also shown similar results. **Abdelrahman W et al.**[29] have

demonstrated cardiac and neurological parameters to be significant compared to patients with SLE with and without APS. **Nam et al.**[30] have shown SLICC/ACR damage index, immunological disorders and APS antibodies to be significant compared to patients with SLE with and without APS. This study has shown APS antibodies to be significant among patients with SLE with or without APS. Earlier studies[28,30] have also demonstrated similar results to the current research. Among various echocardiographic parameters, only EF (in correlation to lupus nephritis) was found to be significant (r=0.00013, p 0.56) when compared in patients with SLE with and without APS in this study.

CONCLUSION

In this study, various parameters of patients having SLE were compared with healthy controls where among structural echocardiographic findings, left ventricular internal diameter end diastole, intraventricular septal wall thickness, end-diastolic left ventricular internal diameter end-systole and left ventricular posterior wall end-diastole were statistically significant in patients with SLE. Pulmonary artery systolic pressure (PASP) was found statistically substantial while EF was noticeably significant (in correlation with lupus nephritis) compared to patients with SLE with and without APS in a subgroup analysis only in contrast to the healthy controls. Among various clinical parameters, renal involvement in SLE patients with and without APS was also statistically significant, meriting areas of possibility in terms of diagnosis and management.

LIST OF ABBREVIATIONS

APS	Antiphospholipid syndrome
ACR	American College of Rheumatology
ANA	Antinuclear antibody
APLA	Anti phospholipid antibody
Anti ds DNA	Anti- double stranded deoxyribonucleic acid
Anti SM	Anti smith
AR	Aortic regurgitation
BMI	Body mass index
BP	Blood pressure
CBC	Complete blood count
CRP	C reactive protein
C 3	Complement 3
C 4	Complement 4
EF	Ejection fraction
HR	Hazard ratio
IVSWT	Interventricular septal wall thickness
LVIDD	Left ventricular internal diameter end diastole
LVISD	left ventricular internal diameter end systole
(LVPWd)	Left ventricular posterior wall end diastole

Ethical permission: Dow University of Health Sciences, Karachi, Pakistan IRB letter No. IRB/2759/DUHS/Approval/2022/19.
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Data Sharing Statement: The corresponding author can provide the data proving the findings of this study on request. Privacy or ethical restrictions bound us from sharing the data publicly.

AUTHOR CONTRIBUTION

Kashif SM: Study design, concept, drafting, data interpretation
Naqvi IH: Study concept, data analysis
Alam MT: Data interpretation, drafting
Imam B: Study concept, drafting, quastionaire design
Khan M: Data analysis, interpretation, drafting
Kumar D: Data collection, literature research

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