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Research Article

The Predictive Role of Strain Parameters in Predicting All-Cause Mortality in Diabetic Hypertensive Patients with Normal Left Ventricular Systolic Function in Long-Term Follow-up

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Objective: To demonstrate the relationship of all-cause mortality in the long term and speckle-tracking echocardiography parameters in a cohort of diabetic hypertensive cases that had preserved left ventricle ejection fraction (LV-EF).

Methods: The study included 141 diabetic hypertensive cases with preserved LV-EF were retrospectively analyzed. After applying exclusion criteria, 121 patients were included. Two groups were formed according to out-of-hospital mortality status. Laboratory and echocardiography data were analyzed.

Results: The mean age of the 121 patients was 58.4±8.04 years, and the median follow-up duration was 10.08 years. Echocardiographic left atrial strain parameters, namely left atrium reservoir phase strain (35.7±8.7 vs 29.8±7.3, p-value: 0.047), left atrium conduit phase strain (LAScd%) (17.6±5.8 vs 13.3±4.1, p-value: 0.028), and left atrium reservoir phase peak strain (1.5±0.4 vs 1.22±0.3, p-value: 0.037), were worse in the mortality group. In right ventricular strain evaluation, four-chamber right ventricular strain (RV4CSL%) (26.1±5.4 vs. 20.8±6.2, p-value: 0.005) was also worse in the mortality group. Multivariate analysis revealed that the mean daytime systolic blood pressure (odds ratio [OR]: 1.769, p-value: 0.028), LAScd% (OR: 0.820, p-value: 0.015), RV4CSL% (OR: 0.078, p-value: 0.043) independently predicted mortality. Kaplan-Meier analysis showed that LAScd%≤15.3 and RV4CSL%≤24.8 were predictive of mortality (p-values: 0.023 and 0.016, respectively).

Conclusion: Strain parameters, assessed via echocardiography, can be useful diagnostic and follow-up tools for determining prognosis and guiding early risk factor management in diabetic hypertensive patients, especially in comparison to traditional volumetric parameters.

Keywords: Hypertension, Diabetes mellitus, Strain parameters, Preserved ejection fraction, Mortality

1. INTRODUCTION

The rising prevalence of type 2 diabetes mellitus is concerning.[1] Diabetes mellitus places a significant burden on society due to high healthcare costs and poor patient outcomes.[2] Cardiac dysfunction in diabetes mellitus is often clinically silent, with many patients remaining asymptomatic until later stages of the disease. Even among asymptomatic, normotensive, and well-controlled diabetic cases, it is estimated that around 50% have some degree of cardiac dysfunction.[3] Another well-known risk factor for adverse cardiovascular events is hypertension, which has a high global prevalence. Over time, hypertension results in structural cardiac alterations, including left ventricular hypertrophy, myocardial fibrosis, and ventricular dysfunction. Echocardiography is a valuable diagnostic and follow-up tool in diagnosing and monitoring the end-organ damage caused by diabetes mellitus and hypertension.[4]

Speckle-tracking echocardiography is a sensitive modality for non-invasively detecting early regional and global myocardial dysfunction that cannot be identified using conventional 2D echocardiographic imaging.[5]

In the current study, we sought to explore the predictive role of myocardial strain values in determining all-cause long-term mortality in

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diabetic hypertensive cases that had preserved systolic function of the left ventricle.

2. MATERIAL AND METHODS

The study was approved by the Ethics Committee of SBÜ Trabzon Faculty of Medicine (31.05.2023/10496660-27) in accordance with the Declaration of Helsinki. Informed consent was obtained from all patients'.

This retrospectively designed, single-center, cohort study included a patient population derived from a previous study.[6] Mortality data were obtained from the Medula system, and the relationship between speckle-tracking echocardiography data and mortality was analyzed. The study included diabetic hypertensive patients who consecutively underwent strain evaluation between August 2012 and July 2013**.**

2.1. Study population

Patients who had been receiving treatment for hypertension and diabetes for at least one year were selected. After excluding patients with secondary hypertension, those with a systolic/diastolic blood pressure of >130/80 mmHg were evaluated. Further excluded from the study were patients with echocardiographic wall motion abnormalities (regional or global), left ventricular ejection fraction (LV-EF) < 50%, coronary artery disease causing significant stenosis, ongoing anginal complaints or positive stress tests, chronic liver and kidney disease, malignant arrhythmia, atrial fibrillation, high-grade heart block, valve disease (moderate and above), history of ischemic or hemorrhagic stroke, or sleep apnea. Lastly, 20 patients who were non-compliant with ambulatory blood pressure monitoring (ABPM) readings and/or had poor echocardiographic images were excluded. As a result, the sample consisted of 121 patients.

Demographic and clinical information of the patients were obtained when they first applied to the hospital. We examined fasting glucose, lipid markers, creatinine, and HbA1c levels. The calculation of the glomerular filtration rate was undertaken using the Modification of Diet in Renal Disease formula. Body mass index was determined by dividing weight in kg by height in square meters, and body surface area was obtained as follows: $(\text{weight}^{0.425} \times \text{height}^{0.725}) \times 0.007184$. All patients underwent 24-hour ABPM and echocardiography.

2.2. ABPM

We used the Agilis-CDABPM (ELA Medical, France, 2002) device for 24-hour ABPM. We recorded blood pressure at 15-minute intervals during the day and at 30-minute intervals at night. Readings were considered valid if ≥80% of measurements were recorded. In addition, at least 14 daytime measurements and at least seven nighttime measurements were required for analysis. The patients' reported wake and sleep times were individually corrected.

2.3. Echocardiography

The echocardiographic examination did perform with the Philips IE33 system (Philips Medical Systems, Andover, MA, USA). Data acquisition completed by a 5-1 MHz sector transducer. Strain imaging was undertaken using EchoPAC™ software, version 108.1.12 (GE Medical Systems, Horten, Norway). Four-chamber right ventricular strain analysis (RV4CSL) was performed by manually adjusting boundaries of the right ventricle using the four-chamber apical view, with the software automatically detecting and adjusting the contour. Measurements were averaged from six segments (three from the septum and three from the free wall). Right ventricular strain measurements were taken during maximum ventricular contraction (right ventricular peak systolic strain). Left atrial strain was similarly analyzed using automated contours in the apical four-chamber view, with manual adjustments made to optimize the imaging. Six automatically separated segments were evaluated. The wall thickness was adjusted to 2–3 mm. The imaging was optimized with manual adjustments, starting from the mitral valve annulus and progressing along the endocardial border of the left atrium lateral wall, the left atrium roof, and the left atrium septum wall, and ending at the opposite tricuspid annulus to avoid including the pericardium. Segments that did not

allow for visualization of atrial wall motion were excluded from the analysis through manual manipulations. End diastole was defined as the beginning of the cardiac cycle for left atrial strain, marked by the R wave on the electrocardiogram. Strain parameters were measured across different cardiac phases (LASr: reservoir phase strain, LAScd: conduit phase strain, LASct: contraction phase strain, pLASRr: reservoir phase peak strain rate, pLASRcd: conduit phase peak strain rate, and pLASRct: contraction peak strain rate). All echocardiograms were measured and evaluated by a cardiologist blinded to the patients' conditions, according to the guidelines set out by the American Society of Echocardiography and the European Association of Cardiovascular Imaging[7].

2.4. Statistical analysis

Data were analyzed using SPSS software (Version 23.0, SPSS, Inc., Chicago, IL). The normality of the data distribution was assessed using visual and analytical (Kolmogorov-Smirnov) methods. Levene's test was used to test homogeneity of variances. Continuous variables were presented as mean ± standard deviation, and categorical variables as percentages. The chi-square or Fisher's exact test (when the chi-square test did not meet assumptions due to expected low cell counts) was used to compare categorical groups. Normally distributed parameters were assessed using a two-tailed Student's t-test, while the Mann-Whitney U test was used for continuous variables that were not normally distributed. A p-value of <0.05 was considered statistically significant.

Parameters showing statistically significant differences between the mortality and non-mortality groups (Table 1) were first evaluated using univariate Cox regression analysis. Parameters that remained significant in univariate Cox regression were further examined using multivariate Cox regression analysis. Sensitivity and specificity of parameters independently associated with cardiovascular mortality were evaluated using receiver operator curve (ROC) analysis. After ROC analysis, Kaplan-Maier plots were created using the cross-sectional values of variables with the highest sensitivity and specificity.

3. RESULTS

The mean age of the 121 patients was 58.4 ± 8.04 years, and the median follow-up duration was 10.08 years. Concerning demographic characteristics, the mortality group had statistically higher values for age (57.2 ± 7.7 vs. 64.2 ± 6.9 years, p-value: 0.001), diabetes mellitus duration (6.4 ± 5.1 vs. 9.2 ± 7.2 years, p-value: 0.041), and hypertension duration (6.48 ± 5.1 vs. 10.5 ± 9.1 years, p-value: 0.003). All systolic blood pressure (SBP) parameters showed significantly elevated values in the mortality group, while the remaining baseline characteristics did not statistically significantly differ (Table 1). A higher rate of patients in the mortality group used calcium channel blockers [26 (26%) vs. 12 (57%), p-value: 0.005]. Laboratory parameters were not significantly different between the mortality and non-mortality groups (Table 2).

Table 1.

Demographic characteristics

	Mortality (-) (n = 100)	**Mortality (+) (n = 21)**	**p value**
Gender (male), n (%)	42 (42)	7 (33.3)	0.315
Age (years)	57.2 ± 7.7	64.2 ± 6.9	<0.001
Hyperlipidemia, n (%)	53 (53)	10 (47.6)	0.417
Current smoking, n (%)	89(89)	17 (81)	0.246
Previous MI, n (%)	5 (5)	2 (9.5)	0.350
Prior CAD, n (%)	25 (25)	7 (33.3)	0.296
Previous PCI, n (%)	18(18)	7 (33.3)	0.103
BMI kg/m^2	32.7 ± 5.1	33.2 ± 5.1	0.705

Table 1. (Continued)

DM duration (years)	6.4 ± 5.1	9.2 ± 7.2	0.041
HT duration (years)	6.48 ± 4.6	10.5 ± 9.1	0.003
Average SBP (mmHg) (Dt)	138.2 ± 17.2	155.5 ± 8.6	<0.001
Average DBP (mmHg) (Dt)	78.4 ± 9.7	82.6 ± 5.5	0.115
Average SBP (mmHg) (Nt)	134.1 ± 19.1	151.5 ± 17.4	0.001
Average DBP (mmHg) (Nt)	72.7 ± 10.4	78.2 ± 10.1	0.060
Office SBP (mmHg)	147.1 ± 14.4	156.4 ±1 2.6	0.031
Office DBP (mmHg)	89.6 ± 11.8	93 ± 10.5	0.278
Overall SBP (mmHg)	137 ± 16.1	153.2 ± 8.5	<0.001
Overall DBP (mmHg)	76.5 ± 9.6	80.5 ± 5.1	0.137

MI: Myocardial infarction, CAD: Coronary artery disease, PCI: Percutaneous coronary intervention, BMI: Body mass index, DM: Diabetes mellitus, HT: Hypertension, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, Dt: Daytime, Nt: Nighttime

Table 2.

Medical treatments and laboratory data

	Mortality (-) (n = 100)	**Mortality (+) (n = 21)**	**p value**
ARB, n (%)	41 (41)	5 (23.8)	0.108
ACEI, n(%)	47 (47)	10 (47.6)	0.573
Beta-blocker, n (%)	39 (39)	9 (42)	0.463
Diuretic n (%)	49 (49)	8 (38.1)	0.252
CaCB, n (%)	26 (26)	12 (57)	0.005
Oral anti-diabetic, n (%)	94 (94)	18 (85.7)	0.188
SGLTi, n (%)	16 (16)	4 (19)	0.492
Insulin, n (%)	14 (14)	5 (23.2)	0.208
Fibrate, n (%)	6 (6)	3 (14.3)	0.191
Statin, n (%)	42 (42)	10 (47.6)	0.636
Blood glucose (mg/dL)	149.6 ± 60	164.5 ± 57.2	0.302
Creatinine (mg/dL)	0.79 ± 0.18	0.81 ± 0.19	0.575
Hemoglobin (g/dL)	13.2 ± 1.2	12.7 ± 1.6	0.094
C-reactive protein (mg/dL)	0.22 (0.09-1.09)	0.2 (0.12-0.29)	0.248
HbA1c (%)	7.9 ± 1.5	8.2 ± 1.7	0.443
eGFR	88.8 ± 18.5	79.8 ± 16.1	0.050

ARB: Angiotensin II receptor blockers, ACEI: Angiotensin-converting enzyme inhibitor, CaCB: Calcium channel blocker, eGFR: Estimated glomerular filtration rate, SGLTi: Sodium-glucose transport protein 2 inhibitor.

Echocardiographic left atrial strain parameters, namely LASr% (35.7 ± 8.7 vs. 29.8 ± 7.3, p-value: 0.047), LAScd% (17.6 ± 5.8 vs. 13.3 ± 4.1, p-value: 0.028), and pLASRr (1.5 ± 0.4 vs. 1.22 ± 0.3, p-value: 0.037), were worse in the mortality group. In the right ventricular strain evaluation, RV4CSL% (-26.1 ± 5.4 vs. -20.8 ± 6.2, p-value: 0.005) was also worse in the mortality group. The groups did not significantly differ in relation to the remaining echocardiographic parameters (Table 3).

Table 3.

Echocardiographic data

	Mortality (-) (n = 100)	**Mortality (+) (n = 21)**	**p value**
LVEF	58.5 ± 6.5	58.1 ± 9.6	0.837
Sm	0.09 ± 0.02	0.08 ± 0.01	0.266
Em	0.11 ± 0.03	0.09 ± 0.02	0.085
Am	0.13 ± 0.03	0.12 ± 0.04	0.757
E/Em	7.5 ± 2.8	8.8 ± 3.6	0.189
E/A	0.94 ± 0.29	0.78 ± 0.22	0.101
LAVI	33.5 ± 11	34.8 ± 12.1	0.326
LAEI	1.15 ± 0.53	1.25 ± 0.56	0.600
GLSs LALASr, %	35.7 ± 8.7	29.8 ± 7.3	0.047
GLSe LALAScd, %	17.6 ± 5.8	13.3 ± 4.1	0.028
GLSa LA LASct, %	18.1 ± 4.5	16.8 ± 4.6	0.387
GLSRs LApLASRr	1.5 ± 0.4	1.22 ± 0.3	0.037
GLSRe LA pLASRcd	1.8 ± 0.4	1.5 ± 0.3	0.485
GLSRa LApLASRct	2.3 ± 0.5	2.2 ± 0.6	0.355
GLS LVGLSLV, %	-18.7 ± 2.7	-18.9 ± 4.1	0.823
GLS RVRV4CSL, %	-26.1 ± 5.4	-20.8 ± 6.2	0.005
AASI	0.49 ± 0.13	0.56 ± 0.17	0.058

LVEF: Left ventricular ejection fraction, Em: Early diastolic tissue velocity, Sm: Systolic tissue velocity, Am: Late diastolic tissue velocity, LAVI: Left atrium volume index, LAEI: Left atrium expansion index, LASr: Strain during reservoir phase, LAScd: Strain during conduit phase, LASct: Strain during contraction phase, pLASRr: Peak strain rate during reservoir phase, pLASRcd: Peak strain rate during conduit phase, pLASRct: Peak strain rate during contraction phase, GLSLV: Left ventricular global longitudinal strain, RV4CSL: right ventricular four-chamber strain, AASI: Ambulatory artery stiffness index

Univariate and multivariate logistic regression analyses were conducted to ascertain independent predictors of mortality. In univariate logistic regression analysis, mean daytime SBP (odds ratio [OR]: 1.769 p-value: 0.028), LAScd% (OR: 0.820 p: 0.015), and RV4CSL% (OR: 0.078 p-value: 0.043) were determined to independently predict mortality (Table 4).

Table 4.

Independent predictors of mortality

	Univariate analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
Age	1.127	1.055-1.204	<0.001			
DM duration	1.075	1.009-1.146	0.025			
HT duration	1.094	1.040-1.150	0.001			
Average SBP (Dt)	1.054	1.024-1.085	<0.001	1.769	1.005-2.943	0.028
Average SBP (Nt)	1.037	1.013-1.061	0.003			
Office SBP	1.058	1.004-1.115	0.036			
Overall SBP	1.048	1.020-1.078	0.001			
eGFR	0.974	0.950-0.999	0.044			
CaCB	3.226	1.375-7.758	0.007			
LASr, %	0.914	0.837-0.997	0.043			
LAScd, %	0.852	0.739-0.982	0.027	0.820	0.698-0.963	0.015
pLASRr	0.130	0.020-0.828	0.031			
RV4CSL, %	1.179	1.046-1.330	0.007	0.078	0.007-0.924	0.043

DM: Diabetes mellitus, HT: Hypertension, SBP: Systolic blood pressure, Dt: Daytime, Nt: Nighttime, eGFR: Estimated glomerular filtration rate, CaCB: Calcium channel blocker, LASr: Strain during reservoir phase, LAScd: Strain during conduit phase, pLASRr: Peak strain rate during reservoir phase, RV4CSL: Right ventricular four-chamber stra

Mean SBP (mmHg) (Dt) ≥ 148.5 mmHg was identified as having 80% sensitivity and 76% specificity in predicting mortality, with positive and negative predictive values (PPV and NPV) of 38.2% and 96.2%, respectively. LAScd ≤ 15.3 had 80% sensitivity and 24% specificity in predicting mortality, with a PPV of 10% and an NPV of 94.5% (Table 5). Kaplan-Meier analysis revealed that LAScd deterioration was associated with mortality (p-value: 0.023) (Figure 1). RV4CSL ≤ 24.8 had 80% sensitivity and 24% specificity in predicting mortality, with a PPV of 23.6% and an NPV of 95.4% (Table 5). According to Kaplan-Meier analysis, RV4CSL deterioration was related to mortality (p-value: 0.016) (Figure 2).

Figure 1.

Kaplan–Meier survival analysis. The Kaplan–Meier curve shows the survival curves according to LAScd

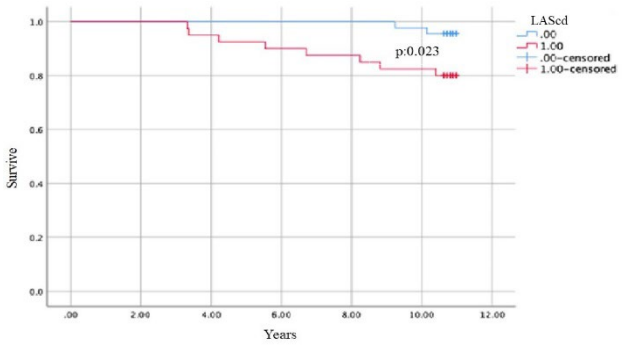
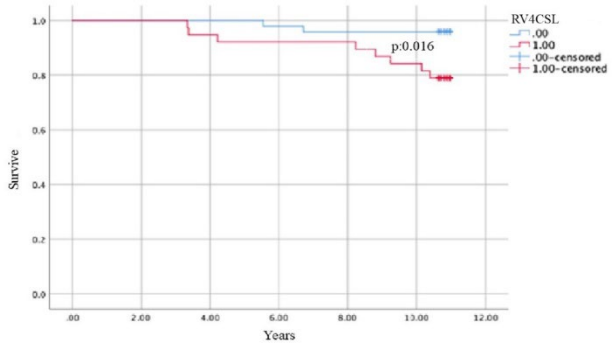


Figure 2.

Kaplan–Meier survival analysis. The Kaplan–Meier curve shows the survival curves according to RV4CSL



4. DISCUSSION

This study showed that right ventricular and left atrial strain parameters, independent of other factors, were correlated with mortality from all causes in diabetic and hypertensive cases. In addition, mean daytime SBP was found to independently predict all-cause death, apart from the strain parameters.

Hypertension-induced cardiac remodeling impairs the balance between collagen types (1 and 3), which are major components of the extracellular matrix.[8] Increased stress, particularly in the subendocardial zone, contributes to heterogeneous myocardial fibrosis. This irregular collagen synthesis and cardiac fibrosis in hypertension patients have been linked to reduced global longitudinal strain and early systolic dysfunction.[9] Hypertension's effect on cardiovascular and mortality from all causes and morbidity has been well-documented in many studies. Consistently, our study revealed that all SBP values were elevated in the mortality group, and mean daytime SBP independently predicted all-cause mortality in multivariate logistic regression analysis. Therefore, detection and control of hypertension should be a priority.

The higher mean BP in the mortality group results in an increase in the use and number of medications. While the use of Angiotensin Converting Enzyme Inhibitors (ACEI)/ Angiotensin receptor blockers (ARB), Diuretic, Beta-blocker was similar in our patient population, this difference naturally emerged in the use of calcium channel blockers (CaCB). As the authors, we do not think that the use of CaCB is directly related to mortality. However, we included CaCB in the statistical analysis in order to provide objective support for other data that will emerge in subsequent studies.

Hypertension also affects left atrial morphology and function. Increased left atrial size and changes in left atrial strain are frequently observed in the tissue Doppler imaging of hypertensive patients.[10] The increasing focus on atrial dimensions and functionality has improved our understanding of how the atria contribute to cardiovascular performance in both healthy and diseased states.[11] Several population-based studies have shown that left atrial analyses can predict outcomes in the long term .[12] Hypertensive and diabetic cases, even with normal left atrial size, often exhibit impaired left atrial deformation mechanics, and the coexistence of both diseases worsens this impairment in an additive manner.[13] Compared to conventional left atrial function parameters, strain parameters are less load-dependent and relatively independent of coupling effects.[14] Reduced left atrial strain is linked to older age, an increased prevalence of atrial fibrillation, hypertrophy of the left ventricle, reduced systolic performance in the left and right ventricles, and impaired left ventricular diastolic functioning.[15]

In a study by Cameli et al., 312 patients were monitored for an average duration of 3.1 years and evaluated in two groups according to the presence of cardiovascular events. Significant deterioration in left atrial parameters was observed in the group with cardiovascular events. The association between worsening left atrial PLAS as categorized by Kaplan-Meier analysis and cardiovascular events was clearly demonstrated. A key finding in that study was that the left atrial strain parameter was more valuable than volumetric parameters for assessing left atrial dysfunction and prognosis.[11] Modin et al. evaluated 385 patients without atrial fibrillation, ischemic heart disease, or heart failure, investigating the relationship between left atrial strain parameters and a composite endpoint of heart failure, cardiovascular mortality, and ischemic heart disease. Although there was no

difference in left atrial enlargement between the groups, a deterioration in LASr values was found in the combined endpoint group.[16] This finding suggests that volumetric parameters are affected later than strain parameters and highlights the importance of strain values in determining prognosis. Similarly, in our study, LAScd, LASr, and pLASRr values were adversely affected in the mortality group, while the groups did not significantly differ in volumetric parameters. LAScd was identified as a parameter that independently predicted mortality, maintaining its significance in multivariate analysis. Both our findings and the literature demonstrate that traditional left atrial assessment parameters may be late in predicting adverse events. Therefore, early intervention, especially in patients with risk factors, can be performed by incorporating functional parameters and strain assessment.

For many years, the significance of right ventricular function was largely overlooked. However, with accumulating evidence from both healthy and diseased populations, the understanding of the significance of the right ventricle has advanced. Assessing right ventricular function using conventional echocardiographic techniques is challenging due to its complex geometry, leading to inconsistent results.[17] Speckle-tracking echocardiography is an advanced modality with the potential of addressing some of these limitations.[18] Lejeune et al. investigated the RV4CSL parameter in the long term in cases of heart failure with preserved EF. RV4CSL was identified as an independent predictor of mortality from all causes. In the same study, evaluation of the patients were in two groups according to RV4CSL revealed that the impaired RV4CSL group had lower left-right ventricular EF and tricuspid annular plane systolic excursion and higher N-terminus pro-B-type natriuretic peptide values.[19] In the current study, while systolic and diastolic function were not significantly different between the mortality and non-mortality groups, RV4CSL was impaired in the mortality group, and this parameter was an independent predictor of all-cause mortality in multivariate logistic regression analysis. Deterioration in RV4CSL without corresponding impairment in traditional parameters may allow time for early intervention in controlling and treating risk factors. In addition, this finding shows the importance of evaluating the heart as a whole rather than focusing solely on the left side in echocardiographic evaluation.

5. CONCLUSION

Hypertension and diabetes mellitus are recognized risk factors for cardiovascular events, and their importance is well-established within the healthcare community. As with any disease, early intervention and preventive measures are crucial for preventing cardiovascular events. Traditional follow-up methods may delay early intervention. Echocardiography is the most commonly used tool for monitoring and detecting the effects of diabetes mellitus and hypertension on the cardiovascular system. Both our study and the literature show that traditional volumetric echocardiography parameters are late predictors of adverse events. Therefore, it is essential to evaluate high-risk patients using functional echocardiographic parameters, even if volumetric echocardiography parameters are normal. Early detection of potential deterioration in functional parameters may allow for tighter control of risk factors and reduced mortality and morbidity. Strain parameters, which provide functional evaluation through echocardiography, should be utilized as diagnostic and follow-up tools for determining prognosis and facilitating early control of risk factors, especially in comparison to volumetric parameters.

Limitations

This study is limited by its single-centered nature and the small sample size. In addition, patient selection was not randomized. The reliability of the results could be enhanced through a multicenter study involving a larger sample. Since the EchoPAC™ program used for strain analysis did not have a specific interface for RV, it was modified with operator support on the modified RV using the LV interface.

Article Information Form

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Authors' Contribution

All authors contributed to substantial contributions to conception and design (AÖ,EE,EK and MGY), or acquisition of data (TG,MA and TT), or analysis and interpretation of data (AÖ,TT, MGY and MÇ), drafting the article or revising it critically for important intellectual content (AÖ,EK and TT) and final approval of the version to be published.

The Declaration of Conflict of Interest/ Common Interest

No conflict of interest or common interest has been declared by authors.

Ethical Statement

The study was performed in accordance with the ethical considerations of the Helsinki Declarations. The study was approved by the ethics committee of SBÜ Trabzon Medicine Faculty, with decision number 31.05.2023/10496660-27

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