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Research Article

Prevalence & Outcome of Advanced Left Ventricular Diastolic Dysfunction among Consecutive Patients Referred for Echocardiography

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ABSTRACT

Aim: To assess the prevalence of advanced left ventricular diastolic dysfunction (LVDD) in a cohort of consecutive patients referred for echocardiography and its association with mortality.

Methods: The cohort included 4,481 (85% hospitalized) patients who underwent echocardiography, had normal or preserved LV systolic function and diastolic function assessment. LVDD was graded as none or mild (0/I) and advanced grade (II/III). Mortality data were derived from the National Israeli Population Registry.

Results: LVDD grade II/III was found in 1,262 patients (28%), was more prevalent among the elderly, females, diabetic and hypertensive patients. Independent predictors associated with LVDD grade II/III (OR; 95% CI) were: age (1-year increment) 1.015 (1.01-1.02), $p < 0.001$; female sex 1.2 (1.04-1.39), $p = 0.012$; hypertension 1.53 (1.30-1.80), $p < 0.001$, while ischaemic heart disease was negatively associated 0.73 (0.63-0.85), $p < 0.001$. 1-year mortality rates were higher among grade II/III LVDD as compared to grade 0/I DD patients, 19% vs. 10.2%, respectively, $p < 0.0001$. Independent predictors for all-cause mortality after adjusting for pertinent variables were: LVDD grade II/III 1.72 (1.40-2.11); age (1-year increment) 1.08 (1.07-1.09) and diabetes 1.54 (1.26-1.70), $p < 0.001$ for all.

Conclusion: LVDD grade II/III was more prevalent among the elderly, females, diabetic and hypertensive patients. Advanced LVDD was a strong independent predictor for all-cause mortality after adjustment for risk factors. Intensive pharmacological therapies at an earlier stage of LVDD may improve patients' outcome.

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Introduction

Left ventricular diastolic dysfunction (LVDD) is associated with the development of heart failure with preserved ejection fraction (HFpEF), atrial fibrillation, and increased risk of cardiovascular (CV) death [1-6]. LVDD is more prevalent among the elderly, females, diabetic and hypertensive patients [6-8]. However, the relative impact of each of these risk factors on the development of LVDD is not clear. Furthermore, although LVDD is associated with an increased risk of CV death, it is not clear whether LVDD itself contributes to an additional mortality risk in the presence of CV risk factors.

The aim of the study was to evaluate in a large cohort of mostly hospitalized consecutive patients referred for echocardiography, the prevalence of advanced LVDD, and to assess its prognostic significance on mortality.

Methods

The study population included 4,481 consecutive patients, 85% hospitalized in cardiology and internal medicine wards, and others who were referred for trans-thoracic echocardiography (TTE) at our tertiary care center, from November 1, 1991, to October 31, 2017. Patients with normal or preserved left ventricular systolic function were included in

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the study. Patients with mitral stenosis were excluded. All patients had Doppler data that enabled the diastolic function assessment.

To evaluate the diastolic function, trans-mitral inflow was recorded using pulsed-wave Doppler in the apical 4 chamber view for measurements of early (E) and late (A) mitral inflow velocities. Early diastolic velocity was assessed at the septal (septal e') and lateral (lateral e') sites of the mitral annulus using pulsed-wave tissue Doppler imaging. The average value of septal e' and lateral e' was used to calculate E/e' ratio. The maximal left atrial (LA) area was measured by planimetry on apical 4-chamber view, and the LA volume by using modified Simpson's rule in apical 4-chamber and apical 2-chamber views at ventricular end-systole. Diastolic function was evaluated according to the 2016 recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging (ASE/EACVI) [9].

In brief, in patients with normal or preserved left ventricular function, four recommended variables and their abnormal cutoff values were used: i) septal e' < 7 cm/sec or lateral e' < 10 cm/sec; ii) average E/e' ratio > 14; iii) peak TR velocity > 2.8 m/sec; iv) LA volume index > 34 mL/m². LVDD was identified when at least 2 out of these 4 variables met the cutoff values. The severity of LVDD was defined according to the following criteria: i) Normal diastolic function (Grade 0); ii) grade I when E/A < 0.8 and E ≤ 50 cm/s; iii) Grade II when E/A ≤ 0.8 and E > 50 cm/s or E/A > 0.8 < 2 and two of the above mentioned variables B, C or D met the cutoff points) iv) Grade III when E/A > 2. LVDD grade II/III was defined as advanced LVDD. All patients' data including demographics, CV risk factors, and echo-Doppler measurements were prospectively collected and stored in the hospital computerized patients charts database. Mortality data were derived and confirmed by the National Israeli Population Registry of the Ministry of Interior.

Statistical Analyses

Patients' characteristics were described by means ± SD for continuous variables and numbers with percentages for categorical variables. The association between categorical variables and LVDD grade II/III were assessed using chi-square test, and the relation between continuous variables and LVDD grade II/III were tested using the unpaired Student's t-test. Multivariable logistic regression model was conducted in order to identify independent variables associated with advanced LVDD. The variables that were included in the analysis were: age, sex,

diabetes, hypertension, history of ischaemic heart disease (IHD), moderate and severe valvular diseases including aortic stenosis and regurgitation and mitral regurgitation, and patients' status during the performance of the echocardiography study (ambulatory versus hospitalized). Odds ratios (ORs) with 95% confidence intervals (CIs) are reported.

The role of LVDD grade II/III on survival time, evaluated from the index echocardiography date are shown by Kaplan-Meier curves and were compared with the use of a log-rank test. In order to assess variables associated with 1-year all-cause mortality, Cox proportional-hazards regression model was obtained with hazard ratios (HRs) and 95% confidence intervals (CI) and included the same parameters that were contained in the analysis performed to identify the independent variables associated with advanced LVDD, including the variable LVDD grade II/III. All tests were two-sided. P-value of < 0.05 was considered statistically significant. Analyses were performed by using SPSS Statistics software, version 25, IBM, Armonk, NY.

Results

The patients' characteristics are presented in (Table 1). It is notable that the patients with LVDD grade II/III were older, more frequently females, had a higher prevalence of diabetes and hypertension, but a lower prevalence of IHD. LVDD grade II/III was more frequent among patients with moderate and severe valvular disease and hospitalized patients. Patients with LVDD grade II/III had lower fractional shortening, left atrial diameter, and Doppler parameters that reflect diastolic dysfunction. The patients' characteristics according to the individual LV diastolic function parameters are detailed in (Table 2). It is notable that in general, these parameters are more frequent with advanced age, among females, diabetic and hypertensive patients, while they were less frequent among patients with IHD. Multivariate logistic regression analysis revealed that the variables independently associated with LVDD grade II/III were: older age, female sex, hypertension, moderate and severe valvular disease, and hospitalization status, whereas diabetes was not. The presence of IHD was associated with a lower risk of LVDD (Table 3A). When 1,204 patients with moderate and severe valvular disease were excluded from the model, female sex was no longer associated with LVDD grade II/III, whereas diabetes became positive (Table 3B).

Table 1: Clinical and Echo-Doppler characteristics of patients with grade 0/I and II/III LVDD.

	LVDD grade 0/I n=3,219	LVDD grade II/III n=1,262	p-Value
Clinical characteristics			
Age (m±SD), years	71±13	76±13	<0.001
Female sex (n,%)	1,513 (47)	719 (57)	<0.001
Diabetes (n,%)	869 (27)	379 (30)	0.028
Hypertension (n,%)	1,996 (62)	959 (76)	<0.001
Ischaemic heart disease (n,%)	1,223(38)	404 (32)	<0.001
Moderate /Severe valvular disease *(n,%)	546 (17)	658 (52)	<0.0001
Hospitalized patients (n,%)	2688(84)	1140 (90)	<0.0001
Echo-Doppler characteristics			
Left Ventricular End Diastolic diameter (cm)	4.8 [4.4-5.1]	4.7 [4.3-4.1]	0.820
Left Ventricular End Systolic diameter (cm)	2.9 [2.6-3.2]	2.9 [2.6-3.3]	0.015
Fractional shortening %	39 [35-44]	38 [33-43]	<0.001

Left Atrial diameter (short axis) cm	4.2 [3.8-4.7]	4.8 [4.4-5.2]	<0.0001
e' septum velocity cm/s	6.4 [5.2-8.0]	6.1 [5.0-7.5]	0.007
e' lateral velocity cm/s	8.4 [6.9-10.2]	8.2 [6.8-10.1]	0.168
E velocity cm/s	76 [62-93]	107 [89-125]	<0.0001
A velocity cm/s	78.3 [64-94]	47 [38-67]	<0.0001
E/A	0.91 [0.73-1.24]	2.23 [1.73-2.73]	<0.0001
E/A >2	0	659 (52.2)	<0.0001
E/e' ratio	10 [7.83-12.823]	14.7 [11.68-18.52]	<0.0001
E/e' >14 (n, %)	571 (18)	310 (25)	<0.001
TR velocity >2.8 m/s (n, %)	930 (29)	1002 (83)	<0.001
Left Atrial volume index ml/m ² >34 (n, %)	282 (49)	672 (97)	<0.001

*Aortic stenosis, aortic regurgitation, mitral regurgitation

Table 2: Patients' characteristics by individual LV diastolic function parameters.*

	E/A			E/e'			TR velocity m/s			Left Atrial volume index ml/m ²		
	<2	≥2	p-Value	≤14	>14	p-Value	≤2.8	>2.8	p-Value	≤34	>34	p-Value
n	3,822	659		3,600	881		2,478	1,932		319	954	
Age (m±SD) years"	72.39±13	72.9±14	0.358	70.9±13	78.7±10	<0.001	68.5±13	77.9±11	<0.001	70.4±12	77.4±11	<0.001
Female (%)	50.2	47.5	0.203	46.2	64.4	<0.001	42.3	60.4	<0.001	49.2	62.1	<0.001
Diabetes (%)	27.3	31.4	0.030	25.1	39.6	<0.001	24.2	32.1	<0.001	25.7	27.1	0.614
Hypertension (%)	65.8	69.2	0.084	62.8	80.5	<0.001	56.5	79.2	<0.001	62.7	78.5	<0.001
Ischaemic heart disease (%)	35.6	37.6	0.030	36.1	35.2	0.630	39.1	31.6	<0.001	38.2	27.0	<0.001

*Diastolic function assessment, 2016 ASE/EACVI [9].

Table 3: Independent predictors for LVDD grade II/III.*

	OR*	95% CI	p-Value
A. All patients			
Age (1-year increment)	1.015	1.01-1.02	<0.001
Female sex	1.20	1.04-1.39	0.012
Hypertension	1.53	1.30-1.80	<0.001
Diabetes	1.16	0.99-1.35	0.067
Ischaemic heart disease	0.73	0.63-0.85	<0.001
Moderate/Severe valvular disease†	4.88	4.00-5.94	<0.001
Hospitalized patients	1.93	1.55-2.42	<0.001
B. Valvular disease patients excluded:			
Age (1-year increment)	1.011	1.003-1.020	0.006
Female sex	0.98	0.81-1.18	0.83
Hypertension	1.55	1.26-1.92	<0.0001
Diabetes	1.29	1.06-1.57	0.012
Ischaemic heart disease	0.61	0.50-0.75	<0.0001

*By logistic regression analysis (see Methods)

†Moderate and severe aortic stenosis, aortic regurgitation, mitral regurgitation

The median follow-up time was 304 (107-636) days. 1-year all-cause mortality was higher among patients with LVDD grade II/III as compared to patients with grade 0/I, 19% vs. 10.2%, respectively, p<0.0001 (Figure 1A). After excluding all patients with moderate and

severe valvular (see methods), 1-year mortality rate was 16% among LVDD grade II/III as compared to 7% among LVDD grade 0/I; p<0.0001 (Figure 1B).

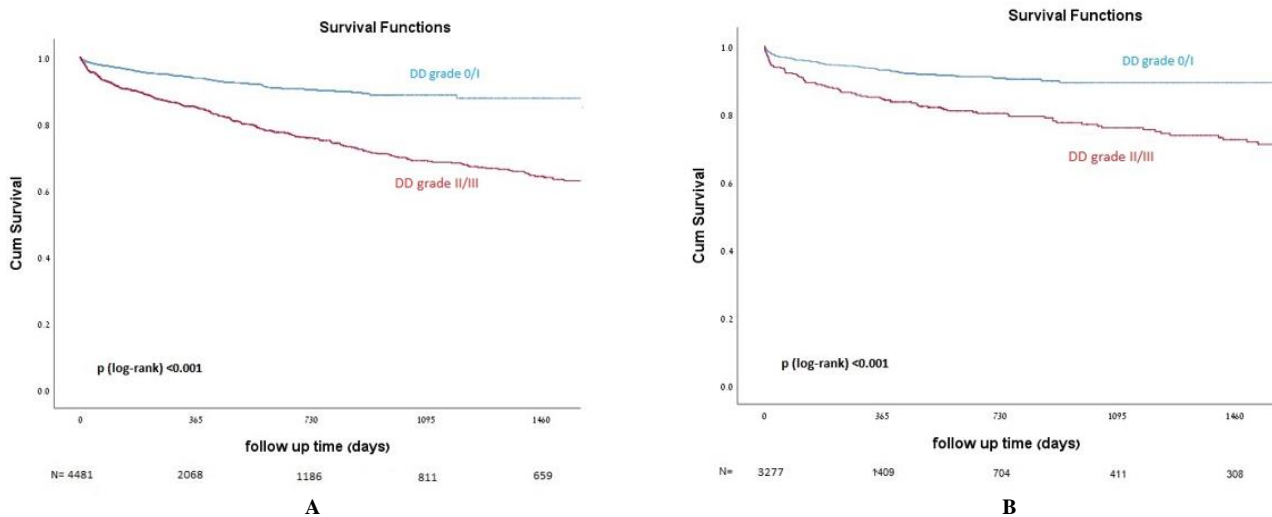


Figure 1: A) Kaplan-Meier cumulative survival curves of the entire cohort, comparing LVDD grade 0/I and LVDD grade II/III. **B)** Kaplan-Meier cumulative survival curves of the cohort excluding patients with moderate and severe valvular disease, comparing LVDD grade 0/I and LVDD grade II/III.

Cox proportional hazard regression analysis revealed that LVDD grade II/III was independently associated with increased all-cause mortality as compared to grade 0/I LVDD (HR=1.72 (1.40-2.11), $p < 0.001$). This

result was also maintained after excluding from the model all patients with moderate and severe valvular disease HR=2.08 95% CI [1.53-2.83] $p < 0.0001$ (Table 4).

Table 4: Independent predictors of 1-year all-cause mortality.*

	HR*	95% CI	p-Value
Grade II/III diastolic dysfunction	1.72	1.40-2.11	<0.001
Diabetes	1.54	1.26-1.7	<0.001
Age (1-year increment)	1.08	1.07-1.09	<0.001
Moderate /Severe valvular disease†	1.93	1.57-2.36	<0.001
Hospitalized patients	1.59	1.15-2.21	0.005

*By Cox proportional hazards-regression model (HR) (see Methods)

†Moderate and severe aortic stenosis, aortic regurgitation, mitral regurgitation

Discussion

Our study included 4,481 consecutive patients (85% hospitalized) referred for echocardiography who had normal or preserved LV systolic function and diastolic function assessment. Of them, 72% had a normal diastolic function or mild dysfunction (grade I), whereas 28% had advanced LVDD grade II/III. The study demonstrated that advanced LVDD was more common among the elderly, female sex, diabetic, hypertensive, moderate and severe valvular disease, and hospitalized patients, whereas less frequent among patients with known IHD. The study demonstrated that advanced LVDD was a strong independent predictor of all-cause mortality.

Prior studies have described the association between CV risk factors and the development of LVDD; however, these studies used non-standardized methods of measurements and definitions for the diagnosis of LVDD [6-8]. Almeida *et al.*, emphasized that the heterogeneity and ambiguity of the different definitions of LVDD led to a significant variability in its reported prevalence and grading. In their study following the release of 2016 ASE/EACVI diastolic function assessment algorithm, a retrospective analysis of a population-based cohort of 1,000 individuals was performed [9, 10]. After exclusion of those with previously known cardiac disease or ejection fraction <50%, the prevalence of LVDD was 1.4% with the 2016 recommendations, 38.1%

with the 2009 recommendations, and 30.4% using the Canberra Study Criteria. Hence, they concluded that the application of the new recommendations resulted in a much lower prevalence of LVDD and that the concordance between the classifications was poor. In a recent study by Gopalakrishnan *et al.*, that also followed the 2016 ASE/EACVI recommendations and was based on more than 20,000 echocardiograms from a single-center, it was demonstrated that there was a 57% decrease in reporting of diastolic dysfunction ($p < 0.001$), grade 1 LVDD decreased by 64% ($P < 0.001$), grade 2 LVDD decreased by 51% ($P < 0.001$), and grade 3 LVDD did not change significantly ($P = 0.18$) [11]. Hence, diastolic function studies published before the release of the 2016 recommendations present miscellaneous non-standardized results. The high prevalence of advanced LVDD observed in our cohort using the 2016 ASE/EACVI recommendations reflects the difference between our study population and the aforementioned ones. In our cohort, most of the patients were hospitalized, and those with significant valvular disease were not excluded from the analyses.

Our study demonstrated that advanced LVDD was more common among the elderly, female sex, hypertensive, and diabetic patients, similarly to Nayor *et al.*, [6]. In an additional article, they concluded that when age- and sex-specific reference limits are used, LVDD was less dependent on age, correlated more powerfully to systolic and diastolic blood pressure,

body mass index, hypertension treatment status, total cholesterol/HDL-cholesterol and diabetes [12].

In our study, the presence of IHD was associated with a lower frequency of advanced LVDD. In contrast, in a study by Lin *et al.*, the extent and severity of obstructive as well as non-obstructive coronary disease by coronary CT angiography were associated with increased measures of LVDD [13]. The prevalence of LVDD increased with a greater number of obstructed vessels. A possible explanation for this contrast is that the information regarding the history of IHD in our study was retrieved from the patients' echo database and was not confirmed angiographically in all patients; hence, it might underestimate the true prevalence of coronary disease in our population. A second possible explanation for our finding may be related to the wide range of medications given to patients with IHD, including beta-blockers, ACEI and ARBS, calcium channel blockers, and nitrates that may actually reduce the risk for the development of advanced LVDD.

The impact of medications on LVDD has not been resolved yet. Several studies have shown that inhibition of the renin-angiotensin aldosterone system (RAAS) with ACEIs or ARBs improve LVDD, also with a combination with beta-blockers or calcium channel blockers; however, others failed to demonstrate such benefit, like the Valsartan in Diastolic Dysfunction (VALIDD) and the perindopril indapamide combination [14-19]. Lan *et al.*, demonstrated that LV mass index and diastolic function improved following SGLT2 inhibitor therapy in people with type 2 diabetes [20]. Our study is retrospective, derived from the departmental electronic database, and hence, the impact of medications on diastolic function was beyond its scope.

Left Ventricular Diastolic Dysfunction (LVDD) and Outcome

In our study, 1-year all-cause mortality rates were 19% among patients with advanced LVDD (grade II/III) as compared to 10.2% among patients with grade 0/I, $p < 0.0001$. The relatively high mortality rates observed in our patient population might be related to the fact that the majority of the patients in both groups were hospitalized and hence were sicker as compared to echo-laboratories that serve mostly outpatients.

Our study has demonstrated that echocardiographic and tissue Doppler imaging (TDI) parameters that assess diastolic dysfunction predict patients' outcome. In accordance with our study, several prior studies have noted that moderate and severe LVDD is associated with increased mortality risk [6, 21, 22]. Mogelvank *et al.*, in their community-based Copenhagen City Heart Study, demonstrated that left ventricular systolic and/or diastolic dysfunction assessed by TDI on 1,036 participants were independent predictors of death in the general population [21]. TDI information had an incremental predictive value when age, body mass index, heart rate, hypertension, diabetes, IHD, and plasma pro-BNP were taken into consideration. Kuznetsova *et al.*, studied the prognostic role of TDI-derived indexes on 793 patients of a general population [22]. After adjustment for conventional cardiovascular risk factors, LV TDI mitral annular e' velocity was a significant predictor of fatal and nonfatal cardiovascular events, as compared with a model including only conventional cardiovascular risk factors. However, mitral annular e' velocity is just one of the parameters required for the evaluation of LVDD. We have demonstrated that advanced LVDD was a strong independent predictor for all-cause mortality after adjustment for age, sex, diabetes, hypertension, and other pertinent variables.

The ASCOT study, which included 980 patients with hypertension but without coronary heart disease demonstrated that E/e' ratio was the strongest predictor of cardiac events by Cox-proportional hazards models, corrected for age, gender, diabetes and systolic blood pressure, and that a unit rise in the E/e' ratio was associated with a 17% increment in the risk of a cardiac events [23]. Blomstrand *et al.*, demonstrated that among 406 middle-aged diabetic patients that E/e' ratio was a strong predictor of myocardial infarction and stroke comparable with HbA1c, superior to global left ventricular longitudinal strain and left ventricular ejection fraction [24]. In patients with diabetes, the E/e' ratio has appeared to independently predict heart failure and mortality [25].

The PARAGON-HF trial tested the efficacy of sacubitril-valsartan in patients with heart failure with preserved ejection fraction (HFpEF). Among the 868 participants who had with TDI data, 96% had 2016 ASE/EACVI criteria for HFpEF. During a median follow-up of 2.8 years, 288 patients experienced heart failure hospitalization or cardiovascular death. Multiple Doppler-based diastolic measures were robustly associated with these outcomes, including higher E-wave velocity, lower TDI septal e' , and higher septal and lateral E/e' ratios were each associated with higher risk for the composite endpoint in adjusted models [26].

Limitations

Our cohort represents mainly hospitalized patients hence reflecting a highly selected population. It is possible that our results may not be applicable to echo Doppler findings in outpatient population.

Conclusion

Utilizing the 2016 ASE/EACVI criteria for the assessment of LVDD revealed high prevalence of advanced LVDD in a cohort of mainly hospitalized patients. Advanced LVDD is more prevalent among the elderly, females, diabetic and hypertensive patients, and provides an independent powerful predictor of all-cause mortality. Patients with earlier stages of LVDD may require intensive medical attention and pharmacological therapies in an attempt to improve their outcome.

Conflicts of Interest

None.

Author Contributions

The research concept and design were outlined by MM and SG. Data acquisition, analysis and interpretation were performed by MM, SG, RF and AB. The manuscript was drafted by MM and SG. All authors contributed to critical revision and approved the final version.

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